biophytis

NEW THERAPEUTICS FOR DISEASES OF AGING

2017 Annual Report

THE BIOTECH SPECIALISED IN DISEASES OF AGING

Société Anonyme [Limited Liability Company] with a Board of Directors and share capital of €2,692,682.60
Registered office: 14, avenue de l'Opéra - 75001 PARIS
Trade and Companies Register (RCS) of Paris 492 002 225

2017 ANNUAL REPORT

AUTORITÉ DES MARCHÉS FINANCIERS

This document is a free non- binding translation, for information purposes only, of the French language "Document de Référence 2017" as submitted to the AMF on July 23, 2018. In the event of any ambiguity or conflict between corresponding statements or items contained in this English translation and the original French version, the relevant statements or items of the French version shall prevail. The auditor's reports apply to the French version of the activity report and the financial statements.

In application of its general regulations, notably article 212-23, the French Financial Markets Authority (*Autorité des Marchés Financiers*, "**AMF**") registered this Annual Report on july 23, 2018 under number R. 18-058. This document cannot be used to support a financial transaction unless accompanied by a prospectus supplement approved by the AMF.

It was prepared by the issuer and is the responsibility of its signatories.

This document is available free of charge on the website of the Company (www.biophytis.com/)

Message from the Chairman

Biophytis' positioning on ageing-associated diseases is unique: on which scientific platform is it based?

Ageing is a complex biological process with multiple causes: genetic, hormonal, metabolic, and even environmental factors lead to the progressive loss of the main body functions (visual, muscular, cognitive, cardiac, respiratory, urinary...) and ultimately death. The field of scientific research in ageing processes is in full expansion. Fortunately, the biological processes at work are universal, affecting all the cells and organs of all living beings, which allows for great research possibilities. Biophytis, in collaboration with SORBONNE UNIVERSITY researchers, is studying these processes with the aim of developing drugs capable of slowing down degenerative processes and the progression of ageing-associated diseases, and that ultimately limit the risk of dependence.

We are not all equal when it comes to ageing: some of us develop age-related diseases such as Alzheimer, AMD, or sarcopenia. These diseases can be defined as specific conditions where an organ of an elderly individual (and the cells of which it is made) undergoes an accelerated or aggravated ageing process. They are yet to be clearly defined, however, from a pathophysiological, clinical and regulatory point of view, and there is no drug treatment available for most of them. Biophytis collaborates with clinicians specialising in these diseases and the relevant regulatory agencies to identify target patient populations and define clinical development plans to evaluate the therapeutic efficacy of our drug candidates.

Our drug candidates are small molecules derived from plant secondary metabolites that modulate the biological processes involved in the ageing of targeted cells and tissues. We have selected the active ingredients of Sarconeos or Macuneos by testing hundreds of molecules from a collection of natural or semi-synthetically derived molecules in cellular models of degenerative diseases, AMD or sarcopenia, without prior knowledge of molecular targets. It is a reverse pharmacology strategy that has allowed us to discover new targets involved in ageing processes and to identify new classes of drug candidates such as Sarconeos, which is in clinical development for sarcopenia and Macuneos which is in clinical development for AMD.

How far along are you in the development of Sarconeos for sarcopenia, your most advanced clinical programme?

Biophytis' primary concern is the development of Sarconeos for sarcopenia. Sarconeos is the most advanced drug candidate in our portfolio and the one that currently represents the most value for our company. In 2016, we developed a particularly ambitious clinical and regulatory development plan, consisting of three clinical studies to meet the challenge of developing a product for this particularly disabling condition for which there is currently no drug treatment. Since then, we have successfully conducted the first clinical study in healthy volunteers (SARA-PK), have

set up the second clinical, observational and international study in patients with sarcopenia (SARA-OBS) and are now launching the third one: an interventional phase 2b study (SARA-INT) that follows the observational study and will enable us to demonstrate the therapeutic efficacy and safety of Sarconeos in the treatment of sarcopenia.

First, having obtained the final results of the SARA-PK clinical study, conducted in 2016 in Belgium, we were able to confirm the right safety and pharmacokinetics profile for Sarconeos in elderly healthy volunteers. We were then able to define the dosages used in the SARA-INT phase 2b clinical trial and file the authorisation applications to start this study in Europe and the United States. We also recruited more than 100 patients with sarcopenia in the SARA-OBS observational study, which was carried out in more than 11 clinical centres in the United States, Belgium, France and Italy. The mobility – gait speed over 400 metres in particular – and the muscular quality of the patients is evaluated for 6 months. Subject to their consent, they will be included progressively in 2018 in the phase 2b SARA-INT study.

We obtained authorisation from the US Food and Drug Agency (FDA), then from the Belgian Federal Agency for Medicines and Health Products (FAMHP) to launch the phase 2b interventional study for Sarconeos in sarcopenia (SARA-INT). We are currently waiting for authorisation in France and Italy. The objectives of SARA-INT are to evaluate the safety and efficacy of two doses of BIO101 (175 mg bid and 350 mg bid) administered orally for 26 weeks vs a placebo in a population of men and women over the age of 65 with a risk of disability. The study should enrol 334 patients in 22 clinical centres in Europe and the United States, about half of which are from the observational study. We expect to include the first patient in the second quarter of 2018, complete the inclusion of patients at the end of the year, obtain the preliminary results in the summer of 2019 and close this study by the end of 2019.

We have become the leading biotechnology company looking for a treatment for sarcopenia. By presenting 8 scientific papers at the ICFSR 2017 and the SCWD 2017, we have actively communicated the progress of our work at these scientific conferences that gather sarcopenia specialists from all over the world. We have also consolidated the industrial property rights to the use of Sarconeos in sarcopenia and other muscular dystrophies, having filed two new patent applications, for a total of 6 families of granted or worldwide patents covering this technology.

> *<u>What level of priority have you assign to the development of Macuneos for AMD?</u>*

Macuneos is Biophytis' second drug candidate in clinical development. In 2016, we postponed the clinical development of this drug candidate, so that it would take over from Sarconeos when the clinical development of the latter product had been completed. As this is now the case, the clinical development of Macuneos is once again at the forefront of our concern. Moreover, as drug candidates intended as a complementary drug for geographic atrophy – also known as advanced dry AMD – have failed in clinical trials, the search for therapeutic alternatives goes on. The medical

community and regulatory authorities now recognise the importance of treating the disease at an earlier stage, the so-called intermediate stage, with the aim of slowing down its progression towards severe forms, geographic atrophy or wet AMD. Macuneos is, to our knowledge, the only drug candidate in clinical development with the potential to be used at this stage. We must, therefore, accelerate its clinical development to demonstrate the effectiveness of Macuneos in the treatment of this particularly debilitating disease.

In 2017, we completed preparations for the launch of the MACA-PK phase 1-2a study, which aims to study the safety, pharmacokinetics and pharmacodynamics of Macuneos in patients with dry AMD. All regulatory non-clinical studies have been completed and the production of clinical batches secured. The clinical trial protocol has been optimised and consists of an initial phase in healthy volunteers in a clinical centre in Belgium (SAD), followed by a second phase in patients with dry AMD recruited from 10 ophthalmology centres in Europe (MAD). We expect to launch this study this summer with the aim of completing the SAD phase at the end of 2018 and thus be able to conduct the MAD phase in 2019.

<u>Why develop Sarconeos and Macuneos for paediatric rare diseases?</u>

The development of Sarconeos for Duchenne muscular dystrophy or of Macuneos for Stargardt disease in the future presents a new opportunity for Biophytis, which perfectly complements development for the main, chronic geriatric conditions. A "rare" disease designation enables companies to accelerate the clinical development of drug candidates up to the Marketing Authorisation (AMM) and benefit from extensive, specific protection. Developing Sarconeos or Macuneos for both a geriatric and a paediatric condition at the same time can reduce the clinical risk and increase the potential of the drug candidate.
These new clinical development projects are the result of years of research on the pharmacological profile of our drug candidates. Our researchers consider that these rare diseases actually lead to accelerated ageing of the target organs and therefore constitute simplified genetic models of age-related diseases. We thus expounded at the WMS 2017 conference on the effects of Sarconeos on mobility and fibrosis in the context of Duchenne muscular dystrophy. We also have some very interesting results from Macuneos in the context of Stargardt disease, which will be presented at ARVO 2018.
We have thus begun to prepare the Sarconeos clinical development plan for Duchenne muscular dystrophy: the MYODA plan. Biophytis' scientific committee has been strengthened by the presence of paediatrician and world-renowned specialist in neuromuscular genetic disease Thomas Voit, Director of the Biomedical Research Centre (BRC) of the Great Ormond Street Hospital for Children NHS Foundation Trust. The MYODA clinical programme is based on two main studies: MYODA-PK, which aims to study the safety, pharmacokinetics and pharmacodynamics of the paediatric formulation of Sarconeos in boys aged 2 to 18 years with Duchenne muscular dystrophy; and MYODA-INT, which will test the safety and therapeutic efficacy of Sarconeos in homeless boys after one year of administration. MYODA-PK could be launched in the second half of 2018 and MYODA-INT in 2019.

Do you have the resources to develop your portfolio of drug candidates?

We replenished Biophytis' capital in 2017 through several capital increase operations, which raised €27.6 million. This means that, at the end of FY2017, the Company's shareholders' equity amounted to €21 million and cash assets were €20 million with financial liabilities of €1 million. Slightly higher losses of € 11 million reflected the investment in the development of Sarconeos and Macuneos. In 2017, we also set up a financing contract with Bracknor, allowing us to draw €9 million in convertible bonds (ORNANEBSA), for an additional financial lifeline. We therefore have access to enough funding for at least 18 months – enough to complete the SARA-INT and MACA-PK studies which are our priority.

We also continued to strengthen the team initially gathered in 2017 on the main campus of SORBONNE UNIVERSITY in Paris (Jussieu) and made up of scientists, pharmacists and clinicians from the academic world or the pharmaceutical industry. The staff has been increased to 22 experienced professionals, experts in their respective fields, who run a network of specialised subcontractors, divided between research and clinical development. Administrative and financial supervisors are assigned only as needed. In 2018, we will continue to develop the team to effectively manage the clinical and regulatory development of Sarconeos and Macuneos, especially in the United States.

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Concordance table: Annual financial report and Management report required by the French Commercial Code

In order to facilitate the reading of this Annual Report, the concordance table below enables the reader, in accordance with article 28 of Regulation EC No. 809/2004 of 29 April 2004, to identify:

- The information required by article L.451-1-2 of the French Monetary and Financial Code in accordance with article 212-13 and 222-3 of the AMF General Regulations, which constitute the annual financial report (the "**Annual Financial Report**", or "AFR"), and

- The parts of the Company management report (the "**Management Report**", or "MR") required by articles L.225-100 et seq., L.232-1 and R.225-102 et seq. of the French Commercial Code, as well as the specific section of the Management Report dedicated to corporate governance as required by articles L.225-37 paragraph 6 et seq. of the French Commercial Code.

Items	Information required by	Paragraph in the Annual Report
1. Annual accounts	AFR	28.1
2. Consolidated accounts	AFR	20
3. Declaration of responsibility by the individuals who take responsibility for the annual financial report	AFR	1.2
4. Statutory auditors' report on the annual accounts and the consolidated accounts	AFR	20.4 and 28.2
5. Risk factors	AFR	4
6. Management report	AFR	20.9
5.1 Information on the Company's activity	MR	N/A
• Activity of the Company during the past financial year	MR	20.9.1
• Presentation of the Company's results, annual accounts and consolidated accounts	MR	20.9.2
• Progress made or difficulties encountered by the Company	MR	20.9.3
• The Company's research and development activities	MR	20.9.4
• Foreseeable evolution of the Company's position and future prospects	MR	20.9.5
• Significant events after the reporting period (balance sheet date)	MR	5.1.6
• Objective and comprehensive analysis of business developments in terms of the volume and complexity of business	MR	20.9.6
• Description of the main risks and uncertainties	MR	20.9.7
5.2 Company legal, financial and tax information	MR	N/A
• Use of the Company's financial securities	MR	5.2.2

Items	Information required by	Paragraph in the Annual Report
• Summary of employee stock ownership status	MR	17.3
• Breakdown of capital	MR	18 and 21.1
• Subsidiaries and investments	MR	7
• Summary of dividends paid	MR	20.6
• Amortisation/depreciation and expenses referred to in article 39.4 of the French General Tax Code	MR	20.9.8
• Information on payment terms	MR	20.9.9
• Information on insider trading (securities transactions by company executives)	MR	15.3
• Table of results	MR	20/09/2010
• Amount of loans due in less than two years granted outside of its main business activity by the Company to microenterprises, SMEs or to intermediate-sized enterprises with which it has economic ties that justify such loans in accordance with article L. 511-6, 3 bis, paragraph 2 of the French Monetary and Financial Code	MR	20/09/2011
• Information relating to the acquisition by the Company of its treasury shares with a view to allocating them to employees and executives in accordance with article L.225-211 of the French Commercial Code	MR	21.1.4
• Injunctions or pecuniary sanctions for anti-competitive practices issued by the French Competition Authority (*Autorité de la concurrence*) in accordance with article L.464-2 of the French Commercial Code	MR	20/09/2012
• Reciprocal shareholding	MR	7.2
• Equity investments and takeovers	MR	20/09/2013
5.3 Corporate governance report included in the Management report pursuant to article L.225-37 paragraph 6 of the French Commercial Code	MR	N/A
• List of all the mandates (directorships) held and functions performed in any company by each corporate officer during the financial year	MR	14.1.2
• Agreements entered into, directly or by intermediaries, between, on the one hand, one of the corporate officers or one of the shareholders holding more than 10% of the voting rights in a company and, on the other hand, another company in which the former holds, directly or indirectly, more than half of the capital, with the exception of agreements relating to transactions concluded under normal conditions	MR	19

Items	Information required by	Paragraph in the Annual Report
• Summary table of the valid delegations of authority granted by the General Shareholders' Meeting concerning capital increases, pursuant to articles L.225-129-1 and L.225-129-2 of the French Commercial Code, including how these delegations of authority were used during the financial year	MR	21.1.6

GENERAL COMMENTS

Definitions

In this Annual Report, and unless otherwise indicated:
*The terms the "**Company**" or "**Biophytis**" refer to the company Biophytis SA, with registered office at 14, avenue de l'Opéra, 75001 Paris, France, entered in the Trade and Companies Register (RCS) of Paris under the number 492 002 225.*

Pursuant to Article 28 of EC Regulation No. 809/2004, the following information is included by reference in this Annual Report:

- The accounts prepared in accordance with IFRS standards and the annual financial statements for the year ended 31 December 2016, presented on pages 208 to 251, and the associated Statutory Auditor's report, presented on page Annual Report filed with the AMF on 28 July 2017 under the number R.17-060.

- The accounts prepared in accordance with IFRS standards and the annual financial statements for the year ended 31 December 2015, presented on pages 192 to 243, and the associated Statutory Auditor's report, presented on page Annual Report filed with the AMF on 28 April 2016 under the number R.16-036.

Warning

This Annual Report contains information on the Company's activity, as well as on the market within which it operates. This information is obtained from studies carried out either by internal or external sources (e.g. sector publications, specialised studies, information published by market research companies, analysts' reports). The Company considers that this information currently provides a faithful portrait of its reference market and of its competitive positioning within it. This information has nevertheless not been verified by an independent expert and the Company cannot guarantee that a third party using different methods to gather, analyse or calculate data on the markets would obtain the same results.

This Annual Report also contains information on the objectives and lines of development of the Company. Such information is sometimes identified by the use of the future or conditional tenses and of terms relating to the time ahead, such as "estimate", "consider", "have as objective", "expect", "intend", "should", "seeks to" and "could" or any other variant or similar terminology. The reader's attention is drawn to the fact that these objectives and lines of development are not historic data and must not be interpreted as a guarantee that the facts and data so stated will occur, that scenarios will occur or that objectives will be achieved. These are objectives which, by their nature, might not be achieved and the information produced in this Annual Report could prove erroneous without the Company being subject in any way to an obligation of updating, subject to the applicable regulations, notably the General Regulations of the French Financial Markets Authority (the "**AMF"**) and MAR European regulation on market abuse.

Investors are also invited to consider the risk factors described in section 4 ("Risk factors"), of this Annual Report before taking their investment decision. The occurrence of all or part of these risks would be likely to have an adverse effect on the Company's activities, position,

financial results or objectives. Moreover, other risks, not yet identified or regarded as insignificant by the Company, could have the same adverse effect and investors could thus lose all or part of their investment.

A glossary containing the principal scientific and technical terms used is presented as an annex to this Annual Report.

1 RESPONSIBLE PERSONS

1.1 PERSON RESPONSIBLE FOR THE ANNUAL REPORT

Mr. Stanislas Veillet,
Chairman/CEO

1.2 DECLARATION BY THE RESPONSIBLE PERSON

Paris, on 23 july 2018,

“I hereby certify, having taken all reasonable measures to this effect, that the information contained in this Annual Report is, to my knowledge, consistent with reality and contains no omission likely to affect its scope.

I have obtained a completion of works letter from the statutory auditor, in which he indicates that he has verified the information concerning the financial situation and financial statements presented in this Annual Report and have read the whole of the Annual Report.

The historical financial information presented in this document has been the subject of the reports of the statutory auditor.

1.3 PERSON RESPONSIBLE FOR FINANCIAL INFORMATION

Mr. Jean-Christophe Montigny
Administrative and financial director
Address: SORBONNE UNIVERSITY BC9, 4 place Jussieu, 75252 Paris cedex 05
Telephone: 01 44 27 23 00
E-mail: investors@biophytis.com

2 LEGAL AUDITORS

2.1 STATUTORY AUDITORS

ERNST & YOUNG AND OTHERS
Address: 1-2 Place des Saisons, Paris La Défense 1, 92400 Courbevoie
Represented by Mr Frédéric MARTINEAU
Appointment date: 10 June 2016
Duration of mandate: 6 years old
Expiry date of mandate: at the General Shareholders' Meeting deciding on the financial statements for the year ended on 31 December 2021

GRANT THORNTON
Address: 29, rue du Pont, 92200 Neuilly-sur-Seine
Represented by Mr. Laurent BOUBY
Appointment date: 16 April 2015
Duration of mandate: 6 years old
Expiry date of mandate: at the General Shareholders' Meeting deciding on the financial statements for the year ended on 31 December 2020

2.2 SUBSTITUTE AUDITORS

AUDITEX
Address: 1-2 Place des Saisons, Paris La Défense 1, 92400 Courbevoie
Represented by Christian Scholer
Appointment date: 10 June 2016
Duration of mandate: 6 years old
Expiry date of mandate: at the General Shareholders' Meeting deciding on the financial statements for the year ended on 31 December 2021

INSTITUT DE GESTION ET D'EXPERTISE COMPTABLE – IGEC
Address: 22, rue Garnier, 92200 Neuilly-sur-Seine
Represented by Mr. Pascal LECLERC
Appointment date: 16 April 2015
Duration of mandate: 6 years old
Expiry date of mandate: at the General Shareholders' Meeting deciding on the financial statements for the year ended on 31 December 2020

3 SELECTED FINANCIAL INFORMATION

3.1 HISTORIC FINANCIAL INFORMATION

The financial information selected and presented below is drawn from the consolidated accounts of the Group, drawn up in accordance with IFRS standards for the financial year ended 31 December 2017 and appearing in section 20.1 “Consolidated financial statements drawn up in accordance with IFRS standards for the financial year ended 31 December 2017” of the Annual Report.

These accounting and operational data selected below must be read in relation to the information contained in sections 9 “Examination of the financial situation and net profit” and 10 “Cash and equity”.

Simplified balance sheet in thousands of euros IFRS Standards	**31/12/2016**	**31/12/2017**
TOTAL ASSETS	**8,393**	**25,947**
Non-current assets	**2,501**	**2,512**
o/w intangible fixed assets	*2,125*	*2,009*
o/w tangible fixed assets	*276*	*313*
o/w other non-current financial assets	*99*	*190*
Current assets	**5,892**	**23,435**
o/w other receivables	*2,827*	*3,578*
o/w cash and cash equivalents	*3,066*	*19,857*
TOTAL LIABILITIES	**8,393**	**25,947**
Total shareholders’ equity	**4,519**	**21,187**
Equity, group’s share	*4,549*	*21,217*
Interests not conferring control	*(30)*	*(31)*
Non-current liabilities	**962**	**821**
o/w commitments to staff	*48*	*114*
o/w non-current financial debts	*913*	*708*
Current liabilities	**2,913**	**3,939**
o/w current financial debts	*176*	*305*
o/w supplier debts and associated accounts	*1,920*	*2,402*
o/w tax and social debts	*722*	*1,118*
o/w other creditors and miscellaneous debts	*94*	*113*

Simplified income statement in thousands of euros IFRS Standards	**31/12/2016**	**31/12/2017**
Operating income	**1,667**	**2,550**
o/w net revenues	-	-
Operating expenses	**(9,609)**	**(12,458)**
Net operating profit	**(7,942)**	**(9,908)**
Net financial income (1)	**(13)**	**(1,501)**
Net profit	**(7,954)**	**(11,409)**
Net earnings per share	*(1.28)*	*(1.24)*

(1) The 2017 net financial income is mainly related to the use of the credit facility taken out with Bracknor Fund Limited (refer to section 9.1 and section 10.1.4 for more details on this credit facility).

Simplified cash flow statements in thousands of euros IFRS	**31/12/2016**	**31/12/2017**
Cash flows linked to operating activities	**(6,633)**	**(8,727)**
O/w internal financing capacity	*(6,848)*	*(8,873)*
(-) Including change in working capital requirements (WCR)	*(216)*	*(146)*
Cash flows linked to investment activities	**(129)**	**(128)**
Cash flows linked to financing activities (1)	**407**	**25,649**
Effect of variations in foreign exchange rates	12	(3)
Change in cash and cash equivalents	**(6,343)**	**16,791**
Opening cash and cash equivalents	9,409	3,066
Closing cash and cash equivalents	3,066	19,857

(1) Flows generated by financing activities in 2017 mainly stem from capital increases, net of fees, amounting to €19.7 million and from the use of the credit facility taken out with Bracknor Fund Limited in the amount of €6 million.

Level of net indebtedness in thousands of euros IFRS Standards	**31/12/2016**	**31/12/2017**
+ Non-current financial debts	913	708
+ Current financial debts	176	305
- Cash and cash equivalents	(3 066)	(19,857)
Total net indebtedness (1)	**(1 977)**	**(18,844)**

(1) The amount of cash and cash equivalents is greater than the amount of financial debt.

4 RISK FACTORS

Investors are encouraged to consider all of the information in this Annual Report, including the factors described in this chapter, before deciding to acquire or subscribe to the Company's shares. As part of the preparation of this Annual Report, the Company conducted a review of risks that it considers, on the date of this basic document, as being likely to have a material adverse effect on the Company, its activity, financial position, prospects, earnings or development.

The attention of investors is drawn to the fact that the list of risks presented in this Chapter 4 is not exhaustive and that other risks, unknown or the realisation of which is not considered on the date of this Annual Report, are likely to have a material adverse effect on the Company, its business, prospects, financial condition, results or development, may exist or might arise.

Biophytis has developed a portfolio of innovative products at different stages of development, which address age-related degenerative diseases.

Concerning the technologies for both products under development, Biophytis is focusing its research and development efforts in the fight against sarcopenia (age-related muscular dystrophy) and age-related macular degeneration (AMD). For these two particularly disabling conditions, the company has proprietary drug candidates Sarconeos, which is entering phase 2b studies, and Macuneos in phase 1/2a studies.

In addition, Biophytis is currently preparing phase 2 clinical development programmes for Sarconeos for Duchenne muscular dystrophy, and Macuneos for Stargardt disease. Both are designated as rare diseases, which provides for a well-defined regulatory framework and an accelerated procedure for obtaining marketing authorisation.

Moreover, the company has extended its research to second-generation products, BIO103 (sarcopenia) and BIO203 (AMD), which are under clinical development.

The company must still pass through many stages before it can market Sarconeos and Macuneos. This marketing, whether by Biophytis or by a licensed third party, may be carried out after having passed through the different clinical stages successfully and obtained the Marketing Authorisation (AMM).

We point out that on the date of this Annual Report, the Company has not signed any license agreement with a pharmaceutical company.

Biophytis therefore draws readers' attention to the risks associated with the absence of revenues while awaiting a first sale of licenses for Sarconeos Macuneos that might occur during the financial year 2019, and those relating to the results of the clinical tests.

The main risk factors linked to the Company or its sector of activity are presented below:

Paragraphs	Types of risk	Risks
4.1.1	Product-related risks	Products under development by the Company must form the object of costly, rigorous and highly regulated preclinical and clinical studies, the number, completion times and outcomes of which are uncertain
4.1.2		The Company may not find partnerships for the clinical and commercial development of its products, which would require significant funding
4.1.3		Interactions with other drugs could delay or prevent the marketing of the Company's products
4.1.4		Despite a specific approach to the treatment of sarcopenia (Sarconeos) and AMD (Macuneos), the Company operates in a competitive environment
4.1.5		The absence of products of the same type on the market for Sarconeos and Macuneos generates many unknowns
4.1.6		Alternative therapeutic solutions, currently at various stages of development, could reduce the size of the Company's potential market
4.1.7		The marketing of the Company's products may not be successful
4.1.8		The Company is dependent on a limited number of suppliers and service providers
4.1.9		Risks linked to dependence on key individuals
04/01/2010		The Company's development strategy could depend on its ability to manage its internal growth
04/01/2011		The liability of the Company may be invoked through its contracting partners and subcontractors
4.2.1	Legal and regulatory risks	Risks associated with a binding and evolving regulatory framework
4.2.2		Specific risks related to preclinical and clinical trials which are necessary to obtain the clinical studies and marketing authorisations for the Company's therapeutic products
4.2.3		Risks linked to the reimbursement and delisting of drugs and treatments
4.2.4		Risks linked to portfolios of patents and licences
4.2.5		Risks linked to liability due to products
4.2.6		Risks linked to potential conflicts which may affect the Company's relationships with its potential licensees
4.3	Industrial risks related to the use of Products hazardous to health and/or to the environment	
4.4.1	Financial risks	Dilution risk
4.4.2		Risks linked to historical losses and forecast losses
4.4.3		Risks linked to the future use of tax losses which may be carried forward
4.4.4		Risks linked to the Research Tax Credit
4.4.5		Risks linked to reimbursable advances and public subsidies
4.5	Insurance and risk coverage	
4.6.1		Liquidity risks
4.6.2		Currency risks

Paragraphs	Types of risk	Risks
4.6.3	Market risk	Credit risk
4.6.4		Interest rate risk
4.6.5		Equity risk
4.7	Extraordinary events and disputes	

4.1 RISKS LINKED TO THE COMPANY'S PRODUCTS

4.1.1. Products under development by the Company must form the object of costly, rigorous and highly regulated preclinical and clinical studies, the number, completion times and outcomes of which are uncertain

The Company conducts preclinical (BIO103 and BIO203) and clinical (Sarconeos and Macuneos) programmes, the principal objective of which is the development and marketing of therapeutic solutions for the treatment of sarcopenia and AMD.

The development of a candidate drug is a long and expensive process, taking place in several distinct phases, each of which is costly and can result in failure or delay in obtaining authorisation and the marketing of the product.

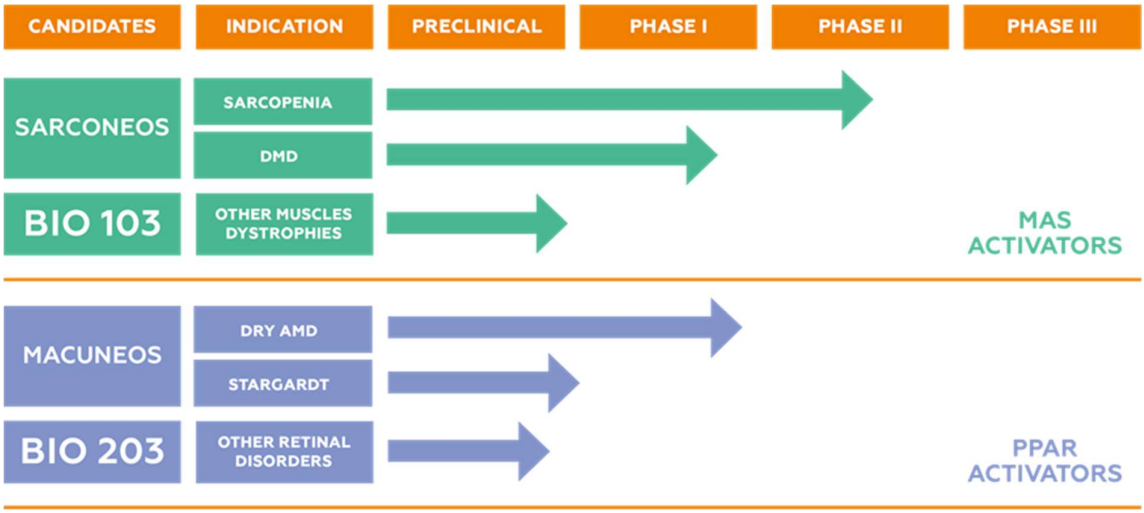
In addition, the regulatory authorities of different countries in which its products could be marketed may have a different interpretation of the results of the Company and may, in any case, request supplementary tests on a discretionary basis or make additional and unforeseen demands during these tests. Consequently, the Company cannot guarantee that clinical trials will lead to marketable results or that these clinical trials will executed within periods which permit profitable marketing.

In general, the development time for a drug for human health is long, often exceeding 10 years, between the discovery of the molecule (candidate drug) and the provision of the drug to patients.
In the case of the development of a drug for a large population, the selection and preclinical phases may last from 2 to 4 years. Phase I (single dose and multiple dose studies) may take between 1 and 2 years, followed by phase II, which may take between 2 and 4 years, and then one or more phases III taking a total of 3 to 5 years. Finally, the Marketing Authorisation may take 1 to 3 years. These approximate durations nevertheless remain highly variable, as a function of the nature of the candidate drugs (new chemical entity, biological product) and the pathologies targeted (rare diseases or acute or chronic therapeutic treatment).

Since the start of its activities in 2006, the Company has developed two technological research platforms. The steps already taken by the Company as at the date of this Annual Report are the following:

The Company may not be able to obtain all regulatory approvals to initiate planned clinical studies; it may encounter difficulties in recruiting patients – it should be noted that recruitment times for clinical trials are becoming longer – and in retaining them for participation in clinical trials. Once recruited, the patients participating in these trials may, at any time and without having to justify themselves, suspend or terminate their participation. If too many patients were to terminate their participation in a clinical trial, the analysis of the results of this study might no longer have a sufficient statistical scope.

The entry into phase-III clinical or marketing of certain candidate drugs will expose wider population samples to the candidate drug in question, which might well reveal safety problems, undesirable side effects, and the absence of effectiveness or interactions not hitherto foreseen or detected. Moreover, phase-III studies can also trigger or aggravate pathologies, whether pre-existing or not or currently unknown, which could delay or interrupt the development of the relevant products. In addition, the completion of certain clinical studies may involve the conclusion of partnerships by the Company, notably for the needs of a large phase-III study. Consequently, the Company will be subject to the risks described in paragraphs 4.1.2 and 4.2.2 of this Annual Report.



4.1.2. The Company may not find partnerships for the clinical and commercial development of its products, which would require significant funding

The Company plans to conduct phase-III clinical trials in a partnership. This approach will require agreements to be reached with pharmaceutical laboratories, which, at present, are not certain to be concluded (see paragraph 4.2.2 below). Moreover, the conduct of these clinical trials will require substantial financial resources, which the Company might not have available. Consequently, the ability of the Company to commit such resources will depend on its ability to obtain adequate financing.

Any delay, failure or inability to obtain such financing or the impossibility of obtaining it at an acceptable cost could delay or prevent completion of phase-III clinical trials for Sarconeos and Macuneos in the country or countries concerned and could consequently have a material adverse effect on the Company, its activity, its prospects, its ability to achieve its objectives, its financial position, cash flow or its operating profit.

4.1.3. Interactions with other drugs could delay or prevent the marketing of the Company's products

The Company's products could have to be used in combination with other drugs. The Company shall conduct studies in order to assess the risks of interactions of its products with other drugs and treatments taken together. These studies cannot, by their nature, cover all possible combinations. Furthermore, there can be no guarantee that the Company's products will not interact negatively with other drugs or treatments not covered by one of the studies or that such interactions will not be revealed once the products have been marketed. These

interactions could have adverse, unacceptable or undetected side effects, or could reduce or destroy the effectiveness of the Company's products, which could diminish the commercial potential of the Company's products, slow their development and consequently, have a material adverse effect on the Company, its activity, its prospects, its ability to achieve its objectives, its financial situation, cash flow or operating profit.

4.1.4. Despite a specific approach to the treatment of sarcopenia (Sarconeos) and AMD (Macuneos), the Company operates in a competitive environment

The Company operates in a competitive market segment (see 6.2.4 and 6.3.4). Pharmaceutical companies, biotechnology companies, institutions, universities and other research organisations, are actively engaged in the discovery, research, development and marketing of therapeutic responses to sarcopenia and AMD.

The Company cannot guarantee that its competitors will not develop alternative products, which will compete successfully with the Company's products, in terms of effectiveness, mode of action, pricing, marketing or being considered by the market as being of similar or superior quality to the Company's products or rendering them obsolete. Nor can the Company guarantee that competitors will not obtain a marketing authorisation for their products before the Company is able to market its own products.

In addition, the Company cannot guarantee that its competitors will not deploy more resources to reduce or limit the prospects of the Company or its products.

4.1.5. The absence of products of the same type on the market for Sarconeos and Macuneos generates many unknowns

The Company develops candidate drugs for the treatment of sarcopenic obesity and of dry AMD. On the date of this Annual Report, there is no drug candidate of this type, for which marketing has been authorised by the competent regulatory authorities.

On account of this, the prospects for growth and profitability of candidate drugs, their harmlessness, effectiveness and acceptance by patients, physicians and paying organisations are uncertain. The preclinical and clinical data on the safety and effectiveness of these candidate drugs are still limited. Not only are tests on animal testing not necessarily predictive of results to be obtained in humans, but the positive results of candidate drugs during the early clinical phases, obtained for a limited number of patients, may not be confirmed by the subsequent phases with a larger number of patients.

4.1.6. Alternative therapeutic solutions, currently at various stages of development, could reduce the size of the Company's potential market

A certain number of alternative and surgical therapeutic solutions intended to combat sarcopenia and AMD form the object of research and are at various stages of development. If these solutions prove effective and/or safe, it could reduce the potential extent of the market for the Company's products.

4.1.7. The marketing of the Company's products may not be successful

In theory, once the marketing authorisation has been obtained for its products, the Company may nevertheless fail to secure the support of the medical community, prescribers and third-party payers.

The growth of the Company and its ability to generate revenues will depend on the degree to which the Company's products are accepted by the market, based on several factors, such as:

- their effectiveness and therapeutic benefit as perceived by prescribers and patients
- the absence of any side effects and adverse drug interactions
- the ease-of-use of the product, linked notably to its mode of administration
- the cost of treatment
- the reimbursement policies of governments and other third-party payers
- the effective implementation of a scientific publication strategy
- the support of opinion leaders in the field of cardiovascular and metabolic diseases
- the development of one or several competing products for the same indication.

The Company and/or its partners may also be affected by controversies involving candidate drugs or other similar therapeutic approaches, albeit which do not compete with those developed by the company, negatively impacting public perception of the therapeutic benefit of these candidate drugs.

Even if the candidate drugs developed by the Company may provide a therapeutic response to a currently unmet need, poor market penetration resulting from one or more of the factors described above would have an adverse effect on their marketing and on the Company's ability to generate profits by way of the agreements that it may conclude with industrial partners, which would have a negative impact on its activity, its prospects, financial condition, results and growth. In the same way, the Company cannot guarantee that the assumptions made and developed more fully in chapter 6 of this Annual Report for determining the characteristics of the market which it targets will be confirmed. In the event of non-realisation of some or all of these assumptions, the size of the market test by the Company could be modified.

4.1.8. The Company is dependent on a limited number of suppliers and service providers

The Company is dependent on third parties for its supply of various raw materials and in particular its active ingredients, included in the manufacture of its clinical products and items necessary for the conduct of its preclinical and clinical trials, as well as service providers, notably CMOs (Contract Manufacturing Organisations) and CROs (Contract Research Organisations) involved in clinical studies.

Any failure or delay on their part could have consequences for the length, cost or even continuation of clinical studies and the quality of data, which must meet strict standards (Good Laboratory Practices, Good Clinical Practices, Good Manufacturing Practices) imposed by the supervisory regulatory authorities and hence delay the start of clinical trials and the marketing of products.

The Company does not currently own or operate any manufacturing facilities.

The Company does not produce drug candidates tested in its preclinical and clinical trials: it has no production facilities and relies largely on third parties to manufacture of its products.

For example, as regards the *Sarconeos* drug candidate, the Company uses, as at the date of this Annual Report, on the one hand, a single manufacturer for the active ingredient, which is

derived from a plant raw material and, on the other hand, a manufacturer of therapeutic units to carry out its clinical trials.

By adopting such a strategy, and even though it has taken into account some of these risks through contractual arrangements, the Company cannot directly control certain key aspects of the development of its products, such as:

- the quality of the product manufactured
- the clinical and commercial quantities that can be provided
- the delivery times for therapeutic units (batches that are pre-packaged and labelled specifically for a given clinical study)
- the compliance with applicable laws and regulations.

4.1.9. Risks linked to dependence on key individuals

Given its stage of development and the innovative character of its products, the Company could lose key employees and not be able to attract qualified new people.

The success of the Company depends largely on the involvement and expertise of its directors and qualified scientific staff, particularly Stanislas Veillet and René Lafont, the two founders of Biophytis, as well as Jean-Christophe Montigny, the administrative and financial.

The temporary or permanent unavailability of these individuals would deprive it of their expertise, their experience and their technical capabilities, which the Company might not be able to replace.

The Company has also implemented and intends to extend a system for the motivation and retention of key individuals in the form of attribution of securities convertible into shares of the Company (warrants for the subscription of founder's shares).
The Company will also need to recruit new executives and qualified scientific staff for the development of its activities, as the company expands in areas requiring additional skills, such as manufacturing, quality assurance, regulatory affairs and medical affairs.

The Company competes with other companies, research organisations and academic institutions to recruit and retain such profiles and may not be able to attract or retain them under conditions deemed as acceptable from a financial viewpoint. This inability could delay or prevent the manufacture and marketing of the Company's products and thus have a material adverse effect on its business, its prospects, its ability to achieve its objectives, its financial situation, cash flow or operating profit.

4.1.10. The Company's development strategy could depend on its ability to manage its internal growth

Within the context of its development strategy, the Company intends to recruit management staff, scientific staff and other staff to develop its operational capacity for the needs of its future clinical developments.

This recruitment will lead to an increase in the Company's payroll. In order to manage this growth and ensure the successful integration of its new staff within the Company, it shall:

- train, manage, motivate and retain an increasing number of employees
- increase the capacity of its existing operational, financial and management IT systems
- manage the outsourcing of the production of its developed drugs

- manage partnership agreements with industrial partners of the Company in charge of the clinical development and marketing of the Company's products.

In order to meet demand within the period agreed with its future partners, the Company may need to conclude new subcontracting agreements.

The inability of the Company to manage growth, or unexpected difficulties encountered during its expansion could have a material adverse effect on its activity, results, financial situation, development and prospects.

4.1.11. The liability of the Company may be invoked through its contracting partners and subcontractors

The Company draws and will draw on co-contractors and subcontractors for all aspects of its activity. This exposes it to every potential demand concerning the activities and observance of obligations by the co-contractors and subcontractors, over which the Company has little or no control. For example, co-contractors and subcontractors use certain regulated materials within the context of their agreement with the Company. If they do not handle these materials appropriately or safely, the liability of the Company may be incurred.

In the same way, the Company may be liable for all or part of the damage, injury or death resulting from an accident involving a co-contractor or subcontractor. The liability incurred may exceed the coverage ceiling set by the insurance contract it by the Company or not be covered by them. Any invoking of the Company's liability, whether or not covered by subscribed insurance policies, could have a significant adverse effect on its activity, prospects, its ability to achieve its objectives, its financial position, cash flow or operating profit.

4.2 LEGAL AND REGULATORY RISKS

4.2.1 Risks associated with a binding and evolving regulatory framework

One of the major challenges for a growing company like Biophytis is to succeed in developing, with partners, products incorporating its technologies in the context of an increasingly constraining regulatory environment. The pharmaceutical industry faces the permanent evolution of its legal and regulatory environment and increased monitoring by the relevant authorities, including the Agence nationale de Sécurité du Médicament et des Produits de Santé [National Security Agency for Medicines and Health Products] ("**ANSM**") in France, the European Medicines Agency ("**EMA**") or the Food and Drug Administration ("**FDA**") in the United States, or other regulatory authorities in the rest of the world. Correspondingly, the public demands more guarantees regarding the safety and effectiveness of drugs.

Health authorities notably organise research and development work, preclinical studies, clinical studies, regulation of pharmaceutical companies and the manufacture and marketing of drugs. This strengthening of the legislative and regulatory framework is common to the whole world, albeit with requirements varying from country to country. In particular, health authorities, including the ANSM, the EMA or the FDA, have imposed increasingly heavy demands, in terms of the volume of data required to demonstrate the effectiveness and safety of a product. These increased requirements have reduced the number of authorised products relative to the number of cases submitted. Furthermore, marketed products also form the object of regular re-evaluation of the benefit/risk ratio after their authorisation. The late discovery of undetected

problems at the research stage can lead to marketing restrictions, removal or withdrawal of the product and to an increased risk of litigation.

In this way, the authorisation process is long and costly and may take several years, with a result which remains unpredictable.

In Europe, USA and other countries, regulations are likely:

- to delay and/or significantly increase the development costs, testing, manufacturing and marketing of products;
- to limit the indications for which the Company is authorised to market its products;
- to impose stricter new requirements, to suspend the authorisation of its products and to demand the halting of clinical trials or of marketing, if unexpected results are obtained during trials or by other researchers on products similar to its own;
- to impose binding labelling.

Lastly, if the Company does not comply with the laws and regulations governing its activities, it could be subject to sanctions, which could include a refusal to allow pending applications, product recalls, sales restrictions, temporary or permanent suspension of its transactions, as well as civil or criminal prosecution.

Insofar as new laws or regulations would entail an increase in the costs of obtaining and maintaining product marketing authorisations or would limit the economic value of a new product for its inventor, the growth prospects of the pharmaceutical industry and the Company could prove to be reduced.

Good clinical practices demand that the recommendations of a monitoring committee for data and safety are followed. Pursuant to these good clinical practices, the Company has established, for each study, a Scientific Committee, the recommendations of which could lead to premature halting or delay the development of the Company's products.

The occurrence of one or more of these risks could have a material adverse effect on the Company's activity, prospects, financial situation, results and development.

4.2.2 Specific risks related to preclinical and clinical trials which are necessary to obtain the clinical studies and marketing authorisations for the Company's therapeutic products

The organisation of preclinical studies on animals and clinical trials on humans is essential for obtaining the Marketing Authorisation (AMM) for products developed by the Company. Their completions usually take over several years and is very expensive.

The regulatory authorisation process for new therapeutic products requires the submission of detailed product characteristics, those of the manufacturing and control process, as well as preclinical and clinical data and all information allowing the harmlessness and potential effectiveness of the product to be established for each indication. It may also require studies after the Marketing Authorisation on a continuous basis, as well as controls of the quality of manufacturing.

These regulatory initiatives are expensive, may take many years and have unpredictable results. Moreover, the authorities may carry out inspections to verify that the drug development is taking place in accordance with current regulations.

As part of the preparation of the clinical studies, additional requirements could be formulated by the authorities of the different countries on the study protocols, the patient characteristics, the treatment durations and the post-treatment follow-up. Differences in the interpretation of results, discrepancies between the regulatory agencies of different countries, requests for further studies to clarify certain points or targeting specific populations, could appear.

Similarly, during clinical trials, it's impossible to determine how fast patients will be recruited, even if the choice of centres and partners will always be adjusted according to the recruitment possibilities. In addition, some requests from regulatory authorities may have an impact on recruitment for new studies by making it more complex and/or by delaying it.

These studies and trials to be conducted by preclinical and clinical research centres, their quality and the interest which they present largely depend on the ability of the Company and its partners to select preclinical and clinical research centres and with regard to trials on humans, to recruit the necessary number of patients within relatively limited time-period, in order to be able to publish results quickly, as well as use good service providers, as appropriate. The remoteness or the geographical dispersion of centres of clinical or preclinical studies may also raise operational and logistical difficulties that could lead to additional costs and delays.

In the event that the Company or its partners are unable to recruit the expected patients, which would cause delays in clinical trials and in the publication of their results, this would result in a delay in adhesion, both of learned societies and of professionals in the relevant medical fields, affecting the marketing of the Company's products, which would be likely have a material adverse effect on the Company, its activity, its financial position, earnings, growth and prospects.

If the Company has conducted preclinical trials and an initial clinical study of its products (Sarconeos and Macuneos), it has not received any marketing authorisation to date from a regulatory agency and it cannot be guaranteed that it will receive the necessary approvals to market its products.

The capacity of the Company to obtain a marketing authorisation for its products will depend on several factors, notably:

- the possibility of continuing with the development of its products (manufacture of batches and tests);
- the fact that the Company or its partners are able to conclude clinical trials successfully, within the allocated deadlines and with the originally planned human, technical and financial resources;
- the fact that its products are approved or not for another indication which has already formed the object of a marketing authorisation; and
- the fact that its competitors do not announce clinical results likely to modify the assessment criteria used by the relevant regulatory authorities.

If the Company does not obtain any marketing authorisation, it will not be able to market its products. Furthermore, its products may not be able to obtain a marketing authorisation for a given geographical area, which could significantly restrict their marketing.

4.2.3 Risks linked to the reimbursement and delisting of drugs and treatments

The conditions for setting sale prices and reimbursement of medicines are beyond the control of pharmaceutical companies. They are respectively decided by commissions and by competent public-sector organisations, as well as by social entities or private insurers. In the current context of controlling expenditure on health and of economic and financial crisis, the pressure on sale prices and the level of reimbursement is increasing, notably on account of price controls imposed by many States and increased difficulty in pertaining and maintaining satisfactory reimbursement rates for drugs.

At the appropriate time, the conditions for determination of prices and reimbursement rates for the Company's products will represent a key factor for their commercial success. The possibility for the Company of receiving royalties from its industrial partner(s) for the sale of its treatments will depend on the circumstances for pricing and reimbursement. If the price negotiation deadlines entail a significant shift in marketing or if a drug of the Company does not secure an appropriate level of reimbursement, its profitability will be reduced accordingly.

Nor can the Company guarantee that it will succeed in maintaining the price level of its drugs or the accepted reimbursement rate over time. Under these conditions, its revenues, profitability and prospects could be significantly altered.

4.2.4 Risks linked to portfolios of patents and licences

- ***The protection offered by patents and intellectual property rights is uncertain***

The economic project of the Company, notably the development of its candidate drugs, depends, among other things, on its ability to obtain, maintain and insure, against third parties, the protection of its patents and patent claims, trademarks and associated request, its other intellectual property or similar rights (notably including its trade secrets, business secrets and know-how) or those which it is permitted to operate within the context of its activities.

It is also important for the success of its activity that the Company is able to provide similar protection for all of its intellectual property rights and this over a sufficiently broad geographical area, i.e. Europe, the United States and other key countries (Canada, China, Korea). The Company devotes significant financial and human efforts to this and intends to continue its policy of protection of new patent filings at its own discretion. The Company believes that its technology is currently effectively protected by patents and patent applications that it has filed and that it has full or joint ownership or an exclusive license, such as that granted by SORBONNE UNIVERSITY and THE CNRS (see Chapter 11 of this Annual Report).

The Company may nevertheless be unable to maintain the protection of its intellectual property rights. In such cases, the Company would lose its technological and competitive advantage.

Intellectual property rights of the Company provide protection for a period which may vary (for example, this duration regarding patents is 20 years from the date of filing of patent applications).

The Company could furthermore encounter difficulties within the context of filing or reviewing some of its patent applications, trademarks or other intellectual property rights currently under review or registration. Indeed, at the time of filing for a patent, other patents or patent applications may constitute an enforceable priority but not yet be published or even if published, may not be known to the Company. Despite the priority searches and the monitoring

which it performs, the Company thus cannot be certain of being the first party to have filed a patent application. In particular, it should be recalled that the publication of patent applications takes place 18 months after the filing of applications themselves (to date, no objection to the Company's patent application has been made). Similarly, on the occasion of the deposit of one of its brands in a country where it is not protected, the Company may find that the trademark in question is not available in this country. A new trademark should then be sought for the given country or an agreement negotiated with the holder of the prior sign. There is thus no certainty that current or future applications for patents, trademarks and other intellectual property rights of the Company will result in issuances or registrations and that these rights will be effectively protected.

In this way, given the recent nature of families of patents which the Company holds in full, it is not possible to determine at present the extent of protection that could reasonably be granted to them.

The mere issuance of a patent, trademark or other intellectual property rights does not guarantee their validity or enforceability. Indeed, any person having an interest may at any time challenge the validity or enforceability of patents, trademarks or relevant applications of the Company before a court or within the context of other specific procedures, which, following such challenges could reduce their scope or result in nullity. Developments, changes or differences of interpretation of the legal framework governing intellectual property in Europe, the US and other countries could allow competitors to use the inventions or intellectual property rights of the Company and develop the products and technologies of the Company without fees. In addition, there are still certain countries which do not protect intellectual property rights in the same way as in Europe or the United States, in which efficient procedures and rules necessary for the defence of intellectual property rights society may not exist. There is thus no certainty that the patents, trademarks and other intellectual property rights of the Company, present or future, will not be challenged or invalidated, nor that they will provide effective protection against competition and third-party patents covering similar inventions.

Consequently, the Company's rights to its patents, trademarks, associated applications and other intellectual property rights may not confer the expected protection against competition. The Company thus cannot guarantee that:

- requests for patents and other rights held, jointly held or licensed by the Company and which are under examination, including recent patent applications of the Company, will effectively result in the issuance of patents, trademarks and other registered intellectual proprietary rights;
- the Company will succeed in developing new inventions which could form the object of a filing or granting of a patent;
- patents or other intellectual property rights granted to the Company will not be challenged, invalidated or circumvented;
- the field of protection conferred by patents, trademarks and other intellectual property rights of the Company is and will remain sufficient to protect the company against competition and against patents, trademarks and intellectual property rights of third parties covering competing devices, products, technologies or developments.

The occurrence of one or more of these risks could have a significant adverse effect on the Company's activity, prospects, financial situation, results and development.

- ***The Company could infringe the intellectual property rights held by third parties***

The success of the Company will depend in part on its ability to develop products and technologies that do not infringe patents or other rights belonging to third parties. It is important, for the success of its activity, that the Company is able to exploit its products freely without them infringing patents or other intellectual property rights, and conversely, without third parties infringing rights, notably intellectual property rights of the Company or of its partners and grantors of licences necessary for the development and exploitation of the Company's R&D programmes.

The Company thus cannot guarantee that:

- there are no patents or other prior rights, notably intellectual property of third parties, likely to cover certain products, processes, technologies, results or activities of the Company and consequently third parties acting against the Company for infringement or breach their rights, with a view to obtaining such damages and/or the cessation of its manufacturing and/or marketing activities of involved products, processes, etc.;
- there are no rights to trademarks or other prior rights of third parties, likely to form the basis for an action for infringement or liability against the Company; and/or
- the domain names of the Company will not form the object, by a third party holding prior rights (e.g. trademark rights), a UDRP ("*Uniform Dispute Resolution Policy*") or related procedure or infringement action.

The growth of the drug research industry and the associated multiplication of the number of filed patents increase the risk that the Company's products and technologies infringe third party rights, notably intellectual property rights.

In the event of occurrence of disputes regarding the intellectual property it uses, the Company may be obliged to:

- cease or arrange for the cessation of the development, sale or use of the product(s) which depend on the disputed intellectual property;
- review the design of some of its products and/or technologies, or in the event of applications concerning trademarks, rename its products, in order to avoid infringing the intellectual property rights of third parties, which may not be possible or may prove long and costly, and could de facto impact the marketing efforts for the relevant products by the Company and/or its partners.

The Company shall thus continue to conduct, as it has done to date, the preliminary studies that seem necessary to it in view of the aforementioned risks before making investments to develop its different products/technologies. It shall notably monitor the activity (particularly in terms of patent applications) of its competitors.

On the day of registration of this Annual Report, however, the Company has not faced any of these situations or been involved in any dispute relating to rights, notably intellectual property rights, held by third parties.

- ***The Company cannot guarantee the absence of infringement of intellectual property rights against it***

Monitoring the unauthorised use of the candidate drugs and technology of the Company and the infringement of its own rights, including intellectual property, is difficult.

The Company thus cannot guarantee that it will be able to prevent and secure indemnification for unauthorised misappropriations or uses of its candidate drugs and its technology, particularly in foreign countries where its rights are less well protected due to the territorial scope of intellectual property rights.

Third parties (or employees of the Company) may use or attempt to use the elements of the Company's technology protected by an intellectual property right, which would create a harmful situation for the Company. The Company may thus be obliged to bring judicial or administrative actions against these third parties and/or employees in order to enforce its rights, including intellectual property rights (patents, trademarks, designs and domain names).

Any dispute or litigation, regardless of the outcome, could entail substantial costs, affect the Company's reputation and negatively influence its result and financial position and may not provide the protection or indemnification sought. Competitors with greater resources than the Company could be more capable of bearing the litigation costs.

On the day of registration of this Annual Report, however, the Company has not faced any of these situations or been involved in any dispute relating to rights, notably intellectual property rights, held by third parties.

- ***The Company might not be able to prevent a disclosure of information by third parties or employees likely to have an impact on future intellectual property rights***

It is important for the Company to protect itself against the unauthorised use and disclosure of confidential information, know-how and trade secrets. Indeed, technologies, processes, methods, know-how and unpatented or unpatentable proprietary data are considered as trade secrets that the Company tries, in part, to protect by confidentiality agreements. Moreover, the rules of return in favour of the Company of the inventions which its employees have been able or could be able to create, as well as their compensation procedures, are governed by article L. 611-7 of the Intellectual Property Code, which is public policy.

Within the context of agreements for collaboration, partnership, research or other types of cooperation between the Company and researchers in academic institutions, as well as with other public or private entities, subcontractors, or any third party joint contractor, various information items of information and/or products may be entrusted to them, in particular for conducting some clinical tests and trials. In these cases, the Company requires the signing of confidentiality agreements. Furthermore, the Company ensures that the collaboration, partnerships or research agreements that it signs will grant it access to full ownership, or at the very least to the joint ownership of the results and/or inventions resulting from this collaboration, where it has effectively participated in the creation of results and/or the invention. The Company also seeks, within the context of the license agreements which it will sign with its partners, to maintain control over the management of patents or only to grant licences in particular areas which it does not exploit.

It cannot be excluded that the arrangements implemented to protect the technology and trade secrets of the Company and/or the know-how implemented will not provide the expected protection or will be infringed, that the Company has no appropriate solutions against such infringements or that trade secrets are disclosed to its competitors or developed independently by them. Moreover, the Company has very limited control over the conditions under which the third parties with which it enters into contracts have recourse to third parties themselves, and

protect their confidential information, regardless of the fact that the company stipulates in its agreements with its contracting partners that they undertake to pass on these confidentiality obligations to their own contracting partners.

Consequently, the rights of the Company to its confidential information, trade secrets and know-how may not confer the expected protection against competition and the Company cannot guarantee:

- that it will not be possible to ensure that its know-how and trade secrets will not be able to be obtained, usurped, circumvented, transmitted without authorisation or used by unauthorised third parties;
- that the competitors of the Company have not already developed a technology, products or devices of similar nature or intended use to those of the Company;
- that no contracting party shall claim the benefit of all or part of intellectual property rights on inventions, knowledge or results of which the Company holds full ownership or joint ownership, or for which it would benefit from a license; or
- that employees of the Company will not claim rights or the payment of additional compensation or a fair price in exchange for inventions in the creation of which they have participated.

The occurrence of one or more of these risks could have a significant adverse effect on the Company's activity, prospects, financial situation, results and development.

4.2.5 Risks linked to liability due to products

The Company is exposed to risks of being held liable, in particular due to products linked to trials, manufacturing and marketing of therapeutic products on humans. It may also be held liable in respect of preclinical of clinical trials in connection with the preparation of tested therapeutic products and unexpected side effects resulting from the administration of these products.

Complaints or proceedings could be filed or brought against the Company by patients, regulatory agencies, regulatory agencies, biopharmaceutical companies and any other third party using or marketing its products. These claims may include complaints resulting from acts of its partners, licensees and subcontractors, over which the Company has no or little control.

The Company cannot guarantee that its current insurance coverage will be adequate to meet the liability claims which may be brought against it. If its liability or that of its partners, licensees or subcontractors is alleged in this way or if it or its partners, licensees or subcontractors are not able to obtain and maintain adequate insurance cover at acceptable cost, or to protect themselves in any way against liability claims for defective products, this could seriously affect the marketing of its products and, in general, affect its activities, prospects, financial position, results and development.

The Company could also form the object of civil or criminal claims, with consequent impairment of its image. In order to limit this risk, the Company has subscribed to insurance policies detailed in this section and shall contract the necessary insurance as its products develop.

4.2.6 Risks linked to potential conflicts which may affect the Company's relationships with its potential licensees

The Company's strategy is to license its candidate drugs to pharmaceutical companies. The conclusion of licensing agreements and their future are thus fundamental for the Company.

Conflicts may nevertheless arise with licensees during execution of agreements with the Company, which may affect their continuation and consequently the manufacture and marketing of the products developed by the Company. This could represent conflicts concerning the conditions of conclusion of agreements or the proper execution, by either party, of its obligations under these agreements. Such conflicts of interest could significantly affect the Company's activity, financial position, results, development and prospects.

4.3 INDUSTRIAL RISKS RELATED TO THE USE OF PRODUCTS HAZARDOUS TO HEALTH AND/OR TO THE ENVIRONMENT

- ***The handling of hazardous materials by the Company's staff of the Company may cause contamination of the environment or cause occupational diseases***

The Company's activities include the controlled storage, handling, use and processing of dangerous substances, toxins, chemical and biological agents.

During its research and development of drug candidates, the Company's researchers may also be required to handle Genetically Modified Organisms (GMOs). Whether these substances are safe for handlers is controlled by the Genetic Engineering Commission;

There are thus not only environmental risks associated with the contamination of the environment but also risks in terms of health (including occupational diseases) associated with handling by the Company's employees of active or toxic products during the research and manufacture of products. These risks also exist for third parties with whom the Company works.

Although the Company believes that the safety and training measures which it takes for the handling and treatment of hazardous materials meet current standards and allow its employees and subcontractors to conduct their activity under good environmental, health and safety conditions, the risk of accidental contamination or professional diseases linked to the handling of hazardous materials cannot be completely eliminated. In the event of an accident, the Company could be held liable for any resulting damage and the liability could exceed the ceiling of the insurance cover contract it by the Company or even not be covered by the subscribed insurance policies.

4.4 FINANCIAL RISKS

4.4.1 Dilution risk

The participation of the Company's shareholders in its share capital could be significantly diluted

Since its creation, the Company has issued and granted stock warrants (BSA) and warrants for founder's shares (BSPCE) to its directors and employees. It has also issued stock warrants (BSA) in connection with the issue of one of the tranches of bonds redeemable in cash or in new or existing shares (ORNANE).

As at the date of this Annual Report, the full exercise of all of the outstanding instruments granting access to the share capital would allow the subscription for 1,706,132 new shares, while generating a dilution equal to 12.672%, based on current capital, and 11.247% based on the fully diluted share capital. These dilution rates should be taken as before the issue of the last 3 tranches of convertible bonds and warrants. The table below shows the remaining dilution under this instrument.

At the date of this document, 2,427,481 new shares were issued in this manner.

Within the context of its policy of motivating its officers and employees and in order to attract and retain qualified staff, the Company may, in the future, issue or attribute shares or new financial instruments providing access to the Company's share capital, which may entail a further dilution, which is potentially significant for the Company's shareholders.

In addition, as part of its financing policy, the Company may, in the future, issue new convertible bond and warrant tranches in the context of the line set up on 3 April 2017, which may result in additional dilution, for the shareholders of the Company.

The table below shows the potential additional dilutions in the event of the drawdown of a new tranche of ORNANEBSAs or in the event of the drawdown in full of the three remaining tranches of the ORNANEBSA line at the date of this document. The calculation summarises the potential dilution in the theoretical case of an issue/conversion/exercise of the notes convertible into shares with share subscription warrants attached at the date of this document, as well as the impact that a 10% price decrease would have on these dilutions.

Effect of the issue on a shareholder owning 1% of the Company before the transaction	As of the date of document		In the event of a 10% decrease	
	Undiluted base	Diluted base	Undiluted base	Diluted base
Before issue	1.00	1.00	1.00	1.00
After issuing, converting, and fully exercising a tranche	0.93	0.93	0.92	0.93
After issuing, converting, and fully exercising the remaining 3 tranches	0.81	0.82	0.79	0.81

4.4.2 Risks linked to historical losses and forecast losses

The Group has recorded operating losses and accumulated a deficit and may never be profitable

Created in September 2006, the Company has recorded operating losses each year, explained by expenses incurred in the development of candidate drugs for the treatment of metabolic and age-related diseases.

At 31 December 2017, the cumulative losses according to the financial statements prepared in accordance with IFRS standards over the last two financial years amounted to a total of €19,363K including a loss of €11,409K for the financial year ended on that date.

In future years, the Group could experience greater operating losses than in the past, as its research and development activities continue, notably on account of:

- the need to conduct new clinical trials in order to approach new market segments, especially for its Sarconeos and Macuneos projects
- the increase in regulatory requirements governing the manufacture of its products.

The increase in these expenses could have a material adverse effect on the Group's activity, financial situation, results, growth and prospects.

4.4.3 Risks linked to the future use of tax losses which may be carried forward

The Group's accumulated losses, which may be carried forward, might not be chargeable against future profits

At 31 December 2017, after taking into account the net loss realised for the year, the Group had tax losses which may be carried forward amounting to €34,558K. These consist of:

- French tax losses of €34,200K which may be carried forward indefinitely

Within France, the use of these deficits is capped at 50% of taxable profit for the financial year, with this limitation applicable to the portion of the profits in excess of €1 million. The unused balance of the deficit is carried forward to subsequent years and is attributable under the same conditions without a limitation as to time.

- tax losses of the US subsidiary of €354K

In the United States, tax losses may be carried forward for 20 years from their date of establishment.

- tax losses of the Brazilian subsidiary of €4K

Within Brazil, the fiscal deficit follows a declining regime: tax losses which may be carried forward are limited to 30% of the accumulated deficit of the previous year.

It cannot be excluded that regulatory or legislative changes in taxation of companies will call into question, as a whole or in part, the possible use of these previous losses to future earnings or may limit their attribution over time.

4.4.4 Risks linked to the Research Tax Credit

The Company may no longer benefit from the Research Tax Credit in future years

In order to finance its activities, the Group has benefited from the Research Tax Credit (Crédit d'Impôt Recherche - "CIR") for its research and development activity in France. This mechanism consists of the French government offering a tax credit to companies which invest significantly in research and development. Research expenditures eligible for the CIR include wages and salaries, depreciation of research material, services outsourced to approved research (public or private) organisations and intellectual property costs.

The amount requested by way of the 2017 CIR is €2,549K.

For the CIR, companies must justify on demand the request of the tax authorities for the amount of the CIR and the eligibility of the research work included in the calculation basis of the mechanism. For the purposes of this justification, the Tax Authority recommends that companies draw up a guide containing all of the items necessary for monitoring this tax credit and in particular demonstrating the eligibility for the CIR of the research work carried out. Despite the absence of a formal scientific report, the Company has technical documentation for its research work and is confident of the quality of these documents for justifying the eligibility of the selected projects.

It cannot be excluded that the tax authorities will contest the eligibility for the CIR of projects selected by the Company or the method of calculating eligible expenses applied by the Company, with the right of clawback exercised until the end the third year following the filing of the special declaration provided for calculating the CIR. Furthermore, changes in tax legislation may affect or limit the CIR mechanisms.

If any of these situations were to occur, this could have an adverse effect on the Company's activity, earnings, financial position, prospects and development.

4.4.5 Risks linked to reimbursable advances and public subsidies

The Company benefits from government advances and in the event of termination of those advances, should have recourse to other sources of funding

During past financial years, the Company has been granted the following reimbursable assistance:

At the date of this Annual Report (amounts in € '000)	**Amount received***	**Amount reimbursed**	**Remaining amount owed**
OSEO - QUINOLIA Project – clinical development of a Quinoa extract acting on Metabolic syndrome	229	155	74
OSEO - MACULIA Project - clinical development of Bixilia with the aim of obtaining a health claim	29	29	-
COFACE – Prospection insurance*	60	-	-
BPI France - SARCOB Project – in vitro, in vivo and pharmacokinetic characterisation of a candidate drug	260	26	234

At the date of this Annual Report (amounts in € '000)	Amount received*	Amount reimbursed	Remaining amount owed
BPI France - Project BIO101 - production of clinical batches, preclinical regulatory and clinical phase of BIO101 for the treatment of sarcopenic obesity	600	-	600
TOTAL	**1,178**	**210**	**908**

** Excluding any costs borne by the Company*
*** The balance of the COFACE advance was considered non-due and was recognised in grants in the 2015 financial year.*

Information on the various advance agreements (repayments, repayment schedule, or specific clauses) are set out in Note 10.1 to the IFRS consolidated financial statements that appear in Section 20.1 of the Annual Report.

In the future, the Company intends to continue to seek aid or subsidies in order to accelerate its development.

In the event the Company does not comply with the contractual conditions provided in the concluded aid agreements, it might have to reimburse the sums paid in advance.

This could deprive the Company of its financial resources necessary for its research and development projects and it cannot guarantee that it would find the additional financial means, the time or the possibility of replacing these funds by others.

4.5 INSURANCE AND RISK COVERAGE

The amount of expenses paid by the Company for all the aforementioned insurance policies amounted respectively to €57,490 net of tax and € 63,914 net of tax during the years ended 31 December 2016 and 31 December 2017.

The Company considers that these insurance policies adequately cover insurable risks inherent to its activity and that its insurance policy is consistent with practices in its sector of activity. The Company does not expect any particular difficulty in maintaining appropriate insurance levels in the future, within the limits of market conditions.

The Company cannot guarantee however that it will always be able to maintain and if necessary, obtain the similar insurance coverage at acceptable costs, which could lead it to accept more expensive insurance policies and/or assume a higher level of risk. This, in particular, as it develops its activities.

In addition, the Company is not yet protected in case of a wrongdoing attributable to the Company's products that would adversely affect the health of the patients given the stage of development of the products.

Insurance policy	Insurer	Covered risks	Amount of guarantees	Expiry/Duration
Company Multi-Risk	**AXA**	Premises located SORBONNE UNIVERSITY 4 place Jussieu 75005 Paris 1) Fire and related events 2) Natural disasters 3) Natural events 4) Water damage 5) Theft - vandalism: property damage 6) Theft - vandalism: damage to movable assets 7) Broken windows 8) Liability as lessee 9) Amicable or judicial defence 10) Guarantee of materials (electrical damage and breakages)	1) € 90,000 2) € 90,000 3) € 90,000 4) € 30,000 5) Guaranteed 6) € 20,000 7) € 20,000 8) Guaranteed 9) Guaranteed 10) € 30,000	**In force** Duration of one (1) year (with tacit renewal) Possibility of annual advance termination subject to a prior notice of two (2) months before the expiry date, which is the anniversary of the agreement, i.e. 1 January.
Civil liability of the company	**CNAHardy**	<u>Civil liability before the delivery of the products or receipt of the works</u> 1. All guaranteed losses, except A, B and C, without being able to exceed, for: 2. Bodily injury 3. All consequential pecuniary and non-pecuniary losses 4. Non-consequential non-pecuniary losses 5. A/ inexcusable wrongdoing; bodily injury 6. B/ damage to entrusted assets;	<u>Limits</u> 1. €7,000,000/claim 2. €7,000,000/claim 3. €2,500,000/claim 4. €300,000/claim 5. € 1,000,000/year of insurance cover 6. € 30,000/year of insurance cover	**In force** Duration of one (1) year with tacit renewal. Possibility of annual advance termination subject to a prior notice of two (3) months before the expiry date, which is the anniversary of the agreement, i.e. 1 January.

Insurance policy	Insurer	Covered risks	Amount of guarantees	Expiry/Duration
		pecuniary and non-pecuniary losses 7. C/ accidental damage to the environment; bodily injury, pecuniary and non-pecuniary losses <u>Civil liability after delivery of products or acceptance of works</u> 8. All damages combined (physical, tangible, and intangible) 9. USA/Canada coverage 10. Defence/Appeal	7. € 500,000/year of insurance cover 8. € 5,000,000/year of insurance cover 9. Guarantee received 10. € 50,000 General deductible €5,000	
Civil Liability for therapeutic tests SARA OBS France	**HDI**	1. Civil liability for therapeutic tests	1 Per patient: € 1,000,000 Per protocol €6,000,000 Per year: € 10,000,000	September 2016-November 2018
Civil Liability for therapeutic tests SARA OBS Italy	**CNAHardy**	1. Civil liability for therapeutic tests	1 Per patient: € 1,000,000 Per protocol €5,000,000.	September 2016-November 2018
Civil Liability for therapeutic tests SARA OBS Belgium	**CNAHardy**	1. Civil liability for therapeutic tests	1 Per patient: € 400,000 Per protocol €3,000,000	September 2016-November 2018
Civil Liability for therapeutic tests SARA OBS USA	**Medmarc**	1. Civil liability for therapeutic tests	1 Per patient: $5,000,000	February 2017-September 2018
Civil Liability for therapeutic tests SARA INT France	**CNAHardy**	1. Civil liability for therapeutic tests	1 Per patient: € 1,000,000 Per protocol €6,000,000 Per year: € 10,000,000	December 2017-June 2019
Civil Liability for therapeutic tests SARA INT Italy	**CNAHardy**	1. Civil liability for therapeutic tests	1 Per patient: € 1,000,000 Per protocol €7,500,000 Per year: € 7,500,000	December 2017-June 2019

Insurance policy	Insurer	Covered risks	Amount of guarantees	Expiry/Duration
Civil Liability for therapeutic tests SARA INT Belgium	**CNAHardy**	1. Civil liability for therapeutic tests	1 Per patient: € 400,000 Per protocol €3,000,000	December 2017-June 2019
Civil Liability for therapeutic tests SARA INT USA	**CNAHardy**	1. Civil liability for therapeutic tests	1 Per patient: € 2,000,000 Per protocol €2,000,000 Per year: € 2,000,000	December 2017-June 2019
Directors' Liability	**AIG**	Professional wrongdoing committed while performing the duties of director	€ 1,000,000/insurance period	**In force** Duration of one (1) year [with tacit renewal] Expiry date of the agreement (every year): February 19
Key individual (individual accident)	**ALBINGIA**	1. Accident 2. Illness	€ 350 per day/365 days	**In force** Duration of one (1) year (with tacit renewal) Possibility of annual advance termination before the anniversary expiry date of the agreement, i.e. on 1 July.
Term life insurance	**METLIFE**	Death and total and irreversible loss of autonomy	€2,000,000	**In force** Duration of one (1) year (with tacit renewal) Possibility of advance termination at each premium payment date, on 15 September of each year.
Machinery breakdown	**ALBINGIA**	Agilent spectrometer	€314,927	**In force** Duration of one (1) year (with tacit renewal)

Insurance policy	Insurer	Covered risks	Amount of guarantees	Expiry/Duration
				Possibility of advance termination on each payment maturity of the premium, on 1 January.
Assistance/repatriation	**ALBINGIA**	Assistance/Repatriation/ Health expenses abroad	Assistance: According to the scale Health €5,000,000	**In force** Duration of one (1) year (with tacit renewal) Possibility of advance termination at each premium payment date, on 8 February of each year.

4.6 MARKET RISK

4.6.1 Liquidity risks

Since its creation, the Group has financed its growth by strengthening its equity base via successive capital increases (including on the occasion of its IPO in July 2015), recourse to bank loans and bonds, obtaining public aid for innovation and reimbursement of CIR receivables.

Significant expenses linked to research and development of candidate drugs have been incurred since the start of the Group's activity, which to date have generated negative cash flows from operating activities. Gross research and development expenses amounted to €9,592,977 as at 31 December 2017 compared to €6,787,760 as at 31 December 2016.

At 31 December 2017, the Group had cash and cash equivalents of €19,857,390.

On the date of the Annual Report, the Company carried out a specific review of its liquidity risk and considers that it is in a position to meet its debt obligations over the next 12 months.

In order to cover its needs after that date, the Company intends to continue its search for the most appropriate financing.

The Group will continue in the future to have significant financing requirements for the development and clinical testing of its candidate drugs. It is possible that the Company will be unable to self-finance its growth, which would lead it to seek other sources of funding, especially through new capital increases.

The level of the Group's financing needs and their staggering over time depend on elements that are largely beyond its control, such as:

- Higher costs and slower progress than anticipated for its research programmes and clinical studies;
- Costs of preparation, filing, defence and maintenance of its patents and other intellectual property rights.

It is possible that the Company may fail to obtain additional capital when it needs it, or that such capital may not be available on acceptable financial terms to the Group. If the necessary funds are not available, the Company may have to delay the clinical trials of its candidate drugs.

To the extent that the Company would raise capital by issuing new shares, the holdings of its shareholders could be diluted.

Debt financing, to the extent it is available, could also include binding commitments for the Company and its shareholders.

The occurrence of one or more of these risks could have a significant adverse effect on the Group, its activity, financial position, earnings, growth and prospects.

4.6.2 Currency risks

The Group's strategy is to favour the euro as its currency within the context of its activity.

The principal risks associated with the currency impact of purchases in foreign currencies are considered to be insignificant.

The Company has two foreign subsidiaries: in Brazil and the USA. On the date of the Annual Report, the activity of these two entities is limited.

In view of these insignificant amounts, the Group has not actively contracted currency hedges at this stage. The Group cannot exclude the possibility that a significant increase in its activity abroad, particularly in the United States, would entail greater exposure to currency risk, thereby obliging the Group to use a suitable policy to hedge such risks.

4.6.3 Credit risk

The Group manages available cash on a prudent basis. Cash and cash equivalents include cash and term deposits.

At 31 December 2017, cash and cash equivalents amounted to €19,857,390, including €10,000,000 in term deposits.

Credit risk is associated with deposits with banks and financial institutions. The Group draws on leading financial institutions for its cash investments and thus does not bear significant credit risk on its cash position.

4.6.4 Interest rate risk

The Company has no exposure to interest rate risk with regard to the asset items on its balance sheet, insofar as its financial investments consist of term deposits.

The company has contracted floating rate debt with BPI France (see details of loans in Note 10.2 of the Notes to the consolidated financial statements prepared in accordance with IFRS in Section 20.1 of this Annual Report).

Given the low level of reference rates, the Company considers that any change of +/-1% would have an insignificant impact (less than € 1,000) on its net income with regard to the amount of the losses generated by its operating activity.

Consequently, the Company does not believe that it is exposed to a significant risk of changes in interest rates.

4.6.5 Equity risk

The Company holds no investments or investment securities which may be traded on a regulated market.

4.7 EXTRAORDINARY EVENTS AND DISPUTES

The Company has not, for the 12-month period preceding the registration date of this Annual Report, been involved in any administrative, criminal, judicial, or arbitration proceedings requiring market disclosure.

There was no event of an exceptional nature entailing a supplementary risk or additional unprovisioned costs during the same period to the knowledge of the Company.

5 INFORMATION ON THE ISSUER

5.1 HISTORY AND EVOLUTION OF THE COMPANY

5.1.1 Legal Name of the Company

The Company has the legal name: Biophytis SA.

5.1.2 Registration location and number of the Company

The Company is registered in the trade and companies register of Paris under the identification number 492 002 225.

The NAF code of the Company is 7211Z.

5.1.3 Date of incorporation and duration

The Company was incorporated on 27 September 2006 for a duration of 99 years expiring on 26 September 2105, unless dissolved in advance or extended.

5.1.4 Registered Office of the Company, legal form and applicable law

The registered office of the Company is located at 14, avenue de l'Opéra, 75001 Paris.

The Company is a Société Anonyme [limited liability company] with a Board of Directors.

The Company, governed by French law, is primarily subject for its operations to L.225-1 et seq. of the Commercial Code.

5.1.5 Principal facility

The principal place of business of the Company is located at the Sorbonne University – BC 9, Bâtiment A 4ème étage, 4 place Jussieu, 75005 Paris, under a Public Property Occupancy Agreement (see 8.1.1).

Telephone: 01 44 27 23 00
Email: investors@biophytis.com
Website: www.biophytis.com

5.1.6 History of the company

September 2006: creation of the Company by Stanislas Veillet in the form of Société par Actions Simplifiée [simplified joint stock company] with a single shareholder.

September 2006: creation of the Scientific Committee consisting of Professors René Lafont (SORBONNE UNIVERSITY) and Daniel Tomé (INRA).

November 2007: filing of the patent application No. 07 59478 for a composition acting on the metabolic syndrome (joint ownership with SORBONNE UNIVERSITY and the CNRS).

March 2008: acquisition by the Company of 99% of the shares held by Stanislas Veillet of Instituto de Biophytis do Brasil Serviços em Análises Tecnicas de Alimentos Ltda, a company governed by Brazilian law registered in the state of Sao Paulo and incorporated in July 2006.

July 2008: capital increase subscribed by Stanislas Veillet and four directors of the Company.

September 2008: obtaining of the FCPI [Innovative investment fund] label by Oséo (BPI France)

December 2008: securing of Young Innovative Company status by the DGFiP [General Directorate of Public Finances].

December 2008: raising of € 800,000, subscribed by an investment fund managed by Seventure Partners, and transformation of the Company into an SAS [simplified joint stock company] with a Board of Directors.

June 2009: appointment of Professor Karine Clément (ICAN) to the Scientific Committee.

June 2009: filing of patent application No. 09 54354 for a composition intended for solar protection (joint ownership with SORBONNE UNIVERSITY).

June 2009: fund raising of € 2.2m, subscribed by several investment funds managed by Seventure Partners and CM-CIC Capital Privé.

September 2009: installation of the Company at the biotech activity park: Biocitech, in Romainville (93).

September 2009: launch of a clinical study of 54 patients, double-blind against placebo on the effectiveness of the solar protection.

September 2010: launch of the clinical study of 60 patients, double-blind against a placebo on weight regain after dieting, carried out with ICAN (Institut du Cardiométabolisme et de la Nutrition, formerly the CRNH).

May 2011: filing of patent application No. 11 54172 for the treatment of age-related macular degeneration (joint ownership with the Institut de la Vision - SORBONNE UNIVERSITY).

November 2011: filing of patent application No. 11 60280 for limiting weight regain after dieting (joint ownership with SORBONNE UNIVERSITY).

December 2011: filing of patent application No. 11 61519 to improve muscular quality (joint ownership with SORBONNE UNIVERSITY).

January 2012: launch of the SARCOB12 project, supported by the Company, involving the Institut de Myologie, ICAN, INRA, the company Metabrain Research and co-funded by the Single Interministerial Fund of € 1.5 million.

July 2012: fundraising of € 1.8m subscribed by Metabrain Research and several investment funds managed by Seventure Partners and CM-CIC Capital Privé.

September 2012: launch of the MACULIA project, supported by the Company, involving the Institut de la Vision and Iris Pharma, which entitled the company to an €0.8 million grant, co-financed by FEDER.

April 2014: end of the SARCOB12 project, proof of concept of BIO101 and BIO103, discovery of the molecular target of candidate compounds.

May 2014: filing of patent application No. 14 54538 for new chemical entities and their therapeutic use (joint ownership with SORBONNE UNIVERSITY, Metabrain Research).

Mai 2014: appointment of Professors Jean Mariani (Institut de la Longévité), José-Alain Sahel (Institut de la Vision), and Thomas Voit (Institut de Myologie) to the Scientific Committee.

September 2014: end of the MACULIA project, proof of concept of BIO201 and BIO203, discovery of the molecular target of the candidate compounds.

February 2015: arrival of Dr Philippe Guillet as Medical Director.

April 2015: filing of the patent application No. 15 53957 for the treatment of macular degeneration (joint ownership with SORBONNE UNIVERSITY and IRIS Pharma).

July 2015: IPO on Alternext Paris (ISIN: FR0012816825; Ticker: ALBPS) with the raising of € 10.035 million, of which € 2 million from existing shareholders (Seventure, CM-CIC Capital Privé) and Metabrain.

July 2015: appointment of Dr Philippe Dupont (University Paris XI) as Director of Operations.

August 2015: fundraising of € 6 million by private placement with a North American investor.

September 2015: launch of production of clinical batches of BIO101 with the US company Patheon, the first stage of Phase 2b clinical trials for sarcopenic obesity.

November 2015: launch of the subsidiary Biophytis Inc. in Cambridge, USA.

December 2015: appointment of Dr Peter J. Dilda (University of Paris V) as Director of Research and Professor Roger A. Fielding (Harvard University) as Scientific Advertiser within the context the SARCOB program.

April 2016: confirmation of Professor Jean Mariani (Institut de la Longévité), Professor René Lafont and Professor Jose-Alain Sahel (Institut de la Vision); and the appointment of Doctor Philippe Guillet, Professor Roger A. Fielding (Tufts University, Harvard Medical School) and Doctor Ivana Kim (Eye & Ear Infirmary Boston, Harvard Medical School) as members of the Scientific Committee for a period of five (5) years. Professor Jean Mariani was appointed Chairman of the Scientific Committee.

April-May 2016: Several scientific papers at the ICFSR 2016 (Philadelphia) on sarcopenia, and ARVO 2016 (Seattle) on ophthalmology.

July 2016: Authorisations received for the SARA-PK clinical study to determine the safety of Sarconeos (BIO101) and to evaluate pharmacokinetics and pharmacodynamics in healthy, young, and elderly volunteers following a single ascending dose and multiple ascending doses.

October 2016: Launch of the production of clinical batches of Macuneos (BIO201) with the American company Patheon.

November 2016: Authorisations received in France and Belgium to conduct the SARA-OBS clinical study, a 6-month observational study on more than 300 patients, during which time multiple parameters of the severity and the evolution of the condition will be monitored. The study is to be conducted in Europe and the United States. The data obtained will allow a better characterisation of the patients with sarcopenia who will subsequently be recruited in the phase 2b study (SARA-INT).

November 2016: End of the investigation period of the SARA-PK clinical trial.

December 2016: several scientific papers at SCWD 2016 (Berlin).

December 2016: The Company establishes its main office on the campus of the Pierre et Marie Curie University (Paris) near its scientific partners: The Institute of Biology Paris Seine (IBPS), the Institute of Myology, and the Institute of Vision.

March 2017: Final results from the SARA-PK clinical study received. Their analysis confirms the good pharmacokinetic profile in healthy elderly subjects, confirms the therapeutic window of the Sarconeos product, and specifies the dosages that will be used in the SARA-INT phase 2b clinical trial.

March 2017: First clinical centres of the SARA-OBS study open in Belgium and France.

April 2017: Financing of the Company secured by:

- A capital increase subscribed by several private investors, including Bracknor Fund, and the management, amounting to €3.7 million, carried out by the issue of 1,310,431 new shares at a unit price of €2.85.
- A credit facility is set up with Bracknor Fund for up to €15 million in the form of 5 tranches of €3 million in bonds redeemable in cash or new or existing shares, with warrants ("ORNANEBSA").

April 2017: 4 scientific and clinical works presented at the ICFSR 2017.

April 2017: Filing of patent application No. 17 53775 for a new pharmaceutical-grade compound (joint ownership with SORBONNE UNIVERSITY).

May 2017: First patient added to the SARA-OBS clinical study in the United States.

May 2017: First tranche of the bonds redeemable in cash and/or new and/or existing shares is drawn, giving rise to the issue of (i) 330 bonds redeemable in cash and/or new and/or existing shares with a value of €10,000 and (ii) 225,225 stock warrants with an exercise price of €3.33. All bonds issued were subsequently converted.

July 2017: Second tranche of the bonds redeemable in cash and/or new and/or existing shares is drawn, giving rise to the issue of (i) 300 bonds redeemable in cash and/or new and/or existing shares with a value of €10,000 and (ii) 205,959 stock warrants with an exercise price of €3.6415. All bonds issued were subsequently converted.

August 2017: Dr Manfred Horst (former MSD) appointed as Director of Business Development.

August 2017: Filing of patent application No. 17 58071 for the use of a family of compounds in the treatment of myopathies (joint ownership with SORBONNE UNIVERSITY).

September 2017: Positive results of Sarconeos in a model of Duchenne muscular dystrophy presented at the World Muscle Society International Conference 2017.

September 2017: Scientific work on Macuneos in the protection of the retina presented at the 2017 Euretina Congress.

October 2017: Capital increase of €10.4 million through private investment and the issuance of 1,989,000 new ordinary shares at a unit price of €2.85, offered to qualified investors.

October 2017: Authorisation obtained from the US Food and Drug Agency (FDA), to launch the phase 2b interventional study for Sarconeos in sarcopenia (SARA-INT) in the United States.

October 2017: Dr Thomas Voit (University College London) appointed to the Scientific Committee.

October 2017: Capital increase of €7.5 million through private investment and the issuance of 1,513,000 new ordinary shares at a unit price of €5.00, offered to qualified investors.

December 2017: Authorisation obtained from the Belgian Federal Agency for Medicines and Health Products (FAMHP), to launch the phase 2b interventional study for Sarconeos in sarcopenia (SARA-INT) in Belgium.

December 2017: Several scientific and clinical works on Sarconeos presented at the SCWD 2017.

February 2018: Filing of patent application No. 18 51778 for the use of a family of compounds for the prevention of loss of muscle strength during immobilisation (joint ownership with SORBONNE UNIVERSITY).

March 2018: Several scientific and clinical works on Sarconeos presented at the ICFSR 2018.

May 2018: FDA (Food and Drug Administration) and EMA (European Medicines Agency) grant Orphan Drug status to drug candidate Sarconeos in Muscular Dystrophy or Duchenne Muscular Dystrophy (DMD).

May 2018: Inclusion of the first patient in Phase 2b clinical trial of Sarconeaos (SARA-INT) to treat sarcopenia, at the Clinical Center of Liege (Belgium).

May 2018: At the Ordinary General Meeting of May 16, 2018, the shareholders decided (i) to renew mandates of Mr. Stanilas Veillet, Mr. Jean-Gérard Galvez and Mrs. Nadine Coulm as director for a period of three (3) years, which will terminate at the end of the Ordinary General Meeting called to approve the financial statements for the year ended December 31, 2020, (ii) the non-renewal of the mandate of Mrs. Marie-Claire Janailhac Fritsch and Mrs. Micheline Kergoat as director and (ii) the appointment of Mr. Dimitri Batsis and Mr. Eric Keith Rowinsky as director for a duration of three (3) years, which will terminate at the end of the Ordinary General Meeting called to approve the financial statements for the year ended December 31, 2020.

At the meeting of the Board of Directors on May 16, 2018, the directors decided to:

- Audit committee: (i) appoint Mrs. Jean Franchi and renew the mandate of Mrs. Nadine Coulm as a member of the audit committee and (ii) renew the mandate of Mrs. Nadine Coulm as Chairman of the Audit Committee;

- Compensation and governance committee: (i) appoint Mr. Dimitri Batsis and to renew the mandate of Mr. Jean-Gérard Galvez as a member of the Remuneration and Governance Committee and (ii) renew the mandate of Mr. Jean-Gérard Galvez as Chairman of the Remuneration and Governance Committee; and

- Chairman and Chief Executive Officer: renew the mandate of Mr. Stanilas Veillet as Chairman and Chief Executive Officer for the duration of his mandate as a director, being the end of the Ordinary General Meeting called to approve the financial statements of the Company financial year ended December 31, 2020, under the same conditions as those stipulated by the Board of Directors on May 22, 2015.

June 2018: Appointment of Dr Samuel ANGUS (The Hebrew University of Jerusalem, Israel) as Medical Director.

5.2 INVESTMENTS

5.2.1 Principal investments made during the last two financial years

Amounts in thousands of euros	31/12/2016	31/12/2017
Intangible fixed assets	*2*	*4*
Tangible fixed assets	**127**	**123**
*of which materials and tools **	*79*	*82*

Including financial leasing

The main investments in the financial years presented relate to the acquisition of laboratory equipment.

5.2.2 Principal investments in progress

No significant investment has been made since 1 January 2018.

The Company does not use complex financial tools. Excess cash is placed on term accounts renewed monthly.

5.2.3 Principal investments made

The Company does not currently plan to make significant investments in tangible and intangible fixed assets in future years and for which the Company's management bodies have made firm commitments.

Investments in research and development do not fulfil the capitalisation criteria since the Company has not obtained yet marketing authorisation for one of its drugs, so that they are not capitalised.

6 OVERVIEW OF ACTIVITIES[1]

Biophytis is a biotechnology company created in 2006, specialised in age-related diseases. It develops innovative therapeutic solutions for degenerative age-related conditions, for which there is currently no treatment, in order to protect muscular and visual functions. In line with this, Biophytis focuses its research and development efforts in the fight against sarcopenia (age-related muscular dystrophy) and against age-related macular degeneration (AMD). For these two particularly disabling conditions, the company has the proprietary drug candidates Sarconeos, which is entering phase 2b studies, and Macuneos, in phase 1/2a studies.

In addition, Biophytis is currently preparing phase 2 clinical development programmes for Sarconeos for Duchenne muscular dystrophy, and Macuneos for Stargardt disease. Both are designated as rare diseases, which provides a well-defined regulatory framework and an accelerated procedure for obtaining marketing authorisation.

Biophytis' financial model is to ensure that projects are carried out until proof of clinical efficacy on patients is obtained, and then to license the technologies to pursue development in partnership with a pharmaceutical company.

Located on the campus of Sorbonne University (Paris), Biophytis benefits from high-quality research collaborations with the Institut de Biologie Paris Seine (Biology Institute Paris Seine), the Institut de Myologie (Myology Institute) and the Institut de la Vision (Vision Institute).

[1] The words in italics are explained in the glossary (section 26)

6.1 TRANSLATIONAL RESEARCH ON DEGENERATIVE AGEING PROCESSES

BIOPHYTIS develops small molecules, derived from natural substances, to increase biological resilience to cellular stress and thus fight against ageing and age-related diseases.

Living organisms are continually subjected to physical or chemical stresses of very diverse nature, which can affect their functioning. The tissues and cells of these organisms defend themselves against these stresses by various resilience mechanisms such as the production of antioxidant substances and the activation of enzymatic mechanisms of detoxification, or the replacement of damaged molecules or cells. With advancing age – or because of a genetic defect –as stress builds up, these resilience mechanisms lose their effectiveness, due to altered cell and organ function, leading to the accumulation of various 'wastes' which are at the origin of multiple pathological conditions.

Plants produce a very large number of molecules, particularly secondary metabolites which are useful for their own protection, but which are also likely to have beneficial effects in those who consume them because the signalling pathways they activate are conserved during the course of evolution. Plant secondary metabolites are already at the origin of many drugs used in the treatment of metabolic or inflammatory diseases. Some of these metabolites act against cellular distress and organ dysfunction, restoring the effectiveness of protective mechanisms, and thus enable the development of drugs to treat age-related diseases.

Biophytis has identified such compounds from a unique collection of natural plant substances. After having tested their efficacy on cellular and animal models of age-related diseases, Biophytis determined their mechanism of action. This approach is known as reverse pharmacology, which has enabled the elucidation of original chemical structures that activate targets that increase biological resilience to stress and slow down ageing. Biophytis has developed a portfolio of drug candidates under development for the treatment of age-related diseases. Two drug candidates are in clinical development - Sarconeos for the treatment of sarcopenia and a genetic muscular dystrophy (Duchenne muscular dystrophy), and Macuneos for the treatment of age-related macular degeneration (AMD) and a retinopathy of genetic origin (Stargardt disease).

The aging of the population massively affects Western societies, as well as in Japan, China and Russia. The elderly population of these societies already represents several hundred million people, causing the appearance of rapidly expanding epidemics with particular characteristics (neurodegenerative diseases, loss of mobility, AMD, etc.). This population is expected to double by 2050 to reach two billion people, including 500 million with physical degeneration (sarcopenia, osteoarticular diseases), 400 million with visual degeneration (AMD) and 135 million with cognitive degeneration (Alzheimer, senile dementia, etc.)[2]. Such

[2] Source WHO – EWGSOP

diseases can be very debilitating for patients and, in the absence of therapeutic treatment, result in an economic cost estimated in the tens of billions of euros.

Moreover, considering how advanced these diseases are on diagnosis and our current knowledge, it is unlikely that they can be cured, implying that the patients will have to undergo *chronic therapy* for several years in order to block or slow down the development of the condition. This raises the problem of whether treatment is acceptable, both in terms of its mode of administration and potential side-effects on the organism. By focusing on candidate families formulated from active ingredients to which the body is already naturally exposed by nutrition, Biophytis has identified compounds offering, in principle, an extremely favourable pharmacological profile.

6.1.1 Degenerative processes, science of ageing

In the human species, life expectancy at birth and life expectancy at age 65 have increased considerably: the former owing to the decrease in infant mortality and the improvement of health conditions since the beginning of the twentieth century, the latter due to a more recent decline in morbidity in elderly persons thanks to advances in medicine. Humans live on average for 80 years and their death occurs after a slow ageing process, during which their physical and cognitive performance gradually declines at different rates depending on the individual. Various degenerative diseases of identified, or at least identifiable origins, come with this functional decline associated with so-called “normal” ageing, which is very common, but not inevitable. These “pathologies”, or conditions, whose frequency increases significantly with age, therefore bear names related to the functions concerned: neurodegenerative diseases (Parkinson, Alzheimer, etc.), alteration of sensory functions (deafness, age-related macular degeneration [AMD], etc.), impaired osteomuscular functions (sarcopenia, osteoporosis, fragility, etc.), cardiac conditions (cardiomyopathy), renal disease (kidney failure). It should be noted that these pathologies, which are generally “chronic”, are very often co-occurring in the same elderly patient (polypathology) can often trigger “decompensations” of other organs with the occurrence of acute complications on the occasion of various stresses even minor ones (falls, fractures, infections). The combination of these pathologies and complications unavoidably leads to the morbid weakening of the patient.

The ageing of the body does not affect all individuals equally, some maintaining their functions much longer than others. Longevity very often depends on two types of factors: genetic factors known as “gerontogenes”, and environmental factors. Individual genetic factors are at play even within the same species, as shown by comparison between monozygotic (“identical”) and dizygotic (“fraternal”) twins, where the latter type shows greater variability in age of death. Environmental factors also play a very important role, especially physical activity, the quality of nutrition and even exposure to harmful substances (pollutants, toxins) or stress. For “well-preserved” individuals, prolonged good health corresponds to what is often termed “healthy ageing”, which is, therefore, a fundamental objective for many research efforts aimed at slowing down/delaying functional deterioration and maintaining autonomy and good quality of life[3]. To achieve this, it is necessary first to understand what causes ageing.

There is no easy answer to this question. Owing to the recent boom in genetics and the biology of ageing, we are now able to understand the main phenomena and mechanisms of ageing at the cellular and molecular levels. These mechanisms are not independent, and their effects are likely to beadditive, or even synergistic.

[3] Balistreri CR.2018. Anti-inflamm-ageing and/or anti-age-related disease emerging treatments: a historical alchemy or revolutionary effective procedures? *Mediators of Inflammation* 2018: article ID 3705389.

First of all, there is a fundamental question: Are the mechanisms that allow a whole organism or a cell to live for a long time the same? To answer this, it is essential to tackle these two levels of study, that is the longevity of the whole organism vs the longevity of single cells.

Metabolic pathways and ageing

Within each cell, thousands of biochemical reactions take place involving many molecules essential to the proper functioning of the body. These processes are collectively termed "metabolism". Different metabolic pathways form particularly complex and finely regulated networks, due to a very dynamic cellular environment.

Which pathways affect longevity in a coordinated and harmonious manner throughout the body and which gene networks do they involve? The first and best-known regulatory pathway was that of insulin. In 1993, Cynthia Kenyon discovered the first gene capable of increasing the lifespan of the *C. elegans* nematode: the DAF-2 gene[4]. Subsequently, the entire network of genes involved in this pathway was identified: its activation allows the DAF-16 protein to penetrate into the cell nucleus, which in turn stimulates the expression of genes that oppose the ageing process. The DAF-16 protein has a human counterpart in the FOXO3 protein which plays a similar role. DAF-2 is the equivalent in *C. elegans* of the insulin receptor in humans, hence the name of this signalling pathway that is found in many species, from Drosophila to mammals, including the mouse and humans, even if the receptor is more complex in the latter ones[5]. The set of target genes in this pathway was then identified in several cell types. It is associated with a so-called mTOR (mammalian target of rapamycin) pathway, which is involved in numerous molecular/metabolic regulations.

There is another metabolic pathway relevant to longevity: that of calorific restriction. Longevity can be increased experimentally by reducing the calorific intake by 30 to 40%, without, of course, creating a deprivation, whether in yeast, worms, mice or primates, and even in humans[6]. But, in practice, calorific restriction cannot be applied to all humans! The idea is rather to find molecules that mimic the effect of calorific restriction. There are many genes involved; we can cite sirtuins, a class of proteins that regulate the metabolism of lipids and glucose and which are activated, among other things, by a component of wine, resveratrol. Activation of these genes acts on mitochondria. Mitochondrial metabolic pathways are also currently the subject of many studies in the biology of ageing.

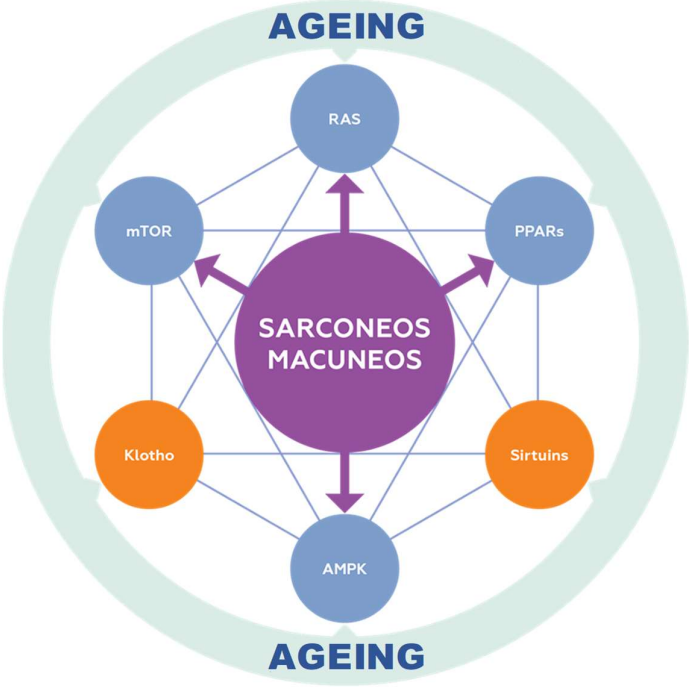
Of course, it was tempting to see if particularly long-lived humans had specific variants of some of these gerontogenes and if they also played a role in our species, but the results are not very convincing at the moment with the exception of FOXO3, the counterpart in humans of DAF-16.

[4] Kenyon C, Chang J, Gensch E, Rudner A, Tabtiang R. 1993. A *C. elegans* mutant that lives twice as long as wild type. *Nature* 366 (6454: 461-464.

[5] Martins R, Lithgow GJ, Link W. 2016. Long life FOXO: unraveling the role of FOXO proteins in aging and longevity. *Aging Cell.* 15: 196-207.

[6] Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, Ravussin E. 2018. Metabolic slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging. *Cell Metabolism* 27: 1-11.

Cell protective and deleterious mechanisms



As these metabolic pathways of longevity are identified, it is crucial to understand how the effect, at the level of the entire organism, of these various metabolic pathways, and their possible activation by environmental factors, regulate the mechanisms that allow a given cell population (yeast, bacteria, human cell culture etc.) to live more or less longer.

Over time, a whole series of entangled phenomena take place at the cellular level. One of the great discoveries of the biology of ageing is that these phenomena are found in all cells – in heart, liver and kidney cells, as well as neurons. Very briefly, there are two types of such mechanisms: phenomena that harm the cell and those that protect it. During ageing, unfortunately, deleterious phenomena tend to increase and protective phenomena to decline. Cellular deterioration is, therefore, due to an increase over time of several toxic or deleterious processes.

In the course of our life, most of our organs are “refurbished” in some way, owing to cell multiplication or division. As early as 1965, Leonard Hayflick showed that after about fifty divisions, almost every cell put in a culture medium ceases to multiply[7]. Such behaviour indicates a state of senescence, which can lead to a state of quiescence, or cellular “rest”, but these cells can also continue to age. They are then absorbed and “digested” by cells of the immune system, macrophages (a phenomenon known as phagocytosis). With age, this cleaning system becomes less effective, senescent cells accumulate and they secrete molecules responsible for chronic inflammations, often associated with age-related diseases (this is called the inflammasome)[8]. The study of these phenomena could lead to the

[7] Hayflick L. 1965. The limited in vitro lifetime of human diploid cell strains. *Exp. Cell Res.* 37: 614-636.
[8] Ventura MT, Casciaro M, Gangemi S, Buquicchio R. 2017. Immunosenescence in aging: between immune cells depletion and cytokines up-regulation. *Clin. Mol. Allergy* 15: 21. doi: 10.1186/s12948-017-0077-0.

development of a new class of so-called “senolytic” drugs, aimed at reducing the number of toxic senescent cells.

Another key breakthrough is the discovery of the role of telomeres and telomerase in maintaining the integrity of the genome, in controlling ageing and in cell proliferation. This discovery won the 2009 Nobel Prize in Medicine for Elizabeth Blackburn, Carol Greider and Jack Szostak. Telomeres are repetitive DNA sequences at the ends of chromosomes that protect them from deterioration. However, they are shortened with each cell division. When their length reaches a threshold limit, the cell stops dividing and enters senescence. Thanks to telomerase, however, the phenomenon is not inevitable[9,10]. In reality, this enzyme is able to replenish the ends of the chromosomes, although less and less effectively with age. In 2011, Harvard researchers succeeded in reversing the ageing process by modifying the activity of this enzyme. However, poorly controlled telomerase activity can also induce abnormal cell division leading to immortal cells whose production can lead to cancers associated with ageing.

Among the phenomena that degrade the cell, there is also “oxidative stress”, i.e., the production of free radicals (“reactive oxygen species” [ROS] or “reactive nitrogen species” [NOS]) which, in small doses, are essential for the good cellular function, but become toxic in large quantities. This excess may be due to overproduction or, on the contrary, to a decrease in the mechanisms of elimination of free radicals and antioxidant defence (antioxidant enzymes such as catalases, peroxidases, superoxide dismutases), or a decrease in quantity of small antioxidant molecules (glutathione, vitamins C and E, quinones, etc.) whether endogenous or obtained from food[11]. An important phenomenon, often related to oxidative stress, is inflammation, the intensity of which increases during ageing (referred to as “inflamm-ageing”)[12] and the study of which has been revolutionised by the discovery of molecular mediators of inflammation, particularly the family of inflammatory cytokines or interleukins. These mechanisms place mitochondrial dysfunction and the exaggerated production of free radicals as an early mechanism common to all ageing pathologies[13]. Free radicals actually cause inflammatory processes that develop with age, and this chronic inflammation has damaging consequences for the function of many cell types and tissues[14].

Finally, cells can commit suicide! Such cell death exists in different forms, including autophagy and apoptosis (also called “programmed cell death”). Cell suicide is a natural and physiological phenomenon during the development of the embryo and whose signalling pathways are well known now, but it can be reactivated during ageing and in certain pathologies. Over time, proliferation falters and apoptosis gains ground.

As we have already said, there also exist cell protective phenomena. All living organisms have mechanisms of response to different forms of cellular stress, whether acute and repeated or chronic. These mechanisms prevent too much damage from accumulating in the cells, and

[9] Blackburn EH, Epel ES, Lin J. 2015. Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection. *Science* 350 (6265) : 1193-1198.
[10] Da Silva Neto Trajano LA, Lima Trajano ET, dos Santos Silva MA, Stumbo AC, Mencalha AL, de Souza da Fonseca a. 2018. Genomic stability and telomere regulation in skeletal muscle tissue. *Biomed Pharmacother.* 98: 907-915.
[11] Fusco D, Colloca G, Lo Monaco MR, Cesari M. 2007. Effect of antioxidant supplementation on the aging process. *Clinical Interventions in Aging* 2 (3): 377-387.
[12] Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, Panourgia MP, Invidia L, Celani L, Scurti M, Cevenini E, Castellani GC, Salvioli S. 2007. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev*. 128: 92-105.
[13] Theurey P, Pizzo P. 2018. The aging mitochondria. *Genes* 9: 22, doi: 10.3390/genes9010022.
[14] Dalle S, Rossmeislova L, Koppo K. 2017. The role of inflammation in age-related sarcopenia. *Front. Physiol.* 8: 1045. doi: 10.3389/fphys. 2017.01045

affect the maintenance of vital functions, especially during ageing. This biological ability of an organism to compensate for cellular stress and to remain functional is called “biological resilience”. Multiple mechanisms underlie this resilience. They rely on complex and often interconnected molecular signalling pathways that act at the cell and organ level through intercellular communication, but also at the level of the whole organism through humoral and immune communication phenomena. They are in particular under the control of transcription factors and nuclear receptors, which as true “guardians” of the cell are able to perceive stress signals and coordinate the collective response of gene networks to maintain the functional balance of the cell. These “guardians” act broadly in relation to metabolism, the “quality control” of cellular components, cell survival and the maintenance of stem cell reserves.

These mechanisms include those that ensure that proteins remain in good working condition (thanks to chaperone proteins), or, on the contrary, those that remove proteins that age poorly. In cells, “small factories” producing several hundred proteins, called proteasomes, are responsible for eliminating “old” proteins[15]. The problem is that proteasomes themselves age, and their efficiency in digesting old proteins decreases over time. There is also the phenomenon known as autophagy which promotes the “recycling” of cellular content. In most situations, autophagy is beneficial to the cell because it allows its survival, but if it is exacerbated, it can cause cell death. “Waste accumulation” may, therefore, occur in a manner that becomes toxic for the cells; this term must be used in a very broad sense to include both altered proteins (i.e., non-functional proteins such as amyloid peptide, oxidised proteins, glycated proteins) and metabolic waste (lipofuscins, nitrogenous waste, etc.).

There are other protectors of the cell: specialised enzymes, like the famous PARPs, which can repair, within the double strands of DNA, lesions induced by many factors, including free radicals (see above). These lesions can block or corrupt the replication (or synthesis) of DNA[16]. More generally, over time, cellular DNA (nuclear and/or mitochondrial) accumulates mutations resulting from errors during its duplication (somatic mutations) in a random manner and these cause deleterious effects.

These resilience mechanisms are present in all types of cells and tissues, but their effectiveness can vary between organs and individuals and it decreases during ageing. How robust these biological resilience mechanisms are plays a key role in healthy longevity and resistance to age-related diseases.

Ageing organs

In conjunction with the actual ageing process (the effect of time on organisms and cells), there are also diseases whose frequency increases with age (neurodegenerative diseases, vascular diseases, joint diseases, etc.). These diseases have specific causes that medicine now seeks to identify more and more precisely, and which often act predominantly on particular organs. It is necessary to underline an important pathophysiological issue here; in the affected organs, these pathological processes generally act on the elementary phenomena that we have already described for ageing itself, and this conjunction explains why the frequency of these diseases increases a lot with age.

The different cells of the human body are not affected in the same way. In the particular case of nerve cells, which do not divide, the metabolic disturbances will result in their gradual death. The loss of neurons cannot be compensated indefinitely by the plasticity of the remaining cells and the reorganisation of their connections (hence the decline in cognitive functions during

[15] Vilchez D, Saez I, Dillin A. 2014. The role of protein clearance mechanisms in organismal ageing and age-related diseases. *Nature Communications* 5 : 5659

[16] Vida A, Márton J, Mikó E, Bai P. 2017. Metabolic roles of poly (ADP-ribose) polymerases. *Semin. Cell Dev. Biol.* 63: 135-143.

neurodegenerative diseases)[17]. In another area, the loss of motoneurons will have consequences on the muscles they innervate (axonal "dieback" theory in sarcopenia), and thus the mobility of individuals; loss of cells from the retinal pigment epithelium (modified neurons) and associated photoreceptors will lead to the progressive loss of central vision (AMD).

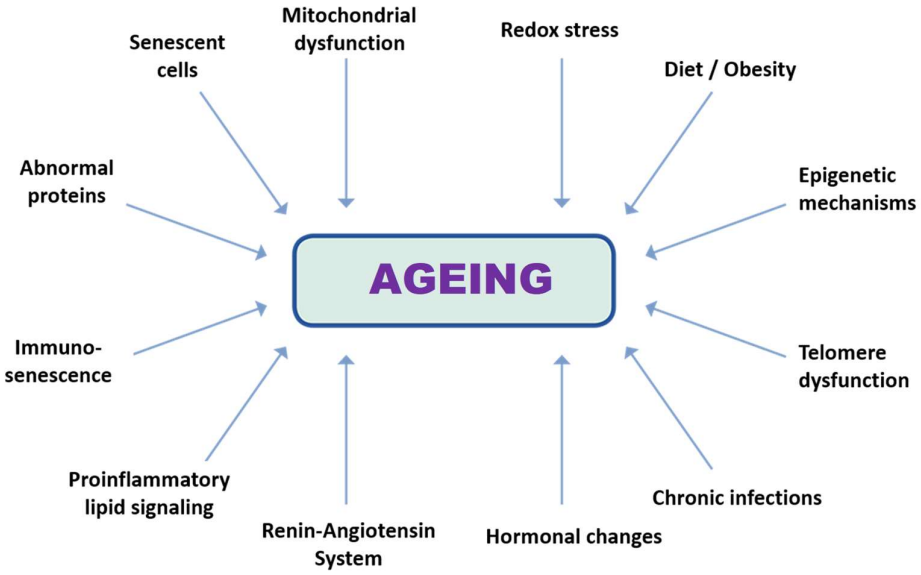
Other organs, on the other hand, have their components renewed regularly. This phenomenon is particularly dramatic in the case of the epithelium of the digestive tract and the liver, but is also important for other organs such as skeletal muscle, which can be damaged during repeated physical exercises. The important regenerative capacity of the latter depends on the presence of satellite cells (muscle stem-cells), the number of which will gradually decrease during ageing[18].

Ageing is obviously a complex, multi-factorial process and it manifests itself differently depending on the organs considered. It may/should thus be tackled in its earlier stages, in a manner adapted to the target.

As regards non-renewable cells, it is a question of keeping them in good condition, and thus of "helping" them to defend themselves against internal or external aggressions, and in particular against oxidative stress. Different strategies are possible: (1) consuming plant or synthetic antioxidant substances, (2) increasing the enzymatic antioxidant defences of the cells, (3) strengthening survival mechanisms, (4) improving mitochondrial function or (5) inhibiting certain ROS-producing enzymes (oxidases). With respect to renewable cells, it is also advantageous to protect them, in order to reduce the use of regenerative processes, which could become exhausted. But it could also be interesting to act on stem cells, in order to favour the maintenance of their population and/or their proliferation (preservation of the restorative capacity).

Finally, one should remember that the various organs communicate with each other, and that these numerous communications involve molecules that are diffusible over short distances (autocrine or paracrine factors) or longer distances (hormones), which is essential for coordinating the activity of the different organs. The ageing of the endocrine glands and the age-related changes in hormones are therefore important to consider, as the ageing of an organ is not an autonomous process without consequences on the ageing of other organs (e.g. *cachexias* associated with heart or kidney failure). We will analyse the subject later considering the involvement of the endocrine system in sarcopenia[19].

[17] Yaron A, Schuldiner O. 2016. Common and divergent mechanisms in developmental neuronal remodeling and dying back neurodegeneration. *Current Biology* 26: R628-R639.
[18] Bigot A, Duddy WJ, Ouandaogo ZG, Negroni E, Mariot V, Ghimbovschi S, Harmon B, Wielgosik A, Loiseau C, Devaney J, Dumonceaux J, Butler-Browne G, Mouly V, Duguez S. 2015. Age-associated methylation suppresses SPRY1, leading to a failure of re-quiescence and loss of the reserve stem cell pool in elderly muscle. *Cell Reports* 13: 1-11.
[19] Vitale G, Cesari M, Mari D. 2016. Aging of the endocrine system and its potential impact on sarcopenia. *Eur J Internal Medicine* 35: 10-15.



The mechanisms behind ageing (according to Fougère et al., 2017, modified)[20].

Case of early-onset degenerative diseases

Some gene mutations cause rare diseases (also known as "orphan" diseases) that result in the early appearance of symptoms that are similar to those observed during "normal" ageing. Apart from the particularly dramatic and extremely rare case of progeria, which causes a general accelerated ageing[21], there are various pathologies that affect more particularly an organ for which the deficient gene plays an essential role. We can cite the case of skeletal muscles (genetic myopathies) or the retina (e.g., Stargardt disease), whose pathologies ressemble sarcopenia and AMD, respectively. In muscle, Duchenne muscular dystrophy is characterised by a great fragility of muscle fibres and an early exhaustion of regenerative capacities, and in the retina, Stargardt disease is accompanied by an accumulation of metabolic waste linked to photo-oxidation.

The treatments contemplated in the context of ageing obviously cannot claim to correct genetic anomalies, but they may:

- slow down degenerative processes in the absence of gene therapy or cell therapy treatments, or indeed
- supplement these when they exist.

In order to slow down ageing (and related pathologies), one possible strategy is to take advantage of knowledge from traditional medicines, which have identified plants with active ingredients and no toxic effects. Let us recall that plants have been, and continue to be, the source of many drugs, or active molecules from which analogues have been derived to become drugs[22,23]. Starting from natural molecules that have proven to have beneficial effects on an organ being studied, it is possible to develop research programmes to better understand how they act (identify the receptor(s) they target). This approach corresponds to what is known as

[20] Fougère B, Boulanger E, Nourhashémi F, Guyonnet S, Cesari M. 2017. Chronic inflammation: accelerator of biological aging. *J. Gerontol. A Biol. Sci. Med. Sci.* 72 (9): 1218-1225.
[21] Strandgren C, Revêchon G, Carvajal AC, Eriksson M. 2017. Emerging candidate treatment strategies for Hutchinson-Gilford progeria syndrome. *Biochem. Soc. Trans.* 45: 1279-1293.
[22] David B, Wolfender JL, Dias DA. 2015 The pharmaceutical industry and natural products: historical status and new trends. *Phytochem Rev.*, 14: 299-315.
[23] Harvey AL, Edrada-Ebel R, Quinn RJ. 2015 The re-emergence of natural products for drug discovery in the genomics era. *Nature Reviews Drug Discovery* 14: 111-129.

reverse pharmacology (see § 6.1.2) [24], which represents an alternative to classical pharmacology, which screens for active molecules on a target, but is then often faced with adverse effects on other targets, rendering these molecules unusable.

6.1.2 The development strategy for candidate medicines

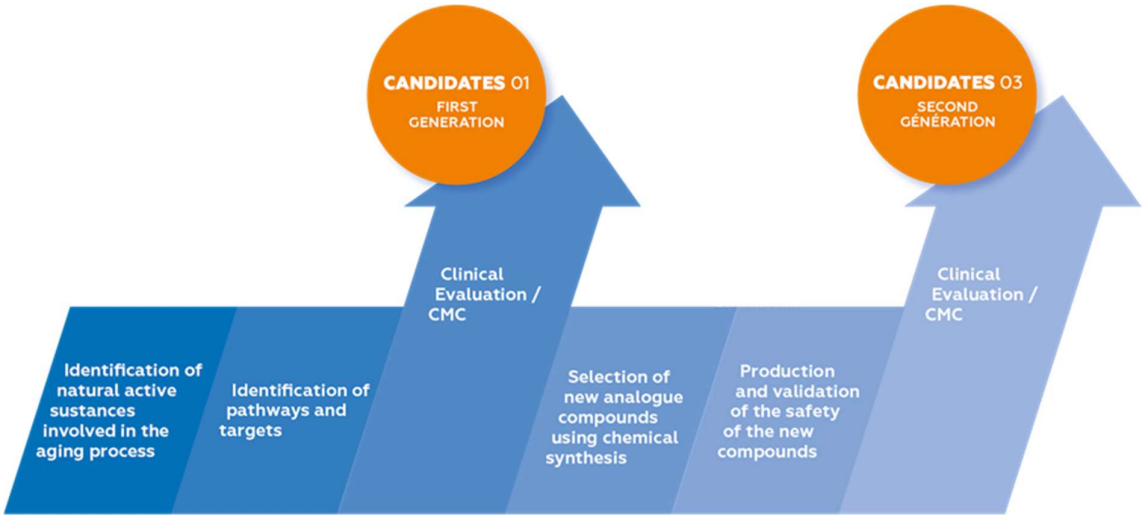
The 1990s saw the development of combinatorial chemistry associated with high-throughput screening assays on new molecular targets with high potential. The advent of this new pharmacology that enabled researchers to identify highly selective, refined molecules offered great promise. However, and in a relatively paradoxical way, the pharmaceutical industry has gone through a productivity crisis linked to a considerable increase in the failure rate in the development candidates (secondary effects, toxicity, ineffectiveness in humans, etc.) and to an explosion in the ratio of R&D costs to registered products.

Plant *secondary metabolites* are molecules with a diversity greatly exceeding that generated by synthesis for *chemical libraries* of the most important small molecules. They derive from the process whereby plants defend themselves against their environment and from co-evolution with different predatory or pathogenic species; they are naturally "bioactive" and seem to show that the pharmacophores found in natural molecules are better than those obtained by combinatorial chemistry. This original property means that they still account for most new medicines discovered: more than 50% of the drugs registered by the FDA in the last 30 years derive from natural active ingredients (Li & Vederas, 2009[25], David et al., 2015[26])

It should be evident by now that natural active molecules continue to represent an important source of medicinal drugs. However, the targets for most of these remain unknown. As a result, the high-throughput systems on pre-identified targets developed in recent decades are not directly applicable to the characterisation of natural molecules. In terms of drug development, it is therefore necessary to implement so-called reverse pharmacology for natural compounds that have proven to be, sometimes for a long time, both safe and effective. Reverse pharmacology, as practiced by Biophytis, is initiated by a phenotypic test of natural compounds. Unlike classical pharmacology, reverse pharmacology moves from the clinic to the laboratory with the objective of identifying the molecular target and the mechanism of action of the compound. The collected information then makes it possible to improve (1) the structure of the compounds by medicinal chemistry (structure-activity relationship studies), (2) the compounds' metabolic and pharmacokinetic characteristics in order to increase their effectiveness.

Biophytis is developing two categories of candidate medicines for each pathology: first-generation candidates (Series BIO-01), based on the development of the natural active molecule, extracted from the food or medicinal plants, as a pharmaceutical active ingredient; and second-generation candidates (Series BIO-03), based on the development of a proprietary *derivative* of the natural active ingredient, resulting from production by chemical synthesis (or hemisynthesis) of the compound.

[24] Blondeau S, Do QT, Scior T, Bernard P, Morin-Allory L. 2010. Reverse pharmacology: another way to harness the generosity of nature. *Curr. Pharmaceutical Design* 16 (15): 1682-1696.
[25] Li, J.W. and Vederas, J.C. (2009) Drug discovery and natural products: end of an era or an endless frontier? Science 325, 161–165
[26] David B, Wolfender JL, Dias DA. 2015 The pharmaceutical industry and natural products: historical status and new trends. *Phytochem Rev*., 14: 299-315.



The first generation of candidates derived from a process of *phenotypic screening* on cellular and animal models of the pathology, without *a priori* knowledge of the molecular targets. Their nutritional or medicinal origin allows for an accelerated *clinical development* of the candidates by reason of the nutritional exposure of humans to these substances and their very low toxicity. The discovery of the effects of these substances on the ageing process allows their use for the treatment of the targeted pathologies to be patented.

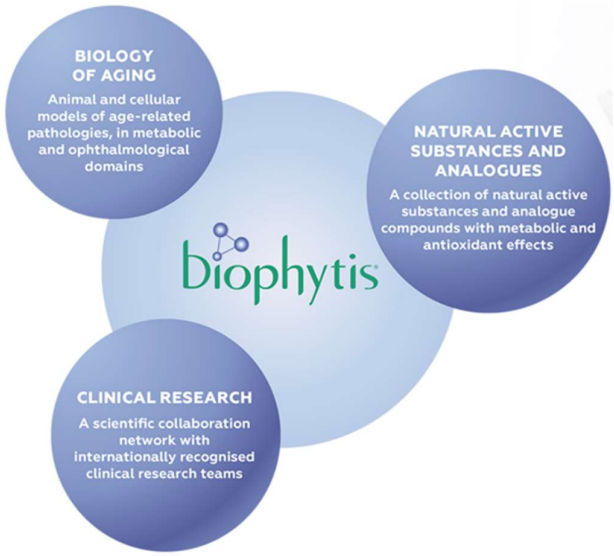
The second generation of candidates has been developed on the basis of a precise understanding of the action mechanisms of the first-generation products, in particular of the molecular targets of the candidates. *Analogues* of the natural active ingredients are synthesised by medical chemistry and selected in previously calibrated cellular models. The synthesis of novel compounds will permit the improvement of their pharmacological properties (in particular the bioavailability of the compounds) and the patenting of the chemical formulas of the candidates for development. Their clinical development requires prior validation in *non-clinical and clinical regulatory studies* (phase 1) in order to confirm whether they are safe for humans.

6.1.3 The translational research platform

Biophytis has developed an original research platform, based on the *screening* of natural active molecules in models of age-related pathologies.

Natural active molecules have been the subject, for some 10 years, of active academic research, to establish their role in the development of chronic age-related pathologies, in particular in degeneration of the eye (notably of the retina), of *skeletal muscle*, or of the vital organs, such as the brain, heart, kidneys or liver. It is well established, for example, that deficiencies of certain *natural active molecules*, such as lutein, a *carotenoid* present in various fruits and vegetables, increases the risk of developing age-related macular degeneration (AMD, AREDS report, 2007)[27]. Tens of thousands of other *natural active molecules* are still poorly characterized. Their effects on little-studied ageing processes thus offer a privileged source of “bioactive” molecules with a potential that remains largely untapped.

[27] AREDS report N°22, 2007. The Relationship of Dietary Carotenoid and Vitamin A, E, and C Intake With Age-Related Macular Degeneration in a Case-Control Study. *Arch Ophthalmol*., 125 (9):1225-1232.



Located on the campus of Sorbonne University (formerly Pierre and Marie Curie University, UPMC), its very first scientific partner, Biophytis has:

(i) set up, in partnership with the Institut de Biologie Paris Seine at Sorbonne University, a collection of natural active ingredients belonging to several chemical classes (triterpenoids, polyphenols and *carotenoids*) derived from food and medicinal plants.

(ii) developed cellular and animal models of age-related pathologies forming the object of its research, in collaboration with the biomedical research teams and *translational research* institutions of Sorbonne University.

SORBONNE UNIVERSITÉ
CRÉATEURS DE FUTURS DEPUIS 1257

INSTITUT DE MYOLOGIE
INNOVER POUR GUÉRIR

INSTITUT DE LA VISION
PARIS

INSTITUT DE BIOLOGIE PARIS SEINE

Sorbonne University: Sorbonne University was formed on 1 January 2018, resulting from the merger of the Pierre et Marie Curie University (UPMC, Paris 6) and the Paris-Sorbonne University (Paris 4). Sorbonne University is based in Paris and specialises in sciences and medicine. It is located in the Jussieu campus (in the Latin Quarter of Paris) for sciences, and in the hospital campuses of Pitié-Salpêtrière, Saint-Antoine, Trousseau and Tenon for medicine. It has 35,000 students. 6,000 lecturers-researchers and researchers work in its 100 research laboratories. In the 2017 Shanghai ranking, the University asserted its position as the leading French research university, ranking 8th in Europe and 40th worldwide.

Institut de Myologie/Institute of Myology: since the start of the 1980s, the directors of the *Association Française contre les myopathies* (AFM-Téléthon) [French Association against myopathies], sufferers and parents of sufferers have established a reference point, bringing together within the public hospital a specialized consultation service, basic and clinical research teams and teaching on muscle and its pathologies. The laboratory of Dr Gillian Butler-Browne has been a partner in the collaborative SARCOB project since 2011. Under the leadership of its new director, Professor Bertrand Fontaine, the world-renowned Institut de Myologie is initiating a transformation in which Biophytis is joining forces by strengthening its collaborations.

Institut de la Vision/Institute of Vision: established at the heart of the CHNO (Centre Hospitalier National of Ophtalmologie des Quinze-Vingts), the Institute of Vision is one of the most important integrated research centres for diseases of vision in Europe. Designed as a place for meeting and exchanges, it brings together basic, clinical and industrial research on the same site. Since 2010, the MACULIA (AMD) project has been directed in collaboration with Valérie Fontaine of the UMRS968 of the Institute of Vision. In 2017, Biophytis began work in collaboration with Florian Sennlaub and Xavier Guillonneau of the team working on inflammation, degeneration and vascular remodelling of retinal pathologies.

Institute of Biology Paris Seine: The Institut de Biologie Paris-Seine (IBPS - FR3631), established on 1 January 2014, gathers all biological research carried out on the Jussieu campus within Sorbonne University, where this discipline has always occupied a central place. The IBPS comprises over 500 people in 5 units and 5 technology platforms. Born out of the common will of the CNRS and Sorbonne University, with which INSERM has joined forces, the IBPS aims to embody Sorbonne University's excellence in biology. Biophytis has established within the IBPS several collaborations with the "Biological Adaptation and Ageing" unit led by Professor Bertrand Friguet. His laboratory is one of the most important in the world in the study of the fundamental mechanisms underlying biological responses to stresses and their development during ageing.

6.1.4 The pipeline

Biophytis has decided to concentrate its research efforts on the degeneration of the muscle and the degeneration of the retina, pathologies for which the selected molecules seem to have the most potential. Sarcopenia (age-related muscular dystrophy) and AMD (age-related macular degeneration) have been given top priority as the major causes of disability in the over-65 age group and no treatment is currently available for them. Since 2017, Biophytis has also invested in adapting its programmes to genetic degenerative diseases: Duchenne muscular dystrophy and Stargardt disease.

The Sarconeos drug candidate and the SARA clinical programme

Sarconeos is the first representative of a new class of drug candidates formulated to activate the MAS receptor (which plays a major role in the renin–angiotensin system), stimulate muscle anabolism, inhibit myostatin, and promote the development of muscle mass in animal models of muscular dystrophies. Sarconeos is being developed for the treatment of Sarcopenia, an age-related muscular dystrophy characterised by a loss of muscle mass and strength, leading to a loss of mobility among seniors. This new pathological condition, for which no drug treatment is available, was first described in 1993 and was recently listed under code M62.84 in ICD-10-CM, (International Classification of Diseases, Tenth Revision, Clinical Modification, based on the WHO classification used in the United States for patient follow-up). It affects up to 10% of the elderly persons in the world.

The SARA programme is a multi-centre clinical programme carried out in 4 countries (USA, France, Belgium and Italy) and aimed at determining the effective therapeutic dose of Sarconeos in a Phase 2b clinical study performed on 334 patients with sarcopenia. It began in 2016, with SARA-PK, a safety and pharmacokinetic study conducted on 30 healthy elderly subjects. The programme includes a sixth-month observational study (SARA-OBS) performed on more than 300 patients with sarcopenia in 11 clinical centres. SARA-OBS launched at the end of 2016. Data from SARA-OBS will enable us to better define the target population for

Sarconeos treatment. After we obtain their consent, we may include patients who participated in the SARA-OBS in the SARA-INT phase 2b study. The objective of SARA-INT is to assess the safety and efficacy of two doses of Sarconeos (175 mg bid and 350 mg bid) administered orally for 26 weeks vs a placebo in a population of men and women over the age of 65 at risk of motor disability, and to estimate the effect of the treatment as concerns the improvement of the physical function and the reduction of the risk of motor disability.

Biophytis is following the regulatory authorisation process for SARA-INT in the 4 countries concerned, which should lead to a unique clinical protocol that meets the requirements of all responsible agencies. We contacted the European Medicines Agency in 2017 for its scientific advice. The authorisations from the US (FDA) and Belgian (FAMHP) agencies were obtained in October and December 2017, respectively. Applications for authorisation were then filed in France and Italy. Lastly, the SARA-INT application is currently being examined in the United States and Belgium by the respective Ethics Committees of the various clinical centres participating in the study.

The first patient has been incorporated into the study in May 2018. Based on the patients previously selected for the SARA-OBS study, the induction of patients will proceed during 2018. As a result, the administration period could end in the first half of 2019, followed by the publication of preliminary results in the summer of 2019.

The Macuneos drug candidate and the MACA clinical programme

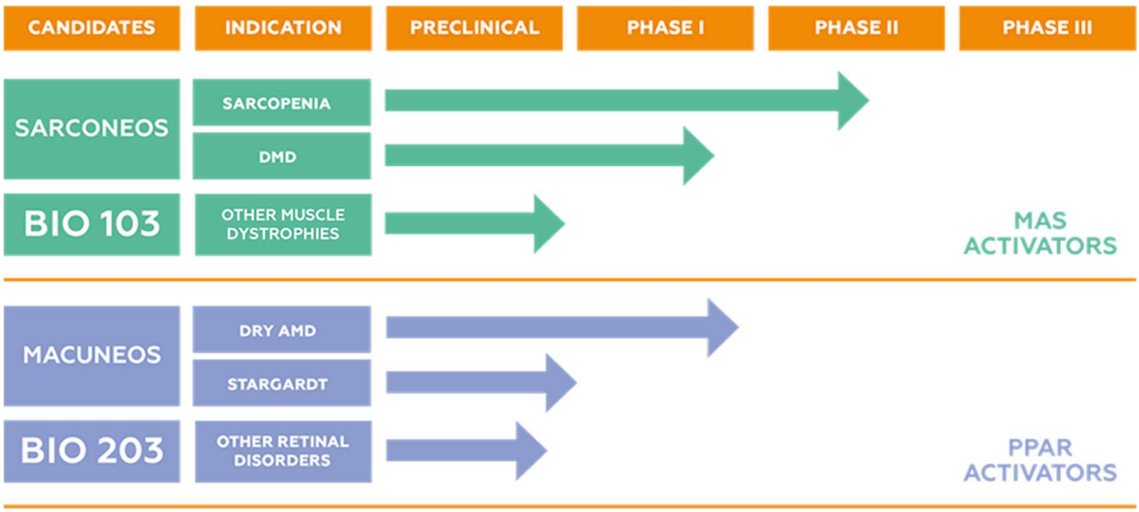
Macuneos is the first representative of a new class of drug candidates intended as PPAR (nuclear receptor) agonists. Macuneos protects the retinal pigment epithelium. Biophytis has demonstrated in animal models that *Macuneos* protects the cells of the retina from the phototoxic effects of A2E in the presence of blue light (photo-oxidative stress), reduces the accumulation of this phototoxic molecule and thus slows down the retinal degeneration process. Macuneos is a drug candidate for dry AMD in its intermediate stage. AMD affects the central part of the retina, known as the macula, leading to serious visual impairment and irreversible loss of central vision after the age of 60. Macuneos comes in capsule form (taken once a day).

The MACA programme is a multi-centre clinical programme carried out in several countries (USA, Europe) and aimed at determining the effective therapeutic dose of Macuneos to slow the progression of the disease in patients with AMD in a Phase 2b clinical study. Two studies, set to begin in the second half of 2018, will be conducted simultaneously prior to the phase-2b interventional study (MACA-INT):

- A pharmacokinetic and safety study on healthy volunteers and elderly patients with intermediate AMD (MACA-PK)
- An observational study to define the target population and pre-recruit patients (MACA-OBS), which will be conducted in Europe and the United States

This clinical-regulatory protocol is aimed at (i) obtaining clinical activity data as early as 2018, (ii) measuring the pharmacokinetics of Macuneos specifically in the patient, before confirming the doses to be administered, (iii) accurately characterising the affected population, before confirming the inclusion criteria of the patients tested.

The process for obtaining regulatory approval is underway, and the single ascending dose (SAD) phase of the study will be set to begin in the autumn of 2018. The results of the SAD phase are expected before the end of 2018.



MYODA clinical programme

Sarconeos has obtained Orphan Drug Disease designation from the FDA, and Biophytis has deposited an application for designation as an orphan medication for Duchenne muscular dystrophy with the EMA. As there are very few drug treatments available, Sarconeos is a drug candidate that has the potential to significantly slow the progression of the disease and could be used alone or in combination with genetic therapy, when the latter is available, in children with Duchenne muscular dystrophy. The staus of ODD or orphan medication could give Sarconeos the advantages associated with orphan drug status, in particular the possibility of early registration (on the basis of a conditional authorisation) and protection for 7 to10 years after receiving the marketing authorisation.

Sarconeos' clinical development plan for Duchenne muscular dystrophy consists of two main clinical studies: a phase 1/2 pharmacokinetic study (MYODA-PK) expected to begin in 2018, and a phase 2/3 efficacy study (MYODA-INT) that could start in 2019.

Second-generation drug candidates

The second-generation drug candidate BIO103 entered the preclinical regulatory phase in 2017 and will be developed to treat muscular dystrophy. BIO203 is currently undergoing optimisation and development as to its dosage (galenic) form and will be ready for preclinical testing in 2018. It will probably be developed to treat a retinopathy other than AMD.

6.1.5 The economic model

Biophytis intends to offer two comprehensive and largely risk-free "technological packages" to pharmaceutical laboratories, which will include the following components:

- A first-generation drug candidate (natural active ingredient) in an advance stage of clinical development, with proof of concept obtained in humans
- Primary indication for a significant portion of the elderly population with significant medical needs that are currently not met
- Second indication for an orphan (rare) genetic condition
- Second-generation drug candidate (active analogue ingredient) which has passed through the regulatory development phases

- An explored and described mechanism of action,
- Characterisation of the effects in several secondary indications.

With the aim of signing one licensing and partnership agreement, either concerning Sarconeos or Macuneos, following the SARA-INT or MACA-PK studies.

It is stated that the economic potentials of the two candidate molecules Sarconeos and Macuneos, presented above, have been simulated presuming marketing authorisation.

Economic potential of Sarconeos

Based on the different studies available on the prevalence of sarcopenia in the American population[28], we obtain the following data on the population that is potentially relevant to *Sarconeos*:

	% of individuals	Number of individuals
American population		308 million
% of the US population between 65 and 79 years of age	10%	31 million
% of the US population over 80 years of age	3.5%	11 million
% of the US population suffering from sarcopenia:		
Between 65 and 79 years of age	30%	9.3 million
Over 80 years of age	50% of	5.5 million
Total US population suffering from sarcopenia		**14.8 million**

Assuming an annual treatment price of €1,000 (conservative assumption, given the sale price of innovative products for comparable pathologies), royalties for Biophytis set at 10% (hypothetical average) under a licensing agreement, and royalties owed by Biophytis to the co-holders of the patents set at 10% (maximum rate), we can project 3 scenarios (at 10, 20 and 30% of the patients for SARCONEOS):

	Scenario 1	Scenario 2	Scenario 3
Patients with sarcopenia	15 million		
Market share of Biophytis (peak sales)	10%	20%	30%
Annual cost of the treatment	1,000		
Peak sales	**€1.5 billion**	**€3 billion**	**€4.5 billion**
Potential royalties for Biophytis (10%)	€150 million	€300 million	€450 million
Royalties payable to the co-holders of the patents (10%)	€15 million	€30 million	€45 million
Net sales for Biophytis	**€135 million**	**€270 million**	**€405 million**

The potential net sales for Biophytis at the peak of sales of SARCONEOS for sarcopenia are estimated between €135 million and €405 million in the US market based on the selected conservative estimates. Since the prevalence of sarcopenia is similar in the European population[29] and only slightly lower in Asia[30], we could double or even triple these figures in a scenario where SARCONEOS is marketed at a global scale for this indication.

[28] Baumgartner, R.N. et al., 1998. Epidemiology of sarcopenia among the elderly in New Mexico, American Journal of Epidemiology, 147, pp. 755-763.
[29] Ethgen O. et al., 2017. The Future Prevalence of Sarcopenia in Europe. A Claim for Public Health Action. Calcif Tissue Int.; 100 (3), 229-234
[30] Shafiee G. et al., 2017. Prevalence of Sarcopenia in the world: A systematic review and meta-analysis of general population studies. J Diabetes Metab Disord 16:21

For Duchenne muscular dystrophy, the prevalence of which is generally less than 1 per 10,000[31] – which would be equivalent to less than 30,000 individuals affected in Europe – the economic model is very different. Biophytis is aware that a price differentiation between the two indications for SARCONEOS will hardly be possible, and that therefore the turnover of the paediatric formulation will probably not exceed a few million. Nevertheless, playing a role in the fight against this terrible genetic disease would have an impact in the medical-scientific community and even on the public, significantly bolstering the SARCONEOS brand. On the other hand, continuing the clinical programme in Duchenne muscular dystrophy allows Biophytis to consider an isolated launch of the product in this indication, in case the results of SARA-INT were delayed or not immediately significant enough and, in this case, we would be able to obtain a "premium" price.

Economic potential of Macuneos

Like sarcopenia, dry AMD is a very common disease and is currently poorly served medically; there are more than 9 million patients in Europe alone[32]. By doubling this figure to reach an overall prevalence assumption, and assuming on the other hand, as for SARCONEOS, an annual treatment price of €1,000, royalties for Biophytis set at 10% under a licensing agreement, as well as royalties owed by Biophytis to the co-holders of the patents set at 11% (maximum rate), we would arrive at the following peak-sales scenarios:

	Scenario 1	Scenario 2	Scenario 3
Patients suffering from dry AMD	18 million		
Market share of Biophytis (peak sales)	10%	20%	30%
Annual cost of the treatment	1,000		
Peak sales	**€1.8 billion**	**€3.6 billion**	**€5.4 billion**
Potential royalties for Biophytis (10%)	€180 million	€360 million	€540 million
Royalties payable to the co-holders of the patents (11%)	€19.8 million	€39.6 million	€59.4 million
Net sales for Biophytis	**€160 million**	**€320 million**	**€481 million**

Lastly, potential net annual sales for Biophytis with *Macuneos* are estimated at between €160 million and €480 million.

Concerning Stargardt disease, the prevalence of which is estimated at just over 1 in 10,000[33], the economic model will be similar to that of SARCONEOS for Duchenne muscular dystrophy; it could mean garnering the support of the medical-scientific community for the MACUNEOS brand for AMD, or commanding a "premium" in case of prior or single marketing.

It is noteworthy that American investment bank HC Wainwright & Co., in a recent report (December 2017: Biophytis: Powered by Plants, Unlocking Phytochemical Potential; Initiating at Buy and € 10 target), using a different model, arrives at figures for SARCONEOS and MACUNEOS that are quite similar (more than $2 billion/year at peak sales).

Immediate economic potential (by partnership)

[31] Ryder S. et al., 2017. The burden, epidemiology, cost and treatment for Duchenne muscular dystrophy: an evidence review. J Rare Dis 12:79
[32] Colijn JM et al., 2017. Prevalence of age-related macular degeneration in Europe: The Past and the Future. Ophthalmology. 124 (12): pp. 1753-1763
[33] Tanna P. et al., 2016. Stargardt Disease: Clinical features, molecular genetics, animal models and therapeutic options. Br J Ophthalmol.; 10: 1136-1142

As a consequence of their frequent occurrence and strong growth, sarcopenia and AMD have formed the object of an intense scientific investment for some 15 years. The understanding of the molecular and physiological mechanisms have gradually become more precise, with better identification of causes, better characterization of the different categories by clinicians and the establishment of regulatory criteria. New markets are opening. In the same way, the public, scientific and also economic interest in muscular and ocular genetic diseases (rare diseases, therefore known as “orphan” diseases) has increased significantly over the last decade.

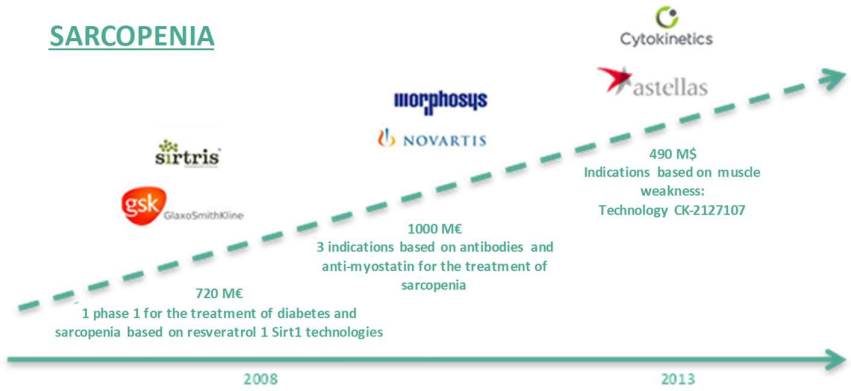
Several of the major pharmaceutical companies count these pathologies amongst their strategic lines for the years 2020-2030 and seek therapeutic solutions, often by entering into agreements with biotechnology companies.

As these are generally new markets (with no drug treatments registered for these indications), the first products to reach the market offer a very high sales potential; Lucentis from Novartis/Roche, the first drug registered to treat exudative AMD (more rare than dry AMD, for which MACUNEOS is developed) currently generates around €3 billion in sales per year.

The licensing agreements signed in recent years are on the scale of this economic potential. Here are some examples:

Year	Licensor	Licensee	Indication(s)	Upfront payment	Estimated total value
2006	Bayer	Regeneron	AMD (wet form)	$75 million	$320 million
2008	Glaxo Smithkline (gsk)	Sirtris	Sarcopenia, diabetes	$720 million	$720 million (buyback)
2013	Novartis	Morphosys	Muscular diseases; AMD	Not made public	> €1 billion
2013	Astellas	Cytokinetics	Muscle weakness	$40 million	$450 million
2016	Pfizer	Bamboo Therapeutics	DMD	$150 million	$495 million
2017	Astellas	Mitobridge	DMD	$225 million	$450 million

Biophytis plans to conclude at least one significant (i.e., comparable to the above examples) licensing agreement



Future economic potential

The domain of degenerative diseases linked to ageing has hardly been explored to date. This is a major public health challenge and its scientific exploration will mobilise a growing number of researchers and investments.

Biophytis is one of the first companies to have implemented a platform and a scientific strategy specifically designed to meet this need. The company is in the process of demonstrating how relevant this strategy is, with its sarcopenia and AMD programmes. Moreover, the approach to treat these age-related diseases also has significant potential in the therapy of degenerative syndromes that could be described as “premature”, related to genetic defects; hence the acceleration of the DMD and Stargardt programmes undertaken by Biophytis.

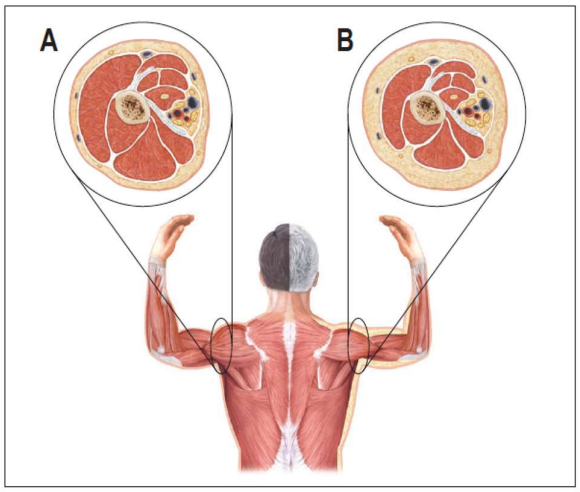
The Company’s ambition is to continue to discover and develop new classes of medicines to treat age-related diseases according to this model:

- Partnership with biomedical research institutions which are experts in a given field of pathologies
- Identification of several families of natural active molecules in *phenotypic* studies
- Description of the mechanism of action, choice of indication and optimisation of drug candidates
- Proof of clinical effectiveness and license with a pharmaceutical company.

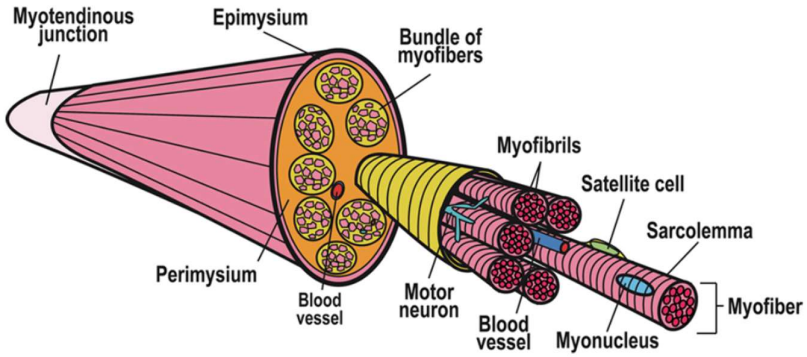
6.2 PROGRAMME TO COMBAT SARCOPENIA AND OTHER MUSCULAR DYSTROPHIES

Muscle loss is the result of a reduction in proteosynthesis, linked to the reduction in anabolising factors, and of an increase in proteolysis. The involvement of the renin–angiotensin system (RAS) in the pathophysiological process leading to sarcopenia has been considered in various studies. In particular, the study of the physical capacity of elderly patients treated with certain ACE (Angiotensin Conversion Enzyme) inhibitors demonstrated that, in certain cases, this treatment could improve the mobility of elderly patients. Biophytis has oriented its work towards the activation of one of the essential parts of the system: the MAS receptor.

6.2.1.1 The regeneration of muscle in maintaining muscular functionality



The *skeletal muscles* represent a very significant fraction of body weight and protein mass (28-35% in a healthy adult). They are a source of important renewal, since the organism produces between 250-300 g of muscle protein every day.



Structure of skeletal muscle (Scime et al., 2009)

Muscle is a tissue composed of contractile cells called *myotubes* (or *muscle fibres*). These *giant multinucleate cells* are rich in actin and *myosin* (two proteins) microfilaments, the principal agents of muscle contraction. Muscle also contains single-nucleus cells, satellite cells, which may multiply and fuse with the myotubes (which occurs following sustained physical exercise or after an injury) or even amongst themselves to form new fibres.

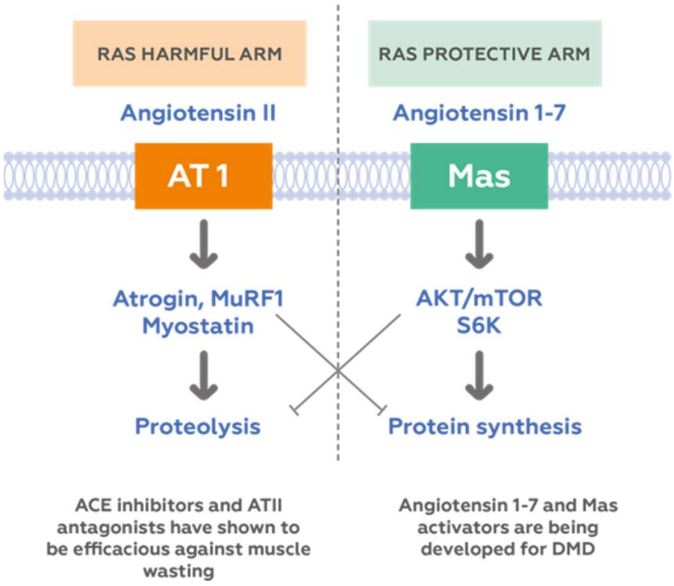
The *skeletal muscles* contain several types of *fibres*. Type II fibres are powerful but rapidly fatigued (IIx fibres in particular), while type I fibres are less powerful, but allow prolonged effort, essentially by consuming fatty acids.

In simplified fashion, the regeneration of muscle depends, on the one hand, on its capacity to synthesise the proteins (actin and *myosin*) that make up the filaments and, on the other hand, on its capacity to produce new muscle cells (*myoblast*) which will fuse with the existing *myotubes* (or which fuse amongst themselves to form new *muscle fibres*). The variations in size of muscles thus depend on those of the size and number of *myotubes*. However, the

capacity of satellite cells to provide for the (partial or total) renewal of the *muscle fibres* is reduced along the elderly (Snijders and Parise, 2017)[34].

The muscle mass is the object of a precise multifactor control mechanism, with stimulating factors, such as testosterone, *IGF-1* and vitamin D, and inhibiting factors, such as *myostatin*, produced by the muscles themselves and acting in an *autocrine* fashion, and angiotensin II. During the ageing process, several hormonal changes occur that may disturb this equilibrium in favour of mechanisms that promote muscle degradation. These effects may be magnified by a reduction in physical activity (Rudrappa et al., 2016, Gomes et al., 2017) [35] .

In sarcopenia, the muscle loss results from a reduction in *proteosynthesis* linked to the reduction in anabolizing factors and an increase in *proteolysis*, which is a consequence of an increase in *catabolizing* factors, primarily of *myostatin*, or even of cell death (*apoptosis*).



There is also a neurodegenerative component of sarcopenia, linked to a reduction in the number of *motoneurons* and of end-plates, which are essential for muscular activity (Lynch and Ryall, 2008)[36]. Aggravating factors, such as malnutrition, renal insufficiency and diabetes, may influence the intensity and age of onset of sarcopenia (Hébuterne, 2003; Pupim et al., 2005; Park et al., 2009; Kim et al., 2010)[37].

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[34] Snijders T, Parise G. 2017. Role of muscle stem cells in sarcopenia. *Curr Opin Clin Nutr Metab Care* 20 (3): 186-190.

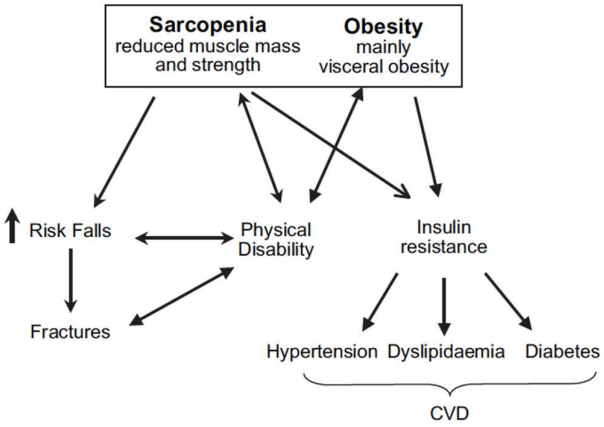
[35] Rudrappa SS, Wilkinson DJ, Greenhaff PL, Smith K, Idris I, Atherton PJ. 2016. Human skeletal muscle disuse atrophy: effects on muscle protein synthesis, breakdown, and insulin resistance – a qualitative review. *Frontiers in Physiology,* doi: 10.3389/fphys. 2016.00361 – Gomes MJ, Martinez PF, Pagan LU, Damatto RL, Cezar MDM, Lima ARR, Okoshi K, Okoshi MP. 2017. Skeletal muscle aging: influence of oxidative stress and physical exercise. *Oncotarget* 8 (12): 20428-20440.s

[36] Lynch GS, Ryall JG. 2008. Role of β-adrenoreceptor signaling in skeletal muscle: implications for muscle wasting and disease. *Physiol Rev*, 88: 729-767.

[37] Hébuterne X, Bermon S, Schneider SM. 2001 Ageing and muscle: the effects of malnutrition, re-nutrition, anfd physical exercise. *Curr Opin Clin Nutr Metab* Care, 4 (4): 295-300. Pupim LB, Heimbürger O, Qureshi AR, Ikizler TA, Stenvinkel P. Accelerated lean body mass loss in incident chronic dialysis patients with diabetes mellitus. *Kidney* Int, 68 (5): 2368-2374. Kim TN, Park MS, Yang SJ, Yoo HJ, Kang HJ, Song W, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. 2010. Prevalence and determinant factors of sarcopenia in patients with type 2 diabetes. *Diabetes Care* 33: 1497-1499.

The ageing of the muscles is accompanied by a reduction in the size of the *fibres*, as well as by a change in the distribution of the types of *fibres*, to the benefit of type I *fibres* (slow and weak *fibres*). The reduction in the size and number of *myotubes* is not always accompanied by a reduction of the size of the muscles, since following the establishment of inflammatory process and excessive nutritional contributions with regard to the physical activity of individuals, these may be infiltrated by *adipocytes*, the multiplication and the development of which will maintain muscle volume, but evidently not its mechanical properties. We may then speak of sarcopenic obesity, a pathology which develops in elderly overweight individuals (Walrand and Boirie, 2007; Zamboni et al., 2008)[38]. In this pathology, the cardio-metabolic risk factors, whether the cardiovascular risk or the risk of diabetes, are exacerbated due to the incapacity of the *skeletal muscle* to fulfil its metabolic function, with it becoming progressively resistant to insulin and to *anabolic* stimulation.

Sarcopenia in obese individuals thus represents an aggravated form of sarcopenia owing to the combination of several unfavourable factors, the deleterious effect on cells of fatty infiltration into the muscles (Kalinkovich and Livshits, 2017)[39], which reduces their *proteosynthetic* capacity and amplifies their degeneration, and excessive weight, which limits mobility (Zamboni et al., 2008)[38]:



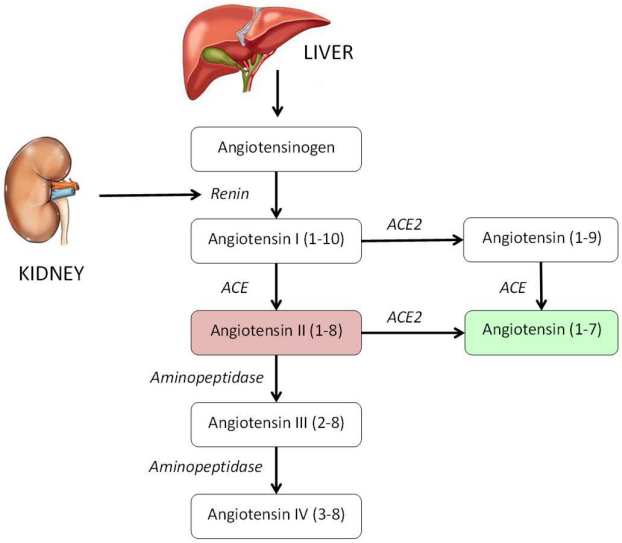
6.2.1.2 The renin-angiotensin system and muscular functionality

The *renin-angiotensin-aldosterone system* classically refers to a hormonal system, which allows an equilibrium to be maintained between Na^+ (sodium) ions and water, termed sodium and water *homeostasis*. In order to achieve this, renin, an enzyme secreted by the kidney, splits *angiotensinogen*, produced by the liver, to form angiotensin I. This is then split by a "conversion" enzyme (ACE) into angiotensin II, which is a *peptide* with very powerful vasoconstrictive properties. The excess of angiotensin II is thus a significant cause of hypertension and the inhibitors of ACE are classically used to treat arterial hypertension.

It was subsequently discovered that this system is much more complex, since it is likely to generate a large number of biologically active *peptides*:

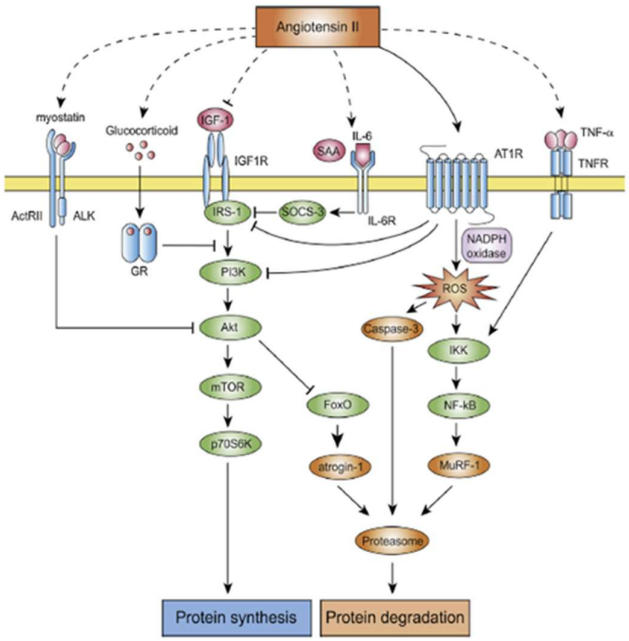
[38] Walrand S, Boirie Y. 2007 Obésité sarcopénique: parle à mon gras, mon muscle est malade (Sarcopenic obesity: talk to my fat – my muscle is sick) *Obésité* 2: 331-338. Zamboni M, Mazzali G, Fantin F, Rossi A, Di Francesco V. 2008. Sarcopenic obesity: a new category of obesity in the elderly. *Nutrition, Metabolism & Cardiovascular Diseases* 18: 388-395

[39] Kalinkovich A, Livshits G. 2017. Sarcopenic obesity or obese sarcopenia: A cross talk between age-associated adipose tissue and skeletal muscle inflammation as a main mechanism of the pathogenesis. *Aging Res Reviews* 35: 200-221.



The physiological roles of all of these components are under study. The involvement of the *renin-angiotensin system* (RAS) in the pathophysiological process leading to sarcopenia was contemplated in various genetic and *pharmacological* studies on animals and humans (Carter and Groban, 2008)[40].

Skeletal muscle cells are the targets of angiotensin II via the AT1R receptor. By virtue of this, it currently appears that angiotensin II plays a major role in the appearance of sarcopenia (Yoshida et al., 2013)[41].



[40] Carter CS, Groban L. 2008. Role of the renin-angiotensin system in age-related sarcopenia and diastolic dysfunction. *Aging Health*, 4 (1): 37-46.
[41] Yoshida T, Tabony AM, Galvez S, Mitch WE, Higashi Y, Sukhanov S, Delafontaine P. 2013. Molecular mechanisms and signaling pathways of angiotensin II-induced muscle wasting: potential therapeutic targets for cardiac cachexia. *Int J Biochem Cell Biol*, 45: 2322-2332.

Angiotensin II plays an essential role in the development of sarcopenia, both directly via its receptor AT1, which causes resistance to insulin and to *IGF-1*, and indirectly through increased production of *myostatin*, glucocorticoids, TNF-α and IL-6 (Yoshida et al., 2013). These effects may also include a reduction in autocrine production of IGF-1 (Brink et al., 2001)[42]. The study of the physical capacity of elderly patients treated with ACE (ACE-I) inhibitors for high blood pressure demonstrated, in epidemiological or interventional studies that, in certain cases, and notably in combination with physical exercise, this treatment could improve the mobility of elderly patients (Buford et al., 2012)[43]. The effect of ACE inhibitors on the physical performance of athletes is moreover well-established by numerous clinical studies, as is the association of an insertion/deletion polymorphism in the ACE gene with response to resistance or endurance exercises (Ma et al., 2013; Nazarov et al., 2001)[44].

Number of patients	Patients	Compound	Result	Authors
641	Hypertensive Women Aged 77-80	ACE Inhibitor	Decreased loss of muscular force and gait speed over 3 years in the treated group	Onder et al. (2002)[45]
2431	Healthy elderly individuals Average age: 73	ACE Inhibitor or Beta blocker	Muscle mass of lower limbs greater in the treated group	Di Bari et al. (2004)[46]
130	Elderly individuals with a mobility problem Average age: 79	ACE Inhibitor (perindopril)	Distance walked in 6 mins Improved in the treated group	Sumukadas et al. (2007)[47]
1929	Elderly individuals with cardiac insufficiency Average age: 60	ACE Inhibitor (enalapril)	Lower risk of weight loss in the treated group	Anker et al. (2003)[48]
424	Elderly individuals with a muscular function problem 70-89	ACE Inhibitor	Physical activity significantly improved, with an improvement in gait speed in users of ACE inhibitors	Buford et al. (2012)[49]

ACE inhibitors were also tested in several clinical studies for treating patients affected by *Duchenne muscular dystrophy*, as a substitute or supplement to *beta blockers*, with very interesting results regarding cardiac insufficiency, and delaying the progression of the *cardiomyopathy* (Viollet et al., 2012)[50].

[42] Brink M, Price SR, Chrast J, Bailey JL, Anwar A, Mitch WE, Delafontaine P. 2001. Angiotensin II induces skeletal muscle wasting through enhanced protein degradation and down-regulates *autocrine* insulin-like growth-factor I. *Endocrinology*, 142 (4): 1489-1496.

[43] Buford TW, Manini TM, Hsu FC, Cesari M, Anton SD et al. 2012 Angiotensin-converting enzyme inhibitor use by older adults is associated with greater functional responses to exercise. *J Am Geriatr Soc*, 60 (7): 1244-1252.

[44] Ma F, Yang Y, Li X, Zhou F, Gao C, Li M, Gao L. 2013. The association of sport performance with ACE and ACTN3 genetic polymorphism: a systematic review and meta-analysis. *PLoS One*, 8 (1): e54685. Nazarov IB, Woods DR, Montgomery HE, Shneider OV, Kazakov VI, Tomilin NV, Rogozkin VA. 2001. The angiotensin converting enzyme I/D polymorphism in Russian athletes. *Eur J Hum Genet*, 9 (10): 797-801.

[45] Onder G, Penninx BWJH, Balkrishnan R, Fried LP, Chavez PHM, Williamson J et al. 2002. Relation between use of angiotensine-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. *Lancet*, 359 (9310): 926-930.

[46] Di Nari M, van de Poll-Franse LV, Onder G, Kritchevsky SB, Newman A, Harris TB et al. 2004. Antihypertensive medications and differences in muscle mass in older persons: the health, aging and body composition study. *J Am Geriatr Soc*, 52 (6): 961-966.

[47] Sumukadas D, Witham MD, Struthers AD, McMurdo MET. 2007 Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. *CMAJ*, 177 (8): 867-874.

[48] Anker SD, Negassa A, Coats AJS, Afzal R, Poole-Wilson PA, Cohn JN et al. 2003 Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. *Lancet*, 361 (9363): 1077-1083.

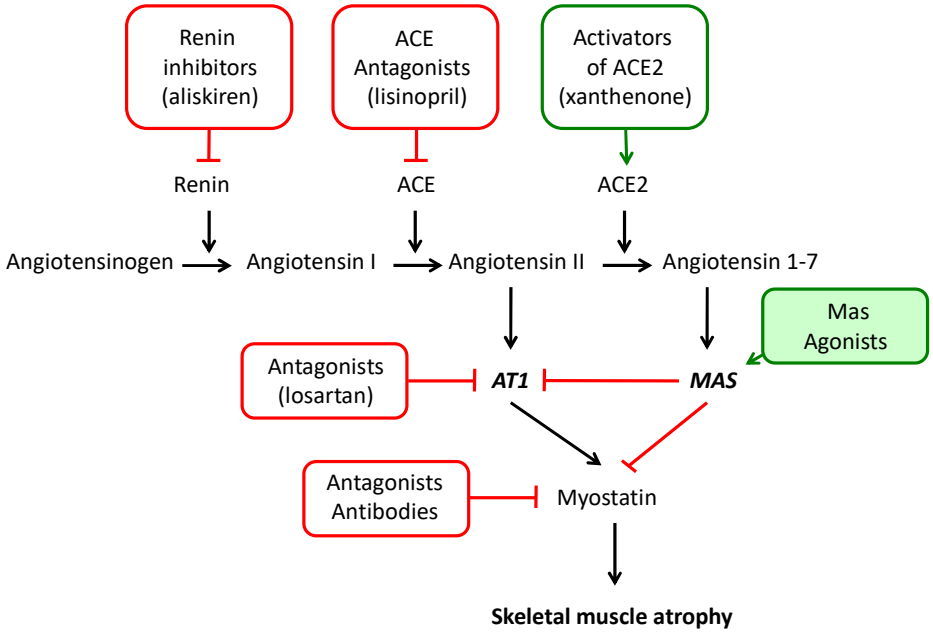
[49] Buford TW, Manini TM, Hsu FC, Cesari M, Anton SD et al. 2012 Angiotensin-converting enzyme inhibitor use by older adults is associated with greater functional responses to exercise. *J Am Geriatr Soc*, 60 (7): 1244-1252.

[50] Viollet L, Thrush PT, Flanigan KM, Mendell JR, Allen HD. 2012. Effects of angiotensin-converting enzyme inhibitors and/or beta blockers on the cardiomopathy in Duchenne muscular distrophy. *Am J Cardiol*, 10: 98-102.

6.2.1.3 Angiotensin 1-7 and the receptor Mas, new actors in the renin-angiotensin system

Other actors in the RAS system seem to be able to act on *muscular functionality*. Angiotensin 1-7, formed by an enzyme known as ACE2 and its receptor (Mas) were recently discovered (Santos et al., 2003)[51]. Angiotensin 1-7, an endogenous *ligand* of the MAS receptor, opposes numerous actions of angiotensin II and is involved in cardiovascular, renal and metabolic regulation. It was recently demonstrated that angiotensin 1-7 has beneficial effects in an animal model of *Duchenne muscular dystrophy* (Acuña et al., 2014; Riquelme et al., 2014)[52].

Developing *agonists* of the MAS receptor to treat sarcopenia, including sarcopenic obesity, is particularly original, with no product of this type mentioned in the scientific literature for treating this indication. It is likely that the stimulation of Mas will not produce exactly the same effects as the inhibition of ACE, or the administration of *antagonists* of the angiotensin II AT1 receptor.



Several studies indicate that the stimulation of Mas could be more effective for stimulating muscular *anabolism* than the inhibition of ACE, and in particular, would have more significant metabolic effects on *adipose tissue* than the inhibition of the ACE.

The challenge here is to limit *polymedication* by treating not the symptoms, but the principle cause of these pathologies in elderly individuals with sarcopenia by combining physical exercise and pharmaceutical intervention.

[51] Santos RAS, Simoes e Silva AC, Maric C, Silva DMR, Machado MP, de Buhr L, et al. 2003 Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas. *PNAS USA,* 100 514): 8258-8263.
[52] Acuña MJ, Pessina P, Olguin H, et al. 2014. Restoration of muscle strength in dystrophic muscle by angiotensin-1-7 through inhibition of TGF-ß signalling. *Human Molecular Genetics*, doi: 10.1093/hmg/ddt514. Riquelme C, Acuña MJ, Torrejón J, Rebolledo D, Cabrera D, Santos RA, Brandan E. 2014. ACE2 is augmented in dystrophic skeletal muscle and plays a role in decreasing associated fibrosis. *PLoS One*, 9 (4): e93449.

6.2.2 Compounds, mechanisms of action, and proofs of concept

Biophytis' compounds are the first non-peptide molecules that are agonists of the MAS receptor to have been the subject of drug development. Tests of the Sarconeos and BIO103 compounds on muscle cells showed a significant increase in protein synthesis and growth in the diameter of myotubes. Furthermore, in animal models treated with Biophytis' compounds, muscles are larger and contain more protein, the expression of a key factor of proteolysis was reduced and that of myogenesis markers increased. Lastly, these compounds are responsible for a significant increase in physical performance in older animals and compensate for the significant loss of mobility due to age.

Biophytis' researchers have directed their interest towards a family of plant molecules, which are *analogues* of insect hormones and are, quite surprisingly, present in medicinal plants used on various continents (Europe, Africa, the Americas, Asia, Oceania). In particular, these plants have *anabolising* and anti-diabetic effect, albeit without it always being established that these molecules are the only active ingredients.

In this family of almost 500 compounds, one molecule is most frequently encountered and is often the most abundant within a complex cocktail. We refer to *20-hydroxyecdysone*. This molecule (a polyhydroxy sterol) was initially the subject of various studies in Japan, Russia and Uzbekistan, which long remained unknown because of the language barrier. But the situation has changed since 1990 and this molecule has sparked further research, especially in the United States and Germany. This molecule is very different from mammalian and human steroid hormones and for this reason, does not interfere with their hormone system. It also has a very low toxicity (LD50 oral > 9 g/kg in mice).

It was on the basis of this molecule that the two candidate drugs *Sarconeos* and BIO103 were developed. The former is based on the natural molecule, while the second is the product of *hemisynthesis* selected after *screening* more than 100 derived molecules. The objective of this *screening* was to select a molecule with improved activity and bioavailability.

Biophytis' drug candidates: *Sarconeos* and BIO103 were chosen for the following properties:

- Their active ingredients stimulate protein synthesis (*hepatocytes*, myocytes) by stimulating the final phase (translation).
- It has hypoglycaemic effects.
- It has hypolipidaemic effects.

6.2.2.1 Mechanism of action of Sarconeos and BIO103: involvement of MAS

Biophytis has determined that the principal mechanism of action of *Sarconeos*, which is responsible for the anabolising muscular effect, involves activation of the MAS receptor.
With various pharmacological effects providing evidence of the membrane effect via a *Gq protein* (Gorelick-Feldman et al., 2010)[53], Biophytis initially prepared conjugates between *Sarconeos* and *serum albumin*, and observed that the compound bound by the 22-OH remained active, while it was incapable of entering cells. This confirmed a membrane action.

[53] Gorelick-Feldman J, Cohick W, Raskin I. 2010. Ecdysteroids elicit a rapid Ca^{2+} flux leading to Akt activation and increased protein synthesis in skeletal muscle cells. *Steroids* 70: 632-637.

On the basis of the observed effects and an exhaustive bibliographic analysis, around 10 candidate receptors were retained and tested (binding test, action of activators or inhibitors). Ultimately, it was proven that the effects of our molecules were very close to those of angiotensin 1-7, with this hypothesis confirmed by the use of two peptide *antagonists* (A-779 and D-Pro^{7}-Ang 1-7), which effectively abolished the different effects of Biophytis' compounds on C_2C_{12}, while they were without effect on the *anabolising* action of *IGF-1*. In the same way, the absence of the MAS receptor following the application of a specific *siRNA* abolishes the effects of *Sarconeos* and BIO103.

Biophytis concluded from this study that these compounds represent the first steroid *agonists* of the MAS receptor and the *a posteriori* analysis of all of the data in the literature on the compared effects of the two compounds and of angiotensin 1-7 agrees with this conclusion, including for the effects on the cardiovascular system (e.g. Wu et al., 2001)[54]. It nevertheless remains possible that certain effects differ, since it was demonstrated that the MAS receptor could respond differently depending on the *peptidic* or *non-peptidic* nature of the *ligand* used (Tirupula et al., 2014; Pernomian et al., 2017)[55].

Under the effect of Sarconeos or BIO103, a set of transduction pathways are activated, which are also activated by angiotensin 1-7: the PI3K/AKT pathway, which is responsible for increasing protein anabolism, and the AMPK/ACC pathway, which is involved in increasing metabolic capabilities (uptake/use of substrates, respiration, ATP production).

The mechanism of action by which *Sarconeos* and BIO103 stimulate *anabolism* in the muscle is shown in the diagram below:

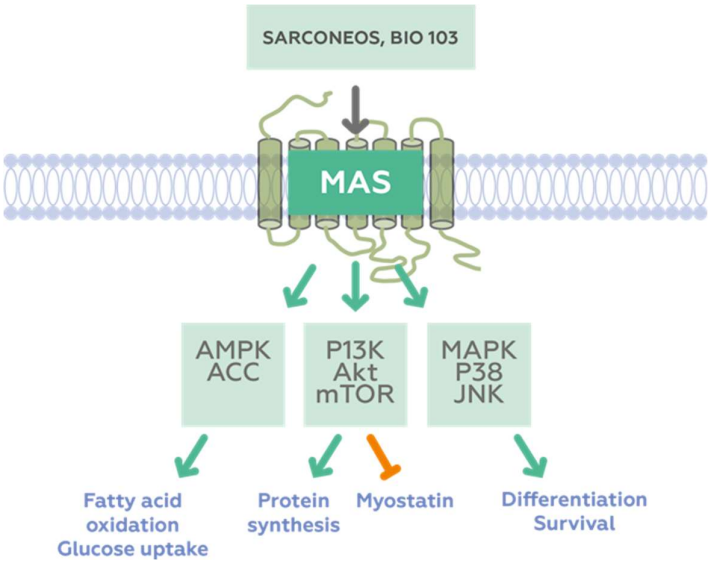


Diagram representing the action mechanism of Sarconeos on muscular anabolism and catabolism

[54] Wu X, Lin J, Liang Z, Shi F. 2001. Beneficial effects of ecdysterone on rat myocardial infarction induced by coronary occlusion. *Zhongcaoyao (Chinese traditional and herbal Drugs)* 32 (8): 721-723.
[55] Tirupula KC, Desnoyer R, Speth RC, Karnik SS. 2014 Atypical signaling and functional desensitization response of mas receptor to peptide ligands. P*LoS ONE*, 9 (7): e103520. Pernomian L, Gomes MS, Tomich de Paula da Salva CH, Rosa JMC. 2017 Reverse induced fit-driven Mas-downstream transduction: looking for metabotropic agonists. *Curr Med Chem* 24: 4360-4367.

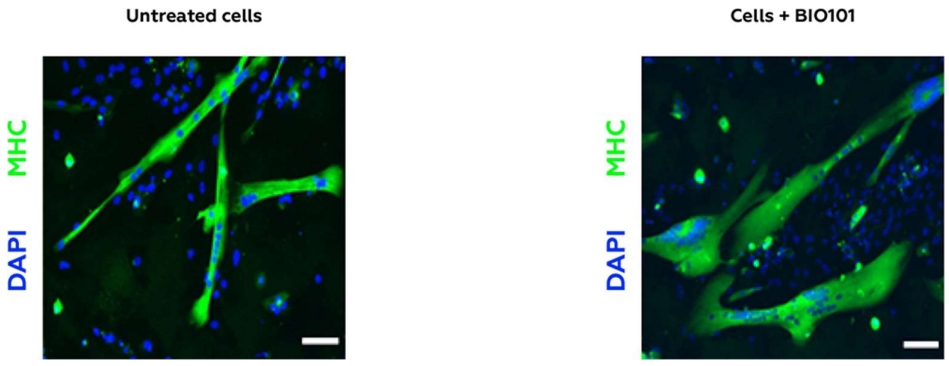
- ***Experiments on muscle cells***

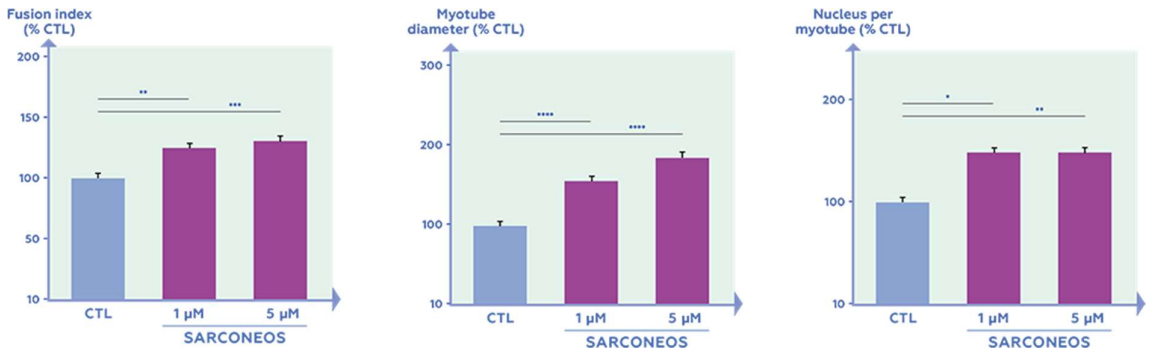
The cells are placed in a medium permitting their proliferation and then their fusion and differentiation into *myotubes*, and it is thus possible to assess the effect of molecules to be tested on these two processes. Several markers were used:

Protocol	Cell culture	Differentiation	Treatment (compound)	Results
Diameter of myotubes	1-2 days	5 days	2-3 days	Increased diameter of myotubes
Protein synthesis	1-2 days	5 days	2-6 hours	Stimulation of protein synthesis
S6K phosphorylation	1-2 days	5 days	2-6 hours	Stimulation of S6K phosphorylation
Myostatin expression	1-2 days	5 days	2-6 hours	Reduced myostatin mRNA

- growth by measuring the diameter of the *myotubes*
- protein synthesis with the aid of a radiolabelled amino acid
- effect on different transduction routes
- measurement of different transcripts (*myostatin*, *proteasome* markers, etc.)

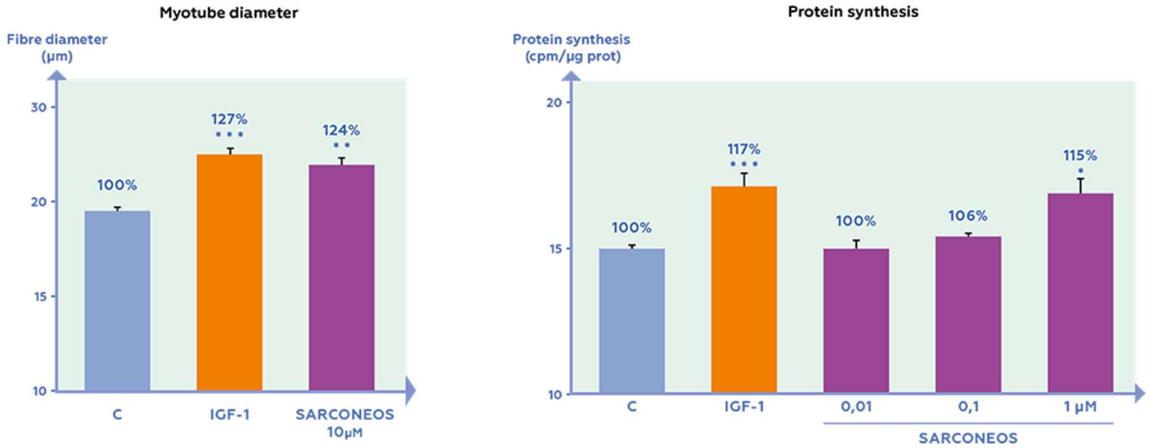
The effect of Sarconeos on the differentiation of myoblasts into myotubes has been studied in murine (mouse) and human models. Both models showed hypertrophic effects characterised by an increase in the fusion index, the diameter of the myotubes and the number of nuclei per myotube.



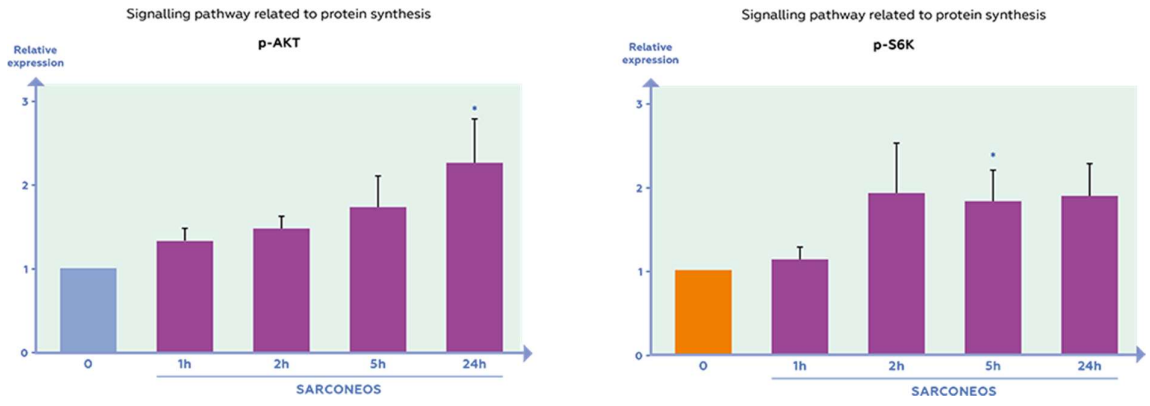


Hypertrophic effect of Sarconeos on human muscle fibres

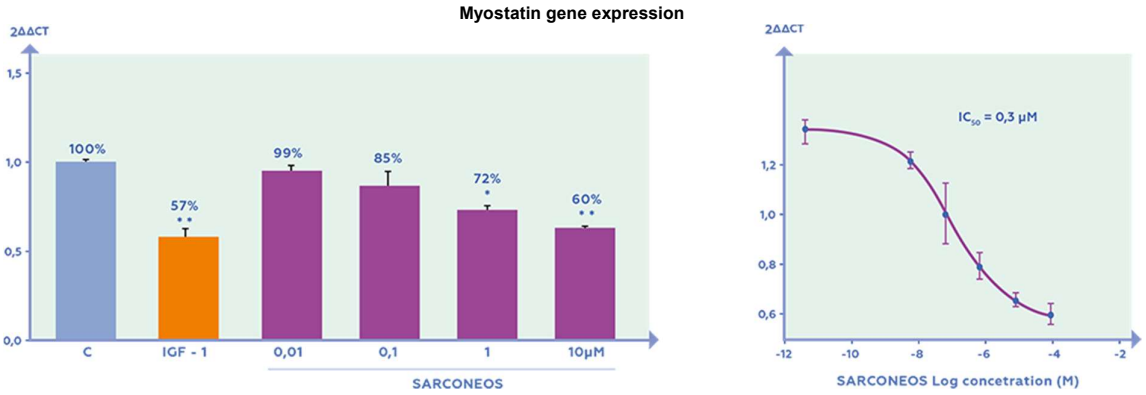
The hypertrophy observed in response to Sarconeos treatment is consistent with a significant increase in protein synthesis, the activation of intracellular transduction pathways involved in protein anabolism and the inhibition of myostatin gene expression in murine myoblasts. AKT and S6K (AKT/mTOR pathway) are activated by phosphorylation.



Hypertrophic effect of Sarconeos consistent with an increase in protein synthesis in murine myotubes

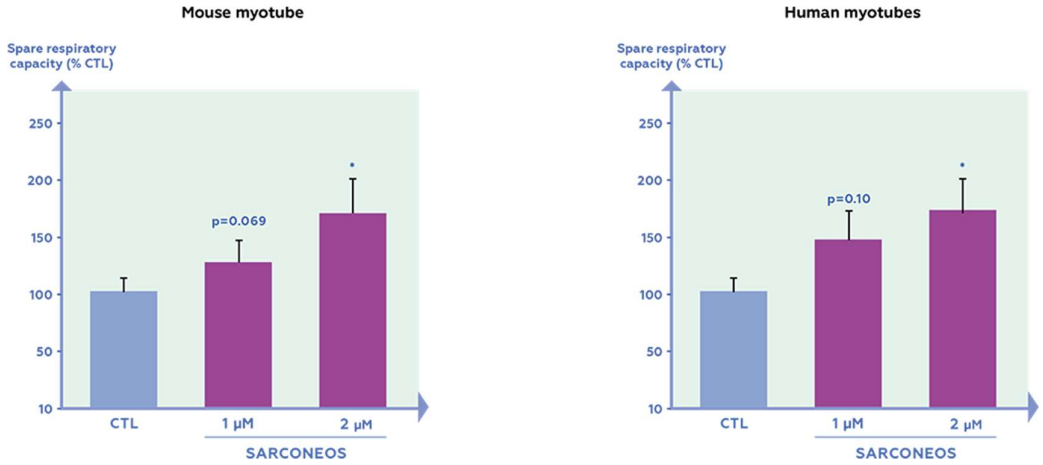


Activation of a transduction pathway involved in Sarconeos proteosynthesis



Dose-dependent inhibition of the expression of myostatin by Sarconeos

Interestingly, the mitochondrial reserve respiratory capacity (RCC) of myotubes is significantly increased by Sarconeos. This metabolic parameter is used to define the amount of ATP that can be produced by oxidative phophorylation in response to a demand for energy[56]. These results were the subject of an oral presentation at the International Congress on Frailty and Sarcopenia Research (ICFSR) held in Miami from 1st to 4th March 2018.



Significant increase in reserve respiratory capacity of myotubes following treatment with Sarconeos

In addition to its anabolic properties, Sarconeos had beneficial effects on muscle energy metabolism[57].

[56] Desler C, Hansen TL, Frederiksen JB, Marcker ML, Singh KK, Juel Rasmussen L. Is There a Link between Mitochondrial Reserve Respiratory Capacity and Aging? Journal of Aging Research 2012: 192503

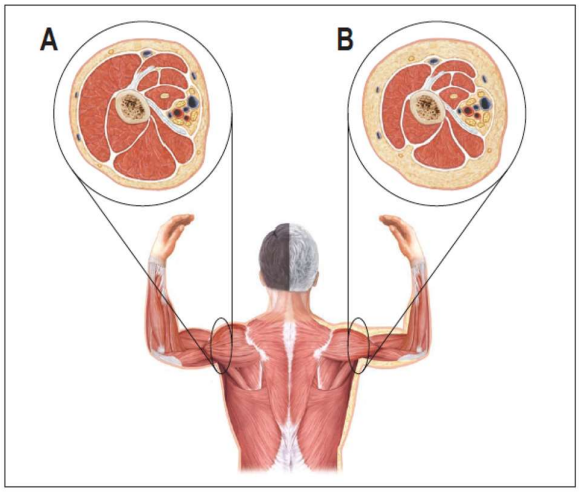
[57] Serova M., On S., Didry-Barca, B., Veillet S., Lafont R., Dilda P. (2018). Combined effects of BIO101 on anabolism and mitochondrial function in skeletal muscle cells. ICFSR 2018, 1-3rd March, Miami, USA. *The Journal of Frailty & Aging*, 7 (1), 72. Abstract OC12.

6.2.3 Sarcopenia

Sarcopenia consists of a loss of muscle mass and function that occurs in the elderly and causes a general deterioration in physical condition. The atrophy of muscle fibres, i.e., the reduction in their diameter and number, is responsible for this reduction in muscle mass. Obesity aggravates sarcopenia and the degradation of functional capacities. The proportion of individuals with sarcopenic obesity is estimated at 31% of the entire population aged over 60 in the United States.

6.2.3.1 Epidemiology

The term "sarcopenia" was initially defined by Irwin Rosenberg in 1989[58] to describe the reduction in skeletal mass during ageing. This word derives from the Greek word *sarx,* meaning "flesh", and *penia* meaning "a lack of". Since 1989, this purely quantitative definition of sarcopenia has evolved to incorporate notions of muscle strength and quality. In 2010, the European Working Group on Sarcopenia in Older People[59] worked on establishing a definition of sarcopenia based on consensus. It insisted on the need to take into account both the loss of mass and the loss of muscle function; sarcopenia is thus now defined as the reduction in mass and in muscle strength, associated with a reduction in physical performance. In 2016, sarcopenia was designated a disease (code M62.84)[60], which clarified the regulatory scope of future drug developments.



The changes in bodily composition during sarcopenia (B) by comparison with young adults (A) correspond to a loss of lean body mass and an increase in adipose tissue, around and between

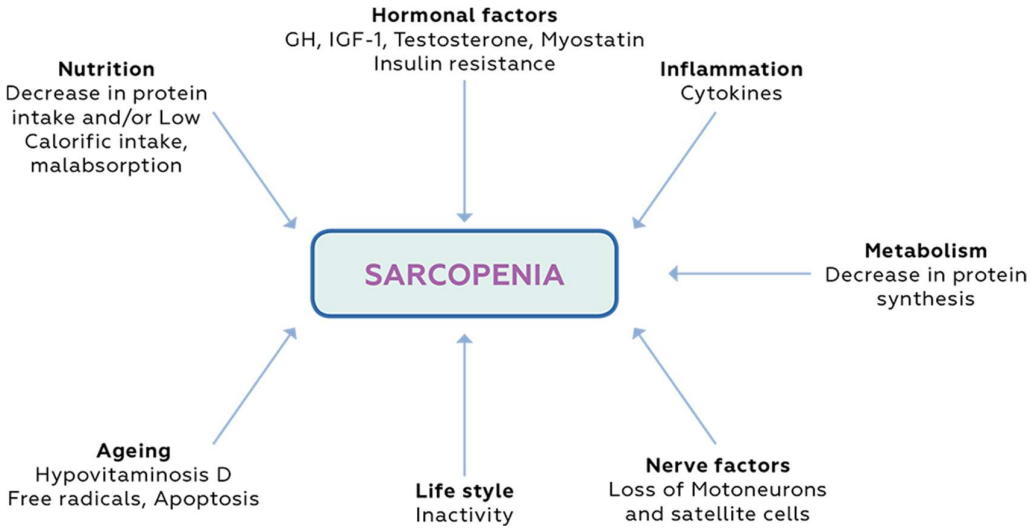
[58] Rosenberg I. 1989. Summary comments: epidemiological and methodological problems in determining nutritional status of older persons. *Am J Clin Nutr*, 50: 1231-1233.
[59] Cruz-Jentoft AJ, Baryens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoulde M, Zamboni M. 2010. Sarcopenia : European consensus on definition and diagnosis. Report of the European Working Group on Sarcopenia in Older People. *Age Ageing*, 39 (4): 412-423.
[60] Anker SD, Morley JE, von Haeling S. 2016. Welcome to the ICD-10 code for sarcopenia. *J Cachexia Sarcopenia* 7: 512-514.

the muscles, which are consequences (among other things) of physical inactivity and inadequate nutrition. These changes are amplified in obese individuals (Benton et al., 2011)[61].

The European Working Group on Sarcopenia in Older People defines three conceptual levels:

- presarcopenia, defined solely by a reduction in muscle mass
- sarcopenia, which associates a reduction of the muscle mass and the reduction in either muscle strength or in performance;
- severe sarcopenia, associating the reduction in mass, force and performance.

Sarcopenia is at the origin of a general deterioration in physical condition. Sarcopenia results in a greater risk of falling, a progressive inability to perform everyday actions, a loss of autonomy, and leads to an increase in hospital stays and mortality. Different studies estimate that up to 25% of individuals aged over 70 and 40% of individuals aged over 80 could develop sarcopenia



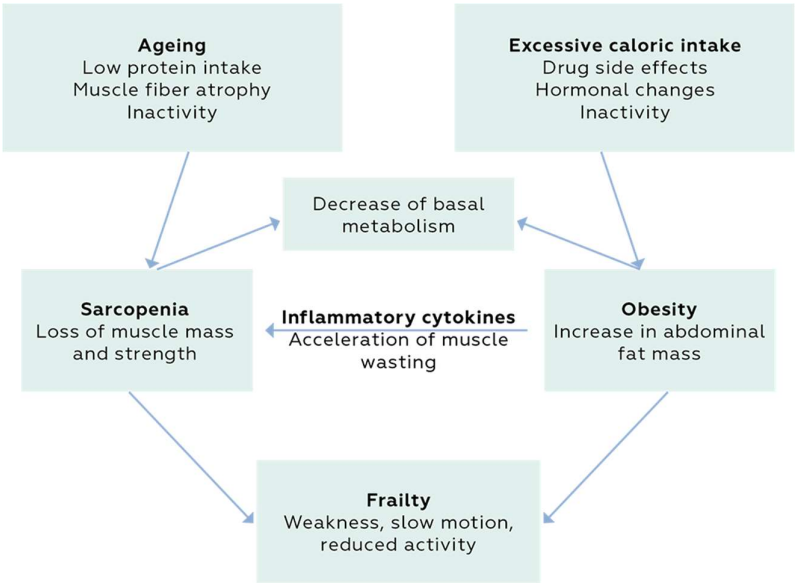
Sarcopenia, a multi-factor pathology (Aussel et al., 2013)[62]

In the SARA clinical programme, the definition of the muscular component of sarcopenia is based on the operational criteria proposed at the initiative of the Foundation for the National Institutes of Health (FNIH: Studenski et al., 2014)[63]. The FNIH reports triggered a re-evaluation of the existing operational definitions of sarcopenia, which represents a change from the definition of the European Working Group on Sarcopenia in Older People (EWGSOP), which was mainly based on expert consensus. The results of the FNIH are based on a meta-analysis of eleven clinical trials involving men and women aged 65 or older, which tested, among various variables, those that best predict gait speed and strength, which are the two functional consequences of sarcopenia.

In 2014, the Foundation for the National Institutes of Health published a series of articles describing updated diagnostic criteria for sarcopenia. These publications have allowed the development of a definition of sarcopenia based on data from a meta-analysis of 11 clinical

[61] Benton MJ, Whyte MD, Dyal BW. 2011. Sarcopenic obesity: strategies for management. *AJN*, 111: 38-44.
[62] Aussel C, Woelffle E, Lemoigne P, Depailler L, Bouillanne O. 2013. Une nouvelle stratégie nutritionnelle pour lutter contre la dénutrition et la sacopénie: le régime protéique pulsé. *Cahiers Nutrition Diététique*, 48: 33-40.

studies and 26,725 participants (mean age: 75.2 ± 6.1 years for men and 78.6 ± 5.9 years for women). This definition takes into account the prevalence of low gait speed (≤0.8m/sec) and weakness (grip-test strength<26kg for men and<16kg for women), in the elderly (≥65 years), expressed in appendicular lean mass (ALM<19.75 kg in men and <15.02 kg in women), or in appendicular lean mass adjusted by body mass index (ALM/BMI <0.789 in men, and <0.512 in women (Studenski et al., 2014[63])). This last definition of sarcopenia, which incorporates body mass index (BMI), is derived from a sensitivity analysis, and makes it possible to better evaluate obese individuals (with sarcopenia). In fact, sarcopenic obesity represents a subgroup of sarcopenia characterised by the loss of muscle mass and function and a concomitant increase in body fat. It mainly affects obese seniors. A higher rate of functional decline has been reported in individuals with sarcopenic obesity. In addition, lipid infiltration into muscle tissue appears to exacerbate sarcopenia, as lipid accumulation prevents the incorporation of amino acids and reduces protein synthesis in muscle (Guillet et al., 2012)[64]; Moreira et al., 2016[65]). The growing population of older people with sarcopenic obesity has a particularly high risk of complications, such as loss of independence, motor disability, and increased morbidity and mortality (Kemmler et al., 2016)[66].



The changes leading to sarcopenia are amplified in obese individuals (= sarcopenic obesity) (after Jarosz and Bellar, 2011)[67]

The most exhaustive study of prevalence, based on the data of the National Health and Nutrition Survey III (1988-1994) estimates the proportion of individuals with sarcopenic obesity at 31% of the entire population aged over 60, i.e., around 20 million individuals concerned by

[63] Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, Ferrucci L, Guralnik JM, Fragala MS, Kenny AM, Kiel DP, Kritchevsky SB, Shardell MD, Dam TT, Vassileva MT. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci. 2014 May; 69 (5):547-58

[64] Guillet C, Masgrau A, Walrand S, Boirie Y. Impaired protein metabolism: interlinks between obesity, insulin resistance and inflammation. Obes Rev. 2012 Dec; 13 Suppl 2:51-7. doi: 10.1111/j. 1467-789X.

[65] Moreira MA, Zunzunegui MV, Vafaei A, da Câmara SM, Oliveira TS, Maciel ÁC. Sarcopenic obesity and physical performance in middle aged women: a cross-sectional study in Northeast Brazil. BMC Public Health. 2016 Jan 16; 16:43

[66] Kemmler W, von Stengel S, Engelke K, Sieber C, Freiberger E. Prevalence of sarcopenic obesity in Germany using established definitions: Baseline data of the FORMOsA study. Osteoporos Int. 2016 Jan; 27 (1):275-81

[67] Jarosz PA, Bellar A. 2011. Sarcopenic obesity: an emerging cause of frailty in older adults. *Geriatric Nursing*, 30 (1): 64-70.

this form of sarcopenia in the USA alone. The only available study of economic impact highlights a cost of US$ 18.5 billion for the health system in the United States, i.e. around US$ 900 per year and per concerned individual.

6.2.3.2 Proof of concept

Several experiments were carried out to assess the activity of *Sarconeos* in animal models – mice and rats – subjected to a fatty diet, in particular within a context of obesity and/or ageing.

In the case of young animals, the molecules were either incorporated into their feed, or administered orally on a daily basis. We shall consider the principal results obtained here:

- the tested molecules limit the appearance of obesity;
- the muscles of the treated animals were more developed and contained more protein
- the expression of *myostatin* is reduced, while that of the markers of myogenesis (*myogenin*, *myoD*) is increased.

Reference	Animal Model	Results
Foucault et al., manuscript in preparation	Young C57Bl/6J mice, fed a high-fat diet	Increase in mass of the *skeletal muscles* Inhibition of the expression of *myostatin* Stimulation of expression of the genes for myogenesis and mitochondrial genes
Mouveaux *et al*., manuscript in preparation	Older GK rats, fed with a fattening diet	Increase in lean mass, reduction in *proteolysis* and *inflammation* of *skeletal muscle* in paws Reduction in body fat
Dilda et al., 2016[68]	Old and adult C57Bl/6J mice, fed with a fattening diet	Significant improvement in the physical performance of older animals
Foucault et al., 2014[69]	Mouse C57Bl/6J 6-8 weeks, fed with a fattening diet, 3-week treatment	Increase in energy expenditure Stimulation of mitochondrial metabolism
Foucault et al., 2012[70]	Mouse C57Bl/6J 6-8 weeks, fed with a fattening diet, 3-week treatment	Reduction in epididymal and subcutaneous body fat

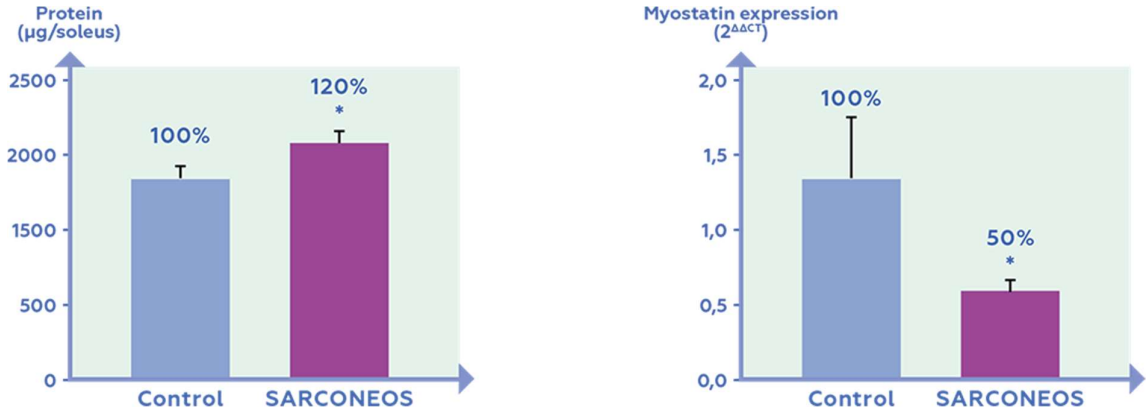
Early work showed Sarconeos had an inhibitory effect on fat gain in animals fed a high-fat diet.

[68] Dilda P.J., Foucault A.S., Serova M., On S., Raynal S., Veillet S., Dioh W., Lafont R. (2016). BIO101, a drug candidate targeting Mas Receptor for the treatment of age-related muscle degeneration. From molecular target identification to clinical development. *Journal of Cachexia, Sarcopenia and Muscle,* 7 (5), 655.

[69] Foucault AS, Even P, Lafont R, Dioh W, Veillet S, Tom. D, Huneau JF, Hermier D, Quignard-Boulangé A. (2014). Quinoa extract enriched in 20-hydroxyecdysone affects energy homeostasis and intestinal fat absorption in mice fed a high-fat diet. *Physiol Behav* 128: 226-231.

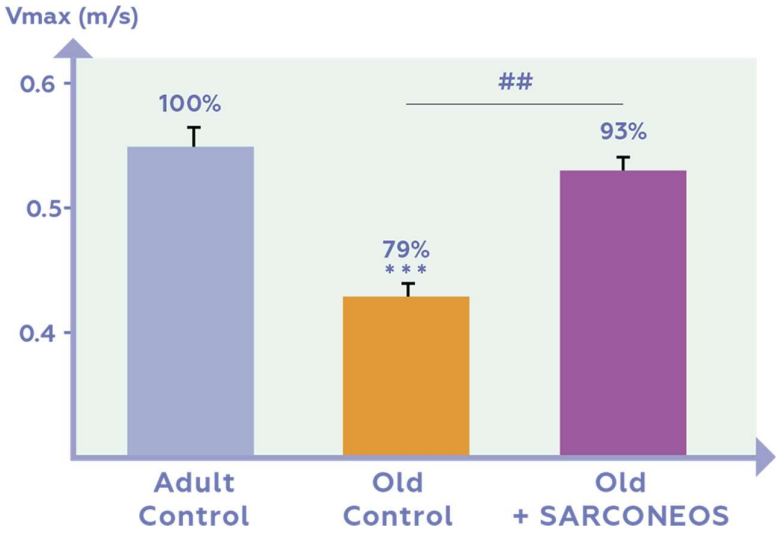
[70] Foucault AS, Mathé V, Lafont R, Even P, Dioh W, Veillet S, Tom. D, Huneau D, Hermier D, Quignard-Boulangé A. (2012). Quinoa extract enriched in 20-hydroxyecdysone protects mice from diet-induced obesity and modulates adipokines expression. *Obesity* 20: 270-277.

This initial work also provided the first evidence demonstrating the *in vivo* activity of Sarconeos on the muscles, thus confirming the data obtained *in vitro* with C2C12 myoblast cultures. In fact, the muscles of young animals treated with Sarconeos contained more proteins and had an inhibited myostatin gene expression compared to the muscles of untreated animals.



Effect of Sarconeos intake on muscle protein (soleus muscle) and myostatin expression after an obesity-inducing diet in young C57Bl/6 mice.

A chronic oral treatment with *Sarconeos* caused a significant increase in physical performance in older animals. Importantly, we have demonstrated in particular that treating older animals with *Sarconeos* makes it possible to compensate for the significant loss of mobility due to age[71].



Effect of Sarconeos intake on maximum running speed in older C57Bl/6 mice.

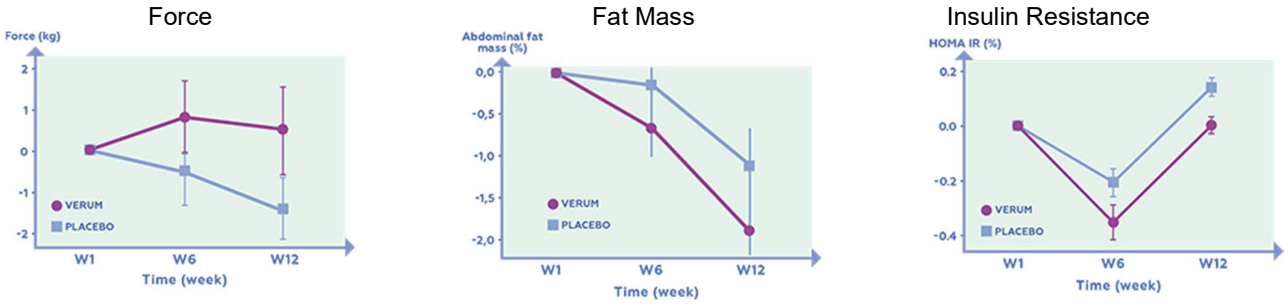
[71] Dilda P.J., Foucault A.S., Serova M., On S., Raynal S., Veillet S., Dioh W., Lafont R. (2016). BIO101 - a drug candidate targeting Mas Receptor for the treatment of age-related muscle degeneration. From molecular target identification to clinical development. *Journal of Cachexia, Sarcopenia and Muscle,* 7 (5), 655.

6.2.3.3 **Clinical studies on healthy volunteers**

QUINOLIA Study

The QUINOLIA clinical study was conducted at the Pitié-Salpêtrière Hospital (Prof. Karine Clément) on obese healthy volunteers after chronic oral administration for 3 months (6 weeks of low calorie diet followed by 6 weeks of normal calorie diet). The studies confirm the absence of toxicity (no serious undesirable event observed) at the studied dosage (40 mg/day). A significant reduction in abdominal body fat (p=0.04) and an increase in insulin sensitivity (p=0.06) were observed. Moreover, the treatment tends to reduce the loss of strength observed during the 6 weeks of low calorie diet (grip test p = 0.09). These results are supported by those of a study carried out on 80 overweight volunteers for a 3-month period at a dosage of 100 mg/ day by the team of Prof. Wuttke of the University of Göttingen (Wuttke and Seidlova-Wuttke, 2013)[72].

Reference	Dosage	Volunteers & Protocol	Results
Foucault *et al.*, manuscript in preparation	40 mg/day	58 obese volunteers (30 verum, 28 placebo) 18-65 years old 3 months, including 1.5 months on a low-calorie diet	Reduction in abdominal fat Reduction in insulin resistance Stabilisation of weight after the diet phase Reduced loss of strength observed during the low-calorie diet phase



Results of the Quinolia study on muscle strength, insulin resistance, and abdominal fat in obese healthy subjects subjected to a low-calorie diet

Moreover, several clinical studies carried out with a concentrated and titrated extract of *Stemmacantha carthamoides* in athletes subjected to intense physical exercise showed that at a dosage of between 30 and 70 mg/day, this preparation increased their physical capacity (Azizov et al.,1998; Gadhzieva et al., 1995)[73], as well as their muscle mass (+6.5%, Simakin et al., 1988)[74]. As for the treatment of elderly populations, it is necessary to optimise the benefits of treatment and the impact on the quality of life.

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[72] Wuttke W, Seidlova-Wuttke D. 2013. Pflanzliche Präparate füt die Therapie klimaterischer und postmenopausaler Beschwerden und Erkrankungen. *Frauenartz* 54 (6): 580-587.

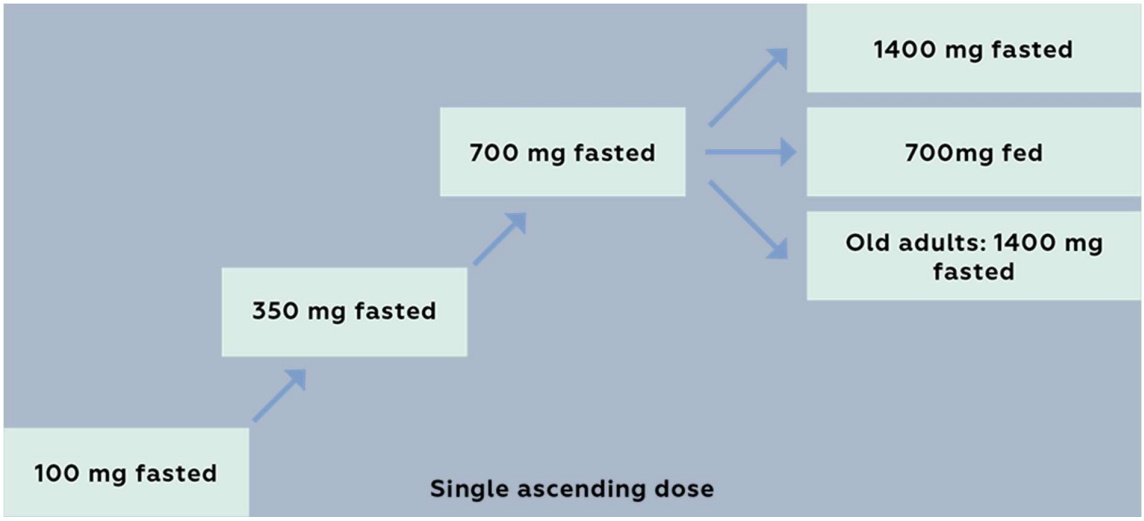
[73] Azizov AP, Seifulla RD, Ankudinova IA, Kondrat'eva II, Borisova IG. 1998 Effect of the antioxidants elton and leveton on the physical work capacity of athletes. *Eksp Klin Farmakol* 61 (1): 60-62.
Gadzhieva RM, Portugalov SN, Paniushkin VV, Kondrat'eva II. 1995. A comparative study of the anabolic action of ecdysten, leveton and Prime Plus, preparations of plant origin. *Eksp Klin Farmakol* 58 (5): 46-48.

[74] Simakin SYu, Panyushkin VV, Portugalov SN, Kostina LV, Martisorov EG. 1988. Combined application of preparation Ecdysten and product Bodrost during training in cyclic sports. *Sports Science Bulletin* N°2, 29-31.

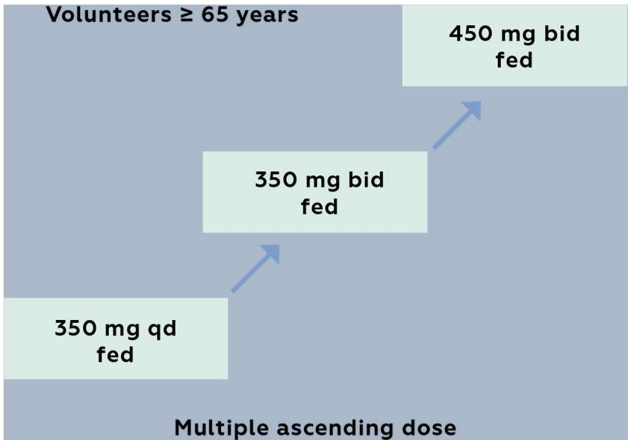
SARA-PK Clinical Study

A clinical safety, pharmacokinetic and pharmacodynamic study was conducted by Biophytis between August and November 2016. We refer to the SARA-PK clinical study to determine safety of Sarconeos and to evaluate its pharmacokinetics and pharmacodynamics in healthy volunteers, both young and elderly, following a single ascending dose and multiple ascending doses for 14 days. The design of this study is presented below:

- The single ascending dose (SAD) involves the oral administration of Sarconeos in installments to 24 subjects in 2 age groups: 2 groups of adults aged 18-55 years in increasing doses ranging from 100 mg to 1400 mg, and 1 group of adults aged 65-85 years in a dose of 1400 mg.
- The multiple ascending dose (MAD) concerns 3 Sarconeos dosages: 350 mg once daily; 350 mg bid (twice daily) and 450 mg bid administered to groups of 10 adults aged 65-85 years over 14 days.



SARA-PK Clinical Study design SAD (Single Ascending Dose).

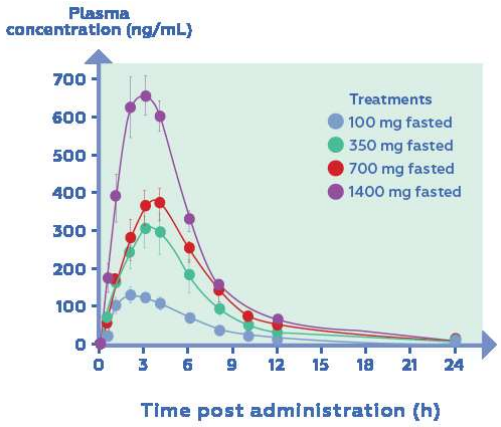


SARA-PK Clinical Study design MAD (Multiple Ascending Dose).

The administration of Sarconeos in single ascending doses (SAD) of 100, 350, 700 and 1,400 mg is well tolerated by both young and elderly volunteers in good health. No serious adverse events were noted during this SAD phase. The only adverse events observed were mild. Furthermore, no abnormalities in vital signs or clinical laboratory parameters were observed in these volunteers.

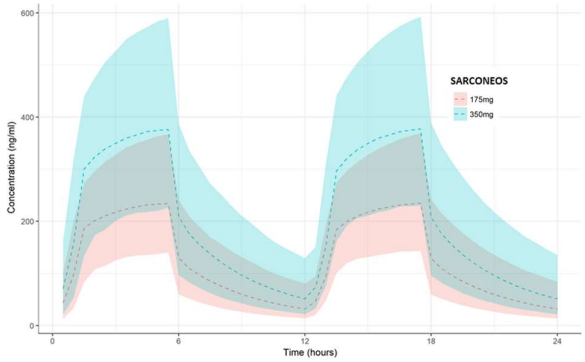
The administration of multiple ascending doses (MAD) for 14 days at 350 mg qd (*quondam die*, once daily), 350 mg bid (*bis in die*, twice daily), and 450 mg bid was also well-tolerated as attested by the absence of serious adverse events at the doses tested. Adverse events were mild, although there were 3 cases of moderate adverse events at the strongest dose (450 mg bid). The vast majority of adverse events resolved themselves on their own before the end of the study.

The study of the SAD pharmacokinetic parameters shows a quasi-proportional increase in Cmax (Maximum concentration: 141-710 ng/mL) and AUCs (area under the curve: 797-4283 ng.h/mL). The absorption of Sarconeos is rapid as corroborated by the Tmax (time in which the maximum plasma concentration was reached) of 2 to 3.5 hours. The pharmacokinetic parameters (Tmax and AUC) were not significantly modified by administration of Sarconeos at 700 mg/day under fasting conditions when compared to adminstration after taking one meal. Similarly, Tmax and AUC are comparable in elderly volunteers and healthy young volunteers at a dose of 1,400 mg/day.



Development of plasma exposure in healthy volunteers under fasting conditions treated with Sarconeos in SAD.

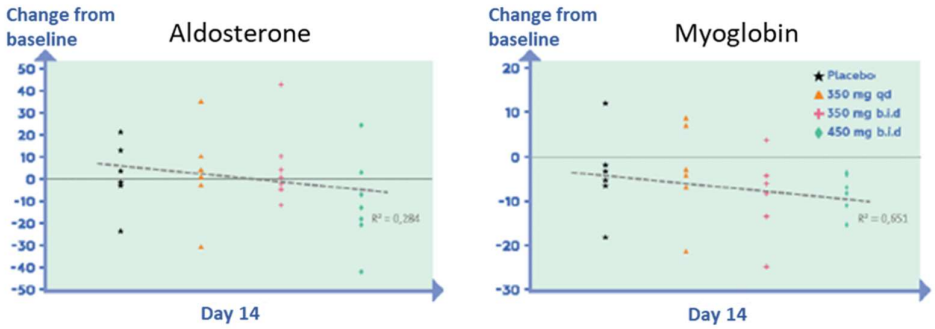
In the MAD phase, there was no accumulation of Sarconeos at 350 mg qd (accumulation ratio of 1.14), whereas a small accumulation was observed at 350 and 450 mg/day bid (accumulation ratio of 1.31). Moreover, on the basis of the short half-life (3-4 hours), and the pharmacokinetic profiles at Day 1 and at the end of the MAD phase (day 14), the steady state is reached from the third day of administration of Sarconeos. A pharmacokinetic data modelling study confirmed the choice of dosage at 350 mg in two doses and 700 mg in two doses. The modelling confirms the very low accumulation of the Sarconeos product; the circulating doses (AUC) are equivalent when administered for 2 weeks (duration of the SARA-PK phase 1 study) as for 26 weeks (duration of the SARA-INT interventional study).



Steady state concentration profile for doses of 175 mg bid and 350 mg bid.

The effects of Sarconeos intake on the evolution of pharmacodynamic markers were evaluated for MAD in an exploratory setting. Very interesting preliminary results showed a tendency towards a decreased plasma level in muscle catabolism markers (myoglobin, creatine kinase) and the renin–angiotensin system (aldosterone and renin). These data are consistent with the proposed mechanism of action of the *Sarconeos* drug candidate. The tendency towards a decreased level of plasma aldosterone accords with Sarconeos acting via the MAS receptor of the renin–angiotensin system. Activation of this protein reduces proteolysis in skeletal muscles, as suggested by a tendency to reduce myoglobin plasma levels in response to Sarconeos administration (Dioh et al., 2017[75]).

The results of the SARA-PK study were the subject of an oral presentation at the International Congress on Frailty and Sarcopenia Research (ICFSR) held in Barcelona from 27 to 29 April 2017.



Effect of Sarconeos treatment for 14 days on the evolution of two pharmacodynamic markers related to the renin–angiotensin system (aldosterone) and muscle catabolism (myoglobin)

The safety, pharmacokinetic and pharmacodynamic results of SARA-PK confirm the favourable drug profile of Sarconeos and allowed us to define which two doses will be tested in SARA-INT, subject to its authorisation by the relevant regulatory agencies: 175 mg bid and 350 mg bid.

[75] Dioh W., Del Signore S., Dupont P., Dilda P.J., Lafont R., Veillet S. (2017). SARA-PK: A single and multiple ascending oral doses study to assess the safety and evaluate the pharmacokinetics of BIO101 in healthy young and older volunteers. ICFSR 2017, 27-29 April, Barcelona. *The Journal of Frailty & Aging*. Abstract OC38, 28

6.2.3.4 Phase 2 studies

The SARA programme is a multi-centre clinical programme carried out in 4 countries (USA, France, Belgium, Italy) and aimed at determining the effective therapeutic dose of Sarconeos in a Phase 2b clinical study performed on 334 patients with sarcopenia. Launched at the end of 2016, the programme includes an observational study (SARA-OBS), followed by an interventional study (SARA-IN). SARA-OBS will follow more than 150 patients with sarcopenia in 11 clinical centres over six months. Early data from SARA-OBS will enable us to better define the target population for Sarconeos treatment. Patients in the SARA-OBS study, about 100 of whom have been recruited since its start in 2017, will be eligible for inclusion in the SARA-INT phase 2b study. The objective of SARA-INT is to assess the safety and efficacy of two doses of Sarconeos (175 mg bid and 350 mg bid) administered orally for 26 weeks vs a placebo in a population of men and women over the age of 65 at risk of motor disability. The study is to include 334 people in 22 clinical centres. Biophytis obtained in the last quarter of 2017 the authorisation of the US Food and Drug Agency (FDA), and then that of the Belgian Federal Agency for Medicines and Health Products (FAMHP) to launch the phase 2b interventional study (SARA-INT). The first patient for SARA-INT started on the 24/05/2018 in Belgium in the Centre at Liège under the supervision of Prof. Olivier Bruyère.

The clinical strategy for the SARA programme has been defined so that the SARA-INT study is a continuation of SARA-OBS. SARA-OBS and SARA-INT thus share governance, inclusion criteria, primary and secondary criteria and the SARA-DATA data management system, named CRO ICON Clinical Research. From a regulatory point of view, these two studies are nevertheless separate from each other, with each having its own objectives, authorisations, design, timetable, results and reports. Their common elements are presented below.

Governance of studies
Dr Roger Fielding, Professor at Tufts University in Boston, USA, is the principal investigator of both the SARA-OBS and SARA-INT studies. Several committees have been created for the management of these studies: the Managing Board; the Steering Committee; the Plenary Committee (made up by all the investigators of the clinical study); the Data Safety Monitoring Board (DSMB) and the Tendering Committee.

The Steering Committee is composed of 4 members representing the two continents participating in the study (Europe and USA). The Steering Committee is chaired by the principal investigator, Prof. Roger Fielding. Prof. Marco Pahor (University of Florida, Gainesville, FL, USA), who was the principal investigator of the LIFE study is the vice-chairman. Professors Olivier Bruyère (University of Liège, Belgium) and Yves Rolland (CHU Purpan, Toulouse, France) are the European representatives. The Medical Director of Biophytis is the secretary of the Steering Committee.

The *DSMB* is composed of 5 experts in geriatrics, sarcopenia, age-related diseases and biostatistics. It meets regularly every quarter for a review of all patient safety data. The main objective of the committee will be to ensure the safety of the patients recruited. In the interventional study, it will meet from the twenty-fifth patient included and will be responsible for performing an interim analysis after follow-up on the 200th patient included. This analysis will re-evaluate the sample size needed for the study and allow the sponsor to decide whether to continue, shorten or stop the study.

Inclusion criteria

The inclusion criteria were validated by the European Medicines Agency (EMA) in June 2017 as part of the scientific advice procedure requested by Biophytis. The criteria selected are (i) age ≥ 65 years, (ii) a Short Performance Physical Battery (SPPB) ≤ 8 (as an index of loss of motor function), (iii) and the sarcopenia criteria of the FNIH (Foundation for the National Institutes of Health) based on DEXA body composition results (an ALM/BMI index <0.789 in men and <0.512 in women or an absolute ALM index <19.75 in men and <15.02 in women). These latter indices, calculated from the measurement of DEXA (dual-energy X-ray absorptiometry) are specific for the lean mass of the upper and lower limbs (Appendicular Lean Mass: ALM) which may be adjusted for body mass index (BMI).

Main criterion and secondary criteria

The primary evaluation criterion of the study is the measurement of the mobility function estimated by the gait-speed-over-400m test. This main criterion was recommended by the EMA in its scientific advice given in June 2017, resulting in the abandonment of the 6-minute walk test initially proposed by Biophytis. This choice was approved by the *Steering Committee* of the SARA program which met at the *European Union Geriatric Medicine Society* (EUGMS) congress in September 2017. This criterion was used in the LIFE study (Pahor et al., 2014[76]) and is currently being evaluated in the SPRINTT observational study. The distance of 400m is the average distance travelled by a healthy elderly person walking at a normal pace in 6 minutes (Simonsick et al., 2001[77]). In addition, the gait speed during the 400 m test is strongly associated with the risk of reduced mobility and reflects the ability to perform everyday activities (Rolland et al., 200[78]).

Two key secondary evaluation criteria were selected: the PF 10 subscore of the SF-36 quality of life questionnaire and the chair stand test, which is one of the subscores of the SPPB test. Several Patient Reported Outcomes will also be used in this study. They make it possible to measure the evolution of the physical condition as felt by the patients. Several other secondary criteria are measured, such as the 6-minute walk test, the appendicular muscle strength of the upper and lower limbs, the physical performance (SPPB test according to Guralnik et al 1994[79]) and body composition measured by DEXA. Several plasma parameters are monitored including safety markers, biomarkers of the renin–angiotensin system (renin, aldosterone), inflammation (IL-6, CRP and hsCRP) and muscle metabolism (N-terminal part of the type II

[76] Pahor M., Guralnik J.M., Ambrosius W.T., Blair S., Bonds D.E., Church D.S., Espeland M.A., Fielding R.A., Gill T.M., Groessl E.J., King A.C., Kritchevsky S.B., Manini T.M., McDermott M.M., Miller M.E., Newman A.B., Rejeski W.J., Sink K.M., Williamson J.D. for the LIFE Study investigators. (2014). Effect of structured physical activity on prevention of major mobility disability in older adults: the LIFE Study randomized clinical trial. *JAMA*. 311(23): 2387-2396.

[77] Simonsick EM, Montgomery PS, Newman AB, Bauer DC, Harris T (2001) Measuring fitness in healthy older adults: the health ABC long distance corridor walk. J Am Geriatr Soc 49:1544–1548.

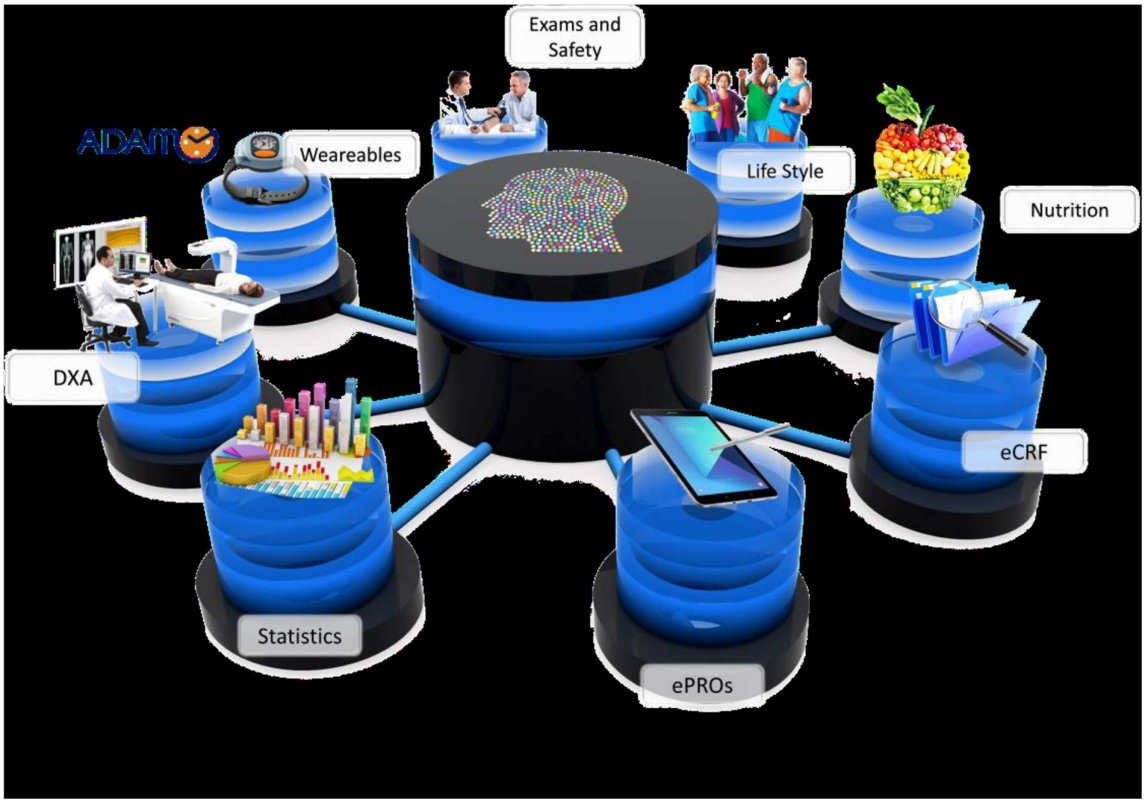
[78] Rolland YM, Cesari M, Miller ME et al (2004) Reliability of the 400-m usual-pace walk test as an assessment of mobility limitation in older adults. J Am Geriatr Soc 52:972-976.

[79] Guralnik JM, Simonsick EM, Ferrucci L, et al. 1994. A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 49: M85–M94

propeptide collagene: PIIINP, myoglobin, creatine kinase MM and creatine kinase MB). Finally, the physical activity of patients in their daily life is monitored throughout the study with an actimeter (ADAMO) developed by the Italian company Caretek.

Data storage and analysis

The collected data is hosted in the SARA-DATA proprietary platform[80] presented in the figure below, developed on behalf of Biophytis by *Blue Companion*. It includes various modules including the electronic observation register (ePRO) of the study, the module containing the body composition data set, the module for measuring the physical performance of patients by actimeter and a module hosting data from the Biobank.



SARA-PK Observational Study

Objectives

The aim of the SARA-OBS clinical study is to characterise sarcopenia, including sarcopenic obesity, in a population of elderly people (aged 65 and over) living in the community and at risk of reduced mobility. The mobility and physical performance of these people, and their body composition, are evaluated for 6 months. At the end of this observation period, patients who consent are included in the SARA-INT phase 2b clinical trial.

[80] Del Signore Su., Dioh W., Zia G., Del Signore St., Veillet S. Patient Reported Outcomes (ePROs) – SarQoL, SF-36 and TSD-OC - in ageing related Sarcopenia. SARA-OBS, a six-month observational clinical trial. ICFSR 2017, 27-29 April, Barcelona. *The Journal of Frailty & Aging*. Abstract P186, 131
Dioh W., Margalef C., Zia G., Veillet S., and Del Signore S. SARA-OBS, an observational study dedicated to characterize age related sarcopenia population suitable for interventional studies. 8th International Conference on Frailty and Sarcopenia Research (ICFSR) March1-3, 2018 Miami, USA. *The Journal Of frailty and Aging* Oral communication

Study design

The design of the study is classically structured around a pre-selection and recruitment period of at least 6 months, followed by a 6-month research phase. The research phase includes 2 main visits, at inclusion and at the end of the study, supplemented by a telephone call at 3 months. This duration of clinical observation is that recommended by the European Working Group on Sarcopenia[81]. The telephone interview at 3 months after inclusion makes it possible to detect whether participants are complaining of a poor physical condition, who can then be invited to bring their end-of-study visit forward.

	Screening & Inclusion	**Characterization**
Month	-0.5 - 0	6 (or End of Study)
Visit Window	+ 1 week	- 1 week
Telephone call		
Informed consent, including secondary research, biobank and DNA tests	X	
Medical history	X	
Physical exam & Anthropometry	X	X
CIRS	X	
SF-MNA	X	
ECG	X	
SPPB	X	X
DEXA	X	X
Inclusion/exclusion criteria	X	
Stair Climb Power Test	X	X
Grip strength/knee extension	X	X
400 m walk (400MW)	X	X
6MWD	X	X
Haematology and Biochemistry	X	X
Urinalysis (dipstick)	X	X
Plasma and Urine collection for biomarkers	X	X
Actimetry	Starting at Month 1 continuously until Month 6	
SF-36	X	X
PAT-D	X	X
SarQoL	X	X
TSD-OC	X	X
Safety measurements including vital signs and weight, AEs evaluation	X	X

Clinical centres

The objective is to recruit 150 patients with sarcopenia in 11 clinical centres in 4 countries at the end of the recruitment period, set today as June 2018. This number is lower than the 300 patients originally planned because of the difficulties in obtaining administrative authorisations

[81] Cruz-Jentoft AJ, Baryens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoulde M, Zamboni M. 2010. Sarcopenia: European consensus on definition and diagnosis. Report of the European Working Group on Sarcopenia in Older People. *Age Ageing*, 39(4): 412-423.

and the low speed of recruitment of the centres. The size of the target population, however, is sufficient to achieve the main objectives of SARA-OBS. The 11 clinical investigation centres have been opened and are active. The centres were opened once the authorisations of the national agencies and ethics committees concerned were obtained in 2017. 111 patients had been included in April 2018 in the 4 countries (United States, Italy, France and Belgium). The inclusion of patients is ongoing in the centres until approval for launching SARA-INT is obtained or until the end of the recruitment period. The following table describes the 11 centres that are open and active:

Country	City/Institution	Investigators	Site initiation visit	Regulatory authorisation obtained	First patient included
USA	Boston Tufts University	Roger Fielding (Principal investigator)	13/04/2017	07/04/2017	30/06/2017
	Gainesville University of Florida	Marco Pahor	11/04/2017	30/03/2017	26/05/2017
	New-York Columbia University	Moïse Desvarieux	30/03/2018	09/03/2018	Q2 2018
France	Toulouse CHU Toulouse	Yves Rolland	23/03/2017	10/11/2016	06/06/2017
	Limoges CHU Limoges	Achille Tchalla	20/12/2017	10/11/2016	Q2 2018
	Lyon CHU Lyon Sud	Marc Bonnefoy	26/04/2017	10/11/2016	26/09/2017
Italy	Rome Sapienza University	Lorenzo Donini	02/05/2017	02/02/2017	25/05/2017
	Rome Campus Biomedico	Raffaelle Antonelli-Incalzi	12/09/2017	02/04/2017	05/10/2017
	Rome Sapienza University	Maurizio Muscaritolli	16/10/2017	06/07/2017	07/11/2017
	Pavie Istituto S. Margherita	Mariangella Rondanelli	13/11/2017	01/10/2017	01/02/2018
Belgium	Liège University of Liège	Olivier Bruyère	22/02/2017	31/10/2016	16/10/2017

Recruitment dynamics

The aim is to recruit 150 patients with sarcopenia in the 11 clinical centres that have opened in the 4 countries (United States, France, Italy, Belgium) before the end of June 2018. The initial objective of the study was to include 300 patients over a period of 6 months, but this objective was revised due to slow progress in obtaining all authorisations, the speed of recruitment observed (1-2 patients per centre and per month) and the priority given to recruitment in the interventional study. In April 2018, more than 111 patients were included in the study in the 4 countries, mainly in the United States and Italy. We hope that the majority of patients enrolled in this study will be included at the end of the observation period in the interventional study by the end of 2018.

Characteristics of the population

A description of the population of the first 84 patients included was prepared and presented at the SCWD 2017 (Dioh et al., 2017)[82] and at the ICFSR 2018 (Dioh et al. 2018, Zia et al., 2018)[8384]. These key data are presented in the table below:

Characteristics	Average	Standard Deviation
Age	78.47	7.87
BMI	30.10	7.29
Women: Men	48: 33	NA
SPPB	6.46	1.63
SPPB gait speed (sec)	0.74	0.18
Chair stand	1.55	0.77
Appendicular Muscle Mass (ALM)	16.53	4.67
Men	19.52	4.96
Women	14.44	3.37
ALM/BMI	0.57	0.14
Men	0.66	0.16
Women	0.51	0.10
6-minute walk test (m)	314.07	98.17
400 m (min)	7.10	3.74
Gait speed over 400 m (m/sec)	0.87	0.27

Patients have an average BMI of 30.1, consistent with observations in other clinical studies such as SPRINTT (in Europe) and LIFE (in the US) that have applied comparable inclusion criteria. The average SPPB score of 6.5/12 is relatively low and corresponds to patients who are at risk of impaired mobility. This score is comparable to that of other studies on sarcopenia (LIFE study with 7.4 ± 1.6 in the physical activity group[85]. The gait speed in the SPPB test is <0.8 m/s, corresponding to the definition of sarcopenia according to the European Working Group on Sarcopenia in Older People (EWGSOP)[86]. Finally, the distance in the 6-minute walk test is 314.07 m, consistent with what is expected for patients with sarcopenia with a mean

[82] Dioh W, Margalef C, Dupont P, Dilda P, Lafont R, Veillet S & Del Signore S. SARA clinical program for evaluating safety and efficacy of Sarconeos in a Phase 2b clinical trial, SCWD 2017

[83] Dioh W, Margalef C, Lafont R, Dupont P, Dilda P, Zia G, Veillet S & Del Signore S. SARA-INT, A double-blind, placebo-controlled, randomized clinical trial to evaluate safety and efficacy of Sarconeos (BIO101). ICFSR 2018

[84] Zia G, Donini L, Dioh W, Margalef M, Veillet S, Feletti L, Del Signore S. Daily mobility profile in age-related Sarcopenia: actimetry baseline data from SARA-OBS, a six-month observational multicentre Clinical Study in EU and US. ICFSR 2018

[85] Pahor M, Guralnik JM, Ambrosius WT, Blair S, Bonds DE, Church TS, Espeland MA, Fielding RA, Gill TM, Groessl EJ, King AC, Kritchevsky SB, Manini TM, McDermott MM, Miller ME, Newman AB, Rejeski WJ, Sink KM & Williamson JD (2014) Effect of Structured Physical Activity on Prevention of Major Mobility Disability in Older Adults: The LIFE Study Randomized Clinical Trial. *JAMA* 311, 2387.

[86] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel J-P, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M & European Working Group on Sarcopenia in Older People (2010) Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 39, 412–423.

age of 78 years and BMI 30.78. This distance is lower than that observed in the Pedredo-Chamizo[87] studies (575.7 ± 91.8 in men and 523.3 ± 83.4 in women) or Gouveia et al., 2013 (461.8 ± 108.6 in men and 392.8 ± 118.2 in women)[88]. The patient population recruited according to the inclusion criteria of the FNIH (Studenski et al., 2014)[82] has, therefore, the desired characteristics (made up of slow walkers, at risk of impaired mobility) to study the effectiveness of a drug treatment.

Regulatory and recruitment schedule

The schedule of the SARA-OBS study presented below provides for an end of inclusions scheduled on 30 June 2018, by which date patients should gradually switch in the second half of 2018 to the interventional study. The final report of the study should be completed in the first half of 2019. We plan to take stock of the study and present the main results at the SCWD in December 2018 in Maastricht (Netherlands) and at the ICFSR in February 2019 in Miami (United States).

SARA-OBS recruitment schedule

Tasks	Stages	Date
Regulatory authorisations	Initial submission to the Ethics Committees (France)	31/08/2016
	Initial approval of the Ethics Committees (France)	22/09/2016
	Initial submission to the Ethics Committees (US)	03/03/2017
	Initial approval of the Ethics Committees (US)	30/03/2017
Opening of the sites	First initiation visit on site	08/02/2017
	Final initiation visit on site	30/03/2018
Patient recruitment	First patient included	18/04/2017
	Last patient included	30/06/2018
	Final visit of the last patient	30/12/2018
Data and report	Database locked	30/01/2019
	Final report	Q1 2019

SARA-INT Interventional Study

Objectives

The objective of the clinical study is to assess the effect of the Sarconeos drug candidate on muscle function of persons with sarcopenia aged over 65, in accordance with criteria proposed by the Foundation for the National Institutes of Health (FNIH)[89]. Two *Sarconeos* doses will be compared with placebo: 350 mg in two doses and 700 mg twice daily at meal times. The general objectives of this study (SARA-INT) are to evaluate the safety and effectiveness of two doses of *Sarconeos* (175 mg bid and 350 mg bid) administered orally for 26 weeks against placebo in a population of people living in the community, aged 65 years or older and at risk of impaired mobility; to estimate the effect of treatment in the target population in improving

[87] Muñoz-Arribas A, Vila-Maldonado S, Pedrero-Chamizo R, Espino L, Gusi N, Villa G, Gonzalez-Gross M, Casajús JA, Ara I & Gómez-Cabello A (2014) [Physical fitness evolution in octogenarian population and its relationship with a sedentary lifestyle]. *Nutr. Hosp.* 29, 894–900.

[88] Gouveia ÉR, Maia JA, Beunen GP, Blimkie CJ, Fena EM & Freitas DL (2013) Functional fitness and physical activity of Portuguese community-residing older adults. *J. Aging Phys. Act.* 21, 1–19.

[89] Studenski et al., 2014. The FNIH Sarcopenia Project: Rationale, Study Description, Conference Recommendations, and Final Estimates. *J Gerontol A Biol Sci* 69(5): 547-558

physical function after a period of 6 months; to estimate the effect of the treatment in reducing the risk of impaired mobility after 6 months of treatment versus placebo.

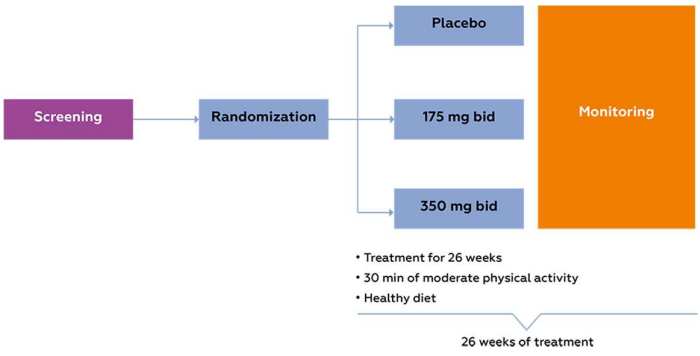
Main criteria and key secondary criteria
The primary evaluation criterion of the SARA-INT study is to evaluate the effect of two daily doses of *Sarconeos* versus placebo on the mobility function as measured by the gait-speed-over-400m test. The difference in absolute value in metres/second observed in each group treated between the beginning and the end of the 6-month study will be compared to that observed in the placebo group. A difference between groups of 0.05 metres/second is considered clinically significant according to the study by Perera et al., (2006)[90].

Two key secondary evaluation criteria are identified: the PF-10 subscore of the SF-36 quality of life questionnaire that will be compared between the treated groups and the placebo group with regard to the difference between the beginning and the end of the clinical investigation phase at 6 months and the chair-to-standing test (SPPB subscore) which will also be compared between the treated groups and the placebo group.

In addition, two subgroups will be considered for the analysis of the results: a “very low speed subpopulation”, defined as having a gait speed over 4 metres of ≤0.8 m/s; and a “subpopulation with sarcopenic obesity” defined by a body fat percentage of >25% for men and >35% for women. Subgroup analyses based on these factors will be performed to better characterise the effects of treatment in patients at risk of impaired mobility.

Study design
The design of the study is similar to that of the SARA-OBS study, with the major difference found in the administration of the product versus placebo. It is composed of the screening/randomisation and investigation phases. Recruitment is estimated at 6 months. The experimental phase includes 2 main visits: the inclusion visit, and the 6-month visit, plus an intermediate visit at 3 months with a reduced number of measurements. A visit focusing on safety is planned after the first month of administration of *Sarconeos*. Telephone interviews take place at 5 months: participants complaining of poor physical function or deterioration of their physical function may be asked to bring the date of their planned visit forward. Participants who see their physical condition worsening may go directly to the end-of-study visit.
A population pharmacokinetic substudy (SARA-POP-PK) is conducted to evaluate pharmacokinetic values after 1 month, 3 months or 6 months of administration in a subgroup of patients in European centres. This study, which is conducted following the recommendations of the Belgian Federal Agency for Medicines and Health Products (FAMHP), makes it possible to determine the levels of exposure of patients during the various visits while evaluating the occurrence of adverse events related to the doses administered.

The figure below shows the different branches of the study.



[90] Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc. 2006 May;54(5):743-9. PubMed PMID: 16696738

The table below presents the design and the main parameters measured in the SARA-INT study.

		Selection	Randomisation & Baseline visit	Visit at M1	Visits at M3, M5 and M6		
Weeks		-8 - 0	Day0	4 +/-3 days)	12 +/- 1 week	21 +/- 1 week	26 - 1 week
Phone call						X	
Main consent form, consent form for secondary research, biobank and genetic research consent form		X					
Demography		X					
Medical history		X					
Concomitant medication		X		X	X		X
Security questions				X		X	
Physical examination and body measurements (anthropometry)		X	X				X
CIRS			X				
SF-MNA			X				
ECG		X					
SPPB		X			X		X
DEXA		X					X
Gall bladder ultrasound		X					X
Inclusion/exclusion criteria		X					
Randomisation			X				
Stair step test			X				X
Grip test/Knee extension test			X				X
400-m walk test		X			X		X
6 min walk test			X				X
Blood sampling	Hematology/biochemistry	X		X	X		X
Urine analysis		X		X	X		X
Urine and plasma sampling for biomarker analysis		X					X
Actimetry			X				X
Patient reported outcomes	SF-36, SarQoL, TSD-OC		X		X		X
Evaluation questionnaire	PAT-D		X				X
Delivery of treatment under study			X	X	X		
Recovery of unused treatment & registration of compliance to the product under study				X	X		X
Safety measures with vital signs and weight			X	X	X		X
Review of adverse events			X	X	X	X	X
Blood sampling for pharmacokinetics (some patients)			X (Day1)	X	X		X
eCRF		X	X	X	X	X	X

Clinical centres

334 patients with sarcopenia have been recruited in about fifteen clinical Investigation centres in Europe (France, Belgium, Italy) and the United States. As SARA-INT is a continuation of SARA-OBS, the 11 SARA-OBS clinical investigation centres will be retained, with additional centres added for a total of 15 to 17 centres. We estimate that at least one-third of the patients

included in SARA-INT will be from the SARA-OBS population, the others being new recruits. The 22 clinical centres of the study are presented in the table below:

Country	City/Institution	Investigators	Site initiation visit	Authorisations obtained	Estimated number of patients
USA	Boston Tufts University	Roger Fielding (Principal Investigator)	Q2 2018	Q2 2018	18
	Gainesville University of Florida	Marco Pahor	Q2 2018	Q2 2018	36
	Houston Michael E. DeBakey VA	Dennis Villareal	26/04/2018	Q2 018	36
	Winston-Salem Bowman Gray Center for Medical Education	Stephen Kritchevsky	23/04/2018	23/04/2018	36
	San Antonio	Nicolas Musi	Q2 2018	Q2 2018	24
	New-York Columbia University	Moïse Desvarieux	Q3 2018	Q3 2018	18
France	Toulouse CHU Toulouse	Yves Rolland	Q3 2018	Q3 2018	12
	Limoges CHU Limoges	Achille Tchalla	Q3 2018	Q3 2018	12
	Paris Hôpital Broca	Olivier Hanon	Q3 2018	Q3 2018	10
	Montpellier CHU Montpellier	Hubert Blain	Q3 2018	Q3 2018	12
	Paris Hôpital Bichat	Agathe Raynaud-Simon	Q3 2018	Q3 2018	12
	Lyon CHU Lyon Sud	Marc Bonnefoy	Q3 2018	Q3 2018	12
Italy	Rome Sapienza University	Lorenzo Donini	Q3 2018	Q3 2018	12
	Rome Campus Biomedico	Raffaelle Antonelli-Incalzi	Q3 2018	Q3 2018	12
	Rome Sapienza University	Maurizio Muscaritolli	Q3 2018	Q3 2018	12
	Genoa University-Hospital San Martino	Samir Sukkar	Q3 2018	Q3 2018	12
	Padua University of Padua	Giuseppe Sergi	Q3 2018	Q3 2018	12
Belgium	Liège University of Liège	Olivier Bruyère	26/04/2018	20/02/2018	12
	Brussels (Free University of Brussels)	Ivan Bautmans	Q2 2018	20/02/2018	12
	Leuven Universitaire Ziekenhuizen	Evelien Gielen	Q3	Q3	12

Regulatory and recruitment schedule
Biophytis sought scientific advice from the European Medicines Agency (EMA) and the US agency (FDA) in the first half of 2017. The comments of these agencies have been incorporated into a new version of the SARA-INT protocol, which has made it possible to file applications for authorisation in the US (FDA) and Belgian (FAMHP) authorities. Authorisations to start this study in these two countries were obtained in the second half of 2017. Taking into account the recommendations of these two agencies, a final version of the protocol was adopted and the applications filed in France and Italy. Biophytis is in discussion with these 2 agencies, answering their questions so as to obtain the authorisations as soon as possible.

The first centres, out of a total of 9, have opened in the United States and Belgium and the recruitment of the first patients has begun in these two countries. Recruitment will start in France and Italy as soon as authorisations are obtained and the centres have opened, probably in Q3 2018. We plan to complete patient recruitment by the end of 2018 to complete the study in the first half of 2019 and report the key results in Q3 2019.
The schedule of the study is presented below:

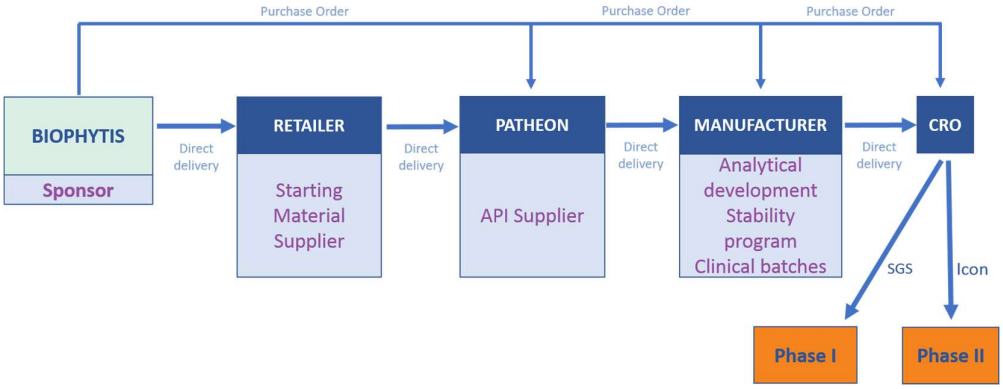
SARA INT

Tasks	Stages	Date
Regulatory authorisations	Initial submission to the competent US authorities (FDA)	25/09/2017
	Initial approval of the competent US authorities (FDA)	01/11/2017
	Initial submission to the competent authorities in Europe (FAMHP)	29/09/2017
	Initial approval of the competent authorities in Europe (FAMHP)	07/12/2017
Opening of the sites	First initiation visit	23/04/2018
	Final initiation visit	Q3 2018
Patient recruitment	First patient included	Q2 2018
	Last patient included	Q4 2018
	Final visit of the last patient	Q2 2019
Data and report	Database locked	Q2 2019
	Final report	Q3 2019

6.2.3.5 CMC – sourcing – supply chain

The Active Pharmaceutical Ingredient (API), BIO101, is an extract of *Stemmacantha carthamoides*, a plant used for both medicinal and food purposes and cultivated in China, and purified for pharmaceutical use (>97% purity of the active molecule), in observance of Good Manufacturing Practices for pharmaceuticals (GMP), by Patheon (Germany) The industrial scale-up and production of the pilot clinical batches began in the third quarter of 2015. The supply chain for clinical batches has been secured both as concerns raw materials and industrial capacity. A first clinical batch (GMP) made it possible to carry out the SARA-PK study whose results are presented above. A new GMP batch was produced for the SARA-INT study.

All the elements necessary for clinical development until the Marketing Authorisations are obtained are covered by this supply chain. Biophytis is also evaluating other ways of obtaining the active ingredient in order to optimise the supply chain in accordance with the estimated future needs of the market.



The diagram above shows the different partners of the current Supply Chain

6.2.3.6 Competitive environment

There is, to date, no molecule registered to treat sarcopenia; the only recommended treatment is 30 minutes of exercise a day, and vitamin D supplementation.

It is increasingly acknowledged, however, that sarcopenia poses a major public health issue, and is steadily increasing as the population ages. It is also acknowledged that an effective pharmacological agent would be a medical and economic boon for those who were to market it[91].

Since then, pharmaceutical companies have launched a plethora of development programmes to treat sarcopenia in the last decade, with different classes of molecules. These are, essentially:

- Substrate molecules for protein synthesis which are amino acids or their *metabolites* (*leucine*, beta-hydroxy-beta-methyl-butyrate (HMB), citrulline, ornithine), as well as rapidly digestible proteins such as lactalbumin.
- Anabolising hormones such as testosterone or its variants (*SARM*s), growth hormone (*GH*), *IGF-1*, vitamin D, ghrelin or progranuline.
- *Myostatin* inhibitors (antibodies, soluble receptors).
- Molecules targeting the renin–anigiotensin system such as ACE inhibitors, *antagonists* of angiotensin II and angiotensin 1-7 (or the *agonists* of the latter).
- *Beta blockers* (inhibitors of β-adrenergic receptors).
- And various natural substances such as polyphenols (resveratrol, isoflavones), triterpenes (ursolic and oleanolic acids), or phytosteroids (brassinosteroids, phytoecdysteroids).

Most of these molecules have failed to demonstrate significant effectiveness, or they had unacceptable side effects during long-term treatment. Sarcopenia is therefore still waiting for a therapeutical breakthrough.

[91] Garber K. 2016. No longer going to waste. *Nature Biotechnology* 34, 458–461

Clinical-stage programmes still in progress are:

Bimagrumab (BYM338) – Novartis in collaboration with Morphosys: Bimagrumab is a human monoclonal antibody that targets ActRIIB. This antibody is capable of inhibiting *myostatin* activity and the activins of skeletal myoblasts to restore Akt signalling (by inhibiting ActRIIB), thereby promoting muscle growth. It is the product of a collaboration between Morphosys (the largest German biotech) and Novartis. Although the phase-2 results for a rare form of muscle weakness have been disappointing, Novartis seems to have decided to launch a large phase 3 study for sarcopenia.

Trevogrumab (REGN1033) – Regeneron: Trevogrumab is a human monoclonal human antibody capable of inhibiting *myostatin* activity by targeting GDF8. Phase-2 results were inconclusive, and partner Sanofi withdrew from the programme. It is now uncertain whether Regeneron will continue the clinical programme for sarcopenia.

Reldesemtiv (CK-2127107) – Cytokinetics in collaboration with Astellas: CK-2127107 is an activator of troponin, a protein located in the sarcomere that is sensitive to calcium. It aims to slow the release of calcium from the regulatory complex involving troponin in fast muscle fibres. Astellas and Cytokinetics are currently planning the clinical development of this molecule for spinal muscular atrophy (SMA).

In conclusion, sarcopenia is still waiting for effective drug treatment. The big pharmaceutical companies had begun a frantic race for the first drug about ten years ago. Following a large number of failures, the range of technologies still in development has been considerably reduced recently.

Nevertheless, Novartis, Astellas and Regeneron continue to invest to be the first to offer an effective drug, and other companies will surely regain their interest in this large potential market.
Sarconeos, which is in clinical phase 2b, is a major opportunity for any partner who decides to participate in this race.

6.2.4 Duchenne muscular dystrophy

6.2.4.1 Epidemiology

Duchenne muscular dystrophy (DMD) is a rare genetic disorder that affects the entire muscular system and whose first symptoms appear in childhood. Progressive muscle weakness develops, causing the loss of walking ability and premature death at around 30 years of age due to respiratory and cardiac complications. Unfortunately, there is currently no cure for DMD. Two products have been approved respectively in Europe and the United States, each of which addresses a small subset of patients, with a relatively low risk–benefit ratio.

Duchenne muscular dystrophy (DMD) is a rare, X-linked recessive inherited disorder affecting 1 in 3,500 boys (Brooke et al., 1989[92]). DMD is the most common muscle dystrophy in children and has a fatal outcome (Emery, 1991[93]; Khurana and Davis, 2003[94]).

DMD is due to the alteration of the dystrophin gene (Walter and Reilich, 2017[95]), which results in the absence of functional dystrophin, leading to progressive muscle weakness, but also to cardiac defects and impaired respiratory function, leading to premature death of patients before the age of 40 (Findlay et al., 2015[96]; Walter and Reilich, 2017). In the European Union, the prevalence of DMD is estimated at 0.81 per 10,000.

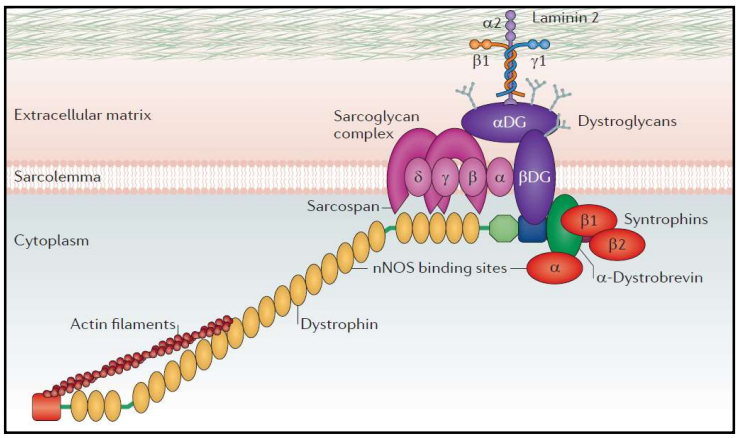


Illustration of DAGC (dystrophin associated glycoprotein complex): Dystrophin is an important link between the cytoskeleton of the muscle fibre and the extracellular matrix (Fairclough et al., 2013)[97].

Dystrophin is a large cytoskeletal protein, which is mainly located under the cell membrane of the muscle fibre. It is associated with several other proteins, forming a complex called DAGC (dystrophin associated glycoprotein complex*)* across the cell membrane, and in connection with the extracellular matrix, outside the muscle fibre. At its other end, dystrophin is linked to actin protein, inside the muscle fibre, and is involved in contraction. Dystrophin is a key mechanical link to the integrity of muscle fibres.

The absence of dystrophin makes the DAGC complex unstable and the membrane of the muscle fibres is severely weakened. Therefore, during muscle contraction, the fibres will become damaged, and will eventually die (necrosis). Muscle tissue regeneration phenomena are set up in parallel, starting from the stem cells of the muscle tissue (the satellite cells). When the regenerative mechanisms are exhausted, degeneration prevails, the muscle fibres are then

[92] Brooke MH, Fenichel GM, Griggs RC, Mendell JR, Moxley R, Florence J, King WM, Pandya S, Robison J, Schierbecker J, et al. 1989 Duchenne muscular dystrophy: patterns of clinical progression and effects of supportive therapy. Neurology. 39 (4):475-81.
[93] Emery AEH. 1991 Population frequencies of inherited neuromuscular diseases--a world survey. Neuromuscul Disord. 1 (1):19-29.
[94] Khurana TS Davies KE. 2003 Pharmacological strategies for muscular dystrophy. Nat Rev Drug Discov. 2 (5):379-90.
[95] Walter MC Reilich P. 2017. Recent developments in Duchenne muscular dystrophy: facts and numbers. J Cachexia Sarcopenia Muscle 8 (5): 681-5.
[96] Findlay AR, Wein N, Kaminoh Y, Taylor LE, Dunn DM, Mendell JR, King WM, Pestronk A, Florence JM, Mathews KD, Finkel RS, Swoboda KJ, Howard MT, Day JW, McDonald C, Nicolas A, Le Rumeur E, Weiss RB, Flanigan KM and United Dystrophinopathy Project. 2015 Clinical phenotypes as predictors of the outcome of skipping around DMD exon 45. Ann Neurol. 77 (4):668-74.
[97] Fairclough RJ, Wood MJ, Davies KE. 2013 Therapy for Duchenne muscular dystrophy: renewed optimism from genetic approaches. *Nautre Reviews Genetics* 14 : 373-378.

replaced by connective tissue (fibrosis) and adipose tissue, resulting in a loss of muscle strength and an intolerance to exercise (Barnabei et al. 2011[98]).

The first clinical signs of the disease develop during childhood. In fact, the first symptoms are usually reported before the age of 5 (Pane *et al*., 2013[99]). DMD evolves according to a very well described progression. The disease manifests itself first in the lower muscles. Around the age of 10 to 12, the use of a wheelchair becomes essential. The muscle tone of the trunk and arms gradually disappears, leading to complications (bronchopulmonary infections and ventilatory complications), as well as severe scoliosis. Around the age of 20, patients develop major respiratory and cardiac failures, which inexorably lead to death around the age of 30.

There is currently no cure for DMD, but palliative, orthopaedic and respiratory treatments improve the quality and expectancy of life. Patients currently receive treatment based on the optimisation of their muscular capacities as well as on the prevention and treatment of cardiac and respiratory complications. The use of corticosteroids makes it possible to extend walking ability by an average of two years.
However, some children do not respond to this treatment which causes adverse effects, including significant bone fragility. Partial cardiac protection is achieved through a combination of ACE inhibitors and beta-blockers. New treatments are in the clinical development stage. Exon skipping involves forcing the cell to produce a shorter, yet functional, version of dystrophin.

Another approach of the same type is to ignore a mutation that interrupts the synthesis of dystrophin prematurely. However, this type of therapy is only targeted at a small number of patients, depending on the exact nature of the mutations that cause their disease. Finally, gene therapy, which offers the possibility of synthesising short versions of dystrophin (mini- or micro-dystrophins) in patients, is faced with a major problem of immune response against these proteins which the body treats as foreign.

In addition to an irreversible decrease in appendicular muscle strength and the onset of exercise intolerance, one of the major complications of the disease is the appearance a fibrosis that particularly affects the heart leading to heart failure (accompanied by dilated hypertrophy). These conditions are life-threatening. The appearance of fibrosis is therefore an irreversible evolution that must be prevented in order to maintain muscle function. In this sense, therapeutic approaches must focus their efforts on:

- maintaining tolerance to exercise
- maintaining muscle strength
- preventing the appearance of fibrosis.

6.2.4.2 Proof of concept

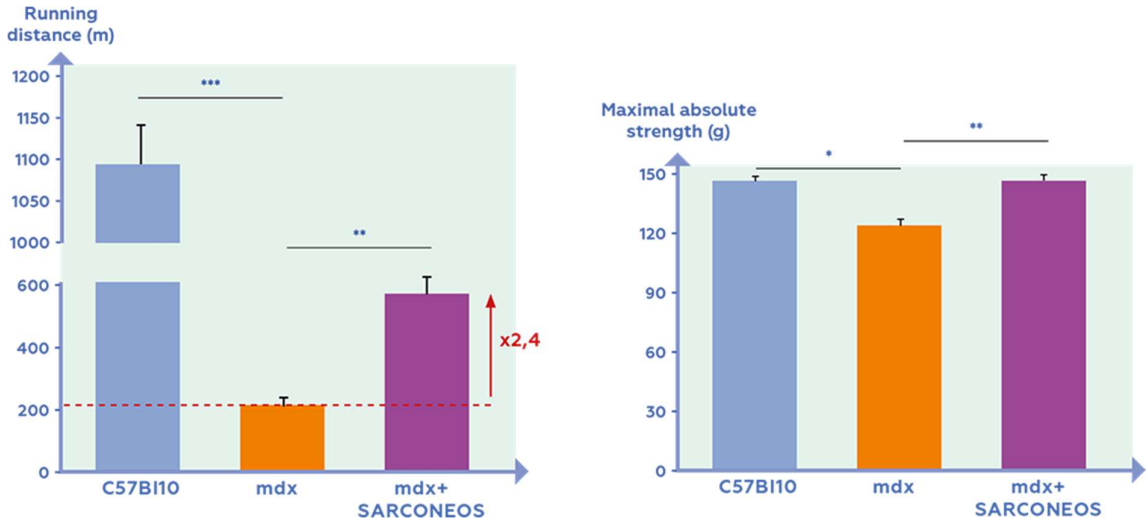
Experiments conducted in animal models

The anabolic effects of Sarconeos have already been demonstrated in young animals, but no work has been done to find out if the same applies to mammals with myopathy, particularly where their muscle function has been altered.

[98] Barnabei M.S., Martindale J.M., Townsend D., Metzger J.M. (2011). Exercise and muscular dystrophy: implications and analysis of effects on musculoskeletal and cardiovascular systems. Compr Physiol. 1 (3):1353-63
[99] Pane M, Messina S, Bruno C, D'Amico A, Villanova M, Brancalion B, Sivo S, Bianco F, Striano P, Battaglia D, Lettori D, Vita GL, Bertini E, Gualandi F, Ricotti V, Ferlini A Mercuri E. 2013. Duchenne muscular dystrophy and epilepsy. Neuromuscul Disord. 23 (4):313-315.

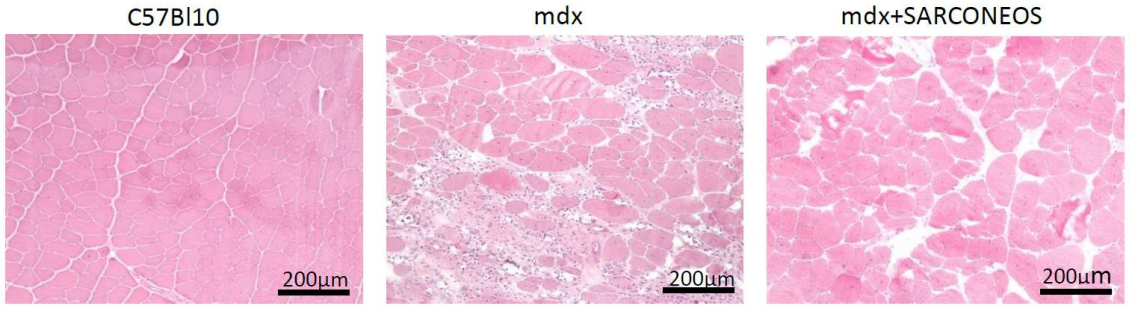
Biophytis therefore focused on a murine (mouse) model of Duchenne muscular dystrophy (mdx mouse), which has a mutation on the dystrophin gene (Bulfield et al. 1984[100]; Maller et al. 1989[101]), to demonstrate the beneficial effects of BIO101 in a context of myopathy. Untreated animals with myopathy (mdx) have very poor physical performance compared with control animals, which do not have the disease (C57Bl10). Mdx animals that receive a daily dose of Sarconeos administered orally show significant improvement in their physical performance with:

- An increase in their running distance (exercise tolerance) by a factor of 2.4
- An increase in absolute muscle strength



Effect of Sarconeos intake on physical performance (running distance and absolute maximum strength) of a mouse model with Duchenne muscular dystrophy (mdx mouse)

The study of muscle histology of mice with myopathy shows that mdx mice exhibit inflammatory infiltration as well as areas of fibrosis compared to healthy muscle in C57Bl10 control mice. In a very interesting way, Biophytis has demonstrated that Sarconeos improves the muscular lesion profile. Indeed, daily treatment of mice with Sarconeos makes it possible to decrease the atrophy of the muscular fibres and the chronic inflammatory foci associated with fibrosis.

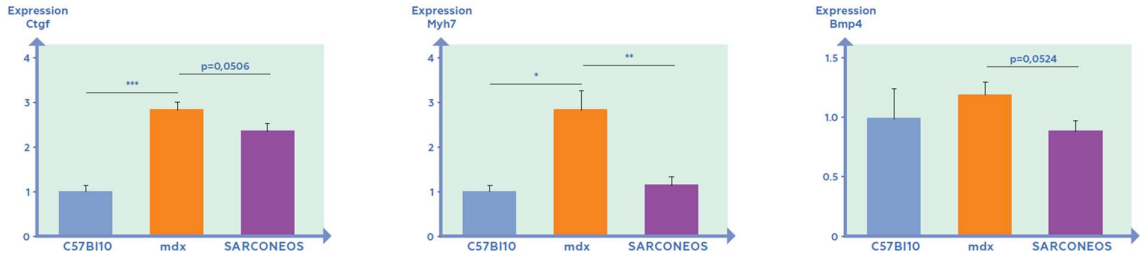


Microscopic observation of mdx mouse muscles receiving Sarconeos shows that the treatment improves the histological profile of mice with myopathy compared to untreated mice (mdx)

[100] Bulfield G., Siller W-G., Wight P-A., Moore K- J. (1984). X chromosome-linked muscular dystrophy (mdx) in the mouse. Proc. Natl. Acad. Sci. USA 81: 1189-1192.

[101] Sicinski P, Geng Y, Ryder-Cook AS, Barnard EA, Darlison MG, Barnard PJ.1989. The molecular basis of muscular dystrophy in the mdx mouse: a point mutation. *Science* 244 (4912), 1578-1580.

At the level of the heart, the analysis of molecular markers made it possible to show that the daily oral treatment of mdx mice by Sarconeos allows the reduction of markers of fibrosis (*ctgf*) as well as markers of cardiac hypertrophy (*myh7* and *bmp4*), which are increased in Duchenne muscular dystrophy.

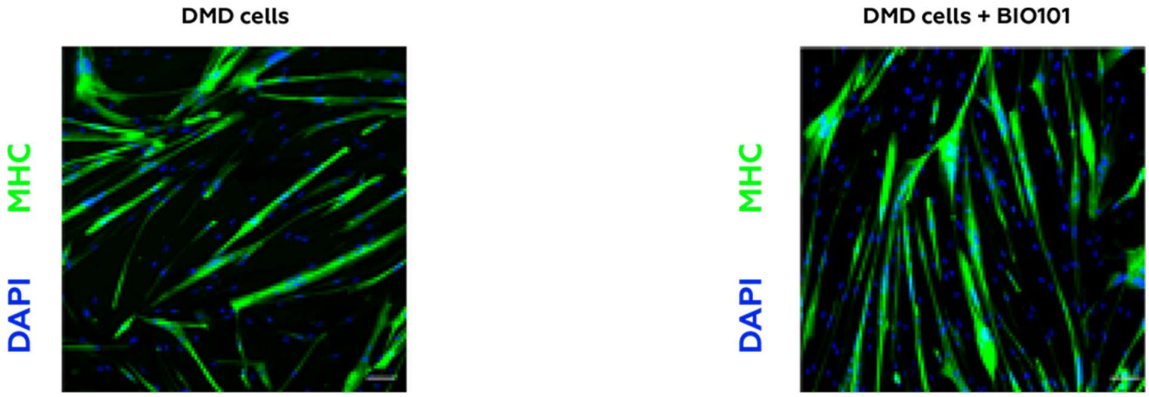


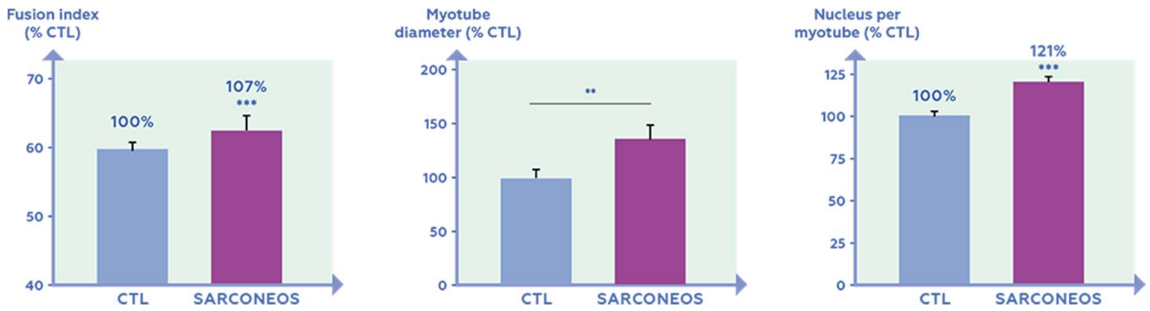
Effect of Sarconeos treatment on cardiac expression of markers of fibrosis (Ctgf) or cardiac hypertrophy (Myh7 and Bmp4) in mdx mice.

Through the use of a paradigmatic animal model of Duchenne muscular dystrophy, Biophytis was able to establish the proof of concept that the use of Sarconeos can be proposed to preserve muscular function, notably muscular strength and tolerance to exercise, and also slow the evolution of myopathies which result in the deterioration of said muscle function, and more particularly the appearance of a fibrosis of the myocardium or skeletal muscle.

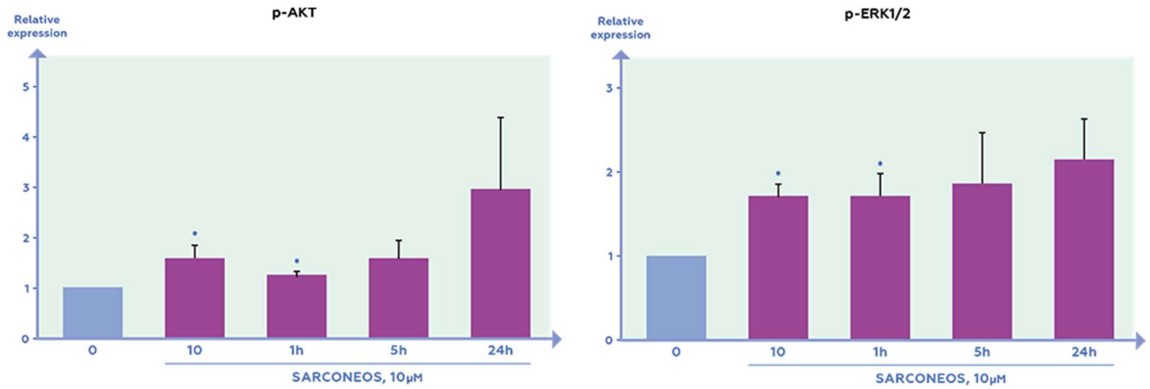
Experiments on cells from humans with DMD

The beneficial functional effects observed in Sarconeos-treated animals are consistent with the results obtained with human cells from a patient with Duchenne muscular dystrophy. Indeed, Sarconeos is responsible for improving the differentiation of DMD myoblasts into myotubes. Moreover, in these same cells, Sarconeos induces significant activation of the AKT/mTOR and MAPK/ERK signalling pathways, respectively, involved in proteosynthesis, proliferation, cell survival and in muscle regeneration and remodelling.



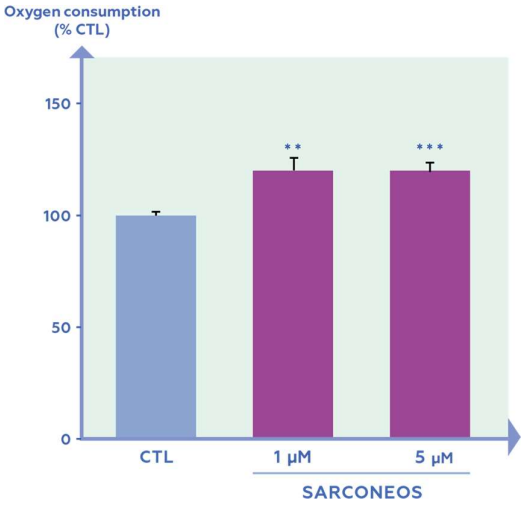


Effect of Sarconeos on three parameters concerning the differentiation of myoblasts from a DMD patient.



Effect of Sarconeos on activation of AKT/mTOR and MAPK/ERK signalling pathways of myotubes from a DMD patient.

Fascinatingly, the beneficial properties of Sarconeos at the anabolic level on myotubes from DMD patients are accompanied by positive effects on energy metabolism. While it is known that there is a decrease in basal mitochondrial respiration in DMD muscle fibres (Schuh et al. 2015[102]), Sarconeos contributes to the restoration of this energy parameter.



Effect of SARCONEOS on basal mitochondrial respiration of myotubes from a DMD patient

[102] Schuh RA, Jackson KC, Khairallah RJ, Ward CW and Spangenburg EE. (2012). Measuring mitochondrial respiration in intact single muscle fibers. Am J Physiol Regul Integr Comp Physiol. 302 (6):R712-9.

6.2.4.1 Clinical programme

The clinical programme of Sarconeos for Duchenne muscular dystrophy (DMD) will consist of 2 main studies: MYODA-PK and MYODA-INT.

The first study, MYODA-PK, is a combined SAD-MAD phase-1 paediatric study. It aims to evaluate the safety, pharmacokinetics and pharmacodynamics of the new paediatric form of Sarconeos in 24 paediatric patients (aged 2-18 years) after single ascending dose (SAD) administered orally and then multiple ascending doses (MAD) administered orally for 4 weeks. We plan 4 SAD doses, from which 3 will be tested in MAD. The safety and acceptability, adverse effects, and pharmacokinetic and pharmacodynamic profiles of BIO101 will be evaluated by age group. Sarconeos will be tested in its new formulation appropriate for paediatrics at a dose of 1 to 10 mg/kg/day.

From a regulatory point of view, a request for Orphan Drug Designation (ODD) in Europe has been filed and the review process for this application formally began on 26 February 2018. In addition, an application for rare (orphan) disease designation will be filed in the United States with the FDA in April 2018.

The award of the Orphan Medication Status by the FDS confers several advantages in the USA including protection for 7 years after marketing authorisation, co-financing of clinical studies by the FDS if approved, and the possibility of accelerated registration.

A request for scientific advice will be submitted to the UK agency MHRA to better prepare the MYODA-PK and MYODA-INT studies.

The European Paediatric Investigation Plan, which is not exclusive to the MYODA clinical studies and applies to the Sarconeos product in general, will also be submitted to the European Agency in the second quarter of 2018.

The second study, MYODA-INT, is a phase-2, randomised, double-blind, placebo-controlled clinical trial. It aims to evaluate the safety and effectiveness of BIO101 in the new oral formulation to be administered to 60 paediatric patients aged 5-12 years with Duchenne muscular dystrophy. A minimum treatment duration of 6 months and a maximum duration of 18 months are currently planned in the design of the study. The primary criterion of this study will be a measure of mobility in children by the 10-metre walk/run test or the sitting-rising test (standing up from the ground). Several other secondary criteria will be selected, including the body composition obtained by Magnetic Resonance Imaging used to measure patients' muscle mass, but also a MyoGrip strength test, a 6-minute walk test, and a Quality-of-Life questionnaire (EQ-5D, HRQL, PedsQL, TSQM). Other exploratory criteria such as actimetry, biomarkers (interleukin, titine, myoglobin, creatine kinase, etc.) as well as a series of questionnaires, will also be evaluated.

Finally, a clinical study (MYODA-EXT) which will be an extension of the MYODA-INT study over the long term will be conducted in boys aged 5 to 18 years.

The studies will be conducted in clinical centres located in France, the United Kingdom, Italy, Belgium and the Netherlands. In order to determine the best design for the different clinical studies and choose the most relevant main and secondary criteria, we have planned to interview the European Medicines Agency (EMA) for its assistance with the phase-2 clinical study protocol.

The schedule of the MYODA studies comprises several phases:

H2 2018:	MYODA-PK begins
H2 2019:	MYODA-INT begins
2019-2021:	MYODA-EXTENSION

6.2.4.2 Competitive environment

Currently, boys with Duchenne muscular dystrophy receive treatment mainly to address their symptoms (rehabilitation, ventilation, nutrition). Such treatment is generally supported by corticosteroids that can extend walking ability and reduce the risk of back deformity, and sometimes by ACE inhibitors to slow the onset of cardiac abnormalities.

They are, however, numerous projects to improve the treatment of this disease that have considerable public impact (see, for example, the impact of Telethon in France), with significant scientific and economic investment not only by biotech companies (some of which have the sole purpose of developing treatments for DMD), but also large pharmaceutical companies.

The approaches are genetic, cellular and pharmacological. The first treatments targeting the genes or acting on genetic transcription have recently been launched to treat certain mutations: Ataluren in Europe and Eteplirsen in the United States.

The scientific community is nevertheless aware that, given the many factors involved in pathogenesis, and the variability of their expression, finding a complete cure of the disease is impossible or very unlikely. New treatments modifying the degenerative process (including Sarconeos) will therefore also play very important roles in treating this terrible disease more effectively. It should be noted that the population likely to respond to the oral administration of Sarconeos is not limited to a subgroup that is numerically limited and corresponds to a specific genetic anomaly, but concerns all patients with DMD.

Currently, the following approaches exist:

Programmes acting on dystrophin and its genetic expression, that:

- Palliate the alteration of the gene: gene therapy
- Correct the gene (for example using meganucleases)
- Modify the anomaly at the level of RNA messenger: transcription of premature stop codons, trans-splicing

- Replace the deficient protein (e.g. by overexpression of utrophin)

Cellular programmes that:

- Contribute new muscle cells: cell therapy.

Pharmacological programmes ("disease-modifiers") that:

- Reduce the destruction of muscle fibres (e.g. anti-proteases, growth factors, calcium channel blockers, NO donors)
- Reduce fibrosis: anti-fibrotic medication
- Offset the loss of muscle mass: anti-myostatin medication
- Improve muscle strength: ACE inhibitors
- Protect heart function: heart failure medication

Biophytis has also shown that Sarconeos acts through several of these approaches at the same time (by acting on strength, mass, fibrosis and muscle anabolism), which is not the case for most other programmes in development (see Table below).

Table: Products under development for DMD
Cell therapy ▪ CAP-1002 / Capricor (Phase I/II)
Gene therapy ▪ Viral vectors for mini- or micro-dystrophin: Solid Biosciences, Uniqure (Phase I) ▪ Epigenetic "rescue" of dystrophin function: Italfarmaco (Givinostat, Phase III) ▪ Antisense oligonucleotides: Sarepta (Eteplirsen, launched in the USA), Biomarin/Prosensa (BMN 44, programme discontinued in Phase II), NS Pharma (Phase II) ▪ Stop codon read-through: Ataluren (PTC Therapeutics, launched in Europe)
Dystrophin analogue ▪ Utrophine (Summit Therapeutics, Phase II)
Drug therapy ("disease modifiers") ▪ Anti-myostatin: Pfizer (Domoagrozumab, Phase II), Roche (RG 6206, Phase II/III) ▪ Analogue TGF-β1: Acceleron (ACE-083, in Phase II for facioscapulohumeral muscular dystrophy) ▪ MAS agonists: RASRx (preclinical), Biophytis (SARCONEOS, Phase I) ▪ Ryanodine (stabilisation of intracellular calcium channels): ARMGO Pharma (ARM 210, Phase I) ▪ Oxidative metabolism: SANTHERA (Idebenone, registered in Israel)

The most advanced pharmacological programmes – potentially direct competitors of Sarconeos – are the anti-myostatin programmes of Pfizer and Roche as well as the Santhera's Idebenone programme (Phase 3 completed, registered in Israel, but the marketing authorisation (MA) application in Europe has been rejected).

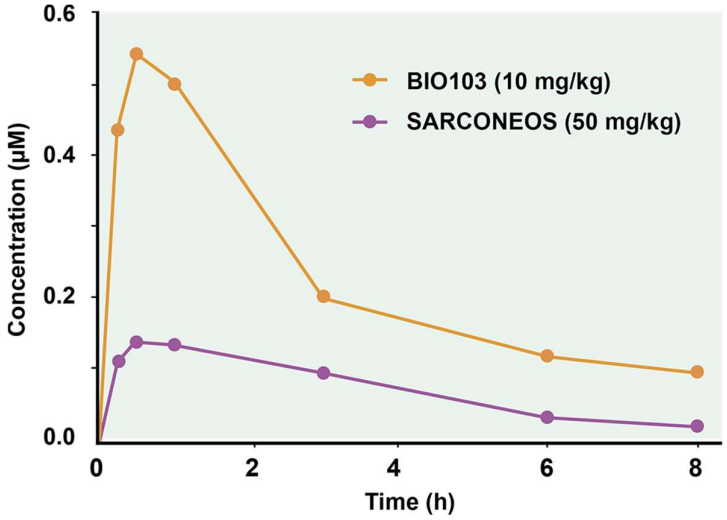
Competition in DMD is therefore expected to be intense. However, with experts and opinion leaders (as well as pharmaceutical companies) mobilising for the activation of MAS, and with

the volume of financial investments committed for this condition, this is a great therapeutic and commercial opportunity.

6.2.5 Development of BIO103 and other muscular dystrophies

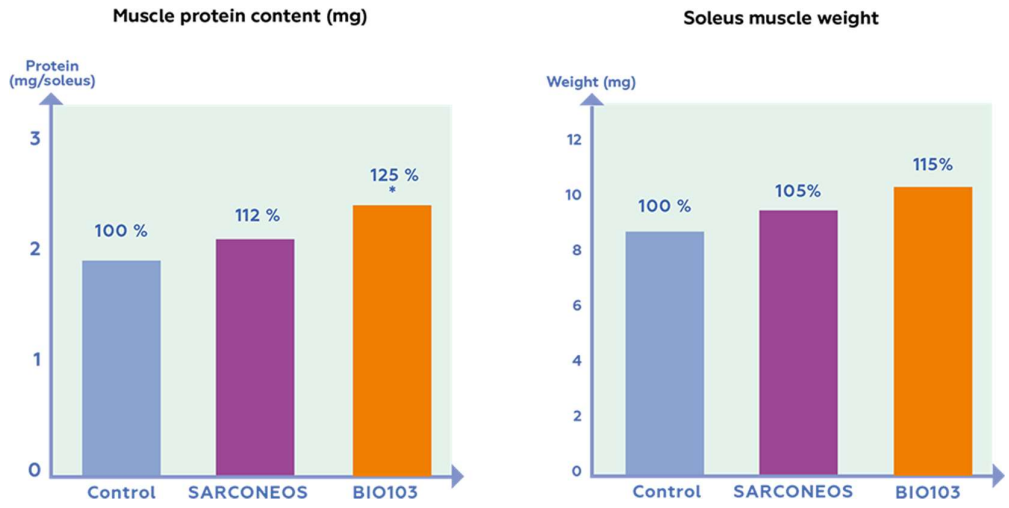
The development of BIO103 involved synthesising more than 150 new chemical molecules, derived through *hemi-synthesis* from *Sarconeos* in more than 5 chemical series, which were assessed in several *in vitro* tests (notably in the muscular cells C_2C_{12}), and *in vivo* (notably in the obese mouse model).

BIO103 was selected at the end of this process and showed an improved pharmacological profile in relation to *Sarconeos*, with higher bioavailability than *Sarconeos* and improved *in vivo* activity in certain animal models



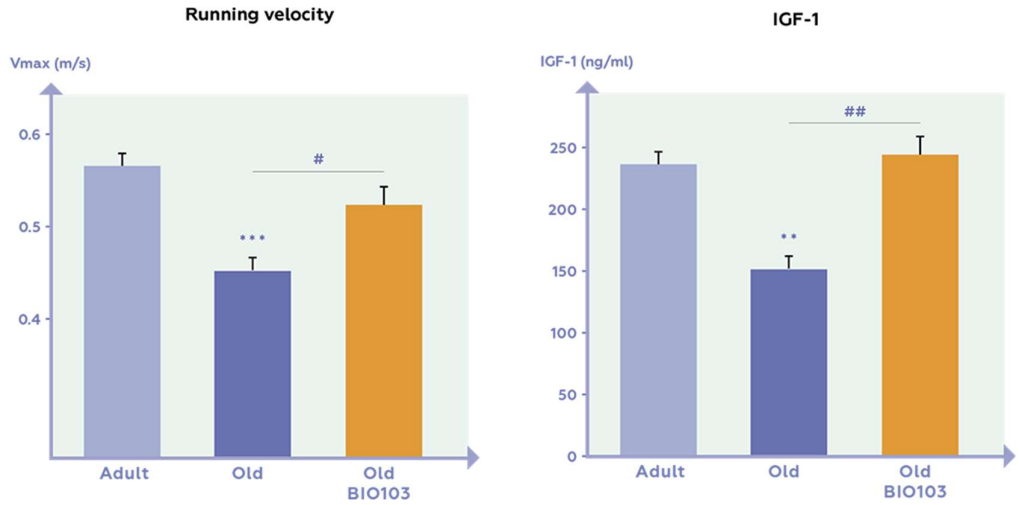
Comparison of BIO103 and Sarconeos plasma levels after oral administration

Similar to what we initially observed with BIO101, BIO103 has anabolic properties. These have been demonstrated in *in vitro* tests on myoblasts as well as in animal models involving young or old animals.



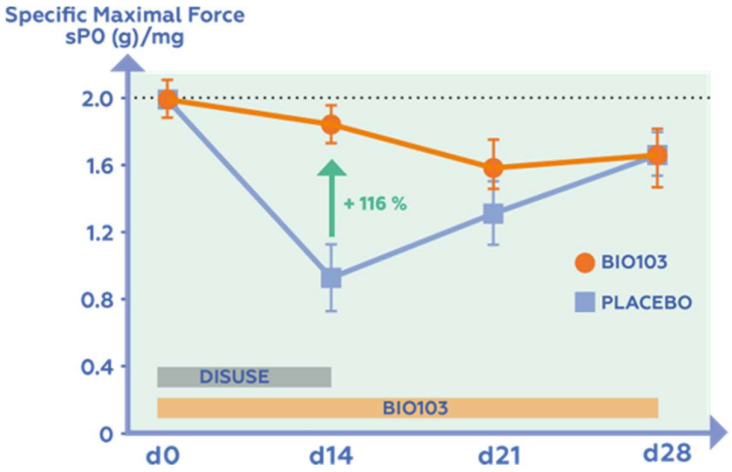
Increased protein content and weight of the soleus muscle after chronic oral treatment with BIO103 in young animals

A chronic oral treatment with BIO103 is responsible for a significant increase in physical performance in older animals. Similarly to what we observed in the case of Sarconeos, we have demonstrated in particular that treating older animals with BIO103 makes it possible to compensate for the significant loss of mobility due to age. This functional improvement is consistent with an increase in muscle mass and a significant increase in the plasma level of IGF-1 in animals treated with BIO103[103].



Increase in plasma levels of IGF-1 and motor performance of older animals after chronic oral treatment with BIO103

Several preclinical programmes are underway to evaluate the potential of BIO103 to treat muscle disorders other than sarcopenia. In particular, BIO103 has demonstrated potential in preventing the loss of muscle strength following immobilisation.



Preservation of maximal specific strength by BIO103 in immobilised mice

Biophytis also intends to evaluate whether BIO103 is safe to use in animals, by compiling a non-clinical regulatory file, and in humans by subsequently conducting an initial phase-1 study.

[103] Dilda P.J., Foucault A.S., Raynal S., Carbonne C., Durand J.D., Veillet S., Dioh W., Lafont R. (2017). BIO103, a second-generation compound for the treatment of sarcopenia. From anabolic properties to the reversion of ageing-related functional loss. ICFSR 2017, 27-29 April, Barcelona. *The Journal of Frailty & Aging*. Abstract P217, 146

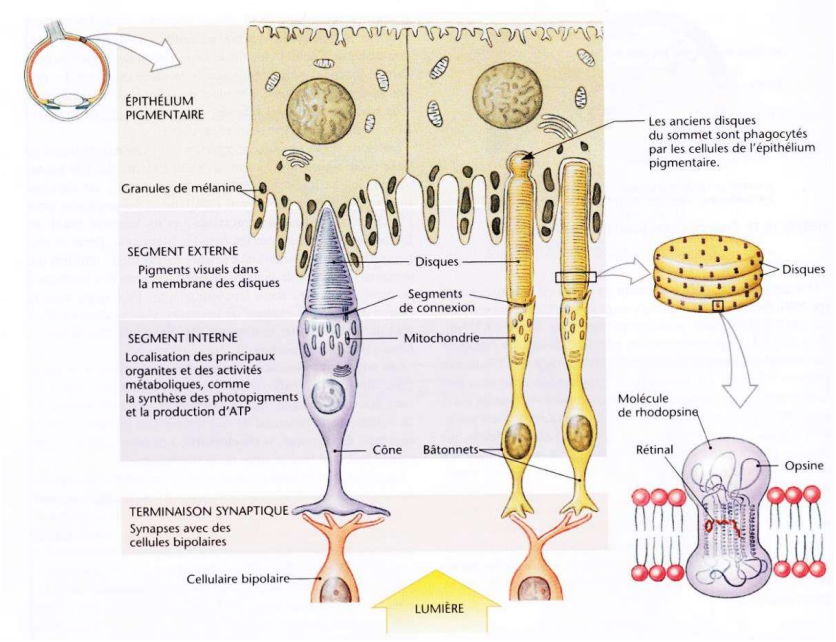
6.3 AGE-RELATED MACULAR DEGENERATION (AMD) PROGRAMME AND RETINOPATHIES

Biophytis has demonstrated that Macuneos protects the cells of the retina from the phototoxic effects of A2E in the presence of blue light (oxidative stress). Macuneos was then administered in two animal models, where retinal degeneration was induced by blue light, demonstrating significant preservation of the retina. In particular, Macuneos proved effective after intravitreal and intraperitoneal administration and following chronic oral administration at a dosage compatible with use in humans.

6.3.1 Retinal pathologies and PPAR receptors

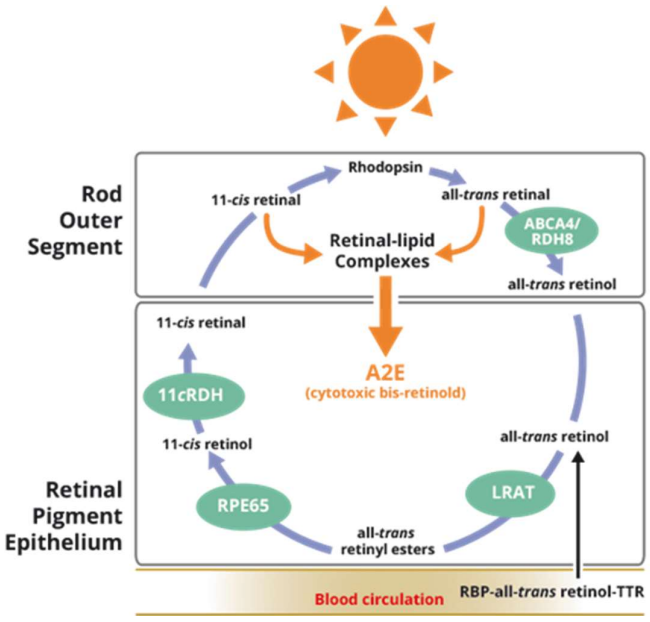
6.3.1.1 Basic data on the pathologies of the eye and retina

In the retina, the *photoreceptor* cells (cones and rods) are associated with a *retinal pigment epithelium* (*RPE*) which ensures the trophic and metabolic functions.
RPE cells have significant *phagocytic activity*, which ensures the renewal of the distal extremities of the photoreceptor cells, thereby contributing to the renewal of the photoreceptor structures (cones and rods).



The connections between the photoreceptors and the retinal pigment epithelium (In "Human Physiology: An Integrated Approach", Dee Unglaub Silverthorn Ed., Pearson Education, 4th edition, 2007)
[Figure in French]

Rhodopsin, a complex made up of the protein opsin and *cis*-retinal, is responsible for photoreception. Under the effect of light, the retinal is *isomerised* and detaches from opsin, and the return to its original form, which is indispensable for its activity, triggers a sequence of complex reactions jointly made possible by the *photoreceptors* and the RPE



Modulation of the visual cycle: A Novel Therapeutic Approach for Treatment of GA in Dry AMD[104]

The different types of retinopathies (related to age or diabetes or a genetic defect)

Photoreceptors and RPE cells are cells whose metabolic activity is very important and are somewhat "fragile". In fact, we know a whole range of retinal pathologies that cause visual impairment to varying degree and evolve at different paces, but which are likely to eventually lead to blindness. We will mention here:

- diabetic retinopathy
- oxygen-induced retinopathy
- macular degeneration (dry and exudative forms)
- Stargardt disease

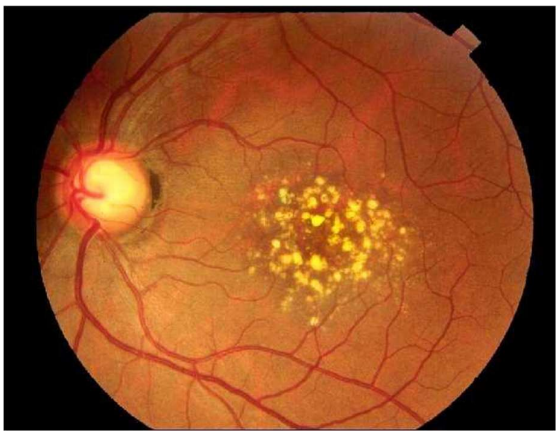
Diabetic retinopathy is a complication in patients with diabetes mellitus that affects the retina. It is manifested by an increased permeability of the capillaries, which causes haemorrhages and defects of irrigation/oxygenation of the retina (Allawi et al., 2015)[105].

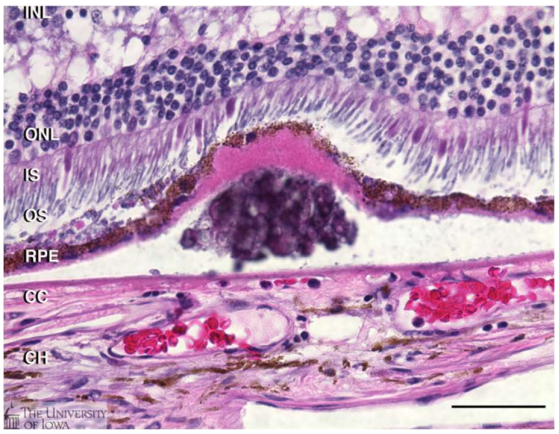
Oxygen-induced retinopathy or retinopathy of prematurity is a condition developed by premature infants exposed to an oxygen-enriched atmosphere and then returned to a normal level of oxygen. These undergo both oxidative stress followed by an under-oxygenation phase that causes significant and poorly controlled neovascularisation (Capozzi et al., 2013)[106].

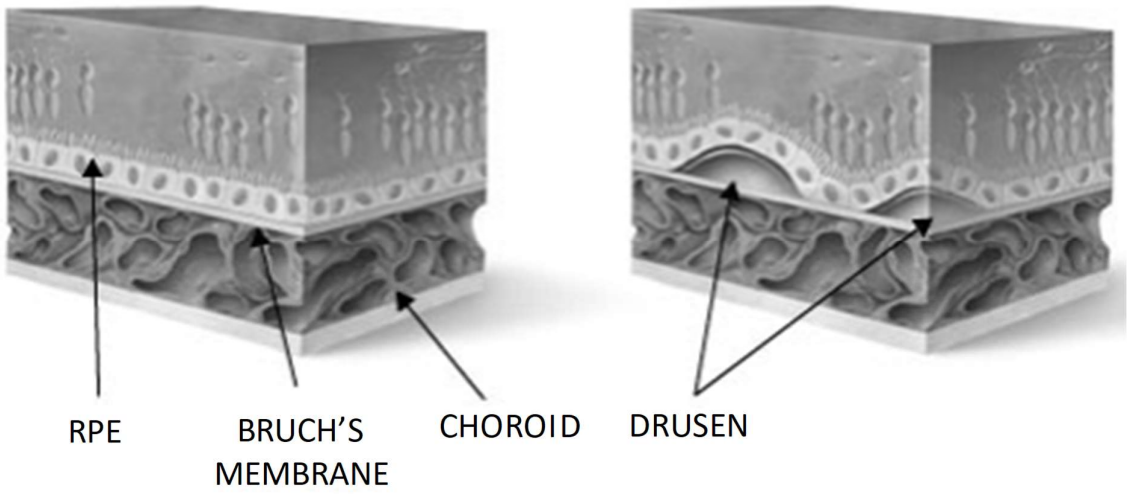
AMD is a multi-factorial disease, related to aging with several associated risk factors, such as the genetic context, gender, diet, hypertension, smoking and sun exposure. AMD is linked to

[104] Mata NL, Kubota R, Dugel PU 2013 Visual Cycle Modulation: A Novel Therapeutic Approach For Treatment of GA In Dry AMD, Retinal Physician, 10: 20-23.
[105] Allawi L, Okhravi N, Lin PF, Koukkoulli A. 2015. Systemic approaches and considerations in the management of diabetic retinopathy. *JSM Ophthalmology*, 3 (3), 1035-1038.
[106] Capozzi ME, McCollum GW, Savage SR, Penn JS. 2013 Peroxisome proliferator-activated receptor-β/δregulates angiogenic cell behaviors and oxygen-induced retinopathy. *Invest Ophthalmol Vis Sci*, 54 (6): 4197-4207.

the accumulation in the RPE of A2E, a by-product of the visual cycle (formed by the dimerization of retinol with an ethanolamine molecule). The accumulation of A2E will disrupt the phagocytosis and digestion activity of RPE cells which accumulate waste. This waste accumulates between the basal membrane of RPE cells and the Bruch membrane which separates the RPE from the choroid, thus forming fluorescent deposits called Drüsen, which deforms the retina and the way images are perceived.







These deposits (Drüsen) contain mainly various forms of A2E molecules that are significantly photo-oxidizable (Marie et al., 2018)[107], and are the origin of inflammatory responses which lead to further disruption of the *RPE* cells. The death of these cells is followed by the death of the *photoreceptors* with which they were associated and the gradual loss of central vision.

Wet, or exudative, AMD is a rarer form of the disease that may result from the previous one and results in haemorrhagic neovascularisation that can quickly cause blindness (Del V Cano et al., 2008)[108].

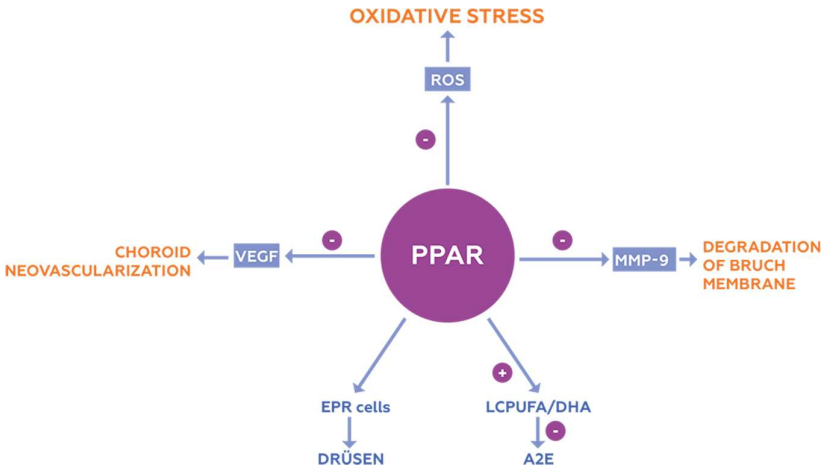
[107] Marie M, Bigot K, Angebault C, Barrau C, Gondoin P, Pagan D, Fouquet S, Villette T, Sahel J-A, Lenaers G, Picaud S. 2018. Light action spectrum on oxidative stress and mitochondrial damage in A2E-loaded retinal pigment epithelium cells. *Cell Death and Disease* 9: art. 287.
[108] Del V Cano M, Gehlbach PL. 2008 PPAR-alpha ligands as potential therapeutic agents for wet age-related macular degeneration. *PPAR Res,* 2008: 821592

Stargardt disease is a pathology of genetic origin affecting the ABCA4 gene that codes for a transporter involved in the visual cycle. This deficiency causes an early accumulation of A2E and is therefore similar to early-stage dry AMD (Lu et al., 2017)[109]. Although the specific mechanisms involved in the onset of different types of age-related retinal disorders differ, evidence points to *oxidative stress* and the resulting *inflammation* as significant contributing factors to the pathogenesis of such disorders.

The role of PPARs

PPARs (peroxisome proliferator activated receptors) are nuclear receptors divided into three classes (PPARα, PPARβ/δ and PPARγ). Various bibliographic data assign them a role in the protection of the retina in various retinal pathologies. In the case of diabetic retinopathy, the effect of fenofibrates (PPARα agonists) is well documented (Chen et al., 2017, Deng et al., 2017)[110]. PPARα also plays a protective role in oxygen-induced retinopathy.

Herzlich et al. (2008)[111] have proposed a general scheme describing the role of PPARs in the protection against AMD, in which they do not specify the class concerned:



A closer look leads us to assign this scheme to PPARγ and wet AMD in particular, but in some ways it is likely to also apply to dry AMD. The filed of PPARs is complex because one is dealing with a family of receptors that share several ligands in common. In addition, important interactions exist between the 3 PPARs, and some authors have in fact posited that they act in triads (Aleshin & Reiser, 2013)[112].

[109] Lu LJ, Liu J, Adelman RA. 2017 Novel therapeutics for Stargardt disease. Graefes Arch Clin Exp Ophthalmol 255 (6): 1057-1062.

[110] Chen Q, Qiu F, Zhou K, Matlock HG, Takahashi Y, Rajala RVS, Yang Y, Moran E, Ma JX. 2017 Pathogenic role of microRNA-21 in diabetic retinopathy through downregulation of PPAR□. *Diabetes*, 66 (6): 1671-1682. Deng G, Moran EP, Cheng R, Matlock G, Zhou K, Loran D, Chen D, Yu Q, Ma JX. 2017 Therapeutic effects of a novel agonist of peroxisome proliferator-activated receptor alpha for the treatment of diabetic retinopathy. *Invest Ophthalmol Vis Sci*, 58 (12): 5030-5042.

[111] Herzlich AA, Tuo J, Chan CC. 2008. Peroxisome proliferator-activated receptor and age-related macular degeneration. *PPAR Research*, article ID 389507.

[112] Aleshin S & Reiser G. 2013. Role of the peroxisome proliferator-activated receptors (PPARs)-α, β/δ and γ triad in regulation of reactive oxygen species signalling in brain. *Biol. Chem.* 394 (12): 1553-1570.

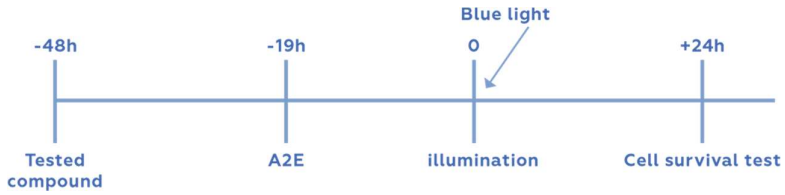
6.3.2 Mechanism of actions and proofs of concept

Biophytis started from the hypothesis that the accumulation of A2E in the retina is responsible for AMD. Biophytis has demonstrated that *Macuneos* protects the cells of the retina from the phototoxic effects of A2E in the presence of blue light (*oxidative stress*), reduces the accumulation of this phototoxic molecule in the animal models and thus slows down the retinal degeneration process, while maintaining the electrical activity of the retina (measured by electroretinography).

These different mechanisms are in the process of being studied by means of different molecular and pharmacological approaches.

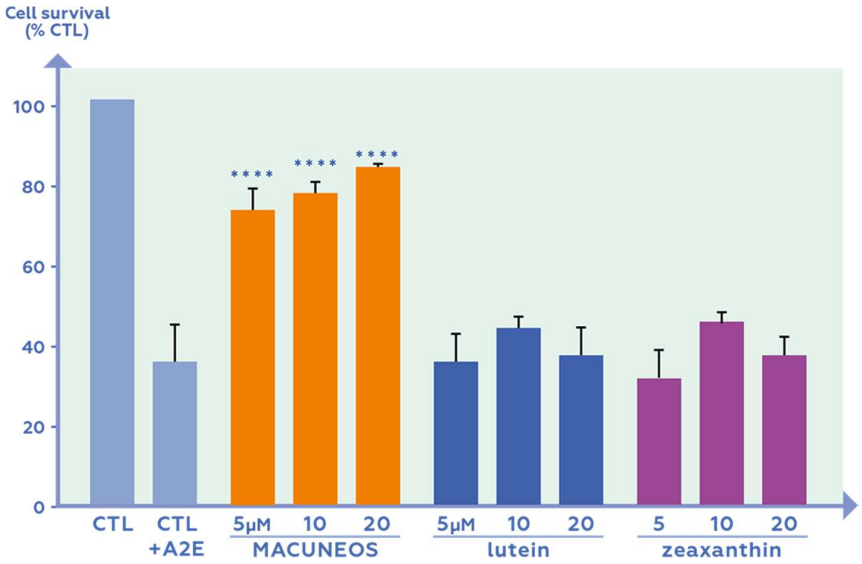
- ***Experiments conducted with EPR primary cultures***

A cellular model comprising primary cultures of pig *retinal pigment epithelium* loaded in A2E and then illuminated with blue light (BL) was developed by the Institute of Vision and used to select the most active natural principles and characterize *Macuneos*. These cells were successively placed in the presence of the compounds to be tested, then A2E, and their survival was measured 24 hours after illumination (diagram). Cells cultivated without A2E served as a negative control.



The compounds are initially tested at a concentration of 20 µM and, depending on the results obtained, with a series of successive dilutions.

Macuneos significantly protects RPE cells exposed to blue light and A2E, and more significantly than those compounds (lutein and zeaxanthin) where the AREDS studies have shown that their deficiency was linked to a high risk of developing dry AMD.

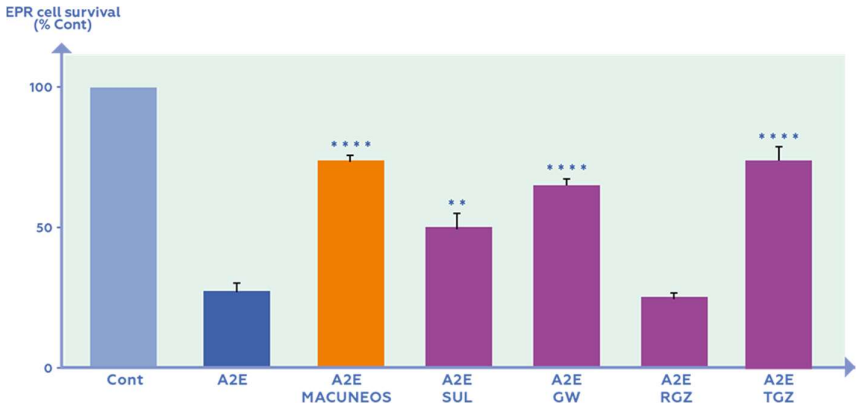


Survival of RPE cells achieved by Macuneos in different concentrations
Comparison with lutein and zeaxanthin at the same concentrations

Measuring the survival rates obtained with several doses of the tested substances enables comparisons to be made between the compounds and to select the most active compounds. This approach resulted in the selection of *Macuneos*, a natural active ingredient, and BIO203, a synthetic molecule that is akin to a natural active ingredient.

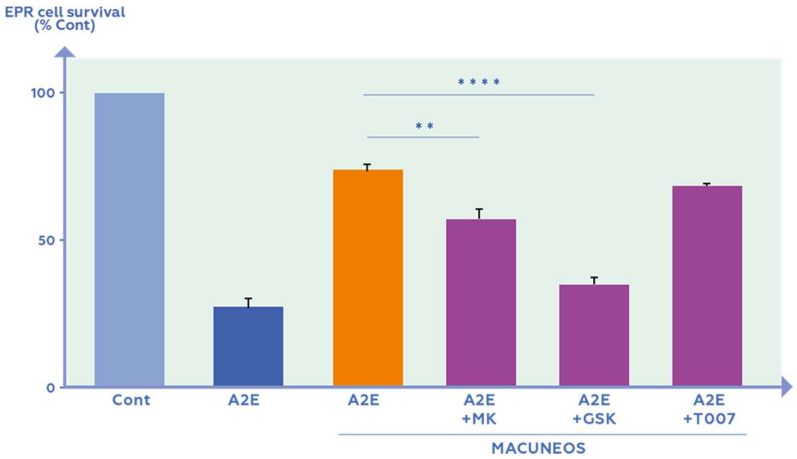
The effects of *Macuneos* involve PPAR receptors. Studies conducted by Biophytis make it possible to specify that Macuneos binds to PPARγ, but does not seem to activate it, while it also interacts with PPARα and PPARβ/δ. The photoprotective effects of Macuneos are also reproduced by PPARα and PPARβ/δ agonists and inhibited by antagonists of the latter.

The study of the effects of PPAR agonists on photoprotection against A2E shows a protective effect of sulindac (a PPARα agonist) and a greater effect of GW0742 (a PPARβ/δ agonist). On the other hand, a pure PPARγ agonist does not provide protection in our model.



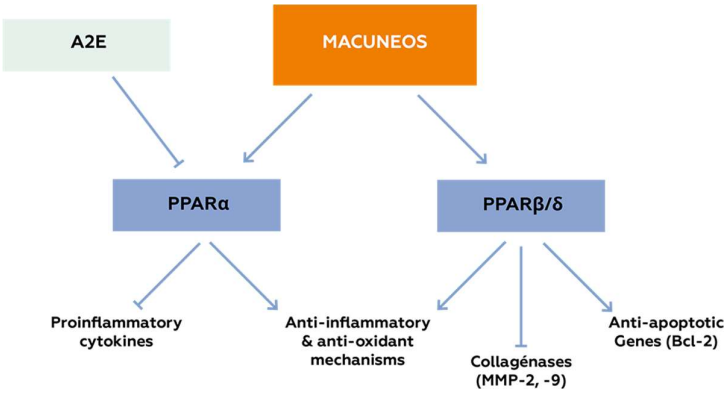
Protective effects of a PPARα agonist (Sulindac) and a PPARβ/δ agonist (GW0742); protective effect of troglitazone (combined PPARα/γ agonist), but not rosiglitazone (PPARγ selective agonist).

The study of the effects of PPAR antagonists on photoprotection against A2E shows that PPARα antagonists weakly and PPARβ/δ antagonists in particular may inhibit the photoprotective effects of Macuneos.



Inhibitory effect of a PPARα antagonist (MK886) and a PPARβ/δ antagonist (GSK3787). Absence of an effect of an inhibitor of PPARγ (T0070907)

In the light of these results, combined with other data, we propose the following scheme:



Macuneos (BIO201) is an agonist of PPAR involved in protecting retinal cells

Macuneos provides protection to A2E-loaded RPE cells in the presence of blue light. The protection conferred by *Macuneos* may be considered at several levels which are mutually compatible:

- *Macuneos* acts as a filter by absorbing blue light
- *Macuneos* reduces the (exogenous) uptake of A2E by the RPE cells (or stimulates its rejection)
- *Macuneos* exhibits antioxidant activity by neutralizing ROS (Tokarz et al., 2013)[113] or stimulates the *antioxidant* defence enzymes
- *Macuneos* has anti-inflammatory and anti-VEGF (vascular endothelial growth factor) properties
- *Macuneos* protects against *apoptosis*

6.3.3 Age-related macular degeneration (AMD)

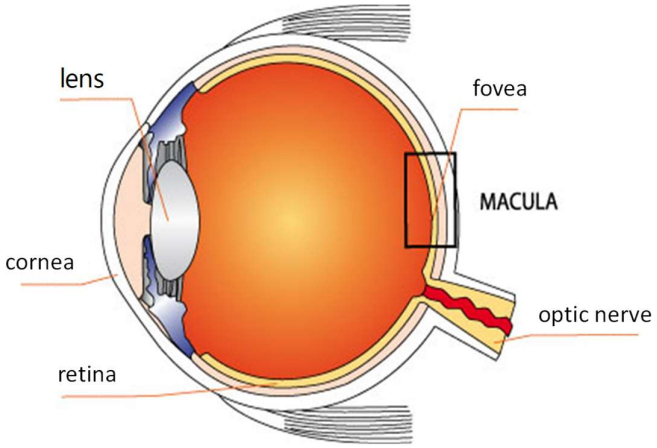
AMD affects the central part of the retina, known as the macula, leading to serious visual impairment and irreversible loss of central vision. The disease is rare before the age of 65, but its prevalence increases exponentially with age. The treatment of early-stage dry AMD called age-related maculopathy (ARM) and late-stage dry AMD called geographic atrophy (GA) represents a potential global market of €30 billion.

6.3.3.1 Epidemiology

Age-related macular degeneration (AMD) causes an irreversible a loss of central vision and gradually leads to blindness. AMD is the leading cause of visual impairment in ageing populations older than 50 years, particularly in Europe and North America. The main risk factors for AMD are age and smoking. Other factors are clearly indicated, particularly genetic factors, which would explain almost 50% of the *phenotypic* variability in several association studies (Priya *et al*. 2012)[114]. The major polymorphism identified as a risk factor for AMD is

[113] Tokarz P, Kaarniranta K, Blasiak J. 2013. Role of antioxidant enzymes and small molecular weight antioxidants in the pathogenesis of age-related macular degeneration (AMD). *Biogerontology* 14: 461-482.
[114] Priya RR, Chew EY, Swaroop A. 2012. Genetic studies of age-related macular degeneration: lessons, challenges and opportunities for disease management. *Ophthalmology*, 119 (12): 2526-2536.

related to the Complement Factor H (CFH) gene that increases, by a factor of 3 to 6, the risk of developing AMD in homozygous carriers (Edwards *et al*. 2005[115]; Haines *et a*l. 2005[116]; Klein *et al*. 2005[117]; Maller *et al*. 2006[118]). Other genetic polymorphisms have been identified in complement genes in particular, which clearly means inflammation plays a part in the pathophysiological process of AMD. Amongst genetic polymorphisms associated with an increased risk of developing AMD (Campagne *et al.* 2014 [119]) one finds polymorphisms of the ARMS2 / HTRA1 genes (Dewan et al. 2006[120]) even though the exact function of these two genes in AMD remains unknown. In conjunction with oxidative stress, all the pathophysiological mechanisms involved in AMD result in the accumulation of A2E in subretinal deposits called Drüsen.



AMD affects the central part of the retina, known as the macula, leading to serious visual impairment and irreversible loss of central vision. The macular function is responsible for central vision and its sharpness is provided by the densely packed *photoreceptor* cells known as cones. The early stage of AMD is characterised by deposits called *Drüsen*, made up of A2E accumulation in particular, which only marginally affect vision. The patient gradually notices some deterioration in his/her central vision, which is then diagnosed by the ophthalmologist; this is the intermediate stage or age-related maculopathy (ARM). Later phases include two forms of AMD: wet AMD, also called exudative or neovascular AMD, characterised by the growth of choroidal neovessels in the subretinal space, or *geographic atrophy* (dry AMD), which is characterised by the loss of retinin pigment epithelium cells and photoreceptors which are the cells needed for the visual cycle. Dry AMD is much more common than wet AMD (Smith

[115] Edwards, A.O., R. Ritter, 3rd, K.J. Abel, A. Manning, C. Panhuysen, and L.A. Farrer. 2005 Complement factor H polymorphism and age-related macular degeneration. *Science*. 308:421-424.
[116] Haines, J.L., M.A. Hauser, S. Schmidt, W.K. Scott, L.M. Olson, P. Gallins, K.L. Spencer, S.Y. Kwan, M. Noureddine, J.R. Gilbert, N. Schnetz-Boutaud, A. Agarwal, E.A. Postel, and M.A. Pericak-Vance. 2005 Complement factor H variant increases the risk of age-related macular degeneration. *Science*. 308:419-421.
[117] Klein, R.J., C. Zeiss, E.Y. Chew, J.Y. Tsai, R.S. Sackler, C. Haynes, A.K. Henning, J.P. SanGiovanni, S.M. Mane, S.T. Mayne, M.B. Bracken, F.L. Ferris, J. Ott, C. Barnstable, and J. Hoh. 2005 Complement factor H polymorphism in age-related macular degeneration. *Science*. 308:385-389.
[118] Maller, J., S. George, S. Purcell, J. Fagerness, D. Altshuler, M.J. Daly, and J.M. Seddon. 2006 Common variation in three genes, including a noncoding variant in CFH, strongly influences risk of age-related macular degeneration. *Nature genetics*. 38:1055-1059.
[119] Campagne, M., J. LeCouter, B.L. Yaspan, and W. Ye. 2014 Mechanisms of age-related macular degeneration and therapeutic opportunities. *Journal of Pathology*. 232:151-164.
[120] Dewan, A., M. Liu, S. Hartman, S.S. Zhang, D.T. Liu, C. Zhao, P.O. Tam, W.M. Chan, D.S. Lam, M. Snyder, C. Barnstable, C.P. Pang, and J. Hoh. 2006 HTRA1 promoter polymorphism in wet age-related macular degeneration. *Science*. 314:989-992.

et al. 2001)[121]. The last stages of these two forms lead to the destruction of the neurosensory retina in the macular region; the progression of exudative (wet) AMD can lead to complete blindness within a few weeks, while the progression of dry AMD is generally slow.

Images illustrating the stages of the disease

AMD in its "wet" and "dry" forms currently affects 30 million people throughout the world. It is estimated that around 500,000 new cases of wet AMD are diagnosed every year throughout the world, and this figure is likely to increase dramatically as the population ages (Scott et al., 1999)[122]. It is estimated that more than 60 million people throughout the world, including 2 million in France, will be affected in 2050, making AMD a major health concern for elderly populations. The disease is rare before the age of 65, but its prevalence increases exponentially with age. The prevalence of the early stages is 1.6% in individuals over the age of 75 (Klein et al. 1997)[123], rising to almost 5% in those aged 75-84, and the frequency increases to 13% in persons aged 85 and over in the population studies. Legal blindness frequently develops over time, because the disease tends to become bilateral in 30% - 40% of patients within 5 years.

Only exudative (or wet) AMD is treated with substantial anti-VEGF intravitreal injections (Avastin®, Lucentis®, Eyla®) taken on a monthly basis, which are very expensive (costing €12,000/year). On the other hand, although "dry" or atrophic AMD represents more than 80% of patients, there is currently no treatment for this form of the disease. Dry AMD (early- and late-onset) thus represents a potential global market of €30 billion in 2023[124]. A laboratory marketing the drug developed by Biophytis under licence would be able to capture a significant share of this market and would pay royalties ranging from 5% to 15% of its turnover to Biophytis.

Serious visual impairment has an enormous impact on the quality of life (Williams et al., 1998)[125]. Individuals who present with a significant reduction in their visual acuity have limited ability to perform everyday tasks and their mobility is restricted as well. Patients with AMD claim that their general quality of life is 20%-25% below that of healthy elderly adults. Psychosocial distress is also associated with AMD, with higher numbers of patients suffering

[121] Smith W, Assink J, Klein R, Mitchell P, Klaver CC, Klein BE, Hofman A, Jensen S, Wang JJ, de Jong PT. 2001 Risk factors for age-related macular degeneration: Pooled findings from three continents. *Ophthalmology*, 108 (4): 697-704.
[122] Scott IU, Smoddy WE, Schiffman J, Feuer WJ, Pappas CJ. 1999. Quality of lire of low-vision patients and the impact of low-vision services. *Am J Ophthalmol*, 128 (1): 54-62.
[123] Klein R, Klein BEK, Jensen SC, Meuer SM, 1997. The five-year incidence and progression of age-related maculopathy: The Beaver Dam Eye Study. *Ophthalmology*, 104 (1): 7-21.
[124] Visiongain. Macular Degeneration (AMD) and Diabetic Retinopathy (DR): World Drug Market 2013–2023. (2012).
[125] Williams RA, Brody BL, Thomas RG, Kaplan RM, Brown SI. 1998. The psychological impact of macular degeneration. *Arch Ophthalmol*, 116: 514-520.

from emotional distress and depression than other elderly adults (Sahel et al, 2007[126]). The cost to society is only now beginning to be revealed. In view of the enormous medical and personnel costs as well as the costs to society and the economy of AMD, there is an urgent need to develop new therapeutic and preventative strategies for AMD.

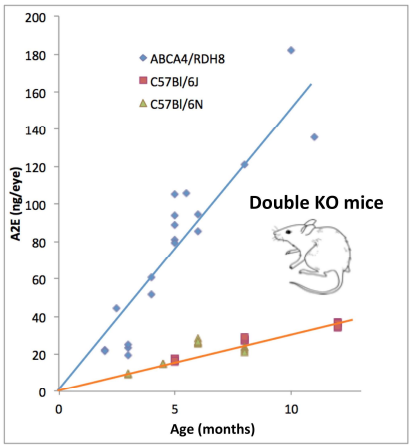
6.3.3.2 *In vivo* proof of concept

The effectiveness of *Macuneos* in slowing down retinal degeneration under the effect of blue light has been evaluated in two animal models for AMD: the mouse and rat.

Reference	Animal Model	Results
Fontaine et al., 2016[127]	Mouse double KO (Abca4-/-/Rdh8-/-) Oral administration, 3 months	Maintenance of a partially normal electroretinogram (A and B waves) Reduction in the accumulation of A2E in the eyes
Fontaine et al., 2016[120]	Mouse double KO (Abca4-/-/Rdh8-/-) Intravitreal administration only Illumination (blue light)	Maintenance of a partially normal electroretinogram (A and B waves) Partial preservation of the integrity of the retina (number of layers of *photoreceptor* nuclei)
Fontaine et al., 2016[120]	Rat Wistar Intra-peritoneal injections (4) and illumination (blue light)	Maintenance of electrical activity of the retina Preservation of *photoreceptors*

(1)- The first animal model used mice in which two genes encoding the proteins involved in the *visual pigment* cycle were absent: the ABCA4 transporter and the retinol dehydrogenase RDH8 (see above). This model was developed by Maeda et al. (2008)[128] and is used under licence.

[126] Sahel JA, Bandello F, Augustin A, Maurel F, Negrini C, Berdeaux GH for the MICMAC Study Group. 2007. Health-related quality of life and utility in patients with age-related macular degeneration. *Arch Ophthalmol.*, 125 (7): 945-951.
[127] Fontaine V., Monteiro E, Brazhnikova E, Lesage L, Balducci C, Guibout L, Feraille L, Elena PP, Sahel JA, Veillet S, Lafont R. 2016. Norbixin protects retinal pigmented epithelium and photoreceptors against A2E-mediated phototoxicity *in vitro* and *in vivo*. PLoS ONE DOI: 10.1371/journal.pone. 0167793,
[128] Maeda A, Maeda T, Golczak M, Palczewski K. 2008. Retinopathy in mice induced by disrupted all-*trans*-retinal clearance. *J Biol Chem*, 283: 26684-26693.

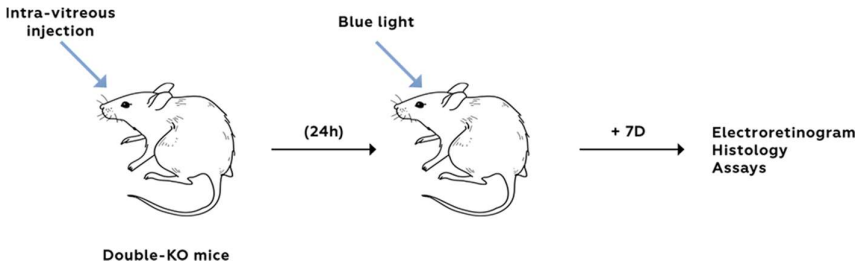


Accumulation of A2E in the animal model for AMD (Mouse ABCA4$^{-/-}$ RDH8$^{-/-}$)

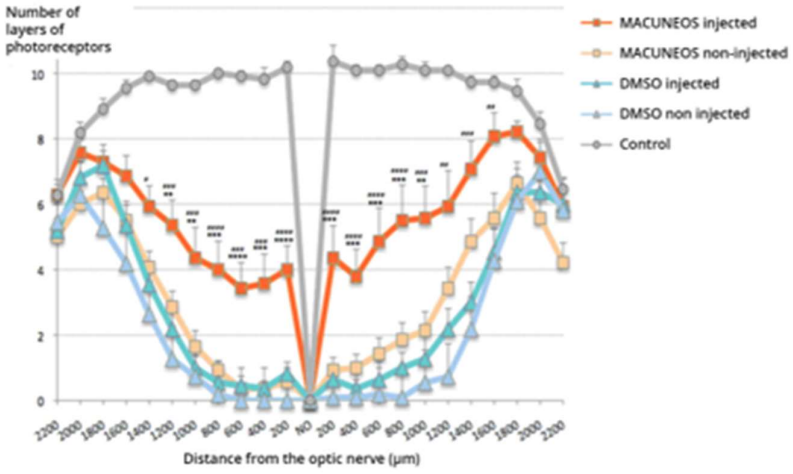
These mice accumulate significant quantities of A2E in the retina early on, making them very sensitive to blue light, and they were consequently a model for studying AMD in accordance with the scientific hypothesis formulated by Biophytis.

These mice were used in two complementary ways:

- ✓ By intra-vitreous injections of the selected compounds:

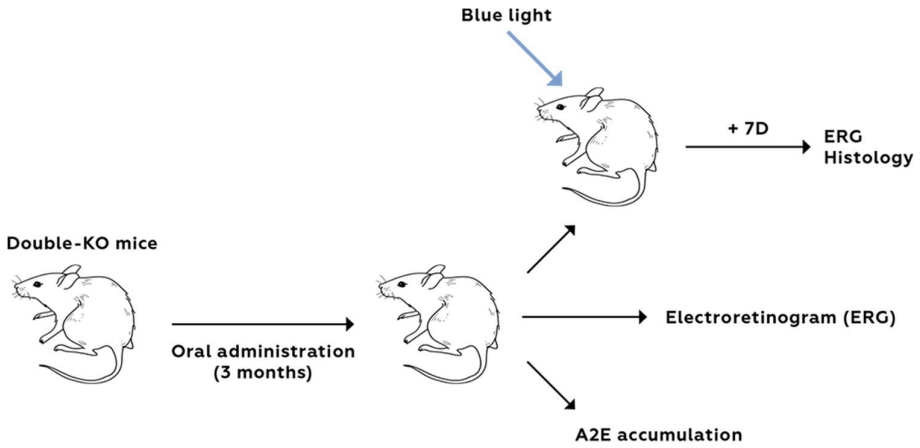


The mice are then subjected to intense blue light. Seven days after the irradiation, an electroretinogram is performed, which makes it possible to measure the retinal function. In addition, a histological analysis makes it possible to assess the number of residual layers of photoreceptors. In this test, *Macuneos* exhibited significant protective activity.

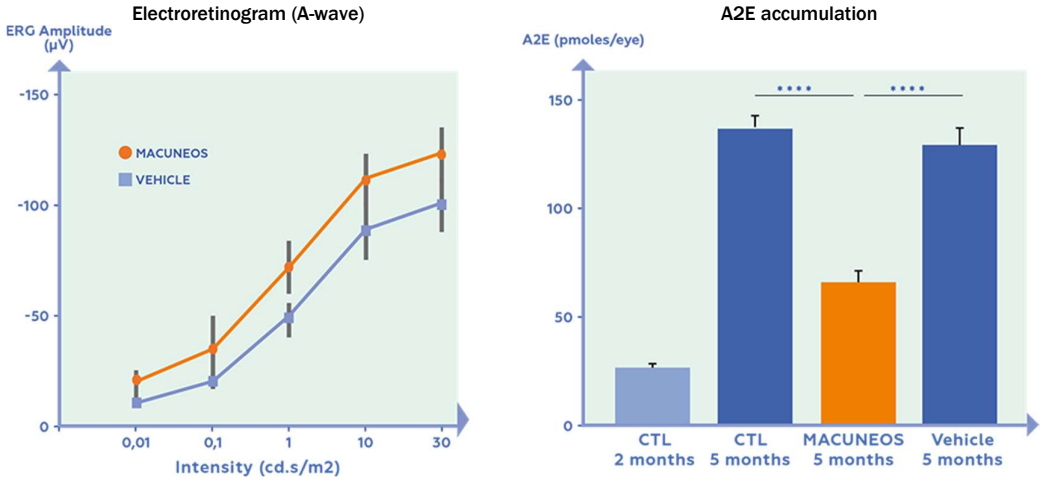


Number of layers of photoreceptors after illumination in mice ABCA4$^{-/-}$ RDH8$^{-/-}$ treated with Macuneos or a control, an intravitreal injection

✓ by chronic oral administration of *Macuneos*, included in the animal feed, over a 3-month period.



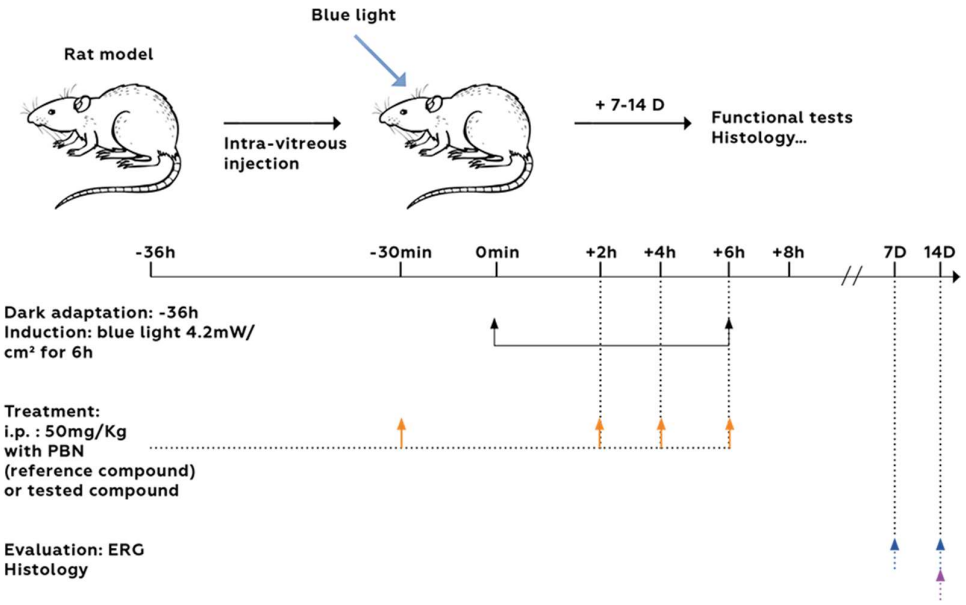
In the treated animals, *Macuneos* proved to be effective. The treated animals showed a less degraded *electroretinogram* than the untreated animals. On the other hand, the eyes of animals who ingested Macuneos contained quantities of A2E that were significantly lower than those measured in untreated animals.



Effects of chronic oral administration of Macuneos on A-Waves of ABCA4$^{-/-}$ RDH8$^{-/-}$ mice and accumulation of A2E in their eyes

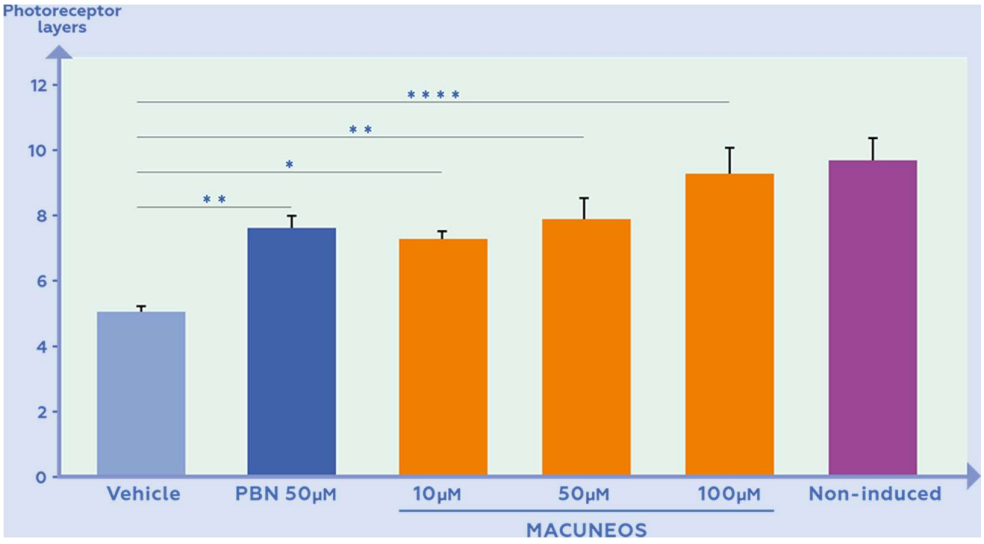
(2)- The second model for AMD was the "blue light" rat model, using normal albino rats in a test for phototoxicity induced by blue light.

In this model, the compounds to be tested were injected intraperitoneally before and during exposure to blue light. An *antioxidant compound*, *PBN* (phenyl-*N*-*tert*-butylnitrone) was used as a positive control and the activity of the compounds to be tested were thus compared to the activity of *PBN*.

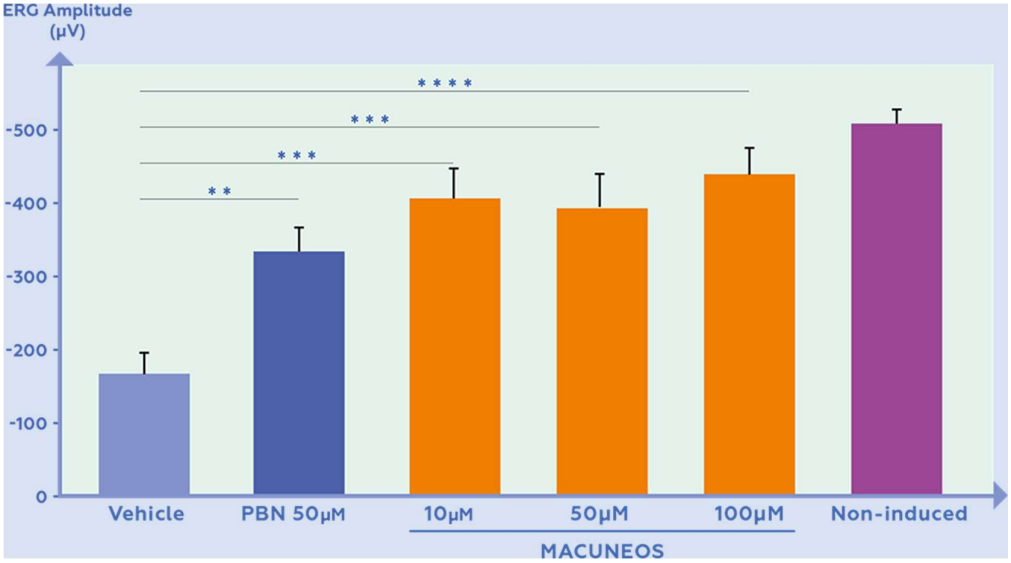


In this test, the compound *Macuneos* exhibited activity that was equivalent to the activity of *PBN*. Macuneos provides significant protection at the structural level (number of layers of photoreceptors) and this results in an improvement in the function of the retina (electroretinogram).

Photoreceptor layers



Electroretinogram – A-wave



Number of layers of photoreceptors and ERG (A waves) in the animal model for AMD (rat Blue Light rat model with intraperitoneal injections).

Macuneos has thus demonstrated its in vitro and in vivo effectiveness and has proven to be more effective than the molecules previously described, in particular other carotenoids. It is also more effective than the reference molecule (PBN) in blue light damage tests in rats.

Macuneos is already suitable for oral administration as it is well absorbed from the gastrointestinal tract, reaching the retina, by following a dose schedule that is compatible with daily oral administration in humans ranging from several dozen mg/day to several hundred mg/day.

6.3.3.3 MACA Clinical Programme

- ***Clinical study with healthy volunteers***

The effects of a concentrated, titrated vegetable extract were assessed in a clinical study conducted by a French *CRO* on healthy volunteers after oral chronic administration over a 3-month period, confirming the absence of toxicity (no serious adverse events associated with the product observed) at the dose studied (35 mg/day). The natural active ingredient may be administered to the general population in doses of up to 300 mg/day and its circulating *metabolite* in humans, on the basis of *Macuneos*, up to 42 mg/day.

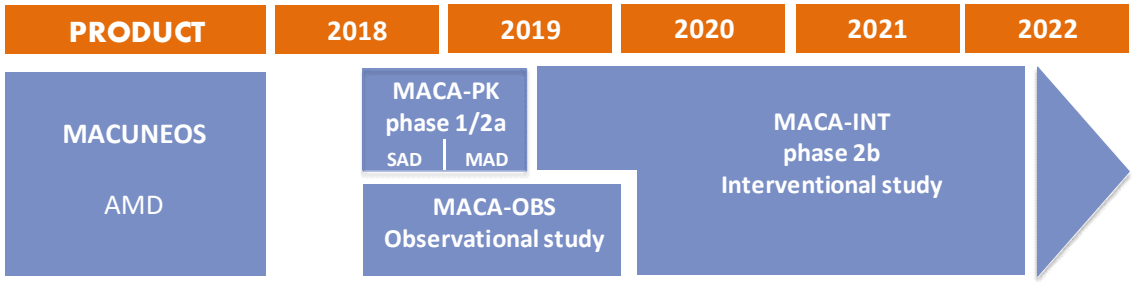
Reference	Dosage	Volunteers & Protocol	Results
Dioh *et al*, proprietary	35 mg/day	47 healthy volunteers (23 verum, 24 placebo) 20- 50 years 3 months	No serious adverse events *MACUNEOS* is the principal circulating *metabolite*

Next stages of development for Macuneos (MACA programme)

The next steps in the development of *Macuneos* aim to determine the therapeutic dose that is effective in slowing disease progression in patients with AMD – the phase 2b MACA programme. Two studies set to begin in the second half of 2018 will be conducted simultaneously prior to the MACA-INT interventional study:

- A pharmacokinetic and safety study on healthy volunteers and elderly patients with intermediate AMD (MACA-PK)
- An observational study (MACA-OBS) that will be conducted in Europe and the United States, aimed at characterising the target population, and at pre-recruiting patients for the MACA-INT study

This new clinical-regulatory programme, in addition to collecting patient safety data, is aimed at (i) obtaining clinical activity data as from 2018, (ii) measuring the pharmacokinetics of Macuneos specifically in patients with AMD, before confirming the doses to be administered, (iii) accurately characterising the population with the disease, before confirming the eligibility criteria of the patients that will be included in the MACA-INT study.



MACA-PK Study

MACA-PK is a randomised, double-blind, placebo-controlled study that will provide on one hand a phase 1 objective which consists of evaluating the safety and pharmacokinetics of Macuneos in 2 stages: Single Ascending Dose (SAD), then Multiple Ascending Dose (MAD). On the other hand, it will cover a phase 2a objective, as the MAD will be undertaken in patients, which will allow the assessment of the first measurements of the biological activity of Macueos in patients affected by AMD. It should result in the first pharmokinetic and safety data for healthy volunteers in 2018 and the first indications of clinical activity in patients affected by AMD from 2019.

The results for safety, pharmokinetics and pharmacodynamics will permit the design of the interventinal study of Phase 2 MACA-INT. Biophytis has called on CRO SGS Life Science Services, which is assisted by the CRO Appletree Medical Group to carry out this study. Ten clinical investigation centres in France, the United Kingdom, Belgium and Hungary are participating in this study. The design of MACA-PK provides for a two-stage process: SAD or “Single Ascending Dose” in healthy volunteers; then MAD or “Multiple Ascending Doses” in patients with dry AMD.

- SAD phase: 40 healthy volunteers over 55 years of age, divided into 5 cohorts of eight patients each, will receive a series of single increasing doses of Macuneos. In each cohort 6 patients will receive one dose of *Macuneos* and 2 patients will receive a placebo. The SAD investigation phase is planned for the second half of 2018 and will be carried out in a specialised phase-1 centre in Belgium in Antwerp. Analyses of

ophthalmological parameters will be performed in a second specialised centre in the same city.

- MAD phase: Three doses of *Macuneos* selected from the SAD data and having the most advantageous safety and pharmacokinetics profiles will be successively tested for 84 days in patients with AMD. The MAD clinical investigation phase will take place in 2019. It includes the assessment of several pharmacodynamic parameters including microperimetry, ERG (electroretinography), dark adaptation, contrast sensitivity, and visual acuity in low light conditions. Patients in MAD will be recruited in 5 French centres, including the CIC Quinze-Vingt Hospital in Paris, 3 centres in the United Kingdom, 1 centre in Hungary and a centre in Belgium.

MACA-OBS Study

MACA-OBS is an observational clinical study that consists of characterising the *Macuneos* treatment target *population* – patients with intermediate dry AMD– and pre-recruiting about one-third of patients who, if they consent, will then be included in the MACA-INT phase-2b study. 120 patients will be recruited from a dozen reference centres in the United States and Europe, including the CIC Quinze-Vingt Hospital in Paris, the Massachusetts Eye and Ear Infirmary (Harvard Medical School) in Boston, the University of Pittsburgh and John Hopkins University in Baltimore. The patients will be monitored for 12 months before being included in MACA-INT. The primary evaluation criterion of the MACA-OBS study will be the change in retinal sensitivity measured by the microperimetry technique, and the patients that will be included will be those with intermediate AMD defined according to the Beckman classification[129] and at stage 3 of the AREDS classification. Such patients exhibit extensive intermediate Drüsen, some large Drüsen (greater than 125 microns in size) with or without non-central geographic atrophy in at least 1 eye. Several quality-of-life questionnaires will also be used to assess their predictive value in the MACA-OBS study.

Regulatory approvals for the start-up of MACA-OBS should be obtained in the second half of 2018 to begin recruiting the first patients in the first half of 2019. The regulatory environment in Europe and the United States is changing as a result of the failure of most drug candidates in clinical development for geographic atrophy, in order to evaluate the efficacy of drug candidates at the intermediate stage. An important meeting was held at the FDA in October 2016 regarding the relevant criteria to be measured in AMD and hereditary retinopathies (Csaky et al., 2017)[130]. In addition, the IMI MACUSTAR European project launched at the end of 2017 with the aim of monitoring a cohort of more than 700 patients at the intermediate stage for 3 years with criteria for assessing the progression of the disease, such as retinal sensitivity measured by the microperimetry technique.

Biophytis has set out to create a steering committee for the MACA study. The committee will approve the protocols of the clinical programme, the main and secondary evaluation criteria, as well as the definition of the population. Dr Ivana Kim will be the principal investigator of the MACA-OBS study, with the participation of Professor José-Alain Sahel from the University of Pittsburgh.

[129] Ferris F.L., Wilkinson, Bird A., Chakravarthy U., Chew E., Csaky K., Sadda S.R. (2013). Clinical Classification of Age-related Macular Degeneration. Ophthalmology 120; 844-851

[130] Czaky K, Ferris III F, Chew EY, Nair P, Cheetham JK, Duncan JL. 2017 Report from the NEI/FDA endpoints workshop on age-related macular degeneration and inherited retinal diseases. *IOVS*, 58 (9): 3456-3463.

MACA-INT Study

The MACA-INT study will be designed according to the results obtained during the MACA-PK study and the MACA-OBS study. The dosage of *Macuneos*, potentially the most effective one that is best tolerated by patients, will have been defined in the MACA-PK study. The criteria for eligibility and evaluation of patients will have been defined during the MACA-OBS study. MACA-OBS patients who have completed their investigation phase will be asked to join the MACA-INT study. The latter is expected to start in the second half of 2019.

The objective of MACA-INT is to determine the therapeutically effective dose of Macuneos in elderly persons suffering from the intermediate dry form of AMD in at least one eye (without loss of visual acuity) and who are likely to develop a severe form (exudative form or geographic atrophy). The applications for the approval of the MACA-INT interventional study in France, in at least one more European country (IMPD Ph2) and in the United States (IND Ph2) should be submitted in the second half of 2019. MACA-INT will involve about 20 clinical investigation centres in Europe and the United States, including the CIC Quinze-Vingt Hospital in Paris, the Massachusetts Eye and Ear Infirmary (Harvard Medical School) in Boston, the University of Pittsburgh, and John Hopkins University of Baltimore. Three hundred patients over 50 years of age with dry AMD defined per the Beckman classification and at stage 3 of the AREDS classification will be randomly assigned to 3 treatment groups: Macuneos at 100 mg, Macuneos at 350 mg and placebo. The main criterion, identical to that of the MACA-OBS study, will be the evolution of retinal sensitivity measured by the microperimetry technique.

The provisional schedule of this study which comprises several phases is as follows:

- H2 2018: MACA-PK SAD study
- H2 2018: MACA-OBS regulatory filings.
- H1 2019: MACA-PK MAD study
- H1 2019: Start of MACA-OBS clinical investigation phase
- H1 2020: Start of MACA-INT

6.3.3.4 CMC – scale-up – sourcing

BIO201, the Active Pharmaceutical Ingredient (API), is manufactured according to the current Good Manufacturing Practices (GMP), by Pathéon at its site in Regensburg, Germany, from achiote seeds (*Bixa orellana*).

The pharmaceutical development of Macuneos has been entrusted to the American subsidiary of a pharmaceutical group at the forefront of atomisation technology. The development of the pharmaceutical form was finalised in 2017. The development of the production process, the industrial scale-up, the production of the technical batches, the validation of the dosage methods as well as the stability studies are planned for the first half of 2018 to produce the clinical batches of the MACA-PK study in the second half.

The current supply chain allows for the complete development of the *Macuneos* project, from the clinical stage to its marketing.

6.3.3.5 Competitive environment

There is currently no registered medication to treat the dry form of AMD. The only drugs that are available on the market are for the treatment of exudative of AMD, i.e. approximately 20% of patients. The sale of preparations used in the treatment of exudative AMD (VEGF inhibitors) accounted for over $5 billion in 2017, notably with Lucentis by Roche/Novartis which dominates the market, and more recently with Eylea by Regeneron/Bayer. These figures demonstrate the significant economic potential of this indication.

For AMD, food supplements have been formulated with generic *antioxidant* compounds, namely minerals and vitamins with *antioxidant properties*, for example zinc, vitamins E and C, and they have demonstrated real, albeit limited, therapeutic effectiveness.

The nutraceutical formula AREDS 1 is considered to be the care norm in the United States for the treatment of the dry form of AMD, reducing the risk of advanced AMD by 25% and vision loss by 19% over five years in certain categories of patients. In Europe, numerous products are available, which are based on a common formulation: Zinc and vitamins E and C, to which a variety of ingredients are added, namely lutein, resveratrol and Omega 3, but in lower doses than those clinically tested and without specifically targeting patient populations.

Recently, some trials with retinal stem cells have brought some hope to patients with dry macular degeneration. Nevertheless, these approaches remain at an experimental, early stage for now.

Despite considerable investment by a number of biotech companies (Acucela, Sirion, Colby, Alexion, Morphosys, Regeneron) and major pharmaceutical companies (Novartis, Roche, GSK) in recent years, there are currently only two pharmaceutical molecules in clinical development for dry AMD (apart from MACUNEOS).

The most recent failures were GSK GSK933776 (anti-beta amyloid, phase 2 inconclusive), Roche's Lampaluzimab (anti-complement factor D, in Phase 3 - Roche has just announced it will discontinue the development of this molecule) and Emixustat by Acucela /Otsaka Pharma (visual cycle inhibitor, inconclusive phase 2b/3 - Acucela is now announcing a phase 2 study for Stargardt disease).

Zimura (anti-complement factor 5) by Ophtotech is currently continuing its phase 2b/3 study. But doubts about the anti-inflammatory mechanism, raised by the failure of Lampaluzimab, seem to have induced the company to pursue other indications – programmes for Stargardt's disease, and for wet AMD (in combination with VEGF inhibitors) have recently been announced.

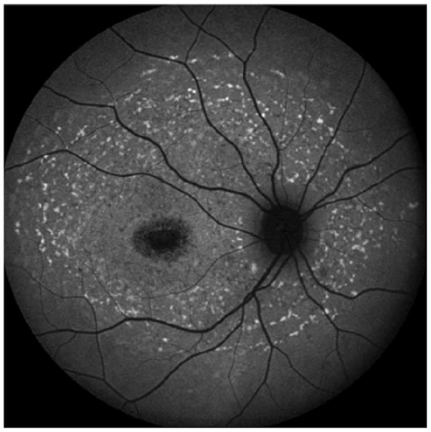
In addition, Apelis Pharmaceuticals is developing the use of another antibody called ***APL-2***, targeting the complement C3 protein in the treatment of AMD. During this development which is at a less advanced stage, in a recent phase II study testing the therapeutic effect of this antibody, a 28% reduction in the rate of progression of the atrophic zone was observed in treated patients compared to the control group. However, the beneficial effect on atrophic AMD in treated individuals is associated with an 18% increase in the occurrence of the neovascular form of AMD in these patients. Therefore, the use of modulation of the complement system as a therapeutic strategy for AMD appears compromised.

Despite a clear medical need and a very significant economic potential, dry AMD is currently almost devoid of promising drug development. The anti-inflammatory and anti-visual cycle mechanisms have not borne the expected results. We hope that MACUNEOS, with its original mechanism of action, will fill this gap.

6.3.4 Stargardt disease

6.3.4.1 Epidemiology

Stargardt disease is the most common hereditary macular dystrophy, with a prevalence of 1/8,000 -1/10,000, and an early onset (patients are usually between 6 and 15 years of age). Stargardt disease is characterised by progressive loss of central vision, slight loss of colour vision and delayed dark adaptation. Peripheral vision, however, remains intact. The decrease in bilateral visual acuity decreases to one-tenth or one-twentieth. As in AMD, macular atrophy with or without paramacular spots and degeneration of the retinal pigment epithelium are observed in the fundus (Tanna et al., 2016)[131].



The pathology is detected by the autofluorescence of the fundus (accumulation of lipofuscins and A2E), and the optical coherence tomography (OCT) showing a disorganisation of the architecture of the retina.
The loss of the retinal function is progressive and its speed is very variable depending on the individual and the mutation of the gene. The nonsense mutations that induce an absence of production of the protein are the most serious and effects appear early on, “missense” genetic mutations which induce the modification of a protein amino acid are at the origin of later pathologies that spare the fovea for some time (“fovea-sparing”).
To date, no treatment is available for this disease.

6.3.4.2 Proofs of concept

Stargardt disease is an inherited autosomal recessive disorder caused by mutations in the ATP-binding cassette gene, subfamily A, member 4 encoding the protein *ABCA4* (a photoreceptor transporter involved in the visual pigment cycle) that causes a loss of central vision bilaterally, following the accumulation of toxic A2E in the cells of the retinal pigment epithelium (RPE).

The ABCA4 protein is produced in photoreceptors. It is one of the proteins involved in phototransduction (the process that transforms the light stimulus into an electrical signal that is transmitted to the brain). During phototransduction, many potentially toxic molecular species are produced that can damage photoreceptors. The ABCA4 protein participates in the elimination from the photoreceptors of one of these substances called N-retinylidene-PE. More than 900 mutations of the ABCA4 gene have been associated with Stargardt disease. The mutated ABCA4 proteins can no longer remove the A2E precursor (A2E-PE). Therefore A2E in the form of lipofuscin (a yellow pigment) accumulates to form deposits similar to the Drüsen observed in AMD. As in AMD, lipofuscin (A2E) accumulation is toxic to retinal cells (photoreceptors and RPE cells) and induces a progressive loss of vision (Sacconi *et al*., 2017[132]). It is important to note that the ABCA4 gene has been identified as a risk factor for AMD. This association has only been established in a negligible percentage of patients with

[131] Tanna P, Strauss RW, Fujinami K, Michaelides M. (2016). Stargardt disease: clinical features, molecular genetics, animal models and therapeutic options. *Br J Ophthalmol* 0-1-6. doi: 10.1136/bjophthalmol. 2016.308823

[132] Sacconi R, Corbelli E, Querques L, Bandello F, Querques G. 2017. A review of current and future management of geographic atrophy. *Ophthalmol Theor* 6: 69-77.

AMD (Fritsche et al., 2012)[133] and is the only example of an association between a gene that is responsible for a monogenic retinal disease and AMD. *Stargardt* disease may thus be regarded as a simple genetic model of AMD, even though this pathology differs in numerous physiopathological aspects.

Photoreceptor protection and BIO201-induced ERG signal in RDH8$^{-/-}$, ABCA4$^{-/-}$ double KO mice, which can be considered both as a model of dry AMD and as an animal model of Stargardt disease is the proof concept that BIO201 can be an effective treatment for Stargardt disease. Clearly, because of its mechanism of action, Macuneos is a good candidate for the treatment of this very debilitating orphan disease for which there is currently no available treatment.

6.3.4.3 Clinical Programme

The phases of the Stargardt programme:

- Startgardt-PK

Initially, a pharmacokinetic and safety study will be conducted in patients aged 6 to 12 years and 13 to 17 years with Stargardt disease from the second half of 2019; the Startgardt -PK will be conducted in Europe and the United States. It consists of adapting the effective therapeutic dose of *Macuneos* in children aged 6 to 12 and 13 to 17 years, which covers the typical age range of patients suffering from Stargardt disease. This study, with a duration of 3 months and which will take approximately 18 months of implementation and follow-up, aims to (i) obtain pharmacodynamic activity data as early as 2020, (ii) measure the pharmacokinetics of Macuneos specifically in children and adolescents, before confirming the doses to be administered, as part of the Startgardt-INT study,

- Startgardt-INT

In a second phase, patients of the Startgardt-PK study will be asked to participate in a phase-2a interventional pilot study (Startgardt-INT) in order to test the effectiveness of Macuneos in delaying the appearance of the visual symptoms in these patients and in inhibiting A2E accumulation and progression of the atrophic zone in the retina of patients with Stargardt disease. The duration of administration will be 6-12 months.

The provisional schedule of this study which comprises several phases is as follows:

- H2 2019: Startgardt-PK MAD study
- H2 2019: Startgardt-INT regulatory filings (ANSM, EMA, FDA)
- H1 2020: Start of the Startgardt-INT clinical investigation phase
- H2 2022: Startgardt-INT: Presentation of results

6.3.4.4 Competitive environment

There is, to date, no registered molecule to treat Stargardt disease; the only recommended treatment consists of a few lifestyle measures: avoiding ultraviolet rays and foods high in vitamin A, and keeping good general health.

[133] Fritsche LG, Fleckenstein M, Fiebig BS, et al. 2012 A subgroup of age-related macular degeneration is associated with mono-allelic sequence variants in the *ABCA4* gene. *IOVS*, 53: 2112-2118.

The discovery of the gene – and the fact that a single gene is responsible – has led to several genetic programmes to treat Stargardt disease. The most advanced is that of Sanofi, undertaken in collaboration with Oxford Biomedica (SAR422459, in Phase 1b/2). It uses a lentiviral vector, injected sub-retinally, to deliver the normal gene to the eye.

Stem cell approaches (stem cells differentiate into functional retinal cells) are also being explored and developed. In 2015, US biotech Ocata Therapeutics announced positive results in patients with Stargardt disease with a cocktail of stem cells. Following the acquisition of the company by Astellas in 2016, nothing has been published on whether the project will be continued.

The pharmacological substances currently in clinical phase for Stargardt disease are ALK-001 from Alkeus Pharma (an analogue of Vitamin A, which is supposed to reduce the accumulation of toxic metabolites of the vitamin), currently in phase 2, as well as Emixustat by Acucela (a visual cycle inhibitor) and Zimura by Ophthotech (a complement C5 inhibitor). Phase 2 trials for Stargardt disease have recently been announced for two of these molecules which had previously been developed for dry AMD.

Like dry AMD, Stargardt disease is, therefore, waiting for a first effective drug to slow the degenerative process that leads to blindness. We believe that MACUNEOS, with its unique and innovative mechanism, may either be such first drug, or play an important role in future treatments of this genetic disorder.

6.3.5 BIO203, other indications

BIO203 is a new molecule selected from synthesised compounds, analogues of the natural active ingredients in animal and cellular models of AMD. The candidate is undergoing optimisation for oral administration, with the aim of improving the targeting of the eye.

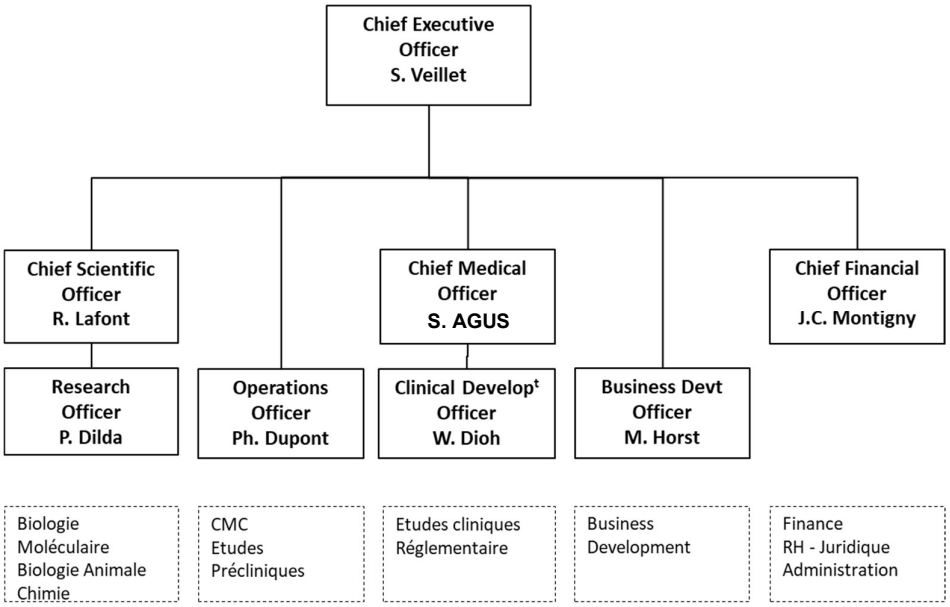
BIO203 will then be able to enter preclinical regulatory development in 2018, then phase 1 in 2019 to assess whether it is safe for use in humans.

BIO203 will probably be developed to treat retinopathies other than AMD.

6.4 ORGANIZATION OF THE COMPANY

6.4.1 Organization

Biophytis has an informal and flexible structure and currently employs 23 people, all management staff, who focus on corporate know-how (and value), while covering a wide range of areas of expertise – including 10 doctors in science, 2 physicians, 2 pharmacists. The additional scientific resources derive from the cooperation with *translational* research institutes. The development work involved in project ownership is entrusted to recognised providers in the sector under the expert guidance of the operations division and the clinical development division.



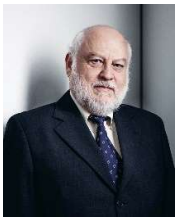
Stanislas VEILLET – Founding Chairman

Degree in Engineering from AgroParisTech, Doctor of Genetics

Degree in Engineering from AgroParisTech, Doctor of Genetics Doctor of Genetics, a graduate of AgroParisTech, Stanislas VEILLET began his career in Brazil as researcher at CIRAD before obtaining a Doctorate in Genetics. He subsequently joined the Cargill Group, where he managed a biotechnology laboratory, then Pharmacia-Monsanto to develop a high-speed genomic analysis platform. His interest in the burgeoning "nutraceutical" industry induced him to accept the challenge of managing the Life Sciences Department of the Danone Group, where he developed several products for the prevention of cardiovascular diseases (Danacol, Danaten).

Motivated by a strong entrepreneurial spirit, he co-founded Biophytis with René Lafont in 2006 with the object of realising the potential of natural active molecules in the treatment of chronic age-related pathologies. He is the author of some ten patents.

René LAFONT – Director and Scientific Founder



Doctor (Ph. D) of Natural Sciences, Emeritus Professor at Sorbonne University

René Lafont studied biology at the Ecole Normale Supérieure in the rue d'Ulm, where he graduated in physiology and biochemistry and then decided to pursue a career in research in the fields of biochemistry and the physiology of insects. He managed a laboratory at the Ecole Normale Supérieure, then at the UPMC, where he was appointed professor in 1985, teaching Comparative Physiology at the Faculty of Sciences and Cellular Biology and the Faculty of Medicine of Pitié-Salpêtrière. After running the Federal Life Sciences Unit at *UPMC*, he became Emeritus Professor in 2008. He is the author of over 180 original

publications, numerous reviews and ten or so patents. He co-founded Biophytis with Stanislas Veillet in 2006, contributing his expertise in the field of natural active molecules.

Doctor SSAmuel AGUS – Medical Director

Doctor of Medicine and holding two PhD in neurology and biostatistics. Samuel AGUS specialized in neurology and neurodegeneration. He has spent over 15 years in clinical development and pharmaceutical industry (such as Solvay and Lundbeck).

Jean-Christophe MONTIGNY – Financial Director

With an engineering degree from AgroParisTech and a degree in Political Science from Paris,
Jean-Christophe spent the first part of his career at Kraft Foods (now Mondelez) where he was primarily involved in growth projects and was successively based in Paris, Vienna, Budapest, and London in finance, marketing, and project management roles. Upon his return to France, he became involved in the SME sector, then as a logical consequence, in 2005 he founded his own company: BLO, an innovative company in the direct marketing sector. Jean-Christophe joined Biophytis in 2009.

Pierre J. DILDA – Director of Research

Doctor of Pharmacology (Paris V), Pierre J. DILDA has spent over 20 years in the pharmaceutical industry (Mayoli Spindler) and academic research. Before joining Biophytis in December 2015, he was responsible for the laboratory at the Lowy Cancer Research Centre (Sydney, Australia) where he was in charge of developing several drug candidates in the field of oncology.

Philippe Dupont – Director of Operations

Doctor of Pharmacy (Paris XI) and holder of an MBA from ESSEC, Philippe DUPONT has spent his entire career in pharmaceutical groups such as Lavipharma, Opodex and Novagali (Santen Group). He joined BIOPHYTIS in July 2015 where he was in charge of project coordination, regulatory studies and production.

Waly Dioh – Director of Development

Doctor of Phytopathology, MBA
Mr DIOH obtained his doctorate at the University of Paris XI. He spent most of his career in the research & development teams at Monsanto, initially in France, then in Saint Louis (Missouri). Dr DIOH joined Biophytis in 2006. He has supervised the two clinical studies on the company's products and is currently managing the SARCOB programme.

Manfred Horst - Business Development Director

Doctor of Medicine (Ludwig-Maximilians-Universität, Munich) and Allergology, he holds an MBA from INSEAD
Dr HORST has more than 25 years of experience in the pharmaceutical industry. He has held senior positions at Ciba-Geigy/Novartis and was CEO of Mercur Value Health Gesundheitspartner (Allianz Group). Prior to joining Biophytis, Dr HORST was Director of Business Development Europe at MSD (Merck & Co.) from 2004 to 2016 and contributed to the conclusion of numerous licensing agreements.

6.4.2 Scientific Committee

Professor Jean MARIANI

Professor Emeritus at Sorbonne University, Director of the Charles Foix Institute of Longevity, hospital practitioner at Charles Foix Hospital.
Expert in neurobiology, development of the central nervous system, synaptogenesis and neuronal death of the normal and pathological nervous system, neurodegenerative diseases.

Professor René LAFONT

Emeritus Professor at the *UPMC*; Laboratory Director; winner of the Karlson Foundation Award (Germany); Jaroslav Heyrovsky Medal from the Czech Academy of Sciences.
Expert in comparative physiology, analytical methods, phytochemistry; author and co-author of 180 original publications and over 50 review articles and book chapters.

Professor José Alain SAHEL

Director of the Institute of Vision; Ophthalmologist; Member of the Academy of Sciences; awarded the CNRS Medal of Innovation 2012; Professor of Biomedical Sciences (Cumberlege Chair) at the Institute of Ophthalmology, University College London; Visiting Professor at the Hebrew University of Jerusalem, Israel.
Pioneer in the field of the artificial retina and ocular regenerative therapies, José-Alain Sahel has given over 250 guest lectures and has authored 280 publications indexed in Pubmed.

Professor Ivana K. KIM

Professor at Harvard Medical School; Director of the Massachusetts Eye and Ear Unit; Graduate of Stanford and Harvard.
Co-director of the Department of Ophthalmology at Harvard Medical School and Director of the Macular Degeneration Unit in Massachusetts Eye and Ear, Ivana Kim is also the principal author of around one hundred international publications.

Professor Roger A. FIELDING

Professor at the Friedman School of Nutrition Science and Policy and at Harvard Medical School; Director of Human Studies at the Jean Mayer USDA Human Nutrition Research centre on Aging
Founding member of Geriatric Studies at the National Institutes of Health, Roger A. Fielding has conducted research on the impact of exercise and physical activity on aging well, age-related changes in the skeletal muscle and alterations of skeletal muscle protein.

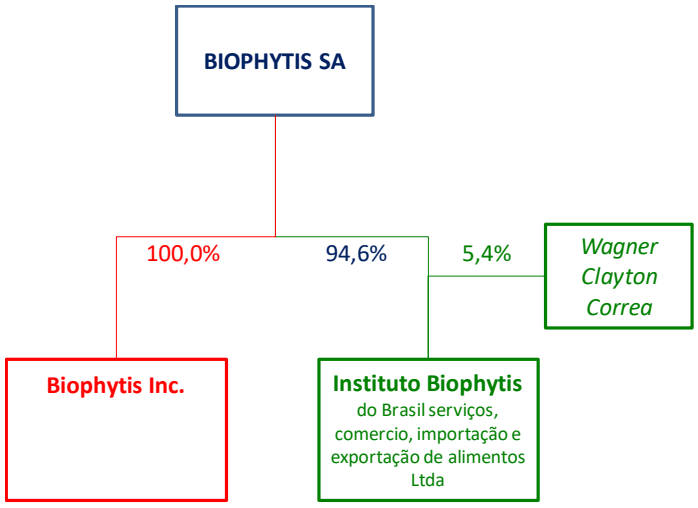
Professor Thomas VOIT

Professor Thomas Voit is the Director of the Biomedical Research Center (BRC) of the Great Ormond Street Hospital for Children NHS Foundation Trust and the Institute of Child Health, University College London. Previously, Professor Voit was at the Pierre et Marie Curie University (Sorbonne), in Paris, where he was Medical and Scientific Director of the Myology Institute and Director of an INSERM/CNRS research centre. Previously he was professor and director of the paediatric department at Essen University Hospital.

7 ORGANISATIONAL DIAGRAM

7.1 ORGANISATIONAL DIAGRAM OF THE COMPANY

The legal organisational diagram of Biophytis is as follows:



Biophytis holds:

- 94.6% of the share capital and voting rights of **Instituto Biophytis** do Brasil Serviços, Comércio, Importação Exportação de Alimentos Ltda, a company governed by Brazilian law, whose second shareholder is Mr. Wagner Clayton Correa, who is also the manager of the subsidiary;

- 100% of the share capital and voting rights of **Biophytis Inc.**, a company governed by the laws of the State of Delaware (USA).

7.2 SUBSIDIARIES AND EQUITY INTERESTS

INSTITUTO BIOPHYTIS DO BRASIL SERVIÇOS, COMERCIO, IMPORTAÇÃO E EXPORTAÇÃO DE ALIMENTOS LTDA.
Date of incorporation: 20 September 2006
Registration: CNPJ / MF No. 08308555 / 0001-07,
Address: Av. Prof. Lineu Prestes, 2242 Cidade Universitaria, in the city of São Paulo, State of São Paulo, CEP 05508-000, Setor D, Bloco 4, CIETEC
Share capital: BRL 898,632.

On the date of this Annual Report, the Company holds 94.6% of the share capital and voting rights of the company BIOPHYTIS INSTITUTO DO BRASIL SERVIÇOS COMÉRCIO, IMPORTAÇÃO E EXPORTAÇÃO DE ALIMENTOS LTDA, a Brazilian company (named BIOPHYTIS BRASIL).

The remaining 5.4% of the share capital is held by Mr. Clayton Wagner Correa, manager of INSTITUTO BIOPHYTIS DO BRASIL.

Since the financial year ended in 2010, INSTITUTO BIOPHYTIS DO BRASIL has not carried out any further activities.

BIOPHYTIS INC.
Date of incorporation: 09 November 2015
Registration: 5873213
Address: CorpoMax Inc., 2915 Ogletown Rd, Newark, DE 19713
Share capital: $ 1,000

On the date of this Annual Report, the Company holds 100% of the share capital and voting rights of BIOPHYTIS INC., a company governed by the laws of the State of Delaware (USA).

Since its creation, Biophytis Inc. has engaged in clinical and regulatory development activities and has partnered with North American investors in the field of human health.

The Company does not hold reciprocal holdings.

7.3 GROUP FINANCIAL FLOWS

INSTITUTO BIOPHYTIS DO BRASIL

Financial flows to the Brazilian subsidiary consist of shareholder loans. No loans were granted during the years presented.

The entire value of the equity interest for a gross amount of €295,000, and receivables for a gross amount of €603,000 have been amortised.

BIOPHYTIS INC.

The Company made current account contributions to its US subsidiary, the amounts of which in the last two financial years are as follows:

- In 2017: €180,000 ($207,000)
- In 2016: €168,000 ($186,000)

The entire value of the equity interest for a gross amount of €1,000, and of the shareholder loan asset for a gross amount of €367,000 have been amortised.

8 PROPERTY, PLANT AND EQUIPMENT

8.1 PROPERTY AND EQUIPMENT

8.1.1 Leased properties

A temporary public property occupancy agreement was concluded between the Company and the Pierre et Marie Curie University (Paris 6), a public scientific, cultural, and professional institution having its registered office at 4, place Jussieu, 75252 Paris Cedex 05 (the "**Pierre et Marie Curie University**"), dated 15 December 2016 with effect from the same day (the "**Public Property Occupancy Agreement**"). The Public Property Occupancy Agreement covers (i) access by the University of Pierre and Marie Curie of 274.85 m² to premises located on the 4th floor of Building A, (ii) access to certain equipment and materials of the FR3631 Institut Biologie Paris Seine Laboratory and (iii) the storing of certain equipment and materials belonging to the Company. The occupancy allowance is annual. The Public Property Occupancy Agreement is concluded for a period of one (1) year, renewable once by conclusion of an amendment agreement. This Public Property Occupancy Agreement may be terminated at any time by giving 3 months' prior notice.

The Public Property Occupancy Agreement covers (i) access by the University of Pierre and Marie Curie to 274.85 m² of premises located on the 4th floor of Building A, (ii) access to certain equipment and materials of the FR3631 Institut Biologie Paris Seine laboratory and (iii) the storing of certain equipment and materials belonging to the Company. The occupancy allowance is annual. The Public Property Occupancy Agreement is concluded for a period of one (1) year, renewable by conclusion of an amendment agreement. By an amendment dated 28 September 2017, the term of the Public Property Occupancy Agreement was extended until 15 December 2018. This Public Property Occupancy Agreement may be terminated at any time subject to a 3 months' prior notice.

The Public Property Occupancy Agreement also contains a confidentiality clause covering the information exchanged during the execution of the agreement, for the duration of the agreement, and for the three (3) years following its expiry.

The occupancy allowance will be revised each year according to the change in the national cost of construction index published by the French National Institute of Statistics and Economic Studies. The Public Property Occupation Convention provides that the indemnity will be paid annually upon signing on a pro rata basis for the occupancy period starting from 15 December 2016. The following payments, equal to one-quarter of the annual allowance, must be paid before the last day of the first month of each quarter throughout the entire period of occupation.

Under the Public Property Occupancy Agreement, the Company incurred a charge of €90,700 during the 2017 financial year.

Moreover, its registered office is at 14, Avenue de l'Opéra, pursuant to a commercial domiciliation agreement concluded with SDM on 6 September 2006, under which the company pays a rent of € 357 net of tax per quarter. This agreement may be terminated at any time subject to a 3 months' prior notice.

The Brazilian subsidiary of the Company rents premises, by way of a non-residential lease, which it uses for the purposes of storing equipment. In this capacity, it currently pays a rent of

€ 6,287 net of tax before expenses, which it is currently under negotiation regarding the reduced activity of the subsidiary.

Address: Rua Hugo Cacuri, 128, Butantã
São Paulo
São Paulo

Surface area: 162 m²

Duration: 5 October 2011 to 4 April 2017

Rent: € 6,287 net of tax per year, excluding expenses

The lease mentioned above has not been renewed.

The company remains domiciled, without premises, at an incubator for innovative businesses within the CIETEC nursery of the Federal University of Sao Paulo (Universidade Federal de Sao Paulo, USP), located at Av. Prof. Lineu Prestes, 2242 – Cidade Universitaria, Campus I – USP – Sao Paulo – SP, CEP 05.508-000 – IPEN – Bloco D, to which the Company is associated.

The US subsidiary is domiciled at the offices of Marie Landel & Associates, its administrative service provider, located at 185 Alewife Brook Parkway, 410, Cambridge, MA 02138, USA, under the terms of the agreement with the provider of 12 October 2015 for an indefinite duration.

8.1.2 Other tangible fixed assets

See section 20.1 note 4.

8.2 ENVIRONMENTAL ISSUES

With the exception of the risks presented in section 4.3 “Risks relating to the use of products hazardous to health and/or the environment”, the nature of the Company’s activities does not entail a significant risk to the environment.

9 ANALYSIS OF FINANCIAL POSITION AND RESULTS

The reader is invited to read the following information regarding the financial position and results of the Company and its subsidiaries with the whole of the Annual Report, notably the consolidated financial statements prepared in accordance with IFRS for the year ended 31 December 2017. The reader may consult the Notes to the financial statements, as included in Section 20.1 of the Annual Report.

Comments on the financial statements presented in Sections 9 and 10 of the Annual Report, are established solely on the basis of the consolidated financial statements prepared in accordance with IFRS, included in Section 20.1 of the Annual Report.

9.1 GENERAL PRESENTATION

9.1.1 GENERAL PRESENTATION

The Company was incorporated on 27 September 2006. It develops novel candidate drugs for the treatment of age-related diseases from natural active molecules involved in the aging process.

The Company devotes its resources to research and development. Research is conducted in collaboration with eminent public institutions. Exploitation and development are at the exclusive liability of the company.

Since its incorporation, the Company has been funded by:

- capital increases;
- an IPO on the Euronext Growth market in Paris in 2015.
- loans from various agencies (OSEO/BPI France, Sopran/Sanofi, SODISID/Arcelor in particular);
- reimbursable advances granted by OSEO/BPI France and Coface;
- bonds loan;
- subsidies granted by the Fonds Unique Interministériel [Single Interministerial Fund] (FUI), the General Council of Seine Saint Denis, and Feder;
- the research tax credit.

9.2 COMPARISON OF ACCOUNTS FOR THE LAST TWO FINANCIAL YEARS

9.2.1 Formation of operating profit and net profit

(I) Revenues

In view of the stage of development of its candidate drugs, the Company does not generate any revenues.

(II) Operating expenses per function

- ***Research and development expenses***

The Company conducts research and development activities in order to develop drugs candidates for the treatment of metabolic and age-related diseases. During the 2017 financial year, the Company:

- continued its efforts on the SARA clinical development programme (Sarconeos drug candidate to treat sarcopenia): end of SARA-PK and launch of SARA-OBS
- accelerated non-clinical studies of the MACA programme (Macuneos to treat AMD).

Research costs were systematically recorded under expenses.

Due to the risks and uncertainties linked to regulatory approval and the research and development process, the six criteria for capitalisation are not considered as met before obtaining the marketing authorisation of medicinal products ("AMM"). Consequently, internal development costs arising before the obtaining of a marketing authorisation, principally consisting of clinical studies costs, are recorded under charges in the Research and development expenses line, as they are incurred.

Research and development expenses break down as follows during the years presented:

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Staff expenses	(1,789)	(2,104)
Other purchases and external expenses	(4,817)	(7,312)
Other	(182)	(177)
Research and development expenses	**(6,788)**	**(9,593)**
Research tax credit	1,604	2,545
Subsidies	62	5
Subsidies	**1,667**	**2,550**
Net research and development expenses	**(5,121)**	**(7,043)**

Personnel costs, including share-based payments, for engineers and research personnel amounted to €2,104K in 2017, an increase of €315K compared to 2016. This change is mainly due to the addition of staff to the research team.

Other purchases and external expenses related to the Group's research activity amounted to €7,312K in 2017 and were up by €2,495K compared to the previous year. This increase is mainly due to an increase in study and research expenses of €2,190K, mainly related to:

- the SARA clinical programme: end of SARA-PK and launch of SARA-OBS
- the acceleration of non-clinical studies of the MACA programme.

The increase in research and development expenses was accompanied by an increase in the research tax credit available to the Group in connection with its research activities in France (€2,545,000 in 2017 compared to €1,604,000 in 2016).

- ***General and administrative expenses***

General and administrative expenses break down as follows during the years presented:

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Staff expenses	(1,145)	(1,257)
Other purchases and external expenses	(1,572)	(1,576)
Other	(103)	(32)
General and administrative expenses	**(2,820)**	**(2,865)**

Personnel costs, including share-based payments, for general management and administrative staff amounted to €1,257K in 2017, compared to €1,145K in 2016.

Other purchases and external expenses amounted to €1,576K in 2017, a similar figure to that for 2016.

(III) Net financial income

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Other financial expenses	(33)	(118)
Amortised cost of convertible bonds	-	(3,145)
Variation in the fair value of derivative liabilities	-	1,756
Other financial income	22	7
Currency gains and (losses)	(1)	0
Total financial income and expenses	**(13)**	**(1,501)**

Financial net income amounted to € (1,501)K at 31 December 2017 compared to € (13)K at 31 December 2016. It mainly consists of the cost of issuing notes convertible into shares with share subscription warrants attached in favour of Bracknor Fund Limited for € (1,389)K in 2017 (amortised cost and change in fair value of derivative liabilities).

(IV) Corporation tax

The Group did not record any corporation tax.

At 31 December 2017, the Group had tax losses of €34,558K, including:

- €34,200K in France
  The use of tax losses in France is capped at 50% of taxable profit for the year, with this limitation applicable to the portion of benefits exceeding € 1 million. The unused balance of the deficit is carried forward to the following years and attributable under the same conditions without limitation in time. The tax rate applicable to Biophytis is the effective rate within France, i.e. 33.33%. This rate will gradually decrease starting in 2018 and drop to 25% from 2022.

- €354K for the US subsidiary
  In the United States, tax losses may be carried forward for 20 years from their date of establishment. The tax rate applicable to Biophytis Inc. is the effective rate in the United States, i.e. 21%.

- €4K for the Brazilian subsidiary

Within Brazil, the fiscal deficit follows a declining regime: tax losses which may be carried forward are limited to 30% of the accumulated deficit of the previous year. The tax rate applicable to Instituto Biophytis Do Brasil is the effective rate in Brazil, i.e. 34%.

Deferred tax assets are recorded as tax loss carry-forwards when it is likely that the Company will have future taxable profits against which it will be possible to offset the unused tax losses. By way of application this principle, no deferred tax asset is recognised in the accounts of the Company in excess of deferred tax liabilities.

(V) Earnings per share

The basic earnings per share are calculated by dividing the net profit attributable to the Company's shareholders by the weighted average number of ordinary shares outstanding during the year. The instruments providing deferred entitlement to the share capital (warrants, founder's warrants, etc.) are considered anti-dilutive because they cause an increase in earnings per share. In this way, diluted earnings per share are identical to basic earnings per share.

	31/12/2016	31/12/2017
Average weighted number of shares circulation	6,202,616	9,188,179
Net profit for the financial year	(7,954)	(11,409)
Basic earnings per share (€/share)	**(1.28)**	**(1.24)**
Diluted earnings per share (€/share)	**(1.28)**	**(1.24)**

9.2.2 Balance sheet analysis

(VI) Non-current assets

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Intangible fixed assets	2,125	2,009
Tangible fixed assets	276	313
Other non-current financial assets	99	190
Total non-current assets	**2,501**	**2,512**

Intangible fixed assets consist of quotas of patents acquired during the financial year 2015 from Metabrain and Iris Pharma for € 1,500K and € 800K respectively.

Property, plant, and equipment mainly consist of laboratory equipment.

Non-current financial assets essentially consist of the cash reserve linked to the liquidity contract implemented in 2015 following the listing of the Company's stock on the Alternext Paris market (now Euronext Growth Paris).

(VII) Current assets

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Other receivables	2,827	3,578
Cash and cash equivalents	3,066	19,857
Total current assets	**5,892**	**23,435**

Other receivables principally include:

- Government debt assets relating to the Research Tax Credit for a total of €2,549K at 31 December 2017 (€2,058K at 31 December 2016).
- deductible VAT and VAT credits amounting to €709K at 31 December 2017 (€471K at 31 December 2016).

Cash and cash equivalents consist of bank accounts and short term deposits with a one month maturity.

(VIII) Shareholders' equity

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Share capital	1,245	2,693
Issue and contribution premiums	19,583	44,708
Treasury shares	(158)	(138)
Conversion differences	4	(0)
Reserves - attributable to Biophytis shareholders	(8,170)	(14,636)
Net income (loss) - attributable to Biophytis shareholders	(7,954)	(11,409)
Shareholders' equity – attributable to Biophytis shareholders	**4,549**	**21,217**
Non-controlling interests	(30)	(31)
Total shareholders' equity	**4,519**	**21,187**

Share capital amounts to 2,692,682.60 as at 31 December 2017. It is divided into 13,463,413 shares, fully subscribed and paid up, with a nominal value of €0.20.

During the 2017 financial year, the Company made several private investments generating a capital increase of €962K and an issue premium of €20,779K. In addition, 630 convertible bonds issued in favour of Bracknor Fund Limited were repaid in new shares generating a capital increase of €482K and an issue premium of €6,339K.

(IX) Non-current liabilities

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Employee benefit obligations	48	114
Non-current financial liabilities	913	708
Total non-current liabilities	**962**	**821**

Commitments to staff consist of the provision for retirement allowances.

Non-current financial debts had the following breakdown:

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Reimbursable advances	797	661
Borrowings from and debts with lending institutions	23	-
Financial debts – Lease financing	94	46
Non-current financial liabilities	**913**	**708**

See section 10 for more information on the financing of the company.

(X) Current liabilities

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Current financial liabilities	176	305
Trade payables	1,920	2,402
Tax and social debts	722	1,118
Other creditors and miscellaneous debts	94	113
Total current liabilities	**2,913**	**3,939**

The increase in trade payables compared to 31 December 2017 is mainly due to the very significant increase in expenses from research and development entrusted to third parties.

Current financial liabilites had the following breakdown:

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Reimbursable advances	96	228
Borrowings from and debts with lending institutions	30	23
Financial debts – Lease financing	44	47
Bank overdrafts	5	7
Current financial liabilities	**176**	**305**

See section 10 for more information on the financing of the company.

10 CASH POSITION AND EQUITY

The reader should also refer to notes 6, 9 and 11 of the notes to the consolidated financial statements prepared in accordance with IFRS in Section 20.1 of the Annual Report.

10.1 INFORMATION ON CAPITAL, LIQUIDITY AND SOURCES OF FINANCING

At 31 December 2017, the net amount of cash and cash equivalents held by the Group (total cash and cash equivalents in assets and bank overdrafts under liabilities) amounted to €19,857K, compared to €3,066K at 31 December 2016.

10.1.1 Capital financing

The Company received a total of € 50,190K (before deduction of expenses linked to capital increases) through contributions from founders, capital increases carried out between 2006 and 2017 and the IPO in 2015.

The following table summarises the principal capital increases by value until the date of this Annual Report:

Periods	Gross amounts raised in € '000	Transactions
2006	267	Contribution by the founders
2008	800	First round of financing completed at a subscription price of € 15.73 per share
2009	2,220	Second round of financing completed at a subscription price of € 11.01 per share
2012	199	Conversion of OCA $_{2011}$ at a subscription price of €11 per share
2012	1,800	Third round of financing completed a subscription price of € 10.28 per share
July-15	10,035	IPO on the Alternext Paris market through a capital increase *(1) (2)*
August-15	6,000	Private investment with a US investor and raising of €6 million via the issue of 666,700 new shares *(1)*
2015	205	Subscription of 270,414 warrants2015D at a price of € 0.60 and of 54,000 warrants2015 at a price of € 0.80
2015	534	Exercise of 80,666 warrants2015D and 6,000 warrants2015
2016	58	Exercise of 28,000 warrants2015
2017	3,734	Private investment of €3.7 million via the issue of 1,310,431 new shares at a price of €2.85 per share *(3)*
2017	10,442	Private investment of €10.4 million via the issue of 1,989,000 new shares at a price of € 5.25 per share *(3)*
2017	7,565	Share capital increase in cash of €7.6 million via the issue of 1,513,000 new ordinary shares at a unit price of €5 offered to industrial or commercial companies, investment funds, organisations, institutions or entities of any form, French or foreign, investing regularly in the health, biotechnology and/or pharmaceutical sectors *(3)*
2017	6,300	Conversion of 630 bonds held by Bracknor Fund *(4)*
2017	31	Exercise of 15,000 founder's warrants$_{2015\text{-}1}$

Total	**50,190**	

(1) The IPO of the company on the Alternext Paris market and the private investment with a U.S. investor generated fees of € 1,383K.
(2) The capital increase within the context of the IPO was partially achieved by offsetting receivables of the Company:

- *debts relating to bonds$_{2015C}$ and $_{2015D}$ for € 1,897K*
- *dent relating to the acquisition of the quota of ownership of the patents with Metabrain and Iris Pharma for € 1,500K and € 800K respectively*
  the shareholder current account for € 60K.

(3) Private investments made during the 2017 financial year generated fees of €2,043K.

(4) This amount includes the conversion of the 30 convertible notes issued in respect of the commitment fee.

10.1.2 Financing by research tax credit

(Amounts in thousands of euros)	**31/12/2016**	**31/12/2017**
Research tax credit	1,604	2,549

The Company has benefited from the research tax credit since its incorporation. The Research Tax Credit ("CIR") for 2016 was reimbursed in 2017. The reimbursement of the 2017 CIR is scheduled for 2018.

10.1.3 Financing by reimbursable advances and subsidies

(XI) Reimbursable advances

The Company benefited from five reimbursable advance programs:

- Four OSEO/BPI France reimbursable assistance grants for innovation;
- a reimbursable advance termed "prospecting insurance" from COFACE.

A reimbursable advance was granted by OSEO on 7 August 2008. This was a non-interest-bearing reimbursable advance of €230K for the "clinical development of an extract of Quinoa active on metabolic syndrome". Following the success of the project and the extension of the repayment terms granted by BPI France (formerly OSEO), this advance is being repaid by means of quarterly payments made between 31 March 2016 and 31 December 2018.

A "prospection insurance" reimbursable advance was granted by the COFACE on 15 September 2008, amended by a rider dated 22 October 2009. The company had to pay a premium corresponding to 3% of the budget covered and repayment was to be based on revenue forecasts and up to a limit of 7% of invoiced revenue. The amortisation period ran from 1 June 2010 to 31 May 2015. The balance of the COFACE advance not used by the Company on 31 May 2015 (€61K) was deemed as not due.

A reimbursable advance was granted by OSEO on 30 August 2010. This was a non-interest-bearing reimbursable advance of €180K for the "clinical development of Biciliate in order to obtain a health claim". Following a partial failure, a supplementary agreement was signed in 2013 to determine the amount of aid as € 29K and to modify the reimbursement schedule accordingly. The last reimbursement was made in 2016.

A reimbursable advance was granted by BPI France on 4 February 2015. This was a reimbursable advance of €260K for the “in vitro, in vivo, and pharmacokinetic characterisation of a candidate drug.” The contract provides that payments are scheduled between the signing date of the agreement and the end of the programme. Following the success of the project and the extension of the repayment terms granted by BPI France (formerly OSEO), this advance is being repaid by means of quarterly payments made between 30 June 2017 and 31 March 2022.

A reimbursable advance was granted by BPI France on 28 November 2016. This is a non-interest-bearing reimbursable advance of €1,100K for the "production of clinical batches, in the preclinical regulatory phase and clinical phase 1 of BIO101, for the treatment of sarcopenic obesity". The contract provides that payments are scheduled between the signing date of the agreement and the end of the programme. At the date of the Annual Report, the Company had received € 600K, on which a registration fee of €33K was charged. If successful, this advance will be repaid in quarterly instalments made between 31 December 2018 and 30 September 2023.

Please refer to Note 10.1 to the IFRS consolidated financial statements in Section 20.1 of the Annual Report.

(Amounts in thousands of euros)	OSEO - Quinolia	OSEO – Maculia	OSEO- Sarcob	BPI - BIO 101	Total
At 31 December 2015	**201**	**4**	**89**	**-**	**293**
(+) Collection	-	-	108	567	675
(-) Reimbursement	(38)	(4)	-	-	(41)
Subsidies	-	-	(12)	(41)	(53)
Financial expenses	14	0	3	2	19
At 31 December 2016	**177**	**-**	**188**	**528**	**893**
(+) Collection	-	-	52	-	52
(-) Reimbursement	(73)	-	(13)	-	(86)
Subsidies	-	-	(5)	-	(5)
Financial expenses	10	-	6	18	35
At 31 December 2017	**114**	**-**	**228**	**546**	**889**

(XII) Subsidies

Since its inception, the Company has benefited from two main subsidy contracts:

A subsidy of up to €520K was granted by the Seine-Saint-Denis General Council and OSEO on 21 December 2011 and on 23 February 2012 for the Sarcob project. Following the notification of the end of the program in 2014, the final amount of the subsidy was set at € 475K (including € 234K from the General Council of Seine-Saint-Denis and € 241K from OSEO).

A subsidy of up to €300K was awarded by the Ile de France Region on behalf of the European Union on 7 June 2013 for the Maculia project. Following the notification of the end of the programme, the final amount of the subsidy was set at €166K.

The Company did not obtain any new significant subsidies since this date.

10.1.4 Financing through borrowings

(XIII) Loans from lending institutions

The Company signed a loan agreement with OSEO on 4 November 2008 for the partial financing of the innovation programme for a total amount of €150K. This loan is being repaid in quarterly $7,500 instalments made between 29 February 2016 and 31 August 2018.

On 31 December 2013, the Company signed a loan agreement with BPI France with the objective of the pre-financing of research and development expenses for the year 2013 eligible for the Research Tax Credit, amounting to € 100K. This loan was fully reimbursed in January 2016.

Please refer to Note 10.2 to the IFRS consolidated financial statements in Section 20.1 of the Annual Report for further details.

(Amounts in thousands of euros)	OSEO - Equity Loan	BPI – CIR Prefinancing loan	Total
At 31 December 2015	**83**	**100**	**183**
(+) Collection	-	-	-
(-) Reimbursement	(30)	(100)	(130)
At 31 December 2016	**53**	**-**	**53**
(+) Collection	-	-	-
(-) Reimbursement	(30)	-	(30)
At 31 December 2017	**23**	**-**	**23**

(XIV) Borrowings and miscellaneous financial debts

On 25 July 2014, the Company signed a € 150K loan agreement with SODISID within the context of a programme to create 10 jobs. This loan was fully reimbursed in 2016. The capital was fully reimbursed in February 2016.

The Company signed a € 30K loan agreement with SORBONNE UNIVERSITY (formerly UPMC) in November 2014 for the partial financing of industrial property costs in connection with French patent application No. 09 54354, entitled “Food composition for solar protection” filed on 25 June 2009 on behalf of the Company. The capital reimbursement was made in 2015.

At 31 December 2017, the balance of this item is nil.

Please refer to Note 10.3 to the IFRS consolidated financial statements in Section 20.1 of the Annual Report for further details.

(Amounts in thousands of euros)	SODISID loan	Total
At 31 December 2015	**150**	**150**
(+) Collection	-	-
(-) Reimbursement	(150)	(150)
At 31 December 2016	**-**	**-**

(XV) Convertible bond with the Bracknor Fund

In April 2017, the Company set up a credit facility with Bracknor Fund for up to €15 million in the form of 1,500 convertible bonds with a nominal value of €10K each, with warrants attached ("**convertible bonds and warrants**"). The Board of Directors decided to set up the credit facility on 3 April, making use of the delegation of authority granted by the tenth resolution of the Combined General Meeting of 10 June 2016.

The 1,500 bonds, with a term of 36 months, require the holder to exercise them, at the Company's request, in tranches of 300 each. Each bond grants rights to 1 convertible bond and warrant. The warrants will be immediately detached from the convertible bonds from the issue of the convertible bonds and warrants.

The convertible bonds have the following characteristics:

- Nominal value: 10K
- No interest
- Conversion terms as follows: N = CA / CP where
    - N is the number of shares that can be subscribed;
    - CA is the nominal value of the convertible bonds;
    - CP is 92% (i.e., 8% discount) of the lowest of the 10 volume-weighted average daily quoted prices of the Company's stock immediately preceding the conversion request date and at least equal to the face value of the action (0.20 €).

It is also specified that the Company may repay in cash according to the following formula: (CA/CP) x Weighted average quoted price on the conversion date.

The Board of Directors shall decide on the issue of:

- An initial tranche of 300 notes convertible into shares with share subscription warrants attached and 30 convertible bonds in respect of the commitment fee on 15 May 2017
- A second tranche of 300 notes convertible into shares with share subscription warrants attached and warrants on 7 July 2017.

The Company may issue 900 additional warrants in favour of Bracknor Fund Limited, which may give rise to a bond issue for an additional maximum amount of €9 million provided that the previous tranche issued is fully repaid.

Summary table of the issue and exercise of the first tranche of Notes convertible into shares with share subscription warrants attached

	TOTAL	Tranche #1	Tranche #2
Issuance date of convertible notes into shares with share subscription warrants attached		15/05/2017	07/07/2017
Number of convertible notes into shares issued*	630	330	300
Number of warrants issued	431,184	225,225	205,959

*: including 30 convertible notes into shares issued as fees related to the issue

	Outstanding shares after conversion	Date	Number	Shares	Date	Number	Shares
Conversion of convertible notes into shares with share subscription warrants attached	1,385,085	16/05/2017	75	306,122	07/07/2017	200	684,931
		26/05/2017	25	102,459	11/07/2017	100	342,465
		31/05/2017	25	104,166			
		02/06/2017	20	85,106			
		08/06/2017	20	85,106			
		09/06/2017	20	85,106			
		09/06/2017	42	178,723			
		09/06/2017	103	438,297			
Exercise of warrants	0	0			0		
Convertible notes into shares hold by Bracknor Fund Ltd	0	0			0		
Warrants hold by Bracknor Fund Ltd	431,184	225,225			205,959		
Total number of shares newly converted	2,412,481	1,385,085			1,027,396		

(See Section 21.1.5 of the Annual Report for more details on the characteristics of this instrument).

10.1.5 Off-balance-sheet commitments

(XVI) Commitments by way of financial debts

Commitments received

Borrowing	Guarantees received	Nominal	Residual amount at 31/12/2017
OSEO seed capital equity loan	- OSEO innovation risk participation for up to 20% of the outstanding loan - OSEO guarantee risk participation as part of the FNG Innovation procedure for 40% of the outstanding loan. - OSEO IDF risk participation for 40% of the outstanding amount of the loan	150	23

Commitments given

Borrowing	Commitments given	Nominal	Residual amount at 31/12/2017

OSEO reimbursable advance - "Quinolia" project	The agreement moreover provides for payment of a reimbursement annuity from 1 January 2009 and until 31 March of each year at the latest, corresponding to: 44% of the proceeds excluding taxes, assignments or granting of licenses, patents or know-how received during the previous calendar year when such transfers or leases related to all or part of the results of the assisted programme and to 44% of the proceeds excluding taxes generated by marketing and in particular, the sale to a third party or use by the beneficiary for the requirements of its own prototypes, pre-series and models, executed within as part of the assisted programme. The due amounts shall be attributed as a priority and for the full amount on the final deadline for payment to OSEO. The application of this mechanism shall not lead the company to pay an amount greater than the aid received.	229	119
BPI France reimbursable advance - "BIO 101"	The agreement moreover provides for payment of a reimbursement annuity from 1 January 2009 and until 31 March of each year at the latest, until 30 September 2023, corresponding to: 35.81 % of the pre-tax proceeds, assignments or granting of licenses, patents or know-how received during the previous calendar year when such transfers or leases related to all or part of the results of the assisted program, and to 35.81 % of the pre-tax proceeds generated by marketing and in particular, the sale to a third party or use by the beneficiary for the requirements of his own prototypes, pre-series, and models, executed within the context of the subsidised program. The due amounts shall be attributed as a priority and for the full amount on the final deadline for payment to BPI. The application of this mechanism shall not lead the company to pay an amount greater than the aid received.	1,100*	600

* Of which €500K will be paid upon completion of the project

(XVII) Property leases

On 31 December 2017, the amount of future rentals regarding the lease signed with SORBONNE UNIVERSITY (formerly UPMC) was as follows:

(Amounts in thousands of euros)	Effective start date of the lease	Lease expiry date	Rental expenses at 31/12/2017	Commitment until the next termination period		
				Up to 1 year	1- 5 years	Over 5 years
Paris - UPMC - laboratory and offices	15/12/2016	15/12/2018	78	87	-	-

10.2 CASH FLOWS

10.2.1 Cash flows linked to operating activities

Cash usage linked to operating activities for the years ended 31 December 2016 and 31 December 2017 amounted to €6,633K and €8,727K, respectively. This increase is mainly due to an increase in study and research expenses mainly related to:

- the SARA clinical programme: end of SARA-PK and launch of SARA-OBS
- the acceleration of non-clinical studies of the MACA programme.

10.2.2 Cash flows linked to investment activities

Cash usage linked to investment activities for the years ended 31 December 2016 and 31 December 2017 amounted to €129K and €1,287K, respectively.

10.2.3 Cash flows linked to financing activities

Cash flow from financing activities are as follows for the years presented:

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Capital increase, net of bond conversion	-	21,742
Expenses associated with capital increases	-	(2,043)
Subscription of warrants	-	22
Exercise of warrants & founder's warrants	58	31
Reimbursable advances received, net of repayments	634	(34)
Collection of subsidies	10	-
Debt issues, net of repayments	(280)	(30)
Gross financial interest paid	(6)	(2)
Bond issues	-	6,000
Interest on the investment account	24	6
Reimbursements of lease financing	(36)	(44)
Change in bank overdrafts	4	2
Cash flows linked to financing operations	**407**	**25,649**

The cash generated by the financing operations in 2017 comes mainly from the raising of funds as well as the issues of notes convertible into shares with share subscription warrants attached under the agreement with Bracknor Fund Limited.

10.3 BORROWING CONDITIONS AND FINANCING STRUCTURE

The information on the financing of the Group's activities is contained in section 10.1 "Information on capital, liquidity and sources of financing" of the Annual Report.

10.4 POSSIBLE RESTRICTIONS ON USE OF CAPITAL

Not Applicable

10.5 EXPECTED SOURCES OF FINANCING FOR FUTURE INVESTMENTS

Not Applicable.

11 RESEARCH AND DEVELOPMENT, PATENTS, LICENCES AND OTHER INDUSTRIAL PROPERTY RIGHTS

11.1 RESEARCH AND DEVELOPMENT

Biophytis is a biotechnology company created in 2006, which develops new classes of drugs against degenerative age-related diseases, for which there is currently little treatment available. **The two most advanced programs are sarcopenia i.e. age-related muscular degeneration (SARCOB program) and age-related macular degeneration (AMD) (MACULIA program).**

Investment in R&D for these two programs enabled the development of two drug candidates entering Phase II, Sarconeos for treating sarcopenia and Macuneos for treating AMD. They have the following characteristics:

- Two large markets under priority focus by health authorities and pharmaceutical companies.
- Two indications without available treatment.
- Convincing proof of concept and a described action mechanism.
- Products tailored to the specific characteristics of patients aged over sixty-five.

For each of the diseases, Biophytis has developed second-generation products, BIO 103 for treating sarcopenia and BIO 203 for treating AMD.

Most of the Company's staff consists of the research and development department made up of 20 individuals with high-level scientific training and more specifically, including 10 doctors of medicine, 2 physicians, and 2 pharmacists. Employees working in research and development are each individually subordinated to the Company by a model employment agreement stipulating a vesting clause for rights, inventions and creations developed by employees to the Company, on payment of supplementary compensation, as appropriate.

The Company records its research and development expenditure under expenses, in accordance with current accounting rules (IAS 38). The amount of gross research and development expenses for the years ended 31/12/2016 and 31/12/2017 amounted respectively to €6,788K and €7,043K, consisting mainly of salaries, internal development costs and fees paid to service providers conducting research and development work on behalf of the Company.

Biophytis' economic model is to take its programs as far as proof of clinical activity of a family of compounds, supplemented by the description of the action mechanism, proof of safety of candidate molecules and their characterisation for *secondary indications*. Then, to conclude partnerships with pharmaceutical companies in order to support the regulatory development as far as commercial launch.

11.2 PATENTS AND PATENT APPLICATIONS

11.2.1 Industrial property protection policy

Patents, patent applications and other intellectual property rights are extremely important in the biotechnology sector.

The intellectual property management strategy developed by Biophytis aims to ensure effective protection of the Company's innovations, both from the perspective of the products developed and geographically, with the aim of protecting future access to markets for its products when they are marketed.

This strategy of protecting Biophytis' innovations is intended to constitute a genuine barrier to the intrusion of third parties into its proprietary domain. Its solid intellectual property portfolio has been built both on the basis of a significant internal research development effort and as part of exclusive research and collaboration agreements with academic institutions (SORBONNE UNIVERSITY, CNRS, Inserm, INRA, AIM) or biopharmaceutical companies (Metabrain Research, Iris Pharma).

The Company's industrial property protection policy covers Biophytis' two key fields of innovation: treatment of sarcopenia (Sarconeos and BIO 103 products) and the treatment of AMD (Macuneos and BIO 203 products). The filed patents thus protect the developed compounds and related therapeutic applications. In this way, most frequently, at least two families of patents protect the use of a candidate drug developed by Biophytis.

The patent filing policy established by Biophytis aims at the initial filing of priority patent applications in France and then the extension of the application by an international patent application through the procedure known as the "*Patent Cooperation Treaty*" (PCT). Various countries among the 142 countries likely to be covered by this procedure are determined according to Biophytis' business strategy for the patent. Two main protection zones are defined:

- Europe and in particular, the major European countries and the United States and Japan, where most of the main major pharmaceutical companies are concentrated;
- the rest of the world and notably the BRIC zone (Brazil, Russia, India, China), and possibly Canada and Australia

This international protection strategy for patents has the objective of securing the first patents in these target areas more rapidly and of placing each innovation in a strong position to obtain the most effective possible protection in all of these countries.

This first level of patent protection will be supplemented by the regulatory protection of the data constituting the registration files for marketing authorisations.

11.2.2 Patents and patent applications of which the Company is the owner or licensee

a) Patent applications

The period of validity of patents is 20 years starting from the date of filing of applications. In the United States, under certain conditions, this validity period may be extended by adding a supplementary period (the "*Patent Term Adjustment*" or "*Patent Term Extension*"). Moreover, the validity of a patent in the biotechnology sector may also be extended by at most 5 years, notably in the majority of European countries and the US, via the filing of a supplementary certificate of protection (CCP).

The average duration for the examination of a patent application is around 3 to 5 years from the start of the examination.

The Company relies on the following patent portfolio, filed with full ownership or joint ownership, or subject to a license for its own benefit that is derived from the two research programs:

Patents relating to the SARCOB program:

- Patent family No. S1 “metabolic syndrome”: the invention protected by these patents is the use of phytoecdysones in the preparation of a composition to act on metabolic syndrome. The patents are equally jointly owned (50/50) by the Company and public partners, it being specified that the Company holds the exclusive exploitation rights under the agreement described in 11.3.2 (I) (hereinafter, “**S I**”).

- Patent family No. S2 “weight stabilisation”: the invention protected by these patents concerns the use of phytoecdysones in stabilising weight after dieting. The patents are jointly equally owned (50/50) by the Company and a public partner, it being specified that the Company holds the exclusive exploitation rights under the agreement described in 11.3.2 (I) (hereinafter, “**S II**”).

- Patent family No. S3 “muscular quality”: the invention protected by these patents is the use of phytoecdysones to improve muscular quality in obese and/or sarcopenic mammals. The patents are jointly owned (50/50) by the Company and public partners, it being specified that the Company holds the exclusive exploitation rights under the agreement described in 11.3.2 (I) (hereinafter, “**S III**”).

- Patent family No. S4 “phytoecdysone analogue”: the invention protected by these patents relates to a process whereby new chemical entities are used in the preparation of medicines. The patents are jointly owned (70/30) by the Company and a public partner, respectively, it being specified that the Company holds the exclusive exploitation rights under the agreement described in 11.3.2 (I) (hereinafter, “**S IV**”).

- Patent Family No. S5 “20-hydroxyecdysone extracts”: the invention protected by this patent relates to a process for extracting purified 20-hydroxyecdysone and the therapeutic use of these extracts to improve muscle function or treat cardiovascular disease. The joint ownership of the S V patent family is governed by the SARCOB consortium agreement specified in 11.3.2 (I) (hereinafter “**S V**”).

- Patent Family No. S6 “20-hydroxyecdysone”: the invention protected by this patent relates to the use of 20-hydroxyecdysone components and its derivatives to treat myopathies and other muscular dystrophies. The patents will be held in joint ownership with SORBONNE UNIVERSITY and the CNRS (hereinafter ""**S VI**”).

- Patent family No. S7 “Loss of muscle strength”: the invention protected by this patent relates to the use of phytoecdysones to prevent loss of muscle strength after immobilisation. The patents are held in joint ownership by the Company and SORBONNE UNIVERSITY (hereinafter “**S VII**”).

Patent family		S I	S II	S II	S IV	S V	S VI	S VII
Application No.		FR 0759478	FR 1160280	FR 1161519	FR 1454538	FR 1753775	FR 1758071	FR 1851778
SARCOB	Sarconeos BIO 103	✔	✔	✔ ✔	✔	✔		✔
	BIO 101					✔	✔	

Patents relating to the MACULIA program:

- Patent family No. MI “Photo-protection”: the invention protected by these patents relates to the use of a composition to protect the skin against sun damage. The patents are 50% jointly owned by the Company anda public partner, it being specified that the Company holdsthe exclusive exploitation rights under the agreement described in 11.3.2 (II) (hereinafter “**M I**”).

- Patent family No. M II “AMD”: This invention relates to the use of compounds to protect the eye against AMD. The patents are 50% jointly owned by the Company anda public partner, it being specified that the Company holds the exclusive exploitation rights under the agreement described in 11.3.2 (II) (hereinafter “**M II**”).

- Patent family No. M III “Composition for protecting retinal epithelial cells”: the invention protected by these patents relate to the use of a composition using norbixin in the treatment of AMD. The patents are 60% jointly owned by the Company and the remaining held by a public partner, it being specified that the Company holds the exclusive exploitation rights under the agreement described in 11.3.2 (II) (hereinafter “**M III**”).

- Patent family No. M IV “Use of 3-deoxhyanthocyanidins for the treatment of eye diseases”: the invention protected by these patents relates to the use of compounds from the family of flavonoids, anthocyanidins, for the treatment, prevention and/or stabilisation of AMD and/or Stargardt’s disease, pigmentary retinopathy and/or diabetic retinopathy. The patents are 50% jointly owned by the Company anda public partner, it being specified that the Company holds the exclusive exploitation rights under the agreement described in 11.3.2 (II) (hereinafter “**M IV**”).

Patent family		M I	M II	M III	M IV
Application No.		FR 0954354	FR 1154172	FR 1553957	FR 1554761
MACULIA	Macuneos BIO 201	✔	✔	✔	✔
	BIO 203		✔		✔

b) Nature and scope of patents or patent applications from the Company

The Company's patents and patent applications reflect the research and development efforts implemented to provide innovative solutions for the treatment of sarcopenia and other muscular dystrophies (SARCOB technology), and the treatment of AMD (age-related macular degeneration) and other retinopathies (MACULIA technology).

(XVIII) SARCOB program for sarcopenia and other muscular dystrophies

- ***S 1***

The invention protected by this patent relates to the use of phytoecdysones in the preparation of a composition to act on metabolic syndrome.

The international patent application (PCT) "use of phytoecdysones in the preparation of a composition to act on metabolic syndrome" has been filed by the Company, the SORBONNE UNIVERSITY and CNRS under the priority of a French patent FR 0759478. The PCT patent application has been extended to Australia, Brazil, Canada, China, Europe, India, Japan, Russia and the United States.

The Company holds 50% ownership of these patents, with the remaining 50% held by SORBONNE UNIVERSITY (25%) and the CNRS (25%).

Priority					
Country	**Date of application**	**Application No.**	**Date of public'n**	**Public'n No.**	**Status of procedure**
FR	30/11/2007	FR0759478	05/06/2009	FR2924346	Granted (19/02/2010)
WO	19/11/2008	WO2008FR052088	11/06/2009	WO2009071804	
AU	19/11/2008	AU2008332981	11/06/2009	AU2008332981	Granted (25/09/2014)
BR	19/11/2008	PI0820455-1	29/09/2015	BR0820455-1	Review in progress
CA	19/11/2008	2,706,821	11/06/2009	CA2706821	Abandoned
CN	19/11/2008	CN200881185514.X	02/11/2011	CN102231986A	Granted (22/01/2014)
EP	19/11/2008	08856497.6	18/08/2010	EP2217255	Review in progress
IN	19/11/2008	3976/DELNP/2010	11/11/2011	452011	Review in progress
JP	19/11/2008	2010-535430	17/02/2011	JP2011504921	Abandoned
RU	19/11/2008	RU2010126625	10/01/2012	RU2010126625	Granted (27/08/2013)
US	19/11/2008	US 12/745,315	10/02/2011	US20110033561	Granted (07/08/2012)

The patent was granted in Australia, China, Russia, and the United States. It has been published in Europe, India, and Brazil. Applications are thus under examination by the regional (EPO) and national offices for these three countries. It was rejected in Japan and the application is deemed withdrawn in Canada.

The patent in the United States and Australia has been granted for a method of reducing fat in a subject by administering pure 20-hydroxyecdysone or 20-hydroxyecdysone in the form of a quinoa extract at a determined dose. We expect to obtain similar patent protection in Europe.

In China and Russia, the patent was granted on the same terms but without any limitation on the dose administered.

- ***S II***

The invention protected by these patents relates to the use of phytoecdysones in stabilising weight after dieting.

The international patent application (PCT) “phytoecdysones for use in stabilising weight after dieting” was filed by the Company and SORBONNE UNIVERSITY under the priority of French patent FR 1160280. The patent application PCT has been extended to China, Europe, Japan, and the United States.

The Company holds a 50% ownership of these patents, with the remaining 50% held by SORBONNE UNIVERSITY.

Priority					
Country	**Date of application**	**Application No.**	**Date of public'n**	**Public'n No.**	**Status of procedure**
FR	10/11/2011	FR1160280	17/05/2013	FR2982489	Granted (27/12/2013)
WO	12/11/2012	WO2012FR052600	16/05/2013	WO2013068704	
CN	12/11/2012	CN201280055214.8	30/07/2014	CN103957727A	Granted (14/09/2016)
EP	12/11/2012	12795522.7	17/09/2014	EP2775859	Granted and validated in the designated European Member States (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HR, HU, IE, IT, LU, NL, NO, PL, PT, RO, SE, TR) (18/01/2017)
JP	12/11/2012	JP2014540542	11/12/2014	JP2014533256	Review in progress modifications (18/01/2017)
JP	13/02/2018	JP 2018-23066			Divisional application
US	12/11/2012	US14/356,646	16/10/2014	US20140309203	Abandoned but continued with a new patent below
US01	22/11/2016	US15/359,477	16/03/2017	US20170071955	Continuity

They have all been published and applications are under review by the national offices. The patent was granted for Europe, validated in 2017 in the selected European contracting countries.

The European patent has been granted for the use of phytoecdysone to avoid weight regain in obese mammals after a low-calorie diet.

- ***S III***

The invention protected by these patents relates to the use of phytoecdysones in improving muscular quality.

International Patent Application (PCT) "phytoecdysones for use in improving the muscular quality of obese and/or sarcopenic mammals" was granted by the Company, SORBONNE

UNIVERSITY and the INRA under the priority of French patent No. FR1161519. The PCT patent application was extended to China, Europe, and the United States.

The Company holds 50% ownership of these patents and50% are held by SORBONNE UNIVERSITY (30%) and the INRA (20%).

Priority					
Country	**Date of application**	**Application No.**	**Date of public'n**	**Public'n No.**	**Status of procedure**
FR	13/12/2011	FR1161519	14/06/2013	FR2983733	Granted (22/12/2017)
WO	13/12/2012	WO2012FR052931	20/06/2013	WO2013088084	
BR	13/12/2012	BR112014014520-2			Under review
CN	13/12/2012	CN201280066803.6	08/10/2014	CN104093409A	Granted (30/06/2017)
EP	13/12/2012	12813926.8	22/10/2014	EP2790706	Review in progress (23/09/2016)
US	13/12/2012	US14/364,249	09/04/2015	US2015099022	Abandoned but continuity with a new patent below
US01	04/12/2016	US15368655	18/05/2017	US20170136041	Continuity

The patent was granted in the France. Granting is pending in China. They have all been published and applications are under review by the other national offices.

- ***S IV***

The invention protected by these patents relates to the products derived from 20-hydroxyecdysones and their use in the preparation of drugs.

The international patent application (PCT) "Products derived from 20-hydroxyecdysones and their use in the preparation of drugs" has been filed by the Company, SORBONNE UNIVERSITY and Metabrain Research under the priority of French patent No. FR1454538. The PCT patent application has been extended to Australia, Brazil, Canada, China, Europe, India, Japan, South Korea, Russia and the United States.

The Company will be the holder on granting of the French patent of 70% of joint ownership of these patents, and 30% will be held by SORBONNE UNIVERSITY.

Country	Date of application	Application No.	Date of public'n	Public'n No.	Status of procedure
FR	20/05/2014	FR1454538	27/11/2015	FR3021318	Granted (28/04/2017)
WO	20/05/2015	WO2015FR051332	26/11/2015	WO2015177419	
AU	20/05/2015	AU2015263121	12/01/2017	AU2015263121	Published
BR	20/05/2015	BR112016027053	15/08/2017	BR112016027053	Published
CA	20/05/2015	CA2949649			Beginning of review in 2020
CN	20/05/2015	CN201580038427 3	22/04/2017	CN106536539	Under review
EP	20/05/2015	15732785.9	29/03/2017	3145942	Under review
IN	20/05/2015	201617043009			Under review
JP	20/05/2015	2017513358	22/06/2017	JP2017516551	Published
KR	20/05/2015	KR10-2016-7035614	09/03/2017	KR20170027319	Published
RU	20/05/2015	RU2016149619			Under review
IL	20/05/2015	IL249062			Under review
US	20/05/2015	US15/311,967	10/08/2017	2017-0226151	Granted (10/04/2018)

The patent was granted in France. It has been published in Australia, Brazil, China, Europe, South Korea and Japan. It has been granted in the United States. It is under review in the other national offices (Russia, India, Israel).

The Examiner has given his approval for several compounds, including BIO103, in the context of the PCT.

- ***S V***

The invention protected by this patent relates to 20-hydroxyecdysone extracts and their use in the preparation of drugs.

The invention was patented on 28 April 2017 under number FR1753775.

The Company will co-own the patent with SORBONNE UNIVERSITY.

Country	Date of application	Application No.	Date of public'n	Public'n No.	Status of procedure
FR	28/04/2017	FR1753775			Under review

The patent has not yet been published or granted in France and has not yet been extended regionally or internationally.

- ***S VI***

The invention protected by this patent relates to the process of obtaining/purifying BIO101 related to sarcopenia and other muscular dystrophies.

The invention was patented on 31 August 2017 under number FR1758071.

The Company will co-own the patent with SORBONNE UNIVERSITY and the CNRS.

Country	Date of application	Application No.	Date of public'n	Public'n No.	Status of procedure
FR	31/08/2017	FR1758071			Under review

The patent has not yet been published nor granted in France and has not yet been extended by regional or international means. [Note: to be updated if necessary because it is scheduled for 28 April 2018 at the latest].

- *S VII*

The invention protected by this patent relates to the use of phytoecdysones to prevent muscle loss after immobilisation.

The invention was patented on 28 February 2018 under number FR1851778.

The Company will co-own the patent with SORBONNE UNIVERSITY.

Country	Date of application	Application No.	Date of public'n	Public'n No.	Status of procedure
FR	28/02/2018	FR1851778			Under review

The patent has not yet been published or granted in France and has not yet been extended regionally or internationally.

(XIX) <u>MACULIA program: AMD and other retinopathies</u>

- ***M I***

The invention protected by these patents relates to the use of bixin and norbixin to protect the skin against sun damage.

The international patent application (PCT) "Food composition intended for solar protection" was filed by the Company and SORBONNE UNIVERSITY under priority of a French patent FR 0954354. A French divisional application FR 1153996 was filed and granted on 16 August 2013. The PCT patent application was extended to Australia, Brazil, Europe, and the United States.

The Company holds 50% ownership of these patents, and 50% held by SORBONNE UNIVERSITY. The co-ownership of the French patent (and of the divisional application) has not yet been registered in the French National Patent Register.

Priority					
Country	**Date of application**	**Application No.**	**Date of public'n**	**Public'n No.**	**Status of procedure**
FR	25/06/2009	FR0954354	31/12/2010	FR2947173	Granted (27/01/2012)
WO	25/06/2010	WO2010FR051323	29/12/2010	WO2010149942	
AU	25/06/2010	2010264314	23/02/2012	AU2010264314	
BR	25/06/2010	PI1010113-6	15/03/2016	PI1010113	Granting pending (23/01/2018)
EP	25/06/2010	10745340.9	02/05/2012	EP2445476	Review in progress (10/05/2017)
FR (divisional application)	10/05/2011	FR1153996	05/08/2011	FR2955767	Granted (16/08/2013)
US	25/06/2010	US13/380,768	14/06/2012	US20120149776	Granted 13/11/2015

The patent was granted in the United States. Granting is pending in Brazil. The application has been published at the European office and is under review. It was abandoned in Australia.

The US patent has been granted for the use of bixin or norbixin, orally and at a fixed dose, to protect against damage to the skin caused by ultraviolet exposure.

- ***M II***

The invention protected by these patents relates to the use of bixin and norbixin to protect the eyes against AMD.

The international patent application (PCT) "use of compounds and composition for the treatment of age-related macular degeneration" was filed by the Company and SORBONNE UNIVERSITY under the priority of a French patent No. FR 1154172. A French divisional application FR 1361229 was filed and granted on 05 August 2016. The PCT patent application was extended to Brazil, Europe, Japan, and the United States.

The Company holds 50% ownership of these patentsand 50% are held by SORBONNE UNIVERSITY (33.33%) and the CNRS (16.7%).

Priority					
Country	**Date of application**	**Application No.**	**Date of public'n**	**Public'n No.**	**Status of procedure**
FR	13/05/2011	FR1154172	16/11/2012	FR2975008	Granted (07/03/2014)
Country	**Date of application**	**Application No.**	**Date of public'n**	**Public'n No.**	**Status of procedure**
WO	14/05/2012	WO2012FR000193	22/11/2012	WO2012156600	
FR (divisional application)	15/11/2013	FR1361229	18/04/2014	FR2996773	Granted (05/08/2016)
BR	14/05/2012	BR11 2013 029318-7	18/04/2017	BR112013029318	Published
EP	14/05/2012	12728639.1	16/04/2014	EP2717891	Granted and validated in the designated European Member States (AT, BE, BG, CH, CZ, DE, DK, ES, FI, FR, GB, GR, HR, HU, IE, IT, LU, NL, NO, PL, PT, RO, SE, TR) (14/09/2016)
JP	14/05/2012	JP2014510851	19/06/2014	JP2014514366	Completed by a new filing JP01 below
JP01	17/02/2017	JP2017278 51	29/06/2017	JP2017114892	Divisional application
US	14/05/2012	US14/117,461	30/10/2014	US20140322371	Abandoned but process continues by filing a divisional application below
US	29/08/2017	US15/688,917			Continuity

The patents have all been published and applications are under review by the national offices. It has been granted for Europe and is currently being validated in the various European contracting countries.

- ***M III***

The invention protected by this patent relates to the use of norbixin in the treatment of AMD.

The international patent application (PCT) "Composition for protecting the cells of the retinal pigment epithelium" was filed by the Company and SORBONNE UNIVERSITY under the

priority of a French patent FR 1553957. The PCT patent application has been extended to Australia, Brazil, Canada, China, Europe, India, Japan, South Korea and the United States.

The Company will hold 60% ownership of these patents, and 40% will be held by SORBONNE UNIVERSITY (13.4%), the CNRS (13.3%) and the INSERM (13.3%). On 5 June 2015, the Company acquired Iris Pharma's 33% ownership of the patents.

Country	Date of application	Application No.	Date of public'n	Public'n No.	Status of procedure
FR	30/04/2015	FR1553957	04/11/2016	FR3035589	Granting pending
WO	28/04/2016	WO2016FR051001	03/11/2016	WO2016174360	
AU	28/04/2016	AU2016256637			Review beginning in 2021
BR	28/04/2016	BR1120170232642			Review beginning in 2019
CA	28/04/2016	CA2984405			Review beginning in 2021
CN	28/04/2016	CN201680037407 9	16/02/2018	CN 107708685 A	Under review
EP	28/04/2016	EP16722319.7	07/03/2018	EP3288551	Published
IN	28/04/2016	IN201717040968			Review beginning in 2019
JP	28/04/2016	JP2017-556593			Review beginning in 2019
KR	28/04/2016	KR10-2017-7034255			Review beginning in 2021
MX	28/04/2016	MX2017/013918			Under review
RU	28/04/2016	RU2017141462			Review beginning in 2019
IL	28/04/2016	IL 255276			Under review
US	28/04/2016	US15/570720			Under review

Granting is pending in France. The patent was published on 7 March 2018 for Europe. It is under review by the other national offices.

- ***M IV***

The invention protected by this patent relates to the use of compounds of the family of flavonoids, anthocyanidins, in the treatment, prevention and/or stabilisation of AMD and/or Stargardt disease, pigmentary retinopathy and/or diabetic retinopathy.

The international patent application (PCT) "Use of 3-deoxhyanthocyanidins for treating ocular diseases" was filed by the Company, SORBONNE UNIVERSITY, the CNRS and INSERM under the priority of French patent FR 1554761. It is being reviewed after publication. Europe was designated in the PCT application.

The Company holds 50% ownership of these patents, and 50% are held by SORBONNE UNIVERSITY (16.7%), the CNRS (16.7%) and the INSERM (16.6%).

Country	Date of application	Application No.	Date of public'n	Public'n No.	Status of procedure
FR	27/05/2015	FR1554761	02/12/2016	FR3036620	Granted
WO	27/05/2015	WO2015FR51262	01/12/2016	WO2016189260	Review in progress

The patent was granted in France and was published by WIPO before being reviewed by the regional or national offices designated in the PCT application.

c) Inventions in progress – know-how

As part of the Company's research and development activities in order to continue the ongoing programs, new inventions developed by the Company should be filed in 2018.

11.2.3 Disputes

To date, no litigation (including any opposition proceedings for patents) relating to intellectual property rights, has been submitted by or against the Company to the courts.

11.3 AGREEMENTS FOR COLLABORATION, RESEARCH, PROVISION OF SERVICES AND LICENSES GRANTED BY THE COMPANY OR GRANTED TO IT

The table below presents for each of the patent families the contractual framework governing (i) research and development, (ii) exploitation and (iii) ownership of the results.

Patents	Research and development agreement	Exploitation agreement	Joint ownership regulation
S I1	N/A	Exploitation agreement between the Company, SATT and Sorbonne University signed on 01/01/2016 with effect from 27 May 2015	Rules between the Company, Sorbonne University and the CNRS signed on 10/07/2008 with effect from 30/11/2007
S II	Consortium agreement dated 22/11/2013		Rules between the Company and Sorbonne University dated 29/03/2016 with effect from 10/11/2011
S III			Rules between the Company, Sorbonne University and the INRA signed on 06/07/2008 with effect from 13/12/2011
S IV			Rules between the Company and Sorbonne University signed on 18/11/2016 with effect from 20/05/2014
S V	Consortium agreement dated 22/11/2013		
S VI	SORBONNE UNIVERSITY/CNRS research collaboration agreement dated 01/07/2016	N/A	N/A
S VII	N/A	N/A	N/A
M I	N/A	Exploitation agreement between the Company, SATTLutech and Sorbonne University signed on 01/01/2016 with effect from 28/05/2015	Rules between the Company and Sorbonne University signed on 10/11/2014 with effect from 25/06/2009
M II	Collaboration agreement dated 20/11/2014		Rules between the Company, Sorbonne University and the CNRS signed on 28/07/2017 with effect from 13/05/2011

M III			Rules between the Company, Sorbonne University, the CNRS and Inserm Transfert SA signed on 16/10*/2017 with effect from 30/04/2015
M IV			Rules between the Company, Sorbonne University, the CNRS and Inserm Transfert SA signed on 18/12/2017 with effect from 27/05/2015

11.3.1 Collaboration, research, service provision and licensing agreements granted by the Company or granted to it

(XX) SARCOB consortium agreement

On 22 November 2013, the Company concluded a consortium agreement with effect from 1 January 2012 for a period of 24 months starting from this effective date and concluded with Metabrain Research, SORBONNE UNIVERSITY, the CRNS, INSERM, AIM (Myology Institute Association) and the INRA. The patents in families S II, S III, S IV and S V were developed under this consortium agreement. While this agreement has now expired with regard to the research and collaboration aspects, it remains in force with regard to the rules governing the transfer of intellectual property rights on the results of research related to family S V patents, for which the negotiation of co-ownership rules is in progress, on a basis similar to the rules made for the families S I, S II, S III and S IV patents described below in 11.3.2. These aspects are developed in 11.3.2.

(XXI) MACULIA consortium agreement

On 27 July 2012, the Company entered into a consortium agreement with SORBONNE UNIVERSITY and Iris Pharma with a view to conducting research on the treatment of the atrophic form of AMD. The duration of this agreement is that of the execution of the tasks described in the agreement increased by 6 months. This agreement has now expired with regard to the research and collaboration aspects and co-ownership rules.

(XXII) MACULIA collaboration agreement

On 20 November 2014, the Company, SORBONNE UNIVERSITY, the CNRS and the INSERM entered into a collaboration agreement following (i) the research agreement of 7 September 2010 between the same parties, and (ii) the consortium agreement of 27 July 2012 between the Company, SORBONNE UNIVERSITY and Iris Pharma. This agreement has a term of six months expiring on 1 April 2015. A first renewal amendment agreement for a further period of six months with retroactive effect from 1 April 2015 onwards, expiring on 30 September 2015, was signed on 26 May 2015. A second renewal amendment agreement taking effect retroactively on 1 October 2015 was signed on 16 February 2016 and expires on 31 December 2016. A third renewal amendment agreement with retroactive effect from 1 January 2017 and

expiring on 31 December 2017, was signed on 13 January 2017. A fourth renewal amendment agreement with retroactive effect from 1 January 2018 for 12 months was concluded.

The object of this collaboration agreement is to continue the research undertaken within the context of the two previous agreements. The successive amendment agreements concluded on 26 May 2015 also modify fees paid by the Company to SORBONNE UNIVERSITY, the CNRS and the INSERM to provide for the payment of a five-figure lump sum, one-half of which is payable on signing, with the balance on expiry of the agreement. The agreement also contains provisions relating to the ownership of research results and the exploitation of the intellectual property so obtained, which are described in 11.3.2.

(XXIII) Inserm research services agreement

On 27 March 2017, the Company, SORBONNE UNIVERSITY and Inserm Transfert SA concluded a research services agreement to study the effect of phytoecdysones on skeletal muscle. The agreement came into force with a retroactive effect from 1 August 2015 for a period of 18 months. Fees paid to the institutions by the Company is a lump sum of several thousand euros. All results from the present agreement shall be the entire and exclusive property of the Company.

(XXIV) SORBONNE UNIVERSITY/CNRS research collaboration agreement

The Society, SORBONNE UNIVERSITY and CNRS have concluded a research collaboration agreement on the effects of BIO 101 and BIO 103 on certain cachexias. The agreement entered into effect on 1 March 2017 for a period of three months. The results obtained from this research collaboration agreement shall be jointly and equally owned by the parties.

By means of an amendment agreement, the parties have decided to (i) extend the collaboration agreement for a period of 12 months until 30/06/2019 and (ii) supplement the program with an additional study to be carried out within a period of 6 months.

(XXV) SORBONNE UNIVERSITY/CNRS research collaboration agreement

The Company, SORBONNE UNIVERSITY and CNRS concluded a collaboration agreement concerning the effects of BIO101 and BIO 103 on the prevention of certain insufficiencies that appearing during the ageing process. The agreement entered into effect on 1 July 2016 for a period of 6 months. The results obtained in the execution of this agreement shall be jointly and equally owned by the parties. The contract was renewed by an amendment agreement dated 22 March 2017 for a period expiring on 31 July 2017.

No renewal amendment agreement has been signed.

Family S VI patents were developed within the context of this collaboration agreement. Moreover, insofar as no independent co-ownership rules have been concluded concerning the the S VI family patents, the co-ownership of the S VI family remains governed by the provisions of the said collaboration agreement.

The agreements described in (I) to (VI) above are significant agreements of the Company under Section 22 of this Annual Report.

(XXVI) SARCOB consortium agreement - SATT Lutech Operating Agreement of 1 January 2016

The Agreement of 22 November 2013 (paragraph 11.3.1 (I)) notably provides that the common results arising from the joint and unseverable inventive and/or intellectual contribution of at least two parties are the joint property of the parties which generated it. Joint ownership rules must be established before any exploitation for any common result protected by an intellectual property title and/or which could give rise to industrial or commercial exploitation.

On 13 April 2015, for the family S IV patents, the Company exercised the exclusive worldwide option to which it was entitled under the consortium agreement to exploit, for commercial and industrial purposes, the joint results of which the Company is joint owner in the field of obesity, sarcopenia, diabetes and sarcopenic obesity. This financial year initiated a 12-month period during which the parties negotiated the terms and conditions of an operating agreement under the terms of which the Company now has an exclusive worldwide exploitation licence.

The negotiations resulted in the conclusion on 27 May 2015, of an agreement between the Company and SATT Lutech, acting in the name and on behalf of SORBONNE UNIVERSITY, the CNRS and the INRA, then an operating agreement between these same parties on 1 January 2016. This agreement annuls and replaces the previous one and entered into effect retroactively on 27 May 2015. It may remain in effect until the expiry or invalidation of the last of the patents. It covers not only the family S IV patents covered by the consortium agreement, but also covers the family S I patents (covered by the exploitation agreement described in paragraph 11.3.2 (I) above) and family S II and S III patents. The contractual structure of the consideration payable by the Company is as follows: firstly, in the year after the first marketing of a product and in any event at the latest, from 2023 onwards, the Company will pay a guaranteed annual minimum, which shall be deducted from the amount of fees effectively due annually. On this point, with regard to the direct exploitation, the agreement provides for an annual royalty for a figure based on the net sales of products, distinguishing between sales of nutraceutical and medicinal products. With regard to indirect exploitation, it provides for annual double-digit royalties based on income received from licensees, distinguishing (i) between the sales of nutraceutical products (double-digit royalties) and drug products (two or one-digit royalties) and (ii) the product development phase (phase 1, 2 or 3) at the time of the conclusion of the licensing agreement.

(XXVII) MACULIA consortium agreement - SATT Lutech Operating Agreement of 1 January 2016

The agreement of 27 July 2012 (paragraph 11.3.1 (II)) provides that common results arising from the joint and unseverable inventive and/or intellectual contribution of at least two parties are the joint property of the parties which generated them. Joint ownership rules must be established before any exploitation for any common result protected by an intellectual property title and/or which could give rise to industrial or commercial exploitation. The joint owner shall decide whether their common results shall form the object of joint patents. The consortium agreement already provides that in case of exploitation by concession of licensing/sub-licenses to third parties, the Company will pay a percentage of the amounts received.

The Company negotiated the terms and conditions of an operating agreement related not only the family S IV patents but also those of families M I, M II and M III, under the terms of which

the Company will benefit from an exclusive and global license. The negotiations resulted in the conclusion on 28 May 2015 of an agreement between the Company and SATT Lutech, acting in the name and on behalf of SORBONNE UNIVERSITY, the CNRS and INSERM, then an exploitation agreement between these same parties on 1 January 2016. This agreement annulled and replaced the previous one and entered into effect retroactively on 28 May 2015. The contractual structure of the consideration payable by the Company is as follows: firstly, in the year following the first marketing of a nutraceutical product and in any event no later than in 2020, the Company will pay an annual guaranteed minimum. In the same way, the Company will pay a guaranteed minimum in the event of marketing of a drug product and in any event no later than from 2026. These amounts will be deducted from the amount of royalties effectively due annually. For direct exploitation, it also provides for an annual royalty of a figure based on net sales of products, distinguishing between sales of nutraceutical and medicinal drugs. For indirect exploitation, it also provides for annual double-digit royalties based on income received from licensees, distinguishing (i) between the sales of nutraceuticals (double-digit royalties) and drug products (one or two-digit royalties) and (ii) the product development phase of these products (phase 1, 2 or 3) at the time of conclusion of the licensing agreement.

(XXVIII) <u>MACULIA collaboration agreement</u>

The collaboration agreement of 20 November 2014 (paragraph (X) (III)) provides that the parties are automatically equal joint owners of the results. Joint ownership rules must be established before any exploitation for any common result protected by an intellectual property title and/or which could give rise to industrial or commercial exploitation.

The Company benefits from an exclusive global option for exploiting the joint results for industrial and commercial purposes in the field of treatment for retinal pathologies studied within the context of the agreement, particularly AMD, Stargardt disease and retinopathies, exercisable during the duration of the consortium agreement and during the 6 months following its expiry or termination. This option has not at this stage been exercised by the Company, since the research conducted as part of the implementation of the cooperation agreement is still in progress and at this stage has not been subject to a patent application within six (6) months from the end of the research.

11.3.3 Agreements on the ownership of industrial property

(XXIX) Joint ownership rules for family S I patents

On 9 July 2008, the Company concluded joint ownership rules with SORBONNE UNIVERSITY and the CNRS and an exploitation agreement for the “metabolic syndrome” patent and associated know-how. With regard to the provisions on the the Company’s exploitation rights concerning the “metabolic syndrome” patent and the associated know-how, the agreement was terminated and replaced by the agreement of 27 May 2015 described in 11.3.2 (II) below. It remains applicable as regards the co-ownership provisions that shall remain in force until the expiry or waiver of the last of the patents.

The ownership of the "Metabolic Syndrome" patent is divided as follows: (i) 50% for the Company, (ii) 25% for the CNRS, and (iii) 25% for the UMPC. The Company is in charge of patent management. In the event of an assignment by one party of its ownership of all or part of the patents or rights to know-how, the other parties shall have a pre-emptive right of first refusal for a period of 60 days.

(XXX) Joint ownership rules for family S II patents

On 21 March 2016, the Company and SORBONNE UNIVERSITY concluded joint ownership rules for family S II patents with retroactive effect from 10 November 2011. The joint ownership regulations shall remain in force until the last of the patents expires or is waived.

The ownership of the patents is divided as follows: (i) 50% for the Company and (ii) 50% for the UPMC. The Company is in charge of patent management. In the event of an assignment by one party of its ownership of all or part of the patents or rights to know-how, the other parties shall have a pre-emptive right of first refusal for a period of 60 days.

Under these rules, the Company has the exclusive exploitation of patents in areas specified by the operating agreement concluded between the Company, SATT and SORBONNE UNIVERSITY on 1 January 2016.

(XXXI) Joint ownership rules for family S II patents

The Company, SORBONNE UNIVERSITY and the INRA concluded on 6 July 2017 a joint ownership rules for the partial assignment of ownership on the family S III patent, with retroactive effect from 13 December 2011. The joint ownership rules shall remain in force until the last of the patents expires or is waived.

The ownership of the patents is divided as follows: (i) 50% for the Company, (ii) 30% for SORBONNE UNIVERSITY and (iii) 20% for the INRA. The Company is in charge of patent management. In the event of an assignment by one party of its ownership on all or part of the patents or rights to know-how, the other parties shall have a pre-emptive right of first refusal for a period of 60 days.

Under these rules, the Company has the exclusive exploitation of patents in areas specified by the operating agreement concluded between the Company, SATT and SORBONNE UNIVERSITY on 1 January 2016.

(XXXII) Joint ownership rules for family S IV patents

On 18 November 2016, the Company and SORBONNE UNIVERSITY concluded joint ownership rules for family S IV patents with effect from 20 May 2014. The joint ownership regulations shall remain in force until the last of the patents expires or is waived.

The ownership of the patents is divided as follows: (i) 70% for the Company and (ii) 30% for SORBONNE UNIVERSITY. The Company is in charge of patent management. In the event of an assignment by one party of its ownership on all or part of the patents or rights to know-how, the other parties shall have a pre-emptive right of first refusal for a period of 60 days.

Under these rules, the Company has the exclusive exploitation of patents in areas specified by the operating agreement concluded between the Company, SATT and SORBONNE UNIVERSITY on 1 January 2016.

The agreements described in (I) to (VIII) above are significant agreements of the Company under Section 22 of this Annual Report.

(XXXIII) Joint ownership rules for family S V patents

The joint ownership of the S V patent family is governed by the SARCOB consortium agreement referred to in 11.3.2 (I).

(XXXIV) Joint ownership rules for family S VI patents

The joint ownership of the S V patent family is governed by the SORBONNE UNIVERSITY/CNRS research collaboration agreement mentioned in 11.3.1 (VI).

(XXXV) Joint ownership rules for family S VII patents

The joint ownership of the S VII patent family is not governed by any agreement. As a result, legal provisions are applicable.

(XXXVI) Joint ownership rules for family M I patents

On 10 November 2014, the Company and SORBONNE UNIVERSITY concluded joint ownership rules for family M I “Photo-protection” patents. The rules shall remain in effect until the later of: (i) the expiry or surrender of the last patent, or (ii) as long as an operating agreement on patents and/or associated know-how is in effect or, until the date on which one of the parties becomes 100% owner of the patents, as the case may be.

Pursuant to these rules, the Company benefits from the exclusive use of patents in the field of foods and drugs for human and animal use, to be completed by an operating agreement to be concluded. The agreement between the Company and SATT Lutech of 27 May 2015, described in paragraph 11.3.2 (I), constitutes the agreement concluded pursuant to these rules.

The ownership of the "Photo-protection" patent is divided as follows: (i) 50% for the Company and (ii) 50% for SORBONNE UNIVERSITY. The Company is in charge of patent management. In the event of an assignment by one party of its ownership on all or part of the patents or its rights to know-how, the other party shall have a pre-emptive right of first refusal for a period of 60 days.

(XXXVII) Joint ownership rules for family M II patents

On 28 July 2017, the Company, SORBONNE UNIVERSITY and the CNRS concluded joint ownership rules for family M II, “AMD”, patents. The rules shall remain in force, except in the event of early termination, until the last of the patents expires or iswaived.

Pursuant to these rules, the Company is entitled to the exclusive global exploitation of patents pursuant to the exploitation agreement with SATT Lutech dated 1 January 2016 as described in paragraph 11.3.2 (II).

The ownership of the “AMD” patent is divided as follows: (i) 50% for the Company, (ii) 33.3% for SORBONNE UNIVERSITY and (iii) 16.7% for the CNRS. The Company is in charge of patent management. In the event of assignment by one party of its joint ownership part, the other parties shall have a right of pre-emption for a period of 60 days.

(XXXVIII) Joint ownership rules for family M III patents

On 16 October 2017, the Company, SORBONNE UNIVERSITY, the CNRS and Inserm Transfert SA concluded joint ownership rules relating to M III family patents “Composition for the protection of retinal epithelium cells”. The regulations shall remain in force, except in the event of early termination, until the last of the following dates: (i) either the expiry or waiver of the last patent, or (ii) aslong as a licence on the patent is in force, or (iii) until the date on which one of the parties becomes 100% owner of the patents, it this happens before.

Under these rules, the Company is entitled to the global worldwide exploitation of patents pursuant to the exploitation agreement with SATT Lutech dated 1 January 2016 as described in paragraph 11.3.2 (II).

The ownership of the patent “Composition for protecting cells of the retinal pigment epithelium” is divided as follows: (i) 60% for the Company, (ii) 13.4% for SORBONNE UNIVERSITY, (iii) 13.3% for the CNRS and (iv) 13.3% for Inserm Transfert SA. The Company is in charge of patent management. In the event of assignment by one party of its joint ownership part, the other parties shall have a right of pre-emption for a period of 60 days.

(XXXIX) Joint ownership rules for family M IV patents

On 18 December 2017, the Company, SORBONNE UNIVERSITY, the CNRS and Inserm Transfert SA concluded joint ownership rules relating to the M IV family patents “Use of 3-deoxhyanthocyanidins for treating ocular diseases”. These rules shall remain in force, except inb the event of early termination, until the last of the following dates: (i) either the expiry or waiverof the last patent, or (ii) as long as a licence on the patent is in force, or (iii) until the date on which one of the parties becomes 100% owner of the patents, it this happens before.

Under these rules, the Company is entitled to the global worldwide exploitation of patents pursuant tothe exploitation agreement with SATT Lutech dated 1 January 2016 as described in paragraph 11.3.2 (II).

The ownership of the patent “Use of 3-deoxhyanthocyanidins for treating ocular diseases” is divided as follows: (i) 50% for the Company, (ii) 16.7% for SORBONNE UNIVERSITY, (iii) 16.7% for the CNRS and (iv) 16.6% for Inserm Transfert SA. The Company is in charge of patent management. In the event of assignment by one party of the joint ownership part, the other parties shall have a right of pre-emption for a period of 60 days.

11.4 OTHER ELEMENTS OF INDUSTRIAL PROPERTY

11.4.1 Trademarks

The Company pays particular attention to the management of its portfolio of brands. For public information purposes and for protection of its rights, it affixes the symbol “®” on its registered trademarks.

The “Biophyta” trademark was acquired back as a precaution, following opposition proceedings from a third-party company.

To date, applications for Brazilian trademarks have all been rejected, apart from the BIOPHYTIS trademark No. 830135081 in class 30, which granting is pending. The BIOPHYTIS trademark No. 830135090 in class 29 has been registered but is the object of a currenbt nullity claim. In addition, there are also trademark applications for MACUNEOS and SARCONEOS currently under review.

The Company is not aware of any other dispute relating to trademarks or opposition against the trademark and in general, its intellectual property is not the object of any dispute.

In total, the Company holds the following 26 trademarks or trademark applications:

- French trademarks:

Trademark	Holder	Status	Filing date	Registration or filing number	Renewal date	Classes
MACUNEOS	Biophytis	Registered	26/02/2016	164,252,454	26/02/2026	3 5 42
SARCONEOS	Biophytis	Registered	26/02/2016	164,252,449	26/02/2026	3 5 42
BIOPHYTIS	Biophytis	Registered	05/06/2012	12 3 924 876	30/06/2022	5 29 30
BIOPHYTIS	Biophytis	Registered	06/04/2009	093,642,120	30/04/2019	3
AROLIA	Biophytis	Registered	17/10/2008	083,605,575	31/10/2018	3 5 29 30 32
	Biophytis	Registered	10/10/2008	083,604,077	31/10/2018	3 5 29 30 32 42
QUINOLIA	Biophytis	Registered	10/10/2008	083,604,074	31/10/2018	3 5 29 30 32
MONOLIA	Biophytis	Registered	10/10/2008	083,604,081	31/10/2018	3 5 29 30 32
BIXILIA	Biophytis	Registered	10/10/2008	083,604,082	31/10/2018	3 5 29 30 32
BIOPHYTIS	Biophytis	Registered	27/03/2006	063,420,081	30/03/2026	5 29 30 32 42

- EU trademarks:

Trademark	Holder	Status	Priority	Filing date	Registration or filing number	Renewal date	Classes
BIOPHYTIS	Biophytis	Registered	Under priority of FR 06 3 420081 of 27/03/2006	26/09/2006	5337159	20/09/2026	5 29 30 32 42
BIOPHYTA	Biophytis	Renewed		12/06/2003	3233376	12/06/2023	3 5 29 30 31

- International trademarks:

Trademark	WO/Country	Holder	Status	Priority	Filing date	Registration or filing number	Renewal date	Classes
BIOPHYTIS	WO	Biophytis	Registered	Under priority of FR 09 3 642 120 of 06/04/2009	10/09/2009	1032737	10/09/2019	3 5 29 30 32 42
	WO/EU	Biophytis	Registered					
	WO/USA	Biophytis	Registered			Serial # 79080361 Reg # 3892827 Due to lack of use, registration 3892827 could only be maintained in 2017 for Class-42 services. A request for a limitation was filed on 16 June 2017, to delete Class 3, 5, 29,30 and 32 products (not exploited) products and a new Class 5 designation was requested and registered on 16 June 2017 - Request SN 79220716 has been provisionally rejected by the Office with a deadline for response set on 9 June 2018 - The response is being prepared		
	WO/CN	Biophytis	Registered					
QUINOLIA	WO	Biophytis	Registered	Under priority of FR 08 3 642 120 of 10/10/2008	10/04/2009	1010571		3 5 29 30 32 42
	WO/EU	Biophytis	Registered					

Trademark	WO/Country	Holder	Status	Priority	Filing date	Registration or filing number	Renewal date	Classes
	WO/CN	Biophytis	Registered					
	WO/JP	Biophytis	Annulled					
MACUNEOS	WO	Biophytis	Registered	Under the priority of MF 4252454 of 26/02/2016	03/08/2016	1343148	03/08/2026	3 5 42
	WO/CN		Registered					3 5 42
	WO/EU		Registered					3 5 42
	WO/IN		Registered					3 5 42
	WO/JP		In progress					3 5 42
	WO/RU		Registered					3 5 42
	WO/USA		Registered			SN 79206825 Registration 5415119 of 06/03/2018		
SARCONEOS	WO	Biophytis	Registered	Under the priority of MF 4252449 of 26/02/2016	03/08/2016	1345067	03/08/2026	3 5 42
	WO/CN		Registered					3 5 42
	WO/UP		Registered					3 5 42
	WO/IN		Registered					3 5 42
	WO/JP		In progress					3 5 42
	WO/RU		Registered					3 5 42

Trademark	WO/Country	Holder	Status	Priority	Filing date	Registration or filing number	Renewal date	Classes
	WO/USA		Registered			SN 79207745 Registration 5398665 of 13/02/2018		3 5 42

- National Brazilian trademark

Brazil is a country with a unique classification, which requires one filing per designated class.

Trademark	Holder	Status	Filing date	Registration or filing number	Renewal date	Classes
BIOPHYTIS	Biophytis	Registered / Nullity action in progress	22/04/2009	830135090	22/11/2021	29
BIOPHYTIS	Biophytis	In progress	22/04/2009	830135081		30
MACUNEOS	Biophytis	In progress	24/08/2016 Under priority of FR 08 3 642 120 of 26/02/2016	911522964		3
MACUNEOS	Biophytis	In progress	24/08/2016 Under the priority of MF 164252454 of 26/02/2016	911523340		5
MACUNEOS	Biophytis	In progress	24/08/2016 Under priority of FR 08 3 642 120 of 26/02/2016	911523391		42

Trademark	Holder	Status	Filing date	Registration or filing number	Renewal date	Classes
SARCONEOS	Biophytis	In progress	24/08/2016 Under the priority of MF 164252449 of 26/02/2016	911523340		3
SARCONEOS	Biophytis	In progress	24/08/2016 Under the priority of MF 164252449 of 26/02/2016	911526676		5
SARCONEOS	Biophytis	In progress	24/08/2016 Under the priority of MF 164252449 of 26/02/2016	911526803		42

- Canadian national trademarks

  At the time of filing, Canada had not adopted the international classification

Trademark	Holder	Status	Filing date	Registration or filing number	Renewal date	Classes
MACUNEOS	Biophytis	In progress	05/08/2016 Under the priority of MF 164252454 of 26/02/2016	1794680		3 5 42
SARCONEOS	Biophytis	In progress	05/08/2016 Under the priority of MF 164252449 of 26/02/2016	1794685		3 5 42

In most countries, including the United States and the European Union, these brands have been changed since the commercial name of pharmaceutical products is subject to prior approval by the competent authorities.

11.4.2 Domain names

The Company has registered the following domain(s):

- biophytis.com;
- biophytis.net;
- biophytis.org;
- biophytis.fr; and
- institut-biophytis.com

These domain names were renewed until March 2017 for biophytis.fr and March 2019 for generic domain names.

12 INFORMATION ON TRENDS

12.1 PRINCIPAL TRENDS SINCE THE END OF THE LAST FINANCIAL YEAR

20 March 2018: The company filed an application for Sarconeos to be designated an Orphan Drug for the treatment of Duchenne muscular dystrophy (DMD), with the European Medicines Agency (EMA) and presented MYODA, the new clinical development programme of Sarconeos for muscular dystrophy or Duchenne muscular dystrophy (DMD).

12.2 KNOWN TRENDS, UNCERTAINTIES, REQUEST FOR COMMITMENT OR EVENTS REASONABLY LIKELY TO INFLUENCE THE COMPANY'S PROSPECTS

Not Applicable.

13 PROFIT FORECASTS OR ESTIMATES

The Company does not intend to make profit forecasts or estimates.

14 ADMINISTRATIVE, EXECUTIVE, SUPERVISORY AND GENERAL MANAGEMENT BODIES

14.1 CORPORATE OFFICERS AND MANAGERS

A summary of the main provisions of the Company's articles of association and internal regulations relating to specialised committees appear respectively in paragraphs 21.2 *"Constitutional articles of association and articles of association"* and 16.3 *"Specialised committees - corporate governance"* of this Annual Report.

14.1.1 Composition of the Board of Directors

On the date of this Annual Report, the members of the Company's Board of Directors are the following:

Member's surname and first name or company name	Office/Position held within the Company	Date of Appointment	Year of renewal/Expiry date of the mandate	Duration of mandate
Stanislas VEILLET	ChairmanChairman/Managing Director	1st appointment when the Company was a French SAS (President): Articles of association of 15 September 2006 1st appointment when the Company was a French SA (as director): Board meeting of 22 May 2015 1st appointment when the Company was a French SA (Chairman/Managing Director): Board meeting of 22 May 2015	Ordinary shareholders meeting approving the financial accounts for the year ended on 31 December 2020	3 years
Jean-Gérard GALVEZ	Independent Director	1st appointment when the Company was a French SAS: Board meeting of 11 June 2009 1st appointment when the Company was a French SA: Board meeting of 22 May 2015	Ordinary shareholders meeting approving the financial accounts for the year ended on 31 December 2020	3 years

Member's surname and first name or company name	Office/Position held within the Company	Date of Appointment	Year of renewal/Expiry date of the mandate	Duration of mandate
Dimitri BATSIS	Director	Shareholders meeting on 16 May 2018	Ordinary shareholders meeting approving the financial accounts for the year ended on 31 December 2020	3 years
Eric Rowinsky	Director	Shareholders meeting on 16 May 2018	Ordinary shareholders meeting approving the financial accounts for the year ended on 31 December 2020	3 years
Jean M. Franchi	Director	Shareholders meeting of 16 June 2017	Ordinary shareholders meeting approving the financial accounts for the year ended on 31 December 2019	3 years

The directors are appointed for a 3-year period.

The Company has chosen to combine the positions of Chairman of the Board of Directors and Managing Director.

The Chairman and Managing Director is appointed for the duration of his mandate as director, i.e. 3 years, namely until the close of the Ordinary General Assembly to be held on 2021 to approve the accounts for the financial year ending 31 December 2020.

The professional addresses of Directors are:

- Stanislas VEILLET 14, avenue de l'Opéra - 75001 PARIS
- Jean-Gérard GALVEZ 375 avenue du Pilon de Saint Clair, 83980 Le Lavandou;
- Nadine COULM 12 rue Paul Hervieu, 75015 Paris;

- Ms Jean M. Franchi: 840 Memorial Drive, 4th Floor, Cambridge, MA 02139;
- Dimitri Batsis: 11 bis avenue de Beaumont, 60260 Lamorlaye; and
- Eric Rowinsky : 215 East 73 road Street, Apt 10a, New York, United States of America

The management expertise and experience of these individuals derive from different previously employment and management functions (see Section 14.1.3).

There are no family ties between the individuals listed above.

To the knowledge of the Company, over the last 5 years, none of these individuals:

- - has been convicted of fraud;
- - has been linked in his/her capacity as a director or corporate officer with a bankruptcy, receivership or liquidation;
- - has been prohibited from managing;
- - has been the subject of official public incrimination or sanctions pronounced by statutory or regulatory authorities;
- has been prevented by a court from sitting as a member of an administrative, executive or supervisory body or from intervening in the management or conduct of affairs of any issuer.

14.1.2 Other company mandates

Other current mandates of the directors

Name	Nature of the mandate	Company
Stanislas VEILLET	Chairman	Biophytis Inc.
Jean-Gérard GALVEZ	Chairman of the Board of Directors Director Director Director Chairman of the Supervisory Board	Implanet SA Polaris SA Echosens SA Personal MedSystem Gmbh Exotec Solutions
Jean M. Franchi	Director Director	International Institute of New England Visioneering Technologies, In
Dimitri Batsis	President	Dimitri Batsis Investissements

Eric Rowinsky	President	Rgenix Inc.

Mandates held by the directors over the last five years which have currently ceased

Name	Nature of the mandate	Company
Stanislas VEILLET	Not Applicable	Not Applicable
Jean-Gérard GALVEZ	Chairman of the Supervisory Board Director Chairmanand Managing Director	Ceprodi SA Columbus Café SA Fastbooking SAS
Jean M. Franchi	NA	NA
Dimitri Batsis	Director and Chairman of the Board of Directors	Drone Volt
Eric Rowinsky	Executive Director Executive Vice Chairman Director Director Director Director Director	Rgenix Inc. Stemline Therapeutics, Inc. Biogen Inc. Fortress Biotech Navidea Biotherapetuics Verastem Inc. Bind Therapeutics

14.1.3 Biographies of the directors

Stanislas VEILLET, Chairman of the Board of Directors and Managing Director of Biophytis

PhD in Genetics and a graduate of AgroParisTech, Stanislas VEILLET began his career in Brazil as researcher at CIRAD before completed his thesis in Genetics. He subsequently joined the Cargill Group, where he managed a biotechnology laboratory, then Pharmacia-Monsanto to develop a high throughput platform for whole genome sequencing. His interest in the burgeoning "nutraceutical" industry induced him to accept the challenge of managing the Life Sciences Department of the Danone Group, where he developed several products for the prevention of cardiovascular diseases (Danacol, Danaten).
Motivated by a strong entrepreneurial spirit, he co-founded Biophytis with René Lafont in 2006 with the object of realising the potential of natural active molecules in the treatment of chronic age-related pathologies. He is the inventor of some dozen patents.

Jean-Gérard GALVEZ, Director of Biophytis

Jean-Gérard GALVEZ has over 30 years of experience in managing High-Tech and Life Science companies, having spent most of his career in United States. After a few years as an engineer with DuPont de Nemours and a dozen years with major US computer groups (Control Data, BancTec), where he was President of subsidiaries and International Vice Presdient, Jean-Gérard joined ActivCard in 1995, a French start-up, as Chairman and managing director. The company designs and markets security and authentication solutions on the Internet. The company relocated to Silicon Valley and was listed on Nasdaq in 2000, raising $ 300 million on a market capitalisation of $ 2 billion.
Jean-Gérard GALVEZ was also one of the directors of the company OKYZ, a French start-up specialising in 3D technologies. The company was sold to Adobe in 2005.
Since his return to France in 2006, Jean-Gerard sat on several corporate boards and regularly acts as consultant on equity financing and restructuring transactions. Jean-Gérard GALVEZ is a graduate of the National Polytechnic Institute of Nancy

(chemical engineering), a post graduate management degree (INP Nancy) and an MBA received from the Stanford Executive Program (California).

Nadine COULM, Director of Biophytis

A graduate of HEC, Nadine COULM (52) began her career at Banque Paribas.

In 1988, she joined the Danone Group, where she was successively in charge of the trading room, international treasurer, director of purchasing management, division finance director and from 2002 onwards, director of investor relations.

In 2006, she was appointed director of financial communication of the Casino Group.

Director of investor relations and financing of the Fnac from January 2013, she contributed to the company's initial public offering and the acquisition of Darty. She joined the Korian Group in March 2016 as director of investor relations and financing.

She is also a member of the Femmes Business Angels network since September 2012.

Jean M. Franchi,
Director of Biophytis

A Chartered Accountant, Jean M. Franchi began her career as a financial analyst at Genzyme where she then held positions in the finance department for more than 15 years. She has been actively involved in the development of the company, which became a leading biotechnology company in the treatment of rare diseases until it was bought by Sanofi in 2011.

She is currently the CFO of Dimension Therapeutics, a biotechnology company for which she participated to the initial public offering on the NASDAQ in 2015. She is responsible for the business strategy and the steering of financial matters as well as the investor relations strategy.

Dimitri Batsis
Director of Biophytis

Dimitri Batsis has been a businessman in the new technologies sector for more than 20 years.

In 1987, he created Zeni-Corporation, a web agency specialized in creation, development and hosting of multi-channel interactive website on various medium. Listed on the Paris stock exchange, the company was acquired by Keyrus in 2007.

Then, he created Drone Volt, a company specialized in professional drones building. The Company was listed on the French stock exchange on 2015 and is doing business in 30 countries.

He is currently a Business Angel and President of Dimitri Batsis Investissements.

Eric Rowinsky
Director of Biophytis

Dr. Rowinsky has more than 25 years of experience in clinical research and drugs development.

Amongst the various functions held after his PhD at Vanderbilt University School of Medecine, he was a researcher at National Cancer Institute, a professor in oncology (UT Health Science Center at San Antonio, Johns Hopkins University) and

director of the drugs development of Cancer Therapy and Research Center of San Antonio. He also exercised strategic function at ImClone Systems, Primrose Therapeutics and Steamline Therapeutics.

In addition to these functions, he is a professor of medicine at NYU, editor in chief of Investigational New Drug and director of several companies (Biogen, Fortress, Verastem, etc).

Dr. Rowinsky received several awards for his research works (American Cancer Society, Emil J. Freireich Award, etc.).

He is currently the President of Rgenix (drugs development for main paths of cancer growth) and oncology scientific director at Clearpath Development (drugs development with biopharmaceutical companies).

14.1.4 Directors of BIOPHYTIS BRASIL

The management of BIOPHYTIS BRAZIL is exercised on an exclusive basis by Mr. Wagner Clayton CORREA (manager) who has an indefinite mandate. The manager has full powers to represent BIOPHYTIS Brazil in its relations with third parties, within the limits of its company object, with the exception of certain specific decisions requiring approval of shareholders. BIOPHYTIS BRAZIL has no other management, administration, or supervisory bodies.

14.1.5 Directors of BIOPHYTIS INC.

The management of BIOPHYTIS INC. is exercised on an exclusive basis by Mr. Stanislas VEILLET (Chairman).

14.2 CONFLICTS OF INTEREST WITHIN THE ADMINISTRATIVE AND GENERAL MANAGEMENT BODIES

The Chairman and Managing Director, Mr. Stanislas VEILLET, the director Mr. Gérard Jean-GALVEZ, also a shareholder of the company H.M CONSEILS are shareholders, directly or indirectly, of the Company and/or holders of securities convertible into shares of the Company.

Apart from these items, on the date of this Annual Report and as far as the Company is aware, there are no actual or potential conflicts between the private interests of members of the Board of Directors of the Company and the interests of the Company.

As far as the Company is aware, there is no potential conflicts of interest between the duties towards the Company of the members of the Board of Directors and their private interests and/or other duties.

In the same way, the Company is not aware, on this same date, of any current or potential conflict between the private interests of the members of the Audit Committee or of the Compensation and Governance Committee and the interests of the Company.

As far as the Company is aware, on the present date, there is no shareholders agreement or agreement between the main shareholders of the Company, under which, a company representative would be selected as a member of an administrative or executive body or as a member of the general management of this latter body.

14.3 LOCK-UP COMMITMENTS BY THE DIRECTORS AND MEMBERS OF THE GENERAL MANAGEMENT

As far as the Company is aware, there are no restrictions accepted by the persons cited in paragraph 14.1.1 *"Composition of the Board of Directors"* of this Annual Report concerning the sale of their interests in the share capital of the Company.

During the financing transaction decided by the Board of Directors of the Company on 3 April 2017, Mr Stanislas VEILLET and Mr Jean-Christophe MONTIGNY agreed not to offer, pledge, lend, give or promise to assign, acquire an option or right to assign or otherwise transfer or dispose in any capacity, directly or indirectly, without the prior consent of INVEST SECURITIES, shares or securities giving an immediate or future right to the shares of the Company they hold, nor enter into any other contract or transaction having equivalent economic effect, or publicly state the intention to carry out one or more of the operations listed above until (1) year following the issuance of the new ordinary shares on 3 April 2018.

15 COMPENSATION AND BENEFITS IN KIND OF THE CORPORATE OFFICERS AND DIRECTORS

15.1 COMPENSATION OF COMPANY REPRESENTATIVES

The information in this chapter is established by referring to the Code of corporate governance for small and medium companies, as published in September 2016 by MiddleNext and approved as a reference code by the AMF. The tables appearing in the AMF recommendation No. 2014-14 are presented below.

At the meeting of the Board of Directors of 24 January 2018, it was decided, on the recommendation of the Compensation Committee, to set the gross annual fixed compensation of Mr Stanislas Veillet at €220,000 for the 2018 financial year. The objectives concerning his variable annual compensation (which is set a maximum of €75,000 for the 2018 financial year) are set annually by the Board of Directors on the recommendation of the Compensation Committee.

Table No. 1: Summary table of compensation and securities awarded to each managing corporate officer

Summary table of compensation and options and sharesgranted to each corporate officer		
	Financial year 2016	**Financial year 2017**
Stanislas VEILLET - Chairman & Managing Director		
Compensation due for the financial year (*detailed in Table 2*)	€ 186,506	€220,242
Value of variable compensation over several years granted during the financial year	- €	- €
Value of options granted during the financial year (*detailed in Table* 4)	- €	€226,440
Value of free shares granted during the financial year *(detailed in Table 6)*	- €	- €
Total	**€186,506**	**€446,682**

Mr Stanislas VEILLET was granted:

- by the Shareholders Meeting of 22 May 2015, 58,500 founder's warrants1-$_{2015}$, whose terms are detailed in paragraph 21.1.5 of this Annual Report. Each of the 58,500 founder's warrants1-$_{2015}$ provide entitles to subscribe to one (1) ordinary share with a nominal value of € 0.20 at a subscription price equal to € 2.06 (i.e. with a premium of € 1.86 per ordinary share);

- by the Board of Directors on 23 September 2015, upon exercise of the authorisation granted by the ShareholdersMeeting of 27 May 2015, 198,800 founder's warrants2-$_{2015}$, whose terms are detailed in paragraph 21.1.5 of this Annual Report. Each of the 198,800 founder's warrants$_{2-2015}$ entitles to subscribe to one (1) ordinary share with a nominal value of €0.20 at a subscription price of €10.70 (with a premium of €10.50 per ordinary share);

- During the 2016 financial year, Mr Stanislas VEILLET was not granted any founder's warrants.

- by the Board of Directors on 21 July 2017, upon exercise of the delegation of authority granted by the Shareholders Meeting of 16 June 2017, 148,000 founder's warrants$_{2017}$, whose conditions are detailed in paragraph 21.1.5 of this Annual Report. Each of the 148,000 founder's warrants$_{2017}$ entitles to subscribe to one (1) ordinary share with a nominal value of €0.20 at a subscription price of €3.30 (with a premium of €3.10 per share).

Table No. 2: Summary table of compensation of managing corporate officer

The following tables show compensation due to managing corporate offices during the financial years ended on 31 December 2017 and 2016 and the compensation received by these same individuals during these financial years.

Summary table of compensation of each managing corporate officer				
	Financial year 2016		Financial year 2017	
	Amounts owed (1):	Amounts paid (2):	Amounts owed (1):	Amounts paid (2):
Mr. Stanislas VEILLET - Chairman – Managing Officer				
Fixed compensation	€150,000	€150,000	€150,000	€150,000
Variable annual compensation	€25,000	€35,000	€50,000	€25,000
Variable multi-year compensation	- €	- €	- €	- €
Extraordinary compensation	- €	- €	- €	- €
Attendance fees	- €	- €	- €	- €
Benefits in kind	€11,506	€11,506	€20,242	€20,242
TOTAL	**186,506**	**€196,506**	**€220,242**	**€195,242**

(1) for the financial year.

(2) during the financial year.

Mr. Stanislas VEILLET has received in accordance with the decision of the Board of Directors of 20 March 2017:

(i) Fixed annual compensation of €150,000 payable over twelve (12) months and variable annual compensation of up to €50,000, payable within two (2) months of the end of the relevant financial year, depending on the annual targets achieved: (a) granting of all authorisations for the launch of the SARA-INT study with the relevant authorities before the end of 2017, (b) recruiting, for the SARA-OBS/INT clinical program, a minimum of 150 patients by the end of 2017, (c) securing the financing of the Company by issuing shares or bonds or other debt, up to €15,000,000 before the end of the 2017 financial year and, lastly (d) granting of the authorisations for the MACA-PK study for the third quarter of 2017

Mr. Stanislas VEILLET also benefits from a "GSC" private unemployment insurance policy, the cost of which is borne by the Company as a benefit in kind.

He may claim reimbursement of expenses incurred within the context of performing his duties as Chairman and Managing Director.

Table No. 3: Attendance fees and other compensation received by non-managing corporate offciers

Table of attendance fees and other compensation received by non-managing corporate officers			
Non-managing corporate officers		**Amounts paid during the financial year 2016**	**Amounts paid during the financial year 2017**
Jean-Gérard GALVEZ	Attendance fees	€18,000	€24,000
	Other compensation	- €	- €
	IFRS value of warrants granted during the financial year	- €	€ 38,336
Micheline KERGOAT	Attendance fees	- €	- €
	Other compensation	- €	- €
	IFRS value of warrants granted during the financial year	- €	- €
Nadine COULM	Attendance fees	€18,000	€24,000
	Other compensation	- €	- €
	IFRS value of warrants granted during the financial year	- €	€ 38,336
Marie-Claire JANAILHAC-FRITSCH	Attendance fees	€18,000	€24,000
	Other compensation	- €	- €
	IFRS value of warrants granted during the financial year	- €	€ 38,336
Jean FRANCHI	Attendance fees	- €	€15,000
	Other compensation	- €	- €
	IFRS value of warrants granted during the financial year	- €	€ 38,336

It being specified that the Board of Directors acknowledged at a meeting dated 24 January 2018, upon recommendation of the Compensation and Governance Committee that not all the objectives have been achieved for 2017 in strictly objective terms. Nonetheless, due to the fact that a significant amount of work was achieved during 2017, particularly in the context of Sarconeos clinical work, it has been decided that the essential part of the work was substantially achieved. Consequently, the Board of Directors decided, upon recommendation of the Compensation and Governance Committee to set, on an exceptional and discretionary basis, the variable compensation of the Managing Director at EUR 50,000 for the 2017 financial year.

The amount of directors attendance fees was set at EUR 5,000 per board at the ordinary shareholders meeting.

Table No. 4: Options to subscribe or purchase shares, founder's warrants or warrants, granted during the financial years ended 31 December 2017, 2016 and 2015 to managing corporate officer by the issuer and by any group company

Warrants (BSA) and founder's warrants (BSPCE) granted to each managing corporate officer by the issuer or by any group company in 2017						
Name of the managing corporate officer	**No. and date of the plan**	**Nature of warrants (warrants or founder's warrants)**	**Value of warrants pursuant to the Black & Scholes method (in euros)**	**Number of warrants granted**	**Exercise price**	**Exercise period**
Stanislas VEILLET - Chairman and Managing Director	BCPCE July 2017 21/07/2017	Founder's warrants	€226,440	148,000	€ 3.30	Until July 2021 May be exercised up to (i) 33% between 21 July 2017 and 21 July 2018, (ii) 66.66%, between 21 July 2018 and September 2017 and (iii) 100%, from 21 July 2019 onwards
TOTAL			**€226,440**	**148,000**		

Warrants (BSA) and founder's warrants (BSPCE) granted to each managing corporate officer by the issuer or by any group company in 2016						
Name of the managing corporate officer	**No. and date of the plan**	**Nature of warrants (warrants or founder's warrants)**	**Valuation of warrants pursuant to the Black & Scholes method (in euros)**	**Warrants awarded**	**Exercise price**	**Exercise period**
Stanislas VEILLET - Chairman and Managing Director	N/A					
TOTAL						

The terms and conditions of the several securities are further described in paragraph 21.1.5 of this Annual Report.

Table No. 5: Options to subscrire or purchase shares, founder's warrants or warrants exercised during the year by each managing corporate officer

Not Applicable

Table No. 6: Free shares granted to each corporate officer during the financial years ended 31 December 2017 and 2016

Not Applicable

Table No. 7: Free shares granted to corporate officers that are currently transferable

Not Applicable

Table No. 8: Granting history of subscription or purchase options, founder's warrants or warrants - Information on founder's warrants/warrants

Information on valid founder's warrants/warrants granted to corporate officers					
	Founder's warrants$_{2015}$	Founder's warrants$_{2015}$	Warrants$_{2015}$	Founder's warrants$_{2017}$	Warrants$_{2017}$
Shareholders meeting	22 May 2015	27 May 2015	27 May 2015	16 June 2017	16 June 2017
Board of Directors meeting	N/A	23 September 2015	04 August 2015	21 July 2017	21 July 2017
Total number of shares which may be subscribed, o/w whose number may be subscribed by:	58,500 (1 founder's warrant$_{2015}$ provides entitlement to 1 share)	198,800 (1 founder's warrant$_{2015}$ provides entitlement to 2 share)	54,000 1 warrant$_{2015}$ provides entitlement to 1 share	354,000 (1 founder's warrant$_{2017}$ provides entitlement to 1 share)	72,000 (1 warrant$_{2017}$ provides entitlement to 1 share)
Issuance price	N/A	N/A	€ 0.80	N/A	€ 0.30
Unit value under IFRS	N/A	N/A	€ 8.88	N/A	€ 2.12
Registered value under IFRS	€ 238 k	€ 1,214k	€ 320 k	€ 226 k	€ 114 k
The Chairman and Managing Director - Mr. Stanislas VEILLET	58,500	198.800	N/A	148.000	N/A
The director – Mr. Jean-Gérard GALVEZ	N/A	N/A	18,000	N/A	18,000
The director – Mrs. Nadine COULM	N/A	N/A	18,000	N/A	18,000
The director – Ms Jean FRANCHI	N/A	N/A	N/A	N/A	18,000
Starting date for exercise	22 May 2015	23 September 2015	24 September 2015	Issuance date (i.e., 21 July 2017)	28 November 2017
Expiry date	22 May 2019	23 September 2019	4 years after the	4 years after the issue date at latest	4 years after the subscription

			subscription date at latest		date at latest
Exercise price per new subscribed share	€ 2.06	€ 10.70	€ 8.40	€ 3.30	€ 3.30
Exercise procedures	The Holder(s) may only exercise the founder's warrants$_{1\text{-}2015}$ if, at the Exercise Date, they are employed by the Company or serve as corporate officer subject to the employees tax regime	The Holder(s) may only exercise the founder's warrants$_{2\text{-}2015}$ if, at the Exercise Date, they are employed by the Company or serve as corporate officer subject to the employees tax regime	N/A	The Holder(s) may only exercise the founder's warrants$_{2017}$ if, at the Exercise Date, they are employed by the Company or serve as Company officer subject to the tax regime of employees The founder's warrants$_{2017}$ may be exercised up to (i) 33.33% between 21 July 2017 and 21 July 2018, (ii) 66.66%, between 21 July 2018 and September 2017 and (iii) 100%, from 21 July 2019 onwards	The founder's warrants$_{2017}$ may be exercised up to (i) 33.33% between the subscription date and the first anniversary of the subscription date, (ii) 66.66% between the first anniversary of the subscription date and the second anniversary of the subscription date and (iii) 100%, from the second anniversary of the subscription date.
Number of subscribed shares to date	0	0	6,000	0	0
Cumulative number of cancelled founder's warrants or warrants	0	0	0	0	0
Founder's warrants or warrants outstanding at the end of the financial year	58,500	198,800	48,000	354,000	72,000

Granting of founder's warrants/warrants to corporate officers is further detailed in paragraph 21.1.5 of this Annual Report.

Table No. 9: Options to subscribe or purchase shares, founder's warrants or warrants and other securities granted to the first ten employees who are not corporate officers and options or warrants exercised by the latter during the 2015, 2016 and 2017 financial years

Options to subscribe shares GRANTED TO THE FIRST 10 EMPLOYEES (WHO ARE NOT CORPORATE OFFICERS) AND OPTIONS EXERCISED BY THE LATTER IN 2017	Total number of granted options /shares subscribed or purchased	Average subscription weighed by share*	No. and date of the plan	Number of granted options /shares subscribed or purchased
Options granted, during the year, by the issuer and any company included in the scope related to the granting of the options, to the ten employees of the issuer and of any company included in this scope, whose number of granted options is the highest (comprehensive information)	194,000	€ 3.30	Founder's warrants July 2017 22/05/2015	194,000
Options held by the issuer and the companies referred to above, exercised during the year by the ten employees of the issuer and those companies, whose number of purchased or subscribed options is the highest (comprehensive information)	15,000	€ 2.06	Founder's warrants May 2015 22/05/2015	15,000

OPTIONS TO SUBSCRIBE SHARES GRANTED TO THE FIRST 10 EMPLOYEES (WHO ARE NOT CORPORATE OFFICERS) AND OPTIONS EXERCISED BY THE LATTER IN 2016	**Total number of granted options /shares subscribed or purchased**	**Average subscription weighed by share***	**No. and date of the plan**	**Number of granted options /shares subscribed or purchased**
Options granted, during the year, by the issuer and any company included in the scope related to the options granting, to the ten employees of the issuer and of any company included in this scope, whose number of granted option is the highest (comprehensive information)	39,700	€ 6.09	Founder's warrant March 2016 15/03/2016	39,700
Options held by the issuer and the companies referred to above, exercised during the year by the ten employees of the issuer and those companies, whose number of options thus purchased or subscribed is the highest (comprehensive information)	28,000	€ 2.06	Founder's warrant May 2015 22/05/2015	28,000

Table No. 10: History of free shares allocation

Not Applicable

Table No. 11: Details of the compensation terms and other benefits granted to managing corporate

Managing corporate officers	Employment agreement		Supplementary pension regime		Indemnities or benefits due or likely to be due to termination or change of function		Indemnities relating to a non-competition clause	
	Yes	No	Yes	No	Yes	No	Yes	No
Stanislas VEILLET – Chairman and Managing Director		X		X	X*			X
Directorship start date:	22/05/2015							
End of mandate:	Shareholders meeting approving the financial accounts ended on 31 December 2017							

BIOPHYTIS BRASIL

Mr. Wagner Clayton CORREA, manager of BIOPHYTIS BRAZIL, no longer receives any compensation.

BIOPHYTIS INC.

Mr. Stanislas VEILLET does not receive any compensation in his capacity as President of BIOPHYTIS INC.

15.2 AMOUNTS PROVISIONED BY THE COMPANY FOR THE PURPOSE OF PAYMENT OF PENSIONS, RETIREMENT PENSIONS AND OTHER BENEFITS IN FAVOUR OF THE COMPANY OFFICERS

No amount has been provisioned or recorded by the Company for the payment of pensions, retirement pensions or benefits in favour of the corporate officers of the Company.

No amount has been provisioned or recorded by BIOPHYTIS BRAZIL for the payment of pensions, retirement pensions or benefits in favour of the Manager of BIOPHYTIS BRAZIL.

No amount has been provisioned or recorded by BIOPHYTIS Inc. for the payment of pensions, retirement pensions or benefits in favour of the President of BIOPHYTIS Inc.

15.3 FREE SHARES, WARRANTS (BSA), OPTIONS TO SUBSCRIBE SHARES OR OTHER SECURITIES GRANTED TO CORPORATE OFFICERS

The following table presents, on the date of this Annual Report, founder's warrants and warrants granted by the Company in favour of its corporate officers.

Holders of the founder's warrants (company officers and directors)	**Founder's warrants$_{1\text{-}2015}$** awarded at the General Meeting of 22 May 2015	Founder's warrants$_{2015}$ attributed at the Board Meeting of 23 September 2015 (by delegation granted by the General Meeting of 27 May 2015)	**Warrants$_{2015}$** attributed at the Board Meeting of 04 August 2015 (by delegation granted by the General Meeting of 27 May 2015)	**Founder's warrants$_{2017}$** awarded at the Board of Directors meeting of 21 July 2017 (by delegation of authority granted by the General Shareholders' Meeting of 16 June 2017)	**Warrants$_{2017}$** awarded at the Board of Directors meeting of 21 July 2017 (by delegation of authority granted by the General Shareholders' Meeting of 16 June 2017)
Stanislas VEILLET Chairman – Managing Director	58,500	198,800	N/A	148,000	N/A
Jean-Gérard GALVEZ Director	N/A	N/A	18,000	N/A	18,000
Nadine COULM Director	N/A	N/A	18,000	N/A	18,000
Jean FRANCHI Director	N/A	N/A		N/A	18,000
TOTAL	**58,500**	**198,800**	**54,000** (Including 48,000 in force to date)	**148.000**	**72.000**

A detailed description of the characteristics of founder's warrants$_{2015}$ and warrants$_{2015}$ mentioned above appears in paragraph 21.1.5 of this Annual Report.

On the date of this Annual Report, (i) exercise of each founder's warrant$_{1\text{-}2015}$ granted on 22 May 2015 entitles to one new ordinary share of the Company with a nominal value of €0.20 at a subscription price of €2.06 and (ii) exercise of each founder's warrant$_{2\text{-}2015}$ grantedon 23 September 2015 entitles to one new ordinary share of the Company with a nominal value of €0.20 at a subscription price of €10.70.

On the date of this Annual Report, exercise of each warrant$_{2015}$ granted on 4 August 2015 entitles to one new ordinary share of the Company with a nominal value of € 0.20 at a subscription price of € 8.40.

On the date of this Annual Report, exercise of each warrant$_{2017}$ granted on 21 July 2017 entitles to one new ordinary share of the Company with a nominal value of €0.20 at a subscription price of €0.80.

On the date of this Annual Report, exercise of each founder's warrant$_{2017}$ granted on 21 July 2017 entitles to one new ordinary share of the Company with a nominal value of €0.20 at a subscription price of €3.30.

15.4 ELEMENTS OF COMPENSATION AND BENEFITS DUE OR LIKELY TO BE DUE BY VIRTUE OF OR SUBSEQUENT TO TERMINATION OF DUTIES OF DIRECTORS OF THE COMPANY

In accordance with the articles of association's provisions, Mr. Stanislas VEILLET may be dismissed, without any reason, from his position as Chairman – Managing Director by the Board of Directors of the Company.

Mr. Stanislas VEILLET benefits from a "GSC" private unemployment insurance policy, whose cost is borne by the Company as a benefit in kind.

15.5 LOANS AND GUARANTEES GRANTED TO THE DIRECTORS

Not Applicable.

16 FUNCTIONING OF THE ADMINISTRATIVE AND MANAGEMENT BODIES

16.1 MANAGEMENT OF THE COMPANY

The Company is a French *société anonyme* with a Board of Directors. The detailed composition of the Board of Directors appears in paragraph 14.1 *"Officers and Directors"*.

The Board of Directors decided upon effective transformation of the Company from a French *société par actions simplifée into a French société anonyme* on 22 May 2015, to combine the functions of Chairman of the Board and Managing Director.

Mr. Stanislas VEILLET has been the Chairman and Managing Director of the Company since 22 May 2015 (it being specified that he had been the President of the Company when it was a French *société par actions simplifiée* since its creation on 15 September 2006).

The mandate of Mr. Stanislas VEILLET as Chairman and Managing Director of the Company has been renewed at the Board Meeting of 16 May 2018 for the period of his Director's term and will terminate after the Ordinary General Shareholders Meeting called to approve, especially the financial statements for the year ended on 31 December 2020.

The Company is represented with regard to third parties by Mr. Stanislas VEILLET.

16.2 INFORMATION ON THE AGREEMENTS BINDING THE DIRECTORS AND THE COMPANY

No contract binds the directors to the Company on the date of this Annual Report.

16.3 BOARD OF DIRECTORS AND SPECIALISED COMMITTEES – CORPORATE GOVERNANCE

16.3.1 Board of Directors

- ***Functioning of the Board of Directors:***

The composition and information regarding the members of the Board of Directors are further detailed in chapter 14 of this Annual Report.

The Shareholders Meeting may allocate a fixed annual amount for attendance fees, as compensation to directors for their activity and based on their attendance, allocated freely among the directors by the Board of Directors.

The internal regulations were adopted by the Board of Directors of 22 May 2015 and amended on 13 June 2016 in order to specify, in particular, the role and composition of the Board of Directors, the principles of conduct and the obligations of the Board of Directors' members in addition to the applicable legal and statutory provisions.

The Board of Directors conducts any control and inspection deemed appropriate. Each director receives all necessary information for performing his/her mission and may request notification of any documents deemed useful.

Each member of the Board of Directors shall undertake to maintain his/her independence of analysis, judgment and action and to actively participate to the works of the Board. He/she shall inform the Board of any conflict of interest which he/she may face. In addition, the internal regulations restate the regulations in effect on the dissemination and use of privileged information and specify that its members must refrain from carrying out transactions on the Company's securities if they have insider information. Each member of the Board of Directors is required to disclose direct or indirect transactions on the Company's shares to the Company and to the AMF.

Pursuant to recommendation 1 of the MiddleNext code, the internal regulations of the Company also provide for the members of the Board of Directors an obligation of absolute confidentiality and an obligation to protect discussion secrecy.

The Company considers that it already has five independent directors (Jean Gérard GALVEZ, Nadine COULM, Jean M. FRANCHI, Dimitri BATSIS and Eric ROWINSKI), pursuant to the provisions of the Code of Corporate Governance for Small- and Mid-Cap Companies, as published in September 2016 by MiddleNext and approved as a code of reference by the AMF, namely:

- Have not been, during the last five years, and are not an employee or managing corporate officer of the Company or of any of its affiliates;
- Have not had in the past two years and do not currently have a significant business relationship with the Company or its group (customer, supplier, competitor, service provider, creditor, or banker, etc.);
- Are not a leading shareholder of the Company nor hold a significant percentage of the voting rights;
- Do not have any close family ties with a corporate officer or key shareholder;
- Have not been, during the last six years, statutory auditors of the company.

- ***Functioning of general management:***

The composition and information relating to members of the general management are further described in Chapter 14 of this Annual Report.

The Managing Director has the broadest powers to act in all circumstances in the name of the Company, subject to the limitations of powers provided for by the Internal Regulations approved by the Board of Directors on 22 May 2015 and amended by the Board of Directors on 13 June 2016.

16.3.2 Specialised committees

The Board of Directors may create committees, determine the composition and powers and, where applicable, the compensation of its members.

Each committee has a study, analysis and advice function on various board decisions related to its area of competence. It also studies the issues and/or projects that the Board or its Chairman may submit to its examination. It has no decision-making powers. It suggests, recommends or gives an opinion, as appropriate, within its field of competence. It has consultative powers and acts under the authority of the Board of Directors, which created it and to which it reports.

The Company has a Compensation and Governance Committee, created on 23 September 2015, a Scientific Committee created on 14 April 2016 and an Audit Committee created on 4 December 2015.

16.3.3 Audit Committee

The Audit Committee meets as often as deemed necessary and at least 4 times a year, two of which shall be before the meeting of the Board of Directors closing the annual and interim financial statements of the Company, Chairman upon the Chairman's convening.

- ***Composition***

The Audit Committee consists of at least 2 members appointed by the Company's Board of Directors. The members of the Audit Committee may or may not be directors or shareholders of the Company, it being specified that as far as possible, two thirds of the members of the Audit Committee shall be independent members and shall, in any event, include at least one independent director.

The Chairman of the Audit Committee is appointed by the Board of Directors of the Company for the duration of his/her mandate as member of the Committee.

The duration of the mandates of the members of the Audit Committee is three (3) years, ending at the first Board of Directors meeting held after the Ordinary Shareholders Meeting approving the financial accounts.

The mandates of the members of the Audit Committee are renewable.

The Audit Committee has consisted, since 16 May 2018, of:

- Nadine COULM, Chairwoman of the Audit Committee, also a director of the Company; and

- Jean FRANCHI also director of the Company.

- ***Powers***

The Audit Committee is responsible for assisting the Board of Directors in:

- ensuring the truthfulness of the financial statements, the quality of internal controls and the quality and relevance of the provided financial information;

- assessing existence and relevance of the financial control and internal audit procedures;

- assessing relevance of the Company's accounting policy;

- examining the annual accounts of the Company, as well as the information issued before their submission to the Board of Directors;

- examining the changes and adaptations of accounting principles and rules used in the context of drawing up of financial statements, as well as their relevance;

- examining the candidates proposed to the positions of statutory auditor or deputy statutory auditor, or proposing appointment of the statutory auditors;

- ensuring independence and competence of statutory auditors and ensuring the proper performance of their duties;

- examining the significant risks for the Company and notably the off-balance-sheet risks and commitments.

To this end, the Audit Committee suggests, gives opinion and recommends the Board of Directors and regularly reports on its mission to the Board of Directors.

- ***Functioning***

The Audit Committee meets as often as deemed necessary and at least twice a year before the meeting of the Board of Directors, closing the annual and interim financial statements of the Company, Chairman upon Chairman's convening.

Convening are sent by any written means (notably by e-mail) with a 5-day prior notice except in cases of emergency. The Audit Committee may also be verbally convened. If all of the members of the Audit Committee are present or represented, the meetings may be held without prior notice.

The Audit Committee may only validly deliberate if at least half of its members are present, participate by videoconference or telecommunications or are represented. As an exception to the above, if the Audit Committee only consists of two (2) members, it shall only validly deliberate if the two (2) members in question are present or participate by videoconference or telecommunications or are represented.

Decisions are taken by a majority of the present or represented members. In the event of a tie, the Chairman shall cast the deciding vote.

Members may be represented by any other member of the Audit Committee subject to two representation mandates per member.

The Audit Committee reports on its mission to the Board of Directors according to modalities agreed with this latter. It also communicates its recommendations, specifications, and opinions.

A written report of each meeting is drawn up.

16.3.4 Scientific Committee

The Scientific Committee meets as often as deemed necessary and at least once (1) a year, Chairman upon Chairman's convening.

- ***Composition***

The Scientific Committee consists of at least five (5) members appointed by the Company's Board of Directors. The members of the Scientific Committee may or may not be directors or shareholders of the Company.

It is specified that no member of the Board of Directors exercising management functions within the Company may be a member of the Scientific Committee.

The Chairman of the Scientific Committee is appointed by the Board of Directors of the Company for the duration of his/her mandate as a Board member.

The duration of the mandates of the members of the Scientific Committee is five (5) years, ending at the first Board meeting held after the Ordinary Shareholders Meeting approving financial statements.

The mandates of the members of the Scientific Committee are renewable.

The Scientific Committee has consisted, since 26 October 2017, of:

- Professor Jean MARIANI, hospital practitioner at Charles Foix Hospital, Director of the Charles Foix Institute of Longevity, Chairman of the Scientific Committee;

- Professor José-Alain Sahel, Ophthalmologist, Director of the Institute of Vision;

- Professor René Lafont, Emeritus Professor at SORBONNE UNIVERSITY, Scientific Director of Biophytis;

- Professor Ivana Kim, Professor at Harvard Medical School, Director of the Unit at the Massachusetts Eye and Ear, Co-director of the Ophthalmology Department of Harvard Medical School and director of the Macular Degeneration Unit at Massachusetts Eye and Ear;

- Professor Roger A. Fielding, Professor at the Friedman School of Nutrition Science and Policy and Harvard Medical School; Human Studies Director at the Jean Mayer USDA Human Nutrition Research centre on Aging;

- Professor Thomas Voit, Director of the Biomedical Research Center (BRC) of the Great Ormond Street Hospital for Children NHS Foundation Trust and the Institute of Child Health, University College London.

- ***Powers***

The Scientific Committee is responsible for assisting the Board of Directors in:

- The study of development plans for nutraceuticals or drug candidates, to formulate an opinion on their scientific or regulatory consistency;

- Analysis of the main scientific or clinical results, to participate in their interpretation and to formulate an opinion whether to continue, redirect or terminate a research project at certain key stages;

- The scientific assessment of new research projects, before they are submitted if they are the subject of an application for subsidies and/or before their actual

start-up, in order to position the project in the global scientific and regulatory context and to specify its innovative character;

- The study of the main scientific and regulatory files prepared by the Company for approval and suggestions for possible additions/improvements, before being filed with the regulatory agencies (EFSA, EMA, etc.).

- ***Functioning***

The Scientific Committee meets as often as deemed necessary and at least once (1) a year, Chairman upon Chairman's convening.

Convening notices are sent by any written means (including by e-mail) with a 5-day prior notice except in cases of emergency. The Scientific Committee may also be convened verbally. If all of the members of the Audit Committee are present or represented, the meetings may be held without prior notice.

The Audit Committee may only validly deliberate if at least half of its members are present, participating by videoconference or telecommunication, or are represented. As an exception to the above, if the Scientific Committee only consists of two (2) members, it shall only deliberate validly if the two (2) members in question are present or participate by videoconference or telecommunication or are represented.

Decisions are taken by a majority of the present or represented members. In the event of a tie, the Chairman shall cast the deciding vote.

Members may be represented by any other member of the Scientific Committee subject to two representation mandates per member.

The Scientific Committee reports on its mission to the Board of Directors according to modalities agreed with the latter. It also communicates its recommendations, specifications, and opinions.

A written report of each meeting is drawn up.

16.3.5 Compensation and Governance Committee

- ***Composition***

The Compensation and Governance Committee consists of at least two (2) members, appointed by the Board of Directors of the Company. The members of the Compensation and Governance Committee may or may not be directors or shareholders of the Company, it nevertheless being specified that the Compensation and Governance Committee shall include at least one independent director.

No member of the Board of Directors exercising management functions within the Company may be a member of the Compensation Committee.

The Chairman of the Compensation and Governance Committee is appointed by the Board of Directors of the Company for the duration of his/her mandate as Committee member.

The duration of the mandates of the members of the Compensation and Governance Committee is three (3) years, ending at the first meeting of the Board of Directors held after the Ordinary Shareholders Meeting approving the financial accounts.

The mandate of the members of the Compensation and Governance Committee is renewable.

The Compensation and Governance Committee has consisted, since 16 May 2018, of:

- Dinitri Batsis, also director of the Company; and

- Jean-Gérard GALVEZ, Chairman of the Compensation and Governance Committee and also a director of the Company.

- ***Powers***

The Compensation and Governance Committee's function is to:

- make recommendations to the Board of Directors (i) on compensation (fixed and variable) of corporate officers and key executives and notably contributing to the review of compensation procedures, setting objectives and bonuses depending on achieved objectives and incentives for the corporate officers; (ii) recruitment, training, development, retention of employees with compensation program; and (iii) the shareholder policy and incentive tools for managers and employees, taking into account the objectives of the Company and individual and collective performance, including the fixing and/or modification of the granting or exercise modalities of securities granted to the corporate officers or employees, and, where appropriate, achievement of objectives permitting texercise of the said securities, as provided under the terms and conditions of the said securities;

- participate in the implementation of the Company's governing bodies;

- identify, assessing and proposing the appointment of independent directors with a view to good governance of the Company;

- decide on any other issue relating to human resources deemed appropriate or which is referred to it by the Board of Directors.

The Compensation and Governance Committee has only consultative powers.

- ***Functioning***

The Compensation and Governance Committee meets as often as deemed necessary and at least twice (2) a year, Chairman upon Chairman's convening.

Convening notices are sent by any written means (including by e-mail) with a 5-day prior notice except in case of emergency. The Compensation and Governance Committee may also be verbally convened. If all of the members of the Compensation and Governance Committee are present or represented, the meetings may be held without prior notice.

The Compensation and Governance Committee will only validly deliberate if at least half of its members are present or participating by videoconference or telecommunications or are represented. As an exception to the above, if the Compensation and Governance Committee consists only of two (2) members, it shall only validly deliberate if the two (2) members in question are present or participating by videoconference or telecommunications or are represented.

Decisions are taken by a majority of present or represented members. In the event of a tie, the Chairman shall cast the deciding vote.

Members may be represented by any another member of the Compensation and Governance Committee subject to two representation mandates per member.

The Compensation and Governance Committee reports on its mission to the Board of Directors according to modalities agreed with this latter. It also communicates its recommendations, specifications, and opinions.

A written report of each meeting is drawn up.

16.3.6 Observers

Article 17.VI of the articles of association provides for the right of the Ordinary Shareholders Meeting to appoint, at its discretion, up to three people, who may be a natural person or legal entity, shareholders or not, for a term of three years expiring at the General Shareholders' Meeting approving the financial accounts for the previous year and held during the year of expiration of their term. This mandate is indefinitely renewable.

The observers are responsible for ensuring the strict compliance with the articles of association and for submitting their observations at the Board of Directors meetings. They have a general and permanent advisory and supervisory mission at the Company. They study issues that the Board of Directors or its Chairman may submit to their examination for an opinion.

Observers shall be convened to each meeting of the Board of Directors, in the same capacity as the directors. They shall only have, either collectively or individualy, advisory powers and shall not have voting rights at Board meetings.

Observers are subject to the same confidentiality obligations as those binding on members of the Board of Directors.

On the registration date of this Annual Report, no observer had been appointed.

16.4 DECLARATION ON CORPORATE GOVERNANCE

Within the context of its development, the Company intends to improve its principles regarding governance by referring notably to the corporate governance Code for companies listed MiddleNext as published in December 2016, insofar as its principles are compatible with the organisation, size, resources and shareholding structure of the Company.

The following table details progress of the Company's reflections on enforcement of the principles of the MiddleNext code:

- the Company considers that it is compliant with the recommendations of the Middlenext code in the table under the heading "Adopted";
- The Company is in the process of reflecting on the recommendations of the Middlenext code with which it considers it is not currently compliant with and are listed in the table under the heading "Ongoing".

On this point, the Company considers that on the date of this Annual Report, it is not yet compliant with the following recommendations of the Middlenext code, and this for the following reasons:

- Implementation of an assessment of the work by the board (R 11): at present, the Company does not carry out a self-assessment of the work of its Board of Directors. In 2018, the Company intends to comply with the recommendation of the MiddleNext Code on the issue and ensure that a self-assessment of the Board is carried out every

year: the Chairman and Managing Director will thus invite the directors once a year, to comment on the functioning of the Board and on the preparation of its work.

- Preparation of "managers" legacy (R 14): The Company considers that it has not complied with the recommendation on the legacy of the "managers" in 2016, bearing in mind that this recommendation is the result of amendments to the MiddleNext Code dated September 2016. The Board of Directors intends, during the financial year 2018, to comply with this new recommendation.
- Stock options and free shares granting (R 18): on the present date, the Company has not yet granted stock options or free shares; it intends to comply with the recommendation of the MiddleNext Code on this subject as soon as it decides on such granting.
- Review of vigilance points (R 19): the Company considers that it has not complied with the recommendation on the review of vigilance points, bearing in mind that this recommendation comes from amendments to the MiddleNext Code dated September 2016. The Company intends to submit to its Board of Directors, during the 2018 financial year, the vigilance points set out by the MiddleNext Code so that the directors may acknowledge and review them.

Recommendations of the Middlenext Code	Adopted	Ongoing
I. Supervisory power		
R 1: Professional ethics of board members	X	
R 2: Conflicts of interest	X	
R 3: Composition of the board - Presence of independent members within the board	X	
R 4: Information of board members	X	
R 5: Organisation of the Board and committees	X	
R 6: Creation of committees	X	
R 7: Creation of internal regulations of the board	X	
R 8: Selection of each director	X	
R 9: Duration of mandates of board members	X	
R 10: Compensation of a director	X	
R 11: Creation of a work assessment process by the Board		X
R 12: Relationship with shareholders	X	
II. Executive power		
R 13: Definition and transparency of compensation of corporate officers	X	
R 14: Preparation of "managers" legacy		X
R 15: Combination of employment agreement and company mandate	X	
R 16: Departure indemnities	X	
R 17: Supplementary pension regimes	X	
R 18: Stock options and free shares granting		X
R 19: Review of vigilance points		X

(I) Internal regulations

On 22 May 2015, the Board of Directors adopted internal regulations containing the headings recommended by the MiddleNext Corporate Governance Code for listed companies, as published in September 2016, the purpose of which is to define its organisation and functioning modalities, in addition to the applicable legal and statutory provisions.

As the new MiddleNext code, published in September 2016, has extended its recommendations on the content of internal rules, which should include information on the

protection of corporate officers and the legacy of managers and key persons, the Company intends to amend its internal rules in order to incorporate these new recommendations.

(II) Combination of mandates of the Chairman of the board of directors and managing director

The Board of Directors Chairman decided to combine the mandates of Chairman of the Board and Managing Director on 22 May 2015

(III) Independent Directors

The Company considers that it already has 5 independent directors (Jean-Gérard GALVEZ, Nadine COULM, Jean FRANCHI, Dimitri BATSIS and Eric ROWINSKY), pursuant to the provisions of the MiddleNext Corporate Governance Code for Small and Mid-Cap Companies, with which the Company intends to comply, namely:

- Have not been, during the last five years, and are not an employee or managing corporate officer of the Company or of any of its affiliates;
- Have not had in the past two years and do not currently have a significant business relationship with the Company or its group (customer, supplier, competitor, service provider, creditor, or banker, etc.);
- Are not a leading shareholder of the Company nor hold a significant percentage of the voting rights;
- Do not have any close family ties with a corporate officer or key shareholder;
- Have not been, during the last six years, statutory auditors of the company.

Jean-Gérard GALVEZ did not receive any compensation in 2016 and 2017 for his term of office as director (€18,000 and €24,000 were nevertheless paid to him in respect of attendance fees for 2016 and 2017, as described above in table 3, paragraph 15.1).

Nadine COULM was appointed director on 22 May 2015. She did not receive any compensation in 2016 and 2017 for her term of office as director (€18,000 and €24,000 were nevertheless paid to her in respect of attendance fees for 2016 and 2017, as described above in table 3, paragraph 15.1).

Ms Jean M. FRANCHI was appointed director on 16 June 2017. She did not receive any compensation during the 2017 financial year for her term of office as director (€15,000 were nevertheless paid to her in respect of attendance fees for 2017, as described above in table 3, paragraph 15.1).

Dimitri BATSIS was appointed director on 16 May 2018. He did not receive yet any compensation during the 2018 financial year for his term of office as director.

Eric Rowinsky was appointed director on 16 May 2018. He did not receive yet any compensation during the 2018 financial year for his term of office as director.

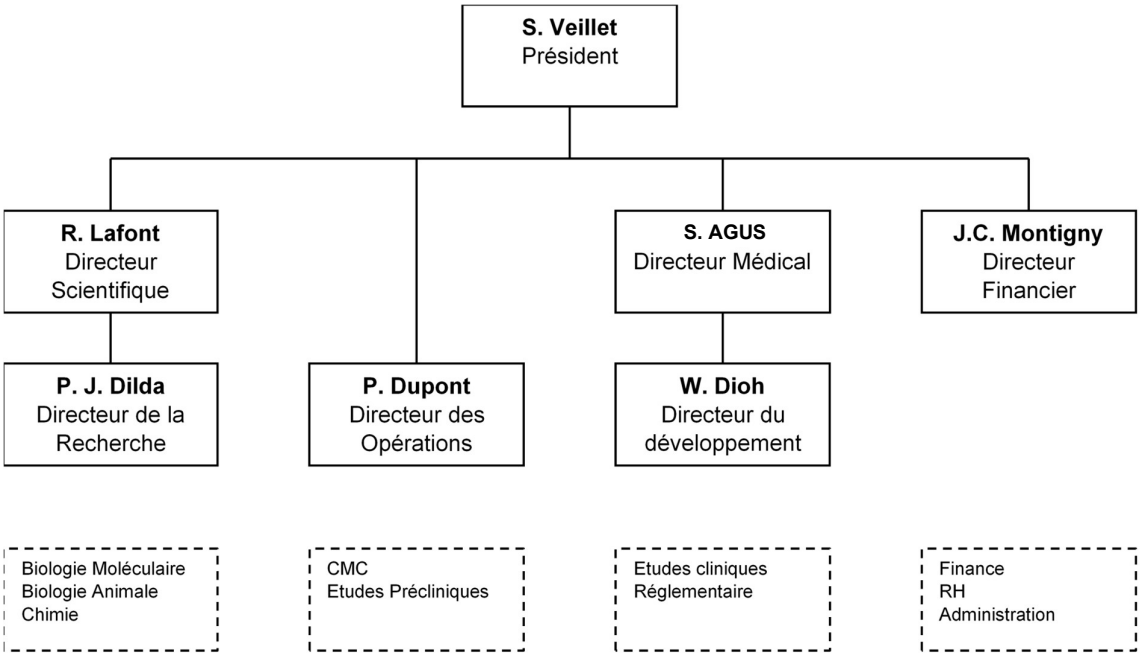
Independent directors receive directors' fees of €3,000 per meeting of the Board of Directors that certain have attended since 22 May 2015.

The Company has no director who represents the employees.

17 EMPLOYEES

17.1 NUMBER OF EMPLOYEES AND ALLOCATION BY FUNCTION

17.1.1 Operational chart on the date of registration of this Annual Report



17.1.2 Number and allocation of employees

On the date of submission of this Annual Report, the Company has 23 employees with indefinite duration employment contracts. The threshold of 20 employees was crossed in 2018.

All the employees are “executive” (*cadre*).

On June 19, 2017, the Company and Ms. Anne-Sophie Foucault (Research Engineer in Charge of Animals) signed a contractual termination form causing termination of the employment agreement on 31 July 2017. This form and the termination protocol were sent to DIRECCTE by registered letter with acknowledgement of receipt on 6 July 2017.

The Chairman and Managing Director of the Company, Stanislas VEILLET does not have an employment agreement. In 2009, the Company subscribed a “GSC” private unemployment insurance policy. Payment by the Company of contributions due under this insurance is regarded as a benefit in kind, subject to social security contributions and charges.

17.1.3 Collective status

The National Collective Bargaining Agreement for “*Retail and wholesale food trade*” until then applied by the Company has been challenged due to a change of activity and attribution of a new APE code, code 7211Z. Employees representatives were informed of this challenge and the application, from 1 January 2018, of the National Collective Bargaining Agreement for the “Pharmaceutical Industry” at the meeting held on 27 October 2017.

Employees representatives were elected on 25 July 2017 (Christine Balducci (Head of Analytical Chemistry) as Employees Representative and Marie-Noelle Ly (Head of Galenic Development) as Deputy Employees Representative).

A collective agreement on hours of work was signed with the employees representatives on 17 November 2017. This agreement provides for an organisation of working hours in days within the framework of an annual fixed period of 216 days worked with a control of the number of days worked and exercise of the right to disconnect.

Internal regulations were adopted on 6 November 2017 as well as a single risk-assessment document.

No unilateral commitment or practice is in effect within the Company.

17.1.4 Clauses of employment agreements

Following the change of collective bargaining agreement and the signing of a collective bargaining agreement on hours of work, new employment contracts were concluded with all employees.

The new employment contracts, prepared on the basis of the same model, contain the following clauses among others:

- a clause on the transfer of the intellectual property of certain inventions (with the exception of the employment contracts of Ms Teylan (Financial Controller), Ms Linard (Admnistrative Assistance) and Jean-Christophe Montigny (Chief Administrative and Financial Officer)),

- a confidentiality clause;

- a non-poaching and non-solicitation clause for a period of 12 months following termination by the employee of his/her duties.

- a non-compete clause for a period of 6 months covering Europe, North America, Japan, China, India, Brazil and Australia regarding the employment contracts of Messrs Dioh (Clinical Development Director), Dilda (Research Director), Dupont (Chief Operating Officer) and Ms Del Signore (Medical Director) with the exception of India in her case.

M. Samuel Agus, from Biophytis Inc., is bound by a non-compete obligation for a period of 6 months following termination of the employment agreement for United States and European Union and a non-poaching obligation related to clinets and employees for the same duration.

No employee of the Company currently benefits from a “golden parachute” clause in the event of termination of his/her employment agreement.

17.1.5 Working hours

In view of the new employment contracts communicated to us, all the employees (with the exception of Messrs. Lafont – Scientific Director – and Montigny and Ms Del Signore who are executive manager “*cadre dirigeant*”) are subject to a fixed agreement for 216 days worked during the year pursuant to the collective agreement of 17 November 2017.

17.1.6 Disputes

There has never been a dispute between the Company and one of its employees (past or present).

17.1.7 Compensation

The Company's gross payroll (gross tax basis) amounted to:

- € 424,263 in 2013;
- € 452,458 in 2014;
- €703.843 in 2015;
- €1,140,367 in 2016;
- €1,339,326 in 2017.

Some employees are eligible for variable compensationn, depending on the achievement of objectives, representing 12 and 20% of their annual compensation.

17.1.8 Mutual and pension coverage

The employees benefit from pension coverage subscribed with Klesia and a health insurance plan subscribed with Humanis. Proceedings were undertaken by the Company in February 2018 with APGIS to subscribe to the pension and medical expenses plan set out by the National Collective Bargaining Agreement for the "Pharmaceutical Industry".

17.2 EQUITY INTERESTS AND STOCK OPTIONS OF THE DIRECTORS

On the date of this Annual Report, the direct and indirect equity interests of the members of general management (the Chairman and Managing Director) and the Board of Directors as well as the number of securities providing access to the Company's share capital are presented in the following table.

The following table reflects the issue of (i) 58,500 founder's warrants$_{2017}$ granted by the Extraordinary and Ordinary Shareholder's Meeting of 22 May 2015 and (ii) 148,000 founder's warrants$_{2017}$ granted by the Board of Directors on 21 July 2017 to Mr Stanislas VEILLET, Chairman and Managing Director.

Member of the Board of Directors	Direct equity interests			Indirect equity interests			Warrants$_{2015}$/ founder's warrants $_{2015}$ Warrants$_{2017}$ Founder's warrants$_{2017}$
	Shares	Percentage		Shares	Percentage		
		Capital	Voting rights		Capital	Voting rights	
Jean-Gérard GALVEZ (1)	0	0%	0%	11,365	0.08%	0.08%	36.000
Stanislas VEILLET (Chairman and Managing Director)	1,469,271	10.91%	10.91%	0	0%	0%	405.300
Nadine COULM	1,250	0.01%	0.01%	0	0%	0%	36,000
Jean FRANCHI	0	0%	0%	0	0%	0%	18,000
Dimitri BATSIS	50	0%	0%	0	0%	0%	0
Eric ROWINSKY	0	0%	0%	0	0%	0%	0
TOTAL	**1,470,571**	**10.92 %**	**10.92 %**	**11,365**	**0,08%**	**0,08%**	**495,300**

(1) Indirectly, due to the fact that H.M Conseils is the owner of some shares (Mr. Jean-Gérard GALVEZ is a shareholder and manager of H.M Conseils).

17.3 EMPLOYEE SHARE OWNERSHIP

On the date of this Annual Report, fourteen employees held a total of 109,210 shares, representing 0.82 % of the share capital on an undiluted basis and 544,900 founder's warrants$_{2015}$ (granting right to 544,900 shares), amounting to 4.32 % of the share capital on a diluted basis (including the founder's warrants$_{2015}$, the warrants$_{2015}$, the warrants$_{2015D}$, the warrants$_{Bracknor}$, the warrants$_{2017}$ and the founder's warrants$_{2017}$).

The Chairman and Managing Director (non-employee) holds 1,469,271 shares representing 10.91% of capital and voting rights of the Company on an undiluted basis and 405,300 founder's warrants$_{1\text{-}2015}$, founder's warrants$_{2\text{-}2015}$, founder's warrants$_{2017}$ (granting right to 405,300 shares), amounting to 12.37% of the share capital on a diluted basis (including the founder's warrants$_{1\text{-}2015}$, founder's warrants$_{2\text{-}2015}$, the warrants$_{2015D}$, the warrants$_{Bracknor}$, the warrants$_{2017}$ and the founder's warrants$_{2017}$)

17.4 INCENTIVE AND PARTICIPATION AGREEMENTS

Not Applicable.

18 PRINCIPAL SHAREHOLDERS

18.1 ALLOCATION OF SHARE CAPITAL AND VOTING RIGHTS

The table below details the shareholding structure of the Company on 26.02.2018.

As far as the Company is aware, there is no concerted action between the Company's shareholders.

	Situation on the registration date of the Annual Report on a non-diluted basis		Situation on the registration date of the Annual Report on a fully diluted basis (3)	
Shareholders	Number of shares	% of share capital and voting rights	Number of shares and founder's warrants$_{1\&2\ 2015}$/ warrants$_{2015}$/warrants$_{2015D}$/warrants$_{bracknor}$/warrants$_{2017}$ and founder's warrants$_{2017}$	% of share capital and voting rights
Founder (1)	***66,666***	0.50%	193,866	1.28%
Directors (2)	***17,365***	0.12%	137,365	0.90%
Stanislas VEILLET – Chairman and Managing Director	***1,469,271***	10.91%	1,874,571	12.37%
Treasury shares at 31/01/2018	***34,909***	0.26%	34,909	0.23%
Floating	***11,832,658***	74.44%	11,832,658	69.80%
Employees (other than founders) and other holders of founder's warrants$_1$	***42,544***	0.32%	460,244	3.04%
Holders of warrants$_{2015D}$	***0***	0.00%	189,748	1.69%
Bracknor	***0***	0.00%	431.184	2.85%
TOTAL	***13,463,413***	***100%***	***15,154,545***	***100%***

(1) A founding natural person who is not a corporate officer.
(2) As of the date of this Annual Report, Mr Jean-Gérard GALVEZ holds, as of the date of this Annual Report, indirectly, by HM Conseils, 11,365 shares.
(3) This table takes account of the 167,000 founder's warrants$_{1\text{-}2015}$ allocated by the Shareholders Meeting of 22 May 2015 still in force, the 384,500 founder's warrants$_{2\text{-}2015}$ issued by the Board of Directors on 23 September 2015, upon exercise of the delegation granted by the Shareholders Meeting of 27 May 2015 still in force, the 20,000 founder's warrants$_{2\text{-}2015}$ issued by the Board of Directors of 4 December 2015, upon exercise of the delegation granted by the Shareholders Meeting of 27 May 2015 still in force, the 39,700 founder's warrants$_{2\text{-}2015}$ issued by the Board of Directors of 15 March 2016, upon exercise of the delegation

granted by the Shareholders Meeting of 27 May 2015, the 48,000 warrants$_{2\text{-}2015}$ issued by the Board of Directors of 4 August 2015, upon exercise of the delegation granted by the Shareholders Meeting of 27 May 2015, and the 189,748 warrants$_{2015D}$ granted to the benefit of the Biophytis$_{2015D}$ Bondholders by the Board of Directors on 10 July 2015, upon exercise of the delegation granted by the Shareholders Meeting of 27 May 2015.

Main Shareholders of Biophytis:

Mr. Stanislas VEILLET, Chairman and Managing Director of the Company.

He co-created BIOPHYTIS with René LAFONT in 2006 in order to develop the potential of natural active molecules for the treatment of chronic age-related diseases.

18.2 SIGNIFICANT SHAREHOLDERS NOT REPRESENTED ON THE BOARD OF DIRECTORS

Not Applicable.

18.3 VOTING RIGHTS OF THE MAIN SHAREHOLDERS

The voting rights attached to capital or dividend shares is proportional to the amount of capital they represent. Each share is entitlement to one vote.

The Extraordinary and Ordinary Shareholders Meeting of 16 June 2017 decided a double voting right for all registered and fully paid-up shares in the name of the same beneficiary for at least two years.

BIOPHYTIS BRASIL

Due to its shareholding percentage in BIOPHYTIS BRAZIL, BIOPHYTIS has the sole power to vote and approve all decisions relating to Biophytis Brasil, with the exception of its transformation into a company of another form.

BIOPHYTIS INC.

Due to its shareholder percentage in BIOPHYTIS INC., BIOPHYTIS has the sole power to vote and approve all decisions regarding BIOPHYTIS INC.

18.4 CONTROL OF THE COMPANY

On the date of this Annual Report, no shareholder or group of shareholders acting in concert controls the Company, pursuant to the provisions of Article L. 233-3 of the Commercial Code.

18.5 AGREEMENTS WHICH MAY LEAD TO A CHANGE OF CONTROL

As far as the Company is aware, no particular element of the articles of incorporation, articles of association, charter or internal regulations of the Company could lead to a change of control.

As far as the Company is aware, there is no concerted action between the Company's shareholders.

18.6 STATUS OF PLEDGES OF COMPANY SHARES

As far as the Company is aware, on the date of this Annual Report, a pledge exists on the shares of the Company, namely:

- 120,000 Company shares held by METABRAIN RESEARCH have been pledged since 18 July 2012 in favour of several banking institutions.

19 TRANSACTIONS WITH RELATED PARTIES

No regulated agreements were entered into during the year ended 31 December 2017.

19.1 INTRAGROUP AGREEMENTS

a. The subsidiary in Brazil

On the date of this Annual Report, the Company has a Brazilian subsidiary, the company INSTITUTO BIOPHYTIS DO BRASIL SERVIÇOS, COMÉRCIO, IMPORTAÇÃO E EXPORTAÇÃO DE ALIMENTOS LTDA.

In recent years, the Company has entered into several agreements for current account advances with BIOPHYTIS Brazil. To this extend, the amount owed by BIOPHYTIS BRASIL to the Company was 291,621.64 Reais (around €73,642) at 31 December 2017. The terms of these loans do not provide for interest or penalty in the event of default or late payment.

The Company entered into a Contract for Scientific and Commercial Collaboration with BIOPHYTIS BRESIL in 2010, under which the Company granted BIOPHYTIS BRESIL the exclusive right to market certain food supplements in Brazil under the BIOPHYTIS® brand. However, as no operational activity has taken place within the subsidiary, this contract is yet to be implemented.

b. The subsidiary in the United States

On the date of this Annual Report, the Company also has a subsidiary in the US, BIOPHYTIS INC.

The Company entered into a current account advance agreement with BIOPHYTIS INC to conduct intra-group re-invoicing by BIOPHYTIS INC. To this extend, the amount owed by BIOPHYTIS INC. was €371,828.71 at 31 December 2017.

The Company entered into on 15 March 2017, with retroactive effect to 1 January 2017, a debt compensation agreement with BIOPHYTIS INC following the Company's provision of a certain number of services that gave rise to a billing generating a significant receivable that should be compensated as part of the proper management of both entities (the "**Debt Compensation Agreement**"). Under the Debt Compensation Agreement, BIOPHYTIS INC. agreed to pay the supplier invoices sent to it by the Company if its resources reasonably allow for it. In addition, the balance of unpaid invoices for which payment has been due shall bear interest at the quarterly average effective rate of floating-rate loans with an initial maturity of more than two years, as used by credit institutions and published by the Bank of France.

19.2 TRANSACTIONS WITH RELATED PARTIES

Not applicable.

19.3 REPORTS OF THE STATUTORY AUDITOR ON REGULATED AGREEMENTS, ISSUED FOR THE FINANCIAL YEAR ENDED 31 DECEMBER 2017

Special report of the Statutory Auditor on regulatory agreements

Grant Thornton
Statutory Auditor
29, rue du pont
92200 Neuilly-sur-Seine Cedex

Ernst & Young et Autres Statutory Auditor
1 / 2 place des Saisons
92400 Courbevoie – Paris la Défense Cedex 1

BIOPHYTIS
French Société anonyme
With capital of €2,692,682.60
14, avenue de l'Opéra
75001 Paris

Shareholders Meeting approving the accounts for the financial year
ended 31 December 2017

Special report of the Statutory Auditor on regulated agreements

Biophytis
Shareholders Meeting approving the accounts for the financial year ended 31 December 2017

To the shareholders of Biophytis,

A statutory auditors of the Company, we hereby submit our report on the regulated agreements.

It is our duty to inform you, on the basis of information provided to us, of the characteristics, the essential procedures and the reasons justifying the company's interest in the notified agreements or which we have discovered during our functions, without having to express an opinion on their usefulness and merits or to investigate the existence of other agreements. It is your responsibility, pursuant to article R. 225-31 of the French Commercial code, to assess the interest associated with the conclusion of these agreements with a view to approving them.

Furthermore, we are responsible, as appropriate, for providing you with the information described in Article R. 225-31 of the Commercial Code regarding the execution during the past financial year of agreements already approved by the shareholders meeting.

We have performed the due diligence that we considered necessary in view of the professional guidelines of the National Society of Auditors relating to this assignment.

AGREEMENTS SUBJECT TO THE APPROVAL OF THE SHAREHOLDERS MEETING

We inform you that we have not been given notice of any agreement authorised and concluded during the past financial year to be submitted for the approval of the shareholders meeting pursuant to provisions of Article L. 225-38 of the French Commercial code.

AGREEMENTS ALREADY APPROVED BY THE SHAREHOLDERS MEETING

We inform you that we have not been notified with any agreement already approved by the shareholders meeting, and whose execution continuedcontinued during the past year.

Neuilly-sur-Seine and Paris-La Défense, 30 April 2018

The Statutory Auditors

Grant Thornton **French member of Grant Thornton International**	**ERNST & YOUNG and Others**
Laurent Bouby Partner	Frédéric Martineau Partner

19.4 SPECIAL REPORT OF THE STATUTORY AUDITOR ON THE REGULATED AGREEMENTS, ISSUED FOR THE FINANCIAL YEAR ENDED 31 DECEMBER 2016

Special report of the Statutory Auditor on regulatory agreements

Grant Thornton
Statutory Auditor
29, rue du pont
92200 Neuilly-sur-Seine Cedex

Ernst & Young et Autres Statutory Auditor
1 / 2 place des Saisons
92400 Courbevoie – Paris la Défense Cedex 1

BIOPHYTIS

French Société anonyme
With capital of €1,506,786.20
14, avenue de l'Opéra
75001 Paris

Shareholders Meeting approving the accounts for the financial year
ended 31 December 2016

Special report of the Statutory Auditor on regulated agreements

Biophytis
Shareholders Meeting approving the accounts for the financial year ended 31 December 2016

To the shareholders of Biophytis,

A statutory auditors of the Company, we hereby submit our report on the regulated agreements.

It is our duty to inform you, on the basis of information provided to us, of the characteristics, the essential procedures and the reasons justifying the company's interest in the notified agreements or which we have discovered during our functions, without having to express an opinion on their usefulness and merits or to investigate the existence of other agreements. It is your responsibility, pursuant to article R. 225-31 of the French Commercial code, to assess the interest associated with the conclusion of these agreements with a view to approving them.

Furthermore, we are responsible, as appropriate, for providing you with the information described in Article R. 225-31 of the Commercial Code regarding the execution during the past financial year of agreements already approved by the shareholders meeting.

We have performed the due diligence that we considered necessary in view of the professional guidelines of the National Society of Auditors relating to this assignment.

AGREEMENTS SUBJECT TO THE APPROVAL OF THE SHAREHOLDERS MEETING

We inform you that we have not been given notice of any agreement authorised and concluded during the past financial year to be submitted for the approval of the shareholders meeting pursuant to provisions of Article L. 225-38 of the French Commercial code.

AGREEMENTS ALREADY APPROVED BY THE SHAREHOLDERS MEETING

We inform you that we have not been notified with any agreement already approved by the shareholders meeting, and whose execution continuedcontinued during the past year.

Neuilly-sur-Seine and Paris-La Défense, 27 April 2017

The Statutory Auditors

Grant Thornton **French member of Grant Thornton International**	**ERNST & YOUNG and Others**
Laurent Bouby Partner	Frédéric Martineau Partner

20 FINANCIAL INFORMATION ON THE ASSETS, FINANCIAL SITUATION AND RESULTS OF THE COMPANY

20.1 CONSOLIDATED FINANCIAL STATEMENTS PREPARED IN ACCORDANCE WITH IFRS FOR THE YEAR ENDED 31 DECEMBER 2017

Consolidated statement of financial position

(amounts in thousands of euros)	Notes	31/12/2016	31/12/2017
ASSETS			
Patents and software	3	2,125	2,009
Tangible fixed assets	4	276	313
Other non-current financial assets		99	190
Total non-current assets		**2,501**	**2,512**
Other receivables	5	2,827	3,578
Cash and equivalents	6	3,066	19,857
Total current assets		**5,892**	**23,435**
TOTAL ASSETS		**8,393**	**25,947**
LIABILITIES			
Shareholders' equity			
Capital	8	1,245	2,693
Issue and contribution premiums	8	19,583	44,708
Treasury shares		(158)	(138)
Conversion differences		4	(0)
Reserves - attributable to Biophytis shareholders		(8,170)	(14,636)
Result - attributable to Biophytis shareholders		(7,954)	(11,409)
Shareholders' equity - attributable to Biophytis shareholders		**4,549**	**21,217**
Non controlling interests		(30)	(31)
Total shareholders' equity		**4,519**	**21,187**
Liabilities			
Employee benefit obligation		48	114
Non-current financial liabilities	10	913	708
Total non-current liabilities		**962**	**821**
Current financial liabilities	10	176	305
Trade payables	12.1	1,920	2,402
Tax and social debts	12.2	722	1,118
Other creditors and miscellaneous debts	12.3	94	113
Total current liabilities		**2,913**	**3,939**
TOTAL LIABILITIES		**8,393**	**25,947**

Consolidated income statement

(in thousands of euros, except for share data)	Notes	31/12/2016 12 months	31/12/2017 12 months
Revenue		-	-
Cost of sales		-	-
Gross Margin		**-**	**-**
Net research and development expenses	13.1	(5,121)	(7,043)
General and administrative expenses	13.2	(2,820)	(2,865)
Net operating profit		**(7,942)**	**(9,908)**
Financial expenses		(35)	(3,293)
Financial income		22	37
Change in the fair value of derivative liabilities		-	1,756
Net financial income	14	**(13)**	**(1,501)**
Profit or loss before tax		**(7,954)**	**(11,409)**
Income taxes		-	-
Net income (loss)		**(7,954)**	**(11,409)**
Attributable to Biophytis shareholders		*(7,954)*	*(11,409)*
Non-controlling interests		*(0)*	*(0)*
Average weighted number of shares circulation		6,202,616	9,188,179
Basic earnings per share (€/share)	16	**(1.28)**	**(1.24)**
Diluted earnings per share (€/share)	16	**(1.28)**	**(1.24)**

Consolidated comprehensive income statement

(amounts in thousands of euros)	31/12/2016 12 months	31/12/2017 12 months
Net profit (loss)	**(7,954)**	**(11,409)**
Non-recurring items in net income		
Actuarial gains and losses	(17)	5
Recurring items in net income		
Currency exchange differences	14	(4)
Comprehensive income (loss)	**(7,957)**	**(11,408)**
Attributable to Biophytis shareholders	*(7,958)*	*(11,408)*
Non-controlling interests	*1*	*0*

Consolidated statement of changes in shareholders' equity

(in thousands of euros, except for share data)	Notes	*Capital - number of shares*	Capital	Share premiums	Reserves and result	Conversion reserve	Treasury shares	Shareholders ' equity - attributable to Biophytis shareholders	nNon controlling interests	Shareholders' equity
At 31 December 2015		*6,195,501*	**1,239**	**19,531**	**(9,082)**	**(9)**	**(50)**	**11,629**	**(31)**	**11,598**
2016 Net income (loss)			-	-	(7,954)	-	-	(7,954)	(0)	(7,954)
Other elements of the global result			-	-	(17)	14	-	(3)	1	(3)
Comprehensive income (loss)			**-**	**-**	**(7,971)**	**14**	**-**	**(7,958)**	**1**	**(7,957)**
Exercise of founder's warrants	8	*28,000*	6	52	-	-	-	58	-	58
Treasury shares acquired			-	-	(65)	-	(108)	(173)	-	(173)
Share-based payments	9		-	-	994	-	-	994	-	994
At 31 December 2016		*6,223,501*	**1,245**	**19,583**	**(16,124)**	**4**	**(158)**	**4,549**	**(30)**	**4,519**
2017 Net income (loss)			-	-	(11,409)	-	-	(11,409)	(0)	(11,409)
Other elements of the comprehensive income			-	-	5	(4)	-	1	-	1
Comprehensive income (loss)			**-**	**-**	**(11,404)**	**(4)**	**-**	**(11,408)**	**(0)**	**(11,409)**
Issue of shares	8	*4,812,431*	962	20,779	-	-	-	21,742	-	21,742
Conversion of bonds	8, 10	*2,412,481*	482	6,339	-	-	-	6,822	-	6,822
Exercise of founder's warrants	8	*15,000*	3	28	-	-	-	31	-	31
Subscription of warrants	9		-	22	-	-	-	22	-	22
Warrants issued on bonds	10		-	-	521	-	-	521	-	521
Treasury shares			-	-	71	-	21	92	-	92
Share-based payments	9		-	-	891	-	-	891	-	891
Capital increase expenses			-	(2,043)	-	-	-	(2,043)	-	(2,043)
At 31 December 2017		*13,463,413*	**2,693**	**44,708**	**(26,046)**	**(0)**	**(138)**	**21,217**	**(31)**	**21,186**

Consolidated cash flows statement

(amounts in thousands of euros)	Notes	31/12/2016 12 months	31/12/2017 12 months
Cash flows generated by operating activities			
Net profit		**(7,954)**	**(11,409)**
Elimination of amortisation/depreciation fixed assets	34	167	204
Provisions, net of reversals	11	6	71
Share-based payment expense	9	994	891
Gross financial interest paid		6	2
Capitalised financial interests		(1)	(1)
Change in fair value of the derivative instruments	10.5	-	(1,756)
Capital gains or losses on disposal of fixed assets		1	2
Subsidy transferred to result		(10)	-
Interest on the investment accounts		(24)	(6)
Discounting/accretion of advances		(34)	29
Impact of the amortised cost of convertible bonds and warrants		-	3,099
Cash flow from operating activities before changes in working capital requirements		**(6,848)**	**(8,873)**
(-) Change in working capital requirements (net of impairment of trade receivables and inventories)		**(216)**	**(146)**
(Decrease) increase of other non-current financial assets		1	(0)
(Decrease) increase in other receivables		*1,404*	*752*
Decrease (increase) in trade payables		*(1,219)*	*(483)*
Decrease (increase) in tax and social debts		*(361)*	*(396)*
Decrease (increase) in other accounts payable and other liabilities		(40)	(19)
Cash flows generated by operating activities		**(6,633)**	**(8,727)**
Cash flow generated by investment activities			
Acquisition of intangible and tangible fixed assets	34	(129)	(128)
Cash flow linked to investment operations		**(129)**	**(128)**
Cash flows linked to financing operations			
Capital increase, net of bond conversion	8	-	21,742
Expenses associated with capital increases		-	(2,043)
Subscription of warrants	9	-	22
Exercise of warrants & founder's warrants	8	58	31
Reimbursable advances received, net of repayments	10.1	634	(34)
Collection of subsidies		10	-
Debt issues, net of repayments	10	(280)	(30)
Gross financial interest paid		(6)	(2)
Bond issues	10.5	-	6,000
Interest on the investment account		24	6
Reimbursements of lease financing	10.4	(36)	(44)
Change in bank overdrafts	10	4	2
Cash flows linked to financing operations		**407**	**25,649**
Effect of variations in foreign exchange rates		12	(3)
Increase (Decrease) in cash		**(6,343)**	**16,791**
Cash and cash equivalents at the beginning of the period		9,409	3,066
Cash and cash equivalents at the end of the period		3,066	19,857

Note 1: General Information about the Company

Created in September 2006, Biophytis is a biopharmaceutical company that develops potential new classes of drugs to treat degenerative diseases related to ageing, especially those affecting muscular and visual functions.

Biophytis is a joint stock company and its registered office is located at 14, Avenue de l'Opéra, 75001 Paris, France (Number of the Trade and Companies Register: 492 002 225 RCS).

Biophytis and its subsidiaries are referred to hereinafter as the "**Biophytis**", the "**Company**" or the "**Group**".

The following information constitutes the notes to the consolidated financial statements for the year ended 31 December 2017 with comparative information for the year ended 31 December 2016.

The consolidated financial statements of Biophytis or the "**Financial Statements"** have been prepared under the responsibility of the management of the Company and have been approved and authorised for publication by the Board of Directors on 26 March 2018.

January 2017

- Grouping of the entire staff of the Company on the Jussieu campus of the Pierre and Marie Curie University (UPMC), the very first scientific partner of the Company.

March 2017

- The Company confirms the excellent pharmacokinetic profile in healthy elderly subjects, the therapeutic window of the Sarconeos product, and determines the dosages that will be used in the SARA-INT phase 2b clinical trial.

- Opening of the first clinical centres as part of the SARA-OBS observational study in Europe and start of patient recruitment.

April 2017:

- Carried out a private investment of €3.7 million via the issue of 1,310,431 new shares at a price of €2.85 per share.

- Setting up of a credit facility with Bracknor Fund of up to €15 million in the form of 1,500 notes convertible into shares with share subscription warrants attached (French acronym "ORNANEBSA") with a nominal value of €10K each.

May 2017:

- Authorisation granted by US regulatory authorities to open two clinical centres and start recruitment of patients with sarcopenia in the United States.

- Issue of an initial tranche of 300 notes convertible into shares with share subscription warrants attached and 30 convertible bonds in respect of the commitment fee in favour of Bracknor Fund. Convertible bonds are accompanied by the issue of 225,225 warrants.
  These 330 bonds were fully repaid by the issue of 1,385,085 shares.

July 2017

- Issue of a second tranche of 300 convertible bonds, with a total nominal value of €3.0 million, accompanied by the issue of 205,959 warrants in favour of Bracknor Fund.
  These 300 bonds were fully repaid by the issue of 1,027,396 shares.

October 2017

- Private investment of €10.4 million with institutional investors in Europe and the United States via the issue of 1,989,000 new shares at a price of €5.25 per share.

- Authorisation obtained from the US Food and Drug Agency (FDA), to launch the phase 2b interventional study of Sarconeos for sarcopenia (SARA-INT) in the United States.

- Private investment of €7.5 million via the issue of 1,513 000 new shares at a price of €5 per share.

December 2017

- Authorisation obtained from the Belgian Federal Agency for Medicines and Health Products (FAMHP), to launch the phase 2b interventional study of the Sarconeos drug candidate for sarcopenia (SARA-INT) in Belgium.

Note 2: Accounting principles, rules and methods

2.1 Principles for preparing the financial statements

Unless otherwise indicated, the financial statements are presented in thousands of euros. Certain amounts may be rounded for the purpose of calculating financial information contained in the financial statements. As a result, the totals in some tables may not exactly match the sum of the previous figures.

Declaration of compliance

The Group has prepared its consolidated financial statements for the years ended 31 December 2017 in accordance with the International Financial Reporting Standards (IFRS), issued by the International Accounting Standards Board (IASB). The term "IFRS" refers to international accounting standards (IAS and IFRS) and interpretative committee interpretations (IFRS Interpretations Committee (IFRS IC) and Standing Interpretations Committee (SIC)) for the year ended on 31 December 2017. Comparative figures are presented for the year ended 31 December 2016.

Due to the listing of the Company's shares on Euronext Growth Paris (formerly Alternext Paris) and pursuant to European Regulation No 1606/2002 of 19 July 2002, the Company's financial statements are also prepared in accordance with IFRS adopted by the European Union (EU), at the date of preparation of the financial statements, for all periods presented.

As at 31 December 2017, all IFRS standards issued by the IASB and mandatory are the same as those adopted by the EU and mandatory in the EU, with the exception of:

- IAS 39 - Financial Instruments: Recognition and Measurement (Revised December 2003), or IAS 39, which the EU has partially adopted;
- IFRIC 22 - Foreign Currency Transactions and Advance Consideration
- IFRIC 23 - Uncertainty over Income Tax Treatments

Going concern

Despite the loss corresponding to €(11,409)K for the 2017 financial year, the Board of Directors approved the accounts under the going concern assumption, taking into account the following elements to cover the future cash requirements of the Company during the next twelve months:

- Cash and cash equivalents available at 31 December 2017 for €19.9 million;
- The possible use of the credit facility set up with Bracknor Fund Limited and which could give rise to additional financing of €9 million.

In order to meet its needs after that date, the Company intends to continue its search for the most appropriate financing.

Accounting methods

The accounting policies adopted for the financial statements for the year ended 31 December 2017 are the same as those used for the year ended 31 December 2016, with the exception of the new standards, amendments and interpretations that are mandatory for the Group as of 1 January 2017:

- Amendments to IAS 12 - Recognition of Deferred Tax Assets for Unrealised Losses
- Amendments to IAS 7 - Disclosures

None of these standards had an impact on the Company's consolidated financial statements.
The recently published but not yet adopted standards that may be applicable to the Company are the following:

- IFRS 15 - Revenue from contracts with customers, published on 28 May 2014 and mandatory as of 1 January 2018.
- IFRS 9 - Financial Instruments, published 24 July 2014 and in force as from 1 January 2018.
- IFRS 16 - Leases, published on 13 January 2016 and mandatory as of 1 January 2019.

The Company has not applied by anticipation any new standards, amendments, or interpretations.
The Company is currently assessing the impacts resulting from the first application of these new standards and does not anticipate any significant impact on its financial statements.

2.2 Use of judgements and estimates

In order to prepare the financial statements in accordance with the IFRS, estimates, judgements and hypotheses were made by the Company's management; these could have affected the reported amounts of assets and liabilities, the contingent liabilities at the date of the financial statements and the amounts reported as income and expenses for the financial year.

These estimates are based on the assumption of going concern and are based on information available when they are drawn up. They are evaluated continuously based on past experience and various other factors considered reasonable that form the basis for assessing the book value of assets and liabilities. Estimates may be revised if the circumstances on which they were based change or if new information arises. The actual results could differ from these estimates on the basis of different hypotheses or conditions.

The main assessments and estimates made by the Group's management include:

- Founders' warrants and warrants for the subscription of shares for employees and managers.
    - The determination of the fair value of payments is based on the Black & Scholes valuation model for options, which takes hypotheses into account regarding complex and subjective variables. These variables include the value of the Company's shares, the expected volatility of the share price over the lifetime of the instrument, as well as the current and future behaviour of the holders of these instruments. There is a high inherent risk of subjectivity from the use of an option pricing model in determining the fair value of payments based on the shares, pursuant to the IFRS 2 standard *"Share-based payments"*.
    - The valuation hypotheses adopted are presented in Note. 9.

- Convertible bonds and warrants: determination of the fair value of the derivative liabilities and equity instruments
    - The determination of the fair value of these instruments is based on the Black & Scholes valuation model for options, which takes into account assumptions on complex and subjective variables. These variables include the value of the Company's shares, the expected volatility of the share price over the lifetime of the instrument. There is a high inherent risk of subjectivity deriving from the use of an option pricing model in determining the fair value derivative liabilities and equity instruments, pursuant to the IAS 32/39 standards.
    - The valuation hypotheses adopted are presented in Note 10.5.

- Non-recognition of deferred tax assets net of deferred tax liabilities:
    - The determination of the amount of deferred tax assets that may be recorded requires management to make estimates both of the period for consumption of tax loss carry-forwards and of the level of future taxable profits, in view of tax management strategies.
    - The accounting principles applied by the Company in terms of recognition of deferred tax assets are specified in note 2.19

2.3 Perimeter and consolidation methods

Biophytis controls all legal entities included in the consolidation.
An investor consolidates an entity if the investor is exposed or entitled to variable returns resulting from his involvement in the entity and if the investor's power over that entity allows the investor to affect his returns. This principle applies to all entities, including structured entities.
To be considered controlling an entity, an investor must hold, cumulatively:

- The power over the entity, i.e. if the investor has effective rights that confer the actual ability to direct the entity's operations having a material impact on returns;
- Exposure or entitlement to variable returns due to its relationship with the entity;
- The ability to exercise its power over the entity so as to affect the amount of returns the investor obtains.

Subsidiaries are consolidated from the date on which the Company acquires control of them. They are deconsolidated starting from the date on which the control ceases to be exercised.
Intra-group transactions and balances are eliminated. The financial statements of the subsidiaries are prepared for the same reference period as that of the parent company, and on the basis of uniform accounting policies.
On the date of publication of these consolidated financial statements, the Company has control over two subsidiaries:

- Instituto Biophytis Do Brasil, a company governed by Brazilian law, registered in the state of Sao Paulo, created in July 2006 and 94.6% held;
- Biophytis Inc., a US company registered in Delaware, created in September 2015 and 100% owned.

2.4 Conversion of foreign currency

For each entity, the Group determines the functional currency and the items included in the financial statements of each entity are measured using that functional currency.
The financial statements of the Company are prepared in euros (€), which is the Group's reporting currency and functional currency.

2.4.1 Recording of foreign currency transactions

Transactions in foreign currencies are translated into the functional currency of the Company at the exchange rates in effect on the date of the transactions. Monetary assets and liabilities denominated in foreign currencies on the closing date are translated into the functional currency at the exchange rate on that date.
Currency gains and losses resulting from the translation of monetary items correspond to the difference between the amortised cost denominated in the functional currency at the beginning of the period, adjusted for the impact of the effective interest and payments for the period and the amortised cost denominated in the foreign currency, converted at the exchange rate on the closing date.
Non-monetary assets and liabilities denominated in a foreign currency, which are measured at fair value, are translated into the functional currency using the exchange rate on the date on which the fair value was determined. Currency differences resulting from these conversions are recorded in the income statement, with the exception of differences arising from the conversion of equity instruments available for sale, of a financial liability designated as a hedge of a net investment in a foreign activity, or instruments qualifying as cash flow hedges, which are recorded directly under shareholders' funds.

2.4.2 Conversion of the financial statements of foreign subsidiaries

The financial statements of entities for which the functional currency is not the euro are converted as follows:

- Assets and liabilities are translated at the closing rate;
- The income statement items are converted at the average rate for the period.
- Shareholders' equity is converted at the historical rate.

Foreign exchange differences resulting from the conversion for consolidation purposes are recognised in shareholders' equity under "Currency conversion reserve".

The exchange rates used for preparing the consolidated financial statements are as follows:

EXCHANGE RATE	Closing rate		Average rate	
(Currency for €1)	31/12/2016	31/12/2017	2016	2017
BRL	3.4305	3.9729	3.8616	3.6043
USD	1.0541	1.1993	1.1066	1.1295

2.5 Intangible fixed assets

Research and development expenses

Research and development costs are recognised as an expense when incurred. Expenses incurred on development projects are recognised as intangible assets when the following criteria are met:

- It is technically possible to complete the intangible asset so it is available for use or sale;
- Management intends to complete, use, or sell the intangible asset;
- There is a possibility of using or selling the intangible asset;
- It can be demonstrated that the intangible asset will generate probable future economic benefits;
- The technical, financial, and other adequate resources necessary for the completion of the development, the use, or the sale of the intangible asset are available;
- Expenditures attributable to the intangible asset during its development can be measured reliably.

According to the Company management, and due to the uncertainties inherent in the development of the Group's products, the criteria required for development costs to be recognised as an asset, as defined by IAS 38, "Intangible assets", are not met.

Patents and software

Costs associated with the acquisition of patents and software are capitalised on the basis of costs incurred to acquire the patents and software in question.

Amortisation duration and expense

When intangible assets have a finite useful life, amortisation is calculated by the straight-line method over this period, i.e.:

Items	Depreciation period
Development costs	Estimated duration of use of the project
Purchased patents	Estimated duration of use of the patents
Metabrain	*19 years old*
Iris Pharma	*20 years old*
Software	3- 5 years

The value of intangible assets is tested as soon as a risk of impairment is identified. The examination of quantitative and qualitative indicators, the main ones being indicators relating to the development of the research and development portfolio, pharmacovigilance, patent litigation and the arrival of competing products, is carried out at each balance sheet date. If there is an internal or external indication of impairment, Biophytis assesses the recoverable amount of the asset. The test consists of comparing the net book value of these assets with their recoverable amount. When the net book value of an asset exceeds its recoverable amount, an impairment loss is recognised for the difference.

2.6 Tangible fixed assets

Tangible assets are valued at their acquisition cost (purchase price and accessory costs) or at their cost of production by the company.

Assets are depreciated on a straight-line basis over their actual useful lives.
They are depreciated on a straight-line basis over the following periods:

Items	Depreciation period
General installations, fixtures and fittings	3- 15 years
Technical installations, materials, and tools	5- 7 years
Office and computer equipment	3- 5 years
Furniture	3- 5 years
Transport equipment	3- 5 years

Depreciation expenses for tangible fixed assets are recorded in the income statement under:

- "General and administrative expenses" for depreciation of plant, fixtures, and miscellaneous fittings; office and computer equipment; furniture.
- "Research and development expenses" for the depreciation of laboratory equipment.

2.7 Lease agreements

Assets financed by finance leases, pursuant to IAS 17 "Lease agreements" standard, which essentially transfer to Biophytis the risks and advantages inherent to their ownership, are recorded as assets in the statement of financial position. The corresponding liability is recorded under "Financial debts".

The lease agreements for which substantially all of the risks and benefits are retained by the lessor, are classified as operating leases. Payments for these simple lease agreements, net

of any incentive measure, are recorded as expenses in the income statement by the straight-line method over the life of the agreement.

2.8 Recoverable value of non-current assets

Assets with an indefinite useful life are not depreciated and are subjected to an annual impairment test.

Depreciated assets are subjected to an impairment test whenever there is an internal or external indication that an asset may have lost value.

2.9 Financial assets

The financial assets of the Company are classified into two categories according to their nature and holding intention:

- financial assets at fair value through the income statement;
- loans and receivables.

All financial assets are initially recorded at their fair value paid plus acquisition costs. All standardised purchases and sales of financial assets are recorded on the payment date.

Financial assets are de-recognised upon the expiry of the rights to receive cash flow from these assets or when they have been sold and the Group has transferred substantially all of the risks and benefits inherent in ownership.

Financial assets at fair value through the income statement

Financial assets at fair value through profit and loss consist of term deposits and are presented under cash and cash equivalents in accordance with IAS 7.
Gains or losses arising from changes in value of "financial assets at fair value through profit or loss" are presented under "net financial income" in the income statement for the period in which they occur.
Other assets may also be voluntarily classified under this category.

Loans and receivables

This category includes other loans, receivables, and trade receivables.

Non-current financial assets include advances and guarantee deposits granted to third parties. Advances and guarantee deposits are non-derivative financial assets with determined or determinable payments which are not listed on an active market.

Such assets are recorded at amortised cost using the effective interest rate method. Gains and losses are recorded in the income statement when the loans and receivables are deregistered or written down.

2.10 Cash, cash equivalents and financial instruments

Cash and cash equivalents recorded in the statement of financial position include bank deposits, cash on hand and short-term deposits with an initial maturity of less than three months.

Cash equivalents are held for trading purposes, are easily convertible into a known amount of cash and are subject to an insignificant risk of changes in value. They are assessed at their fair value and changes in value are recorded under financial income.

For the purposes of the cash flow statement, net cash includes cash and cash equivalents, as defined above, as well as bank overdrafts.

2.11 Fair value of financial instruments

Borrowings and financial debts (excluding derivative liabilities) are initially recognised at fair value and subsequently measured at amortised cost using the effective interest rate (EIR) method.

The fair value of customer receivables and supplier debts is adjusted to their book value, considering the very short payment maturities of these receivables. The same is true of the other receivables and other current liabilities.

The Company has defined three categories of financial instruments according to their valuation methods and uses this classification to present some of the information required by IFRS 7 *Financial Instruments - Disclosures*:

- Level 1: financial instruments listed on an active market;
- Level 2: financial instruments valued based on observable data;
- Level 3: financial instruments valued wholly or partly on unobservable data, where unobservable data is defined as data valued on the basis of assumptions or correlations not based on observable market transactions on the same instrument or on observable market data on the valuation date.

The instruments held by the Company recognised at fair value through profit or loss are term deposits that fall under Level 1, with derivative liabilities falling under Level 3.

2.12 Liquidity agreement

Following its IPO on the Alternext Paris market (now Euronext Growth Paris), the Company signed a liquidity agreement with Invest Securities in order to limit the “intra-day” volatility of the Biophytis stock price.

In this context, the Company provided € 300K to this institution to take long and short positions on the Company’s shares. Shares acquired under this agreement are accounted for as treasury shares of the Company at their acquisition costs.

The result of the disposal of these treasury shares is also recorded directly under shareholders' equity.

The cash reserve linked to the liquidity agreement is presented under “Other non-current financial assets”.

2.13 Government grants

Reimbursable advances

The Company benefits from reimbursable advances: Details of this assistance are provided in Note 10.1.

They are accounted for in accordance with IAS 20 *Accounting for Government Grants and Disclosure of Government Assistance*. Financial advances made at lower-than-market interest rates are measured at amortised cost in accordance with IAS 39 *Financial Instruments:*

- The interest rate advantage is determined by assuming a discount rate corresponding to a market rate on the date of granting. The amount resulting from the interest rate advantage obtained on granting non-interest-bearing reimbursable advances is considered to be a grant recorded as income in the comprehensive income statement.
- The financial cost of reimbursable advances calculated at the market rate is then recorded under financial expenses.

Grants are presented as a debit under “Research and Development”.

These advances are recorded as “Non-current financial debts” and as “Current financial debts” depending on their maturity. In the event of confirmation of pronounced failure, the agreed write-off of the receivable is recorded as a subsidy.

Subsidies

The subsidies received are recorded as soon as the corresponding receivable becomes certain, considering the conditions imposed for granting the subsidy.

Operating subsidies are recorded as a reduction of research and development expenses.

Research tax credit

The Company benefits from certain provisions of the French General Tax Code relating to research tax credits.

The Group benefits from research tax credits relating to specific projects ("research tax credit") granted to companies established in France for the purpose of promoting scientific and technical research. Firms whose expenditures meet the required criteria receive a tax credit that (i) may be deducted from income tax due for the year in which it was granted and for the three following years, or (ii) in certain circumstances, the positive difference between the tax credit and due tax may also be repaid to the Company.
If a company meets certain criteria concerning revenue, workforce, or assets that allow it to be considered as a small or medium-sized enterprise as defined by the European Union, it may request the immediate repayment of the research tax credit. Biophytis meets these criteria.

The Group considers that the research tax credit granted by the French State is a public subsidy, given that the Group receives the credit independently of the tax it pays. The Group recognises this receivable under other current receivables, given the expected repayment

period. Research tax credits are presented in the consolidated income statement as a reduction of research and development expenses.
The research tax credit is subject to audits by the tax authorities.

Employment Competitiveness Tax Credit

The Employment Competitiveness Tax Credit ("CICE") is a French tax mechanism. Revenue is recorded as a reduction in staff expenses. The Company used this tax credit through its research and development efforts.

2.14 Receivables

Receivables are valued at their nominal value. They are, where applicable, depreciated on a case-by-case basis by means of a provision.

Other receivables include the nominal value of the research tax credit recorded at the time the eligible expenditures giving rise to the tax credit were generated.

2.15 Equity

The classification under equity depends on the specific analysis of the characteristics of each issued instrument.

Accessory costs directly attributable to the issue of shares or options on shares are recorded net of tax, as a deduction from equity.

2.17 Share based payments

Since its incorporation, the Company has implemented several remuneration plans paid in equity instruments in the form of warrants or founder's warrants awarded to employees and officers.

Pursuant to the IFRS 2 "*Share-based payment*" standard, the cost of transactions settled in equity instruments is recorded as an expense over the period during which the rights to benefit from the equity instruments are acquired.

The fair value of shares of warrants granted to employees is calculated using the Black-Scholes option valuation model. The same holds for options granted to other natural persons providing similar services, with the market value of these latter not determinable.

All of the assumptions used to value the plans are described in note 9.

2.17 Employee benefit obligation

The French employees of the Company receive the pension benefits provided by French law:

- A retirement indemnity, paid by the Company upon retirement (defined benefit plan);

- Payment of retirement pensions by the Social Security organisations, which are financed by the company and employee contributions (defined contribution plan).

Retirement plans, the related payments and other social benefits classified as defined benefit plans (a regime under which the Company undertakes to guarantee a defined amount or level of payments) are recorded on the balance sheet on the basis of an actuarial evaluation of the commitments on the closing date, reduced by the fair value of the assets of the associated regime which are dedicated to them.

This assessment is based on the use of the projected unit credit method, which takes into account staff turnover and mortality probabilities. Any actuarial differences are recorded under shareholder's equity in "Other elements of comprehensive income".

The payments by the Company for defined contribution plans are recorded as expenses in the income statement during the period to which they relate.

2.18 Borrowings

Financial liabilities are classified into two categories and include:

- financial liabilities recorded at amortised cost and,
- Financial liabilities recorded at fair value through the income statement.

Financial liabilities recorded at amortised cost

Borrowings and other financial liabilities, such as reimbursable advances, are recorded at amortised cost calculated using the effective interest rate. The fraction of financial liabilities of less than one year is presented under "current financial liabilities".

Financial liabilities recorded at fair value via the income statement

Derivative liabilities are recorded at fair value through profit or loss.

During the 2017 financial year, the Company issued convertible bonds and warrants.
This instrument comprises: a debt component (valued using the amortised cost method), a derivative (valued at fair value through profit or loss in accordance with IAS 39) and an equity instrument (valued at fair value at the date of issue in equity instruments in accordance with IAS 32).
The issue costs are allocated to the debt component, the derivative and the equity instrument in proportion to their respective values.
The treatment of this hybrid instrument is detailed in note 10.5.

2.19 Income tax

Tax assets and liabilities due during the financial year and in previous financial years are assessed at the amount expected to be recovered or paid to tax authorities.

The tax rates and regulations used to determine these amounts are those which were adopted or almost adopted on the closing date.

Deferred taxes are recorded using the liability method, for all temporary differences at the balance sheet date between the tax bases of assets and liabilities and their book values in the financial statements as well as on tax loss carry-forwards.

The main temporary differences relate to tax loss carry-forwards.

Deferred tax assets are recorded by way of tax loss carry-forwards when it is probable that the Company will have future taxable profits against which these unused tax losses can be offset. The determination of the amount of deferred tax assets that may be recorded requires management to make estimates both of the period for consumption of tax loss carry-forwards and of the level of future taxable profits, in view of tax management strategies.

2.20 Sector information

The Company operates in a single activity segment: the development of drugs candidates for the treatment of metabolic and age-related diseases.

The assets and the operating loss presented are located in France.

Research and development costs and most of the administrative costs are incurred in France.

2.21 Earnings per share

The basic earnings per share are calculated by dividing the earnings attributable to the holders of Company shares the weighted average number of ordinary shares outstanding during the period.

The diluted earnings per share are determined by adjusting the profit attributable to holders of common shares and the weighted average number of common shares in circulation for the effects of all potentially dilutive common shares.

If the consideration of instruments providing deferred entitlement to equity (warrants, founder's warrants, etc.) generates an anti-dilutive effect, these instruments are not taken into account.

Note 3: Patents and software

(Amounts in thousands of euros)	Patents	Software	Total
GROSS VALUES			
Statement of financial position at 31 December 2015	**2,300**	**12**	**2,312**
Acquisition	-	2	2
Disposal	-	-	-
Transfer	-	-	-
Statement of financial position at 31 December 2016	**2,300**	**14**	**2,314**
Acquisition	-	4	4
Disposal	-	(12)	(12)
Transfer	-	-	-
Statement of financial position at 31 December 2017	**2,300**	**6**	**2,306**
AMORTISATIONS AND DEPRECIATIONS			
Statement of financial position at 31 December 2015	**57**	**11**	**68**
Increase	119	2	120
Decrease	-	-	-
Statement of financial position at 31 December 2016	**176**	**13**	**189**
Increase	119	2	120
Decrease	-	(12)	(12)
Statement of financial position at 31 December 2017	**294**	**3**	**297**
NET BOOK VALUES			
On 31 December 2015	**2,243**	**1**	**2,244**
At 31 December 2016	**2,124**	**1**	**2,125**
At 31 December 2017	**2,006**	**3**	**2,009**

No losses of value were recorded by way of application of the IAS 36 standard.

The Company co-owns certain joint-ownership patents with public partners.

Note 4: Tangible fixed assets

(Amounts in thousands of euros)	Machinery and equipment	Machinery and equipment (leasing - financing)	Installations and fixtures	Of which office, IT equipment, and furniture	Transport equipment	Total
GROSS VALUES						
Statement of financial position at 31 December 2015	**93**	**181**	**28**	**36**	**3**	**342**
Acquisition	79	-	32	16	-	127
Disposal	-	-	(2)	-	-	(2)
Foreign exchange impact	17	-	4	1	1	22
Statement of financial position at 31 December 2016	**189**	**181**	**62**	**53**	**4**	**489**
Acquisition	82	-	12	30	-	123
Disposal	(4)	-	(12)	(19)	(4)	(39)
Exchange impact	(11)	-	(2)	1.	(0)	(15)
Statement of financial position at 31 December 2017	**256**	**181**	**59**	**62**	**0**	**559**
AMORTISATIONS AND DEPRECIATIONS						
Statement of financial position at 31 December 2015	**93**	**5**	**18**	**28**	**3**	**147**
Increase	9	30	2	6	-	47
Decrease	-	-	(1)	-	-	(1)
Foreign exchange impact	17	-	1	1	1	20
Statement of financial position at 31 December 2016	**120**	**35**	**19**	**35**	**4**	**213**
Increase	22	36	15	11	-	84
Decrease	(4)	-	(12)	(18)	(4)	(37)
Exchange impact	(11)	-	(1)	(1)	(0)	(13)
Statement of financial position at 31 December 2017	**127**	**71**	**21**	**28**	**-**	**247**
NET BOOK VALUES						
At 31 December 2015	**-**	**176**	**10**	**8**	**-**	**194**
At 31 December 2016	**69**	**146**	**43**	**17**	**-**	**276**
At 31 December 2017	**130**	**110**	**38**	**34**	**-**	**313**

No losses of value were recorded by way of application of the IAS 36 standard.

Note 5: Other receivables

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Research tax credit (1)	2,058	2,549
Competitive employment tax credits (CICE)	5	9
Value-added tax	471	709
Prepaid expenses (2)	160	251
Suppliers - advance payments	112	49
Other	21	11
Total other receivables	**2,827**	**3,578**

(1) Research tax credit (CIR)

In the absence of taxable income, the receivable against the State relating to the Research Tax Credit is repayable following the year of its recording:

- CIR 2017: €2,549K Reimbursement of the amount is scheduled to take place during the 2018 financial year.

The CIR receivable as at 31 December 20166 included the 2015 CIR and the 2016 CIR, with reimbursements in January 2017 and November 2017, respectively.

(2) Prepaid expenses mainly relate to research services provided by an external service provider.

Note 6: Cash and cash equivalents

The item cash and equivalents had the following breakdown:

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Bank accounts	1,065	9,857
Term deposits	2,001	10,001
Total cash and cash equivalents	**3,066**	**19,857**

At 31 December 2017, the Company held two term deposits maturing in January 2018, with nominal values of €7,000K and €3,000K respectively.

Note 7: Financial assets and liabilities and effects on net profit

The assets and liabilities of the Company were valued as follows for each year:

(Amounts in thousands of euros)	31/12/2017		Value - statement of financial position in accordance with IAS 39		
	Value - Statement of Financial Position	Fair value	Fair value through the income statement	Loans and receivables	Debts at amortised cost
Non-current financial assets	190	190	-	190	-
Other receivables	3,578	3,578	-	3,578	-
Cash and cash equivalents	19,857	19,857	10,001	9,857	-
Total assets	**23,626**	**23,626**	**10,001**	**13,625**	**-**
Non-current financial liabilities	708	708	-	-	708
Current financial liabilities	305	305	-	-	305
Derivative liabilities	-	-	-	-	-
Trade payables	2,402	2,402	-	-	2,402
Total liabilities	**3,415**	**3,415**	**-**	**-**	**3,415**

(amounts in thousands of euros)	31/12/2016		Value - Statement of Financial Position according to IAS 39		
	Value - Statement of Financial Position	Fair value	Fair value through the income statement	Loans and receivables	Debts at amortised cost
Non-current financial assets	99	99	-	99	-
Other receivables	2,827	2,827	-	2,827	-
Cash and cash equivalents	3,066	3,066	2,001	1,065	-
Total assets	**5,992**	**5,992**	**2,001**	**3,991**	-
Non-current financial liabilities	913	913	-	-	913
Current financial liabilities	176	176	-	-	176
Trade payables	1,920	1,920	-	-	1,920
Total liabilities	**3,010**	**3,010**	**-**	**-**	**3,010**

(Amounts in thousands of euros)	31/12/2016		31/12/2017	
	Interest:	Change in fair value	Interest:	Change in fair value
Liabilities				
Liabilities measured at fair value: derivative liabilities	-	-	-	1,756
Liabilities measured at amortised cost: bonds	-	-	(3,145)	-
Liabilities measured at amortised cost: advances	(19)	-	(31)	-

Note 8: Capital

	31/12/2016	31/12/2017
Capital (in thousands of euros)	1,245	2,693
Number of shares, of which	6,223,501	13,463,413
Ordinary shares	6,223,501	13,463,413
Nominal value (in euros)	0.20	0.20

Share capital

At 31 December 2017, share capital was set at € 2,692,682.60.
It is divided into 13,463,413 shares, fully subscribed and paid up, with a nominal value of €0.20.
This number is understood as excluding warrants for the subscription of shares (“BSA”) and “warrants for founder’s shares” (“BSPCE”) granted to certain investors and to certain natural persons, whether or not employees of the Company and not yet exercised.

Development of the share capital

Financial year 2016
Following the exercise of founder’s warrants during the year, the share capital was increased by €5,600 through the issuance of 28,000 new shares with a nominal value of €0.20.

Financial year 2017
The Company made several private investments generating a capital increase of €962K and an issue premium of €20,779K broken down as follows:

- April 2017:
  - Private investment of €3.2 million via the issue of 1,117,449 new shares at a price of €2.85 per share. This transaction generated a capital increase of €223K and an issue premium of €2,961K.
  - Capital increase subscribed by the management of the Company, amounting to €550K, via the issue of 192,982 new shares at a unit price of €2.85. This transaction generated a capital increase of €39K and an issue premium of €511K.

- October 2017:
  - Private investment of €10.4 million via the issue of 1,989,000 new shares at a price of €5.25 per share. This transaction generated a capital increase of €398K and an issue premium of €10,044K.
  - Private investment of €7.6 million via the issue of 1,513,000 new shares at a price of €5 per share. This transaction generated a capital increase of €303K and an issue premium of €7,262K.

In addition, 630 bonds held by Bracknor Fund Limited (see note 10.5) were repaid in new shares generating the issue of 2,412,481 shares with a nominal value of €0.20, representing a capital increase of €482K and an issue premium of €6,339K.

Lastly, following the exercise of founder's warrants during the year, the share capital was increased by €3K via the issue of 15,000 new shares with a nominal value of €0.20.

Distribution of dividends

The Company did not distribute any dividends during the presented financial years.

Capital management

The Group's policy is to maintain a solid capital base in order to preserve the confidence of investors and creditors and to sustain the future development of its activity.

In this capacity, a liquidity agreement was signed with Invest Securities.
On 31 December 2017, under this agreement, 29,909 treasury shares were recorded as a deduction from shareholders' equity and €190K euros in cash were included under non-current financial assets.

Note 9: Warrants and founder's warrants

Warrants awarded to investors

Under the BIOPHYTIS$_{2015D}$ bond agreement, the Company awarded 270,414 warrants$_{2015D}$ on 10 July 2015 for a total non-refundable issue price of €162K. These warrants give the right to acquire a fixed number of Company shares.
Accordingly, pursuant to IAS 32, they are treated as "equity instruments" and are recorded at their issue price in the Company's shareholders' equity.

Type	Characteristics of the plans

	Date of award	Total number of warrants awarded	Date of maturity	Exercise price
Warrants$_{2015D}$	10/07/2015	**270,414**	10/07/2019	€6.00

Type	Date of award	Number of outstanding warrants					Maximum number of shares to be subscribed:
		31/12/2016	Awarded	Exercised	Lapsed	31/12/2017	
Warrants$_{2015D}$	10/07/2015	189,748	-	-	-	189,748	189,748
Total		**189,748**	**-**	**-**	**-**	**189,748**	**189,748**

Warrants

The following table summarises the data relating to option plans issued as well as the assumptions used for valuation pursuant to IFRS 2:

Type	Date of award	Characteristics of the plans			Assumptions used		
		Total number of warrants awarded	Date of maturity	Exercise price	Volatility	Risk-free rate	Total initial IFRS2 valuation (Black & Scholes)
Warrants$_{2015}$	04/08/2015	**54,000**	04/08/2019	€ 8.40	49.77%	-0.18%	**€481K**
Warrants$_{2017}$	21/07/2017	**72,000**	28/11/2021	€ 3.30	59.95%	-0.62%	**€153K**

Type	Date of award	Number of outstanding warrants					Maximum number of shares to be subscribed:
		31/12/2016	Awarded	Exercised	Lapsed	31/12/2017	
Warrants$_{2015}$	04/08/2015	48,000	-	-	-	48,000	48,000
Warrants$_{2017}$	21/07/2017	-	72,000	-	-	72,000	72,000
Total		**48,000**	**72,000**	**-**	**-**	**120,000**	**120,000**

The vesting period of the issued plans is as follows:

Type	Vesting period		
Warrants$_{2015}$	1/3 to 04/08/2015	1/3 to 04/08/2016	1/3 to 04/08/2017
Warrants$_{2017}$	1/3 to 21/07/2017	1/3 to 21/07/2018	1/3 to 21/07/2019

Founders' warrants

The following table summarises the data relating to option plans issued as well as the assumptions used for valuation pursuant to IFRS 2:

Type	Date of award	Characteristics of the plans			Assumptions used		
		Total number of warrants awarded	Date of maturity	Exercise price	Volatility	Risk-free rate	Total initial IFRS2 valuation (Black & Scholes)
Founder's warrants$_{2015-1}$	22/05/2015	**195,000**	22/05/2019	€2.06	49.09%	-0.13%	**€794K**
Founder's warrants$_{2015-2}$	23/09/2015	**424,200**	23/09/2019	€10.70	53.16%	-0.19%	**€2,591K**
Founder's warrants$_{2015-3}$	04/12/2015	**20,000**	04/12/2019	€10.70	53.79%	-0.22%	**€78K**
Founder's warrants$_{2015-4}$	15/03/2016	**39,700**	15/03/2019	€6.09	56.74%	-0.41%	**€83K**
Founder's warrants$_{2017-1}$	21/07/2017	**227,000**	21/07/2017	€ 3.30	54.07%	-0.53%	**€347K**
Founder's warrants$_{2017-2}$	21/07/2017	**127,000**	21/07/2017	€ 3.30	57.25%	-0.65%	**€421K**

Type	Date of award	Number of outstanding warrants					Maximum number of shares to be subscribed:
		31/12/2016	Awarded	Exercised	Lapsed	31/12/2017	
Founder's warrants$_{2015-1}$	22/05/2015	167,000	-	(15,000)	-	152,000	152,000
Founder's warrants$_{2015-2}$	23/09/2015	384,500	-	-	-	384,500	384,500
Founder's warrants$_{2015-3}$	04/12/2015	20,000	-	-	-	20,000	20,000
Founder's warrants$_{2015-4}$	15/03/2016	39,700	-	-	-	39,700	39,700
Founder's warrants$_{2017-1}$	21/07/2017	-	227,000	-	-	227,000	227,000
Founder's warrants$_{2017-2}$	21/07/2017	-	127,000	-	-	127,000	127,000
Total		**611,200**	**354,000**	**(15,000)**	**-**	**950,200**	**950,200**

The acquisition period for the rights of the issued plans is as follows:

Type	Vesting period		
Founder's warrants$_{2015-1}$	Fully vested at the grant date		
Founder's warrants$_{2015-2}$	1/3 to 23/09/2015	1/3 to 23/09/2016	1/3 to 23/09/2017
Founder's warrants$_{2015-3}$	1/3 to 04/12/2015	1/3 to 04/12/2016	1/3 to 04/12/2017
Founder's warrants$_{2015-4}$	1/3 to 15/03/2016	1/3 to 15/03/2017	1/3 to 15/03/2018
Founder's warrants$_{2017-1}$	1/3 to 21/07/2017	1/3 to 21/07/2018	1/3 to 21/07/2019
Founder's warrants$_{2017-2}$	1/3 to 21/07/2017	1/3 to 21/07/2018	1/3 to 21/07/2019

Share-based payment expense recognised for the presented years

Type	31/12/2016				31/12/2017			
	Probable cost of plan to date	Accrued expense at opening	Expense for the financial year	Accrued expense to date	Probable cost of plan to date	Accrued expense at opening	Expense for the period	Accrued expense to date
Warrants$_{2017}$	-	-	-	-	153	-	153	153
Founder's warrants$_{2015-2}$	2,429	1,191	904	2,095	2,429	2,095	335	2,429
Founder's warrants$_{2015-3}$	78	36	31	67	78	67	11	78

Founder's warrants$_{2015-4}$	83	-	59	59	83	59	19	78
Founder's warrants$_{2017-1}$	-	-	-	-	347	-	188	188
Founder's warrants$_{2017-2}$	-	-	-	-	421	-	184	184
Total		**994**					**891**	

Note 10: Borrowings and financial liabilities

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Reimbursable advances	797	661
Borrowings from and debts with lending institutions	23	-
Financial debts – Lease financing	94	46
Non-current financial liabilities	**913**	**708**
Reimbursable advances	96	228
Borrowings from and debts with lending institutions	30	23
Financial debts – Lease financing	44	47
Bank overdrafts	5	7
Current financial liabilities	**176**	**305**
Total financial liabilities	**1,090**	**1,013**

Reconciliation of redemption value/balance sheet value

(Amounts in thousands of euros)	Reimbursement value		Amortised cost	Balance sheet value as at 31/12/2017
	31/12/2016	31/12/2017		
Reimbursable advances	999	966	(77)	889
Borrowings from and debts with lending institutions	53	23	-	23
Financial debts – Lease financing	138	94	-	94
Current bank liabilities	5	7	-	7
Total financial debts	**1,196**	**1,090**	**(77)**	**1,013**

Breakdown of financial liabilities by maturity, in reimbursement value

The maturities of financial debts are broken down as follows:

(Amounts in thousands of euros)	31/12/2017	Current	Non-current	
		< 1 year	1- 5 years	> 5 years old
Reimbursable advances	966	226	740	-
Borrowings from and debts with lending institutions	23	23	-	-
Financial debts – Lease financing	94	47	46	-
Current bank liabilities	7	7	-	-
Total financial liabilities	**1,090**	**303**	**786**	

10.1 Reimbursable advances

The following table presents the evolution of the reimbursable advances:

(Amounts in thousands of euros)	OSEO - Quinolia	OSEO - Maculia	OSEO- Sarcob	BPI - BIO 101	Total
At 31 December 2015	**201**	**4**	**89**	**-**	**293**
(+) Collection	-	-	108	567	675
(-) Reimbursement	(38)	(4)	-	-	(41)
Subsidies	-	-	(12)	(41)	(53)
Financial expenses	14	0	3	2	19
At 31 December 2016	**177**	**-**	**188**	**528**	**893**
(+) Collection	-	-	52	-	52
(-) Reimbursement	(73)	-	(13)	-	(86)
Subsidies	-	-	(5)	-	(5)
Financial expenses	10	-	6	18	35
At 31 December 2017	**114**	**-**	**228**	**546**	**889**

Breakdown of reimbursable advances by maturity, in redemption value

(Amounts in thousands of euros)	OSEO - Quinolia	OSEO- Sarcob	BPI - BIO 101	Total
At 31 December 2017	**119**	**247**	**600**	**966**
Share at less than one year	119	52	55	226
Share at 1 year to 5 years	-	195	545	740
Share over 5 years	-	-	-	-

OSEO reimbursable advance - "Quinolia" project

On 7 August 2008, the Company received from OSEO a non-interest-bearing reimbursable advance of €230K for the "clinical development of an extract of Quinoa active on the Metabolic Syndrome".
Payments were scheduled between the agreement's signing date and the end of the project as follows:

- € 100K on the date of signing of the agreement;
- €80K on the drawdown of funds;
- The €50K balance upon completion of the project.

Since the signing of this agreement, several amendments were signed to postpone the end of the program and the reimbursement maturities.
Following the confirmation of the success of the program, an amendment was signed on 8 July 2013, relating to the fixing of the definitive amount of the aid.

Since the deferral of repayments granted by BPI France (formerly OSEO) on 30 April 2015, repayment terms are as follows:

- € 12.5K/quarter from 31 March 2016 to 31 December 2016 (4 payments)
- € 20K/quarter from 31 March 2017 to 31 December 2017 (4 payments)
- € 25K/quarter from 31 March 2018 to 31 December 2018 (4 payments)

The agreement moreover provides for payment of a reimbursement annuity starting from 1 January 2009 and at latest on 31 March of each year, corresponding to: 44% of the pre-tax proceeds, assignments or granting of licenses, patents or know-how received during the previous calendar year when such transfers or leases related to all or part of the results of the assisted program, and to 44% of the pre-tax proceeds generated by marketing and in particular, the sale to a third party or use by the beneficiary for the requirements of his own prototypes, pre-series, and models, executed within the context of the subsidised program.
The due amounts shall be attributed as a priority and for the full amount on the final deadline for payment to OSEO. The application of this mechanism shall not lead the company to pay an amount greater than the aid received.

Under the IFRS standard, the fact that the reimbursable advance does not include the payment of annual interest may be regarded as the Company having received a zero-interest loan, i.e. under conditions more favourable than market ones. The difference between the amount of the advance at its historic cost and that of the advance discounted at a current market rate (3-month Euribor + 2.5 percentage points = 7.47%) is considered a subsidy received from the government.

OSEO reimbursable advance - "Maculia" project

On 30 August 2010, the Company received from OSEO a non-interest-bearing reimbursable advance of €180K for the "clinical development of Bixilia in order to obtain a health claim".

Payments were scheduled between the agreement's signing date and the end of the project as follows:

- €54K on the agreement's signing date;
- €90K on the drawdown of funds;
- The €36K balance upon completion of the project;

Since the signing of this agreement, an amendment was signed in 2013, having as object the confirmation of the partial failure of the program and a modification of the €29K subsidy and in the reimbursement schedule accordingly.

In this way, the last reimbursement of principal was made during the financial year 2016.

Under the IFRS standard, the fact that the reimbursable advance does not include the payment of annual interest may be regarded as the Company having received a zero-interest loan, i.e. under conditions more favourable than market ones. The difference between the amount of the advance at its historic cost and that of the advance discounted at a current market rate (3-month Euribor + 2.5 points = 3.39%) is considered as a subsidy received from the government.

BPI France reimbursable advance - "Sarcob" project

On 4 February 2015, Biophytis obtained from BPI France a reimbursable advance of €260K for the "in vitro, in vivo and pharmacokinetic characterisation of a drug candidate".

Payments were scheduled between the agreement's signing date and the end of the project as follows:

- € 100K on the date of signing of the agreement;
- € 108K on the call for funds;
- The €52K balance on completion of the project, on 26 June 2017.

Since the signing of this agreement, an amendment was signed to postpone the end of the program and the reimbursement maturities:

Since the deferral of repayments granted by BPI France (formerly OSEO) on 07 November 2016, repayment terms are as follows:

- If successful:
  - € 6.5K/quarter from 30 June 2017 to 31 March 2018 (4 payments)
  - € 13K/quarter from 30 June 2018 to 31 March 2021 (12 payments)
  - € 19.5K/quarter from 30 June 2021 to 31 March 2022 (4 payments)
- In the event of failure or partial success:
  - € 6.5K/quarter from 30 June 2017 to 31 March 2018 (4 payments)
  - € 13K/quarter from 30 June 2018 to 30 September 2019 (6 payments)

The agreement, moreover, provides for payment of a reimbursement annuity starting from 1 January 2009 and at the latest on 31 March of each year, corresponding to: 40% of the pre-tax proceeds, assignments or granting of licenses, patents or know-how received during the previous calendar year when such transfers or leases related to all or part of the results of the assisted program, and to 40% of the pre-tax proceeds generated by marketing and in particular, the sale to a third party or use by the beneficiary for the requirements of his own prototypes, pre-series, and models, executed within the context of the subsidised program.
The due amounts shall be attributed as a priority and for the full amount on the final deadline for payment to BPI. The application of this mechanism shall not lead the company to pay an amount greater than the aid received.

Under the IFRS standard, the fact that the reimbursable advance does not include the payment of annual interest may be regarded as the Company having received a zero-interest loan, i.e. under conditions more favourable than market ones. The difference between the amount of the advance at its historic cost and that of the advance discounted at a current market rate (3-month Euribor + 2.5 points = 2.56%) is considered as a subsidy received from the government.

BPI France reimbursable advance - "BIO 101" project

On 28 November 2016 the Company received from BPI France a non-interest-bearing reimbursable advance of €1,100K for the "production of clinical batches, in the preclinical regulatory phase and clinical phase 1 of BIO101, for the treatment of sarcopenic obesity".

Payments were scheduled between the agreement's signing date and the end of the project as follows:

- €600K on the agreement's signing date;
- The €500K balance on completion of the project upon request by the Company.

The contractual reimbursement dates are as follows:

- If successful: €55K/quarter from 31 December 2018 to 30 September 2023 (20 payments)

- In the event of failure or partial success: € 55K/quarter from 31 December 2018 to 30 September 2020 (8 payments)

The agreement moreover provides for payment of a reimbursement annuity starting from 1 January 2018 and at latest on 31 March of each year until 30 September 2023, corresponding to: 35.81 % of the proceeds net of taxes, assignments or granting of licenses, patents or know-how received during the previous calendar year when such transfers or leases related to all or part of the results of the assisted program and to 35.81 % of the net of tax proceeds generated by marketing and in particular, the sale to a third party or use by the beneficiary for the requirements of its own prototypes, pre-series and models, executed within the context of the subsidised program.
The due amounts shall be attributed as a priority and for the full amount on the final deadline for payment to BPI. The application of this mechanism shall not lead the company to pay an amount greater than the aid received.

Under the IFRS standard, the fact that the reimbursable advance does not include the payment of annual interest may be regarded as the Company having received a zero-interest loan, i.e. under conditions more favourable than market ones. The difference between the amount of the advance at its historic cost and that of the advance discounted at a current market rate (3-month Euribor + 2.5 points = 2.19%) is considered as a subsidy received from the government.

10.2 Debts with lending institutions

The following table shows the evolution of debts with lending institutions.

(Amounts in thousands of euros)	OSEO - Equity Loan	BPI - Research Tax Credit prefinancing loan	Total
At 31 December 2015	**83**	**100**	**183**
(+) Collection	-	-	-
(-) Reimbursement	(30)	(100)	(130)
At 31 December 2016	**53**	**-**	**53**
(+) Collection	-	-	-
(-) Reimbursement	(30)	-	(30)
At 31 December 2017	**23**	**-**	**23**

Change in debts with lending institutions by maturity, in reimbursement value

(Amounts in thousands of euros)	OSEO - Equity Loan
At 31 December 2017	**23**
Less than one year	23
1 year to 5 years	-
Over 5 years	-

OSEO - Equity Loan

On 4 November 2008, the Company obtained an equity loan from OSEO with the object of the partial financing of the innovation program.

The main features of this equity loan are:
- Nominal amount: €150K
- Duration: 8 years, of which 3 years of deferral of amortisation of principal

- Interest rate:
    - During the deferred period: Average 3-month Euribor + 3.20%/year
    - During the amortisation: Average Euribor 3-month + 5%/year
- Interest paid quarterly in arrears

Amendments were signed with the object of extending the loan and an allowance in additional capital.
Since 30 April 2015, the Company has reimbursed principal as follows: € 7,500/quarter from 29 February 2016 to 31 August 2018.

BPI France - Pre-financing loan for the Research Tax Credit

On 31 December 2013, the Company signed a loan agreement with BPI France, having is object the pre-funding of research and development expenses for the year 2013, which are eligible for the Research Tax Credit.

The main features of the loan are:
- Nominal amount: €100K
- Duration: 2 years, including an amortisation grace period of 18 months
- Interest rate: 4.95%
- Interest paid monthly in arrears

On 30 April 2015, BPI France granted the Company a grace period for principal, and the amortisation of principal was made all at once in January 2016.

10.3 Miscellaneous financial debt and borrowings

(amounts in thousands of euros)	SODISID loan
At 31 December 2015	**150**
(+) Collection	-
(-) Reimbursement	(150)
At 31 December 2016	**-**

SODISID loan

On 25 July 2014, the Company signed a loan agreement with SODISID within the context of a programme to create 10 jobs.

The main features of the loan are:
- Nominal amount: €150K
- Duration: 18 months, with reimbursement at the end
- Interest rate: 5%/year
- Interest paid quarterly in arrears

Thus, the capital reimbursement was made in 2016.

10.4 Financial debts – Lease financing

(Amounts in thousands of euros)	Financial debts – Lease financing agreements	Current Share	Non-current share	
			1- 5 years	Over 5 years
At 31 December 2015	**174**	43	131	-
(+) Subscription	-			
(-) Reimbursement	(36)			
At 31 December 2016	**138**	44	94	-
(+) Subscription	-			
(-) Reimbursement	(44)			
At 31 December 2017	**94**	47	46	-

In 2015, the Company entered into a finance lease agreement with a 3-year duration regarding an HPLC system (spectrometer).

10.5 Bonds

(amounts in thousands of euros)	Notes convertible into shares with share subscription warrants attached
At 31 December 2016	**-**
(+) Collection	6,000
(-) Warrant discount	(532)
(-) Derivative liabilities	(1,792)
(+/-) impact of amortised cost	3,145
(-) Reimbursement	-
(-) Conversion	(6,822)
At 31 December 2017	**-**

Issuance of notes convertible into shares with share subscription warrants attached in favour of Bracknor Fund Limited

On April 3, 2017, the Company signed an agreement with Bracknor Fund Limited for the issue of notes convertible into shares with share subscription warrants attached allowing a potential €15 million of funds to be raised at the discretion of the Company.

The Board of Directors shall decide on the issue of:

- An initial tranche of 300 notes convertible into shares with share subscription warrants attached and 30 convertible bonds in respect of the commitment fee on 15 May 2017
- A second tranche of 300 notes convertible into shares with share subscription warrants attached on 7 July 2017.

The Company may issue 900 additional warrants in favour of Bracknor Fund Limited, which may give rise to a bond issue for an additional maximum amount of €9 million provided that the previous tranche issued is fully repaid.

Characteristics of the convertible bonds

The convertible bonds (French acronym: ORNANE) have the following characteristics:

- Nominal value: €10K
- Maturity: 12 months
- No interest
- Conversion terms as follows: N = CA / CP where
    - N is the number of shares that can be subscribed;
    - CA is the nominal value of the convertible bonds;
    - CP is 92% (i.e., 8% discount) of the lowest of the 10 volume-weighted average daily quoted prices of the Company's stock immediately preceding the conversion request date and at least equal to the face value of the action (0.20 €).

It is also specified that the Company may repay in cash according to the following formula: (CA/CP) x Weighted average quoted price on the conversion date.

Characteristics of the warrants

The warrants issued may be exercised for a period of five years from their date of issue. Each warrant entitles the holder to subscribe for one new share of the Company at a fixed exercise price determined on the issue date.

Accounting treatment

In accordance with IAS 39, the debt component is measured using the amortised cost method.

The conversion option is recognised as a derivative liability and is measured at fair value, with changes in fair value recognised in profit or loss in accordance with IAS 39.

Conversion option	**Tranche 1**		**Tranche 2**	
	At issue (15/05/2017)	**31/12/2017**	**At issue (07/07/2017)**	**31/12/2017**
Number of bonds outstanding	330	-	300	-
Maximum number of shares to be subscribed	1,330,645	N/A	1,027,397	N/A
Exercise price	€ 2.48	N/A	€ 2.92	N/A
Expected term	1 months	N/A	1 months	N/A
Volatility	39.87%	N/A	41.02%	N/A
Risk free rate	-0.75%	N/A	0.67%	N/A
Value of the derivative (in €000)	**710**	**-**	**1,046**	**-**
Change in fair value for the period (in €000)		**(710)**		**(1,046)**

** net of fees related to the issue*

Under IAS 39, the discount of 8% is treated as an implicit repayment premium recognised as a financial expense.

At 31 December 2017, all of the Tranche 1 and Tranche 2 convertible bonds had been repaid in new shares, generating the issue of 2,412,481 shares (1,385,085 shares in connection with the convertible bonds$_{T1}$ and 1,027,396 shares in connection with the convertible bonds$_{T2}$).

The warrants issued under this agreement are recognised at fair value at the date of issue as equity instruments in accordance with IAS 32.

Warrants	Tranche 1	Tranche 2
	At issue (15/05/2017)	At issue (07/07/2017)
Number of warrants	225,225	205,959
Exercise price	€ 3.33	€ 3.64
Expected term	3 years old	3 years old
Volatility	53.73%	54.17%
Risk free rate	-0.58%	-0.48%
Value of the equity instrument (in €000)	**215**	**306**

** net of fees related to the issue*

At 31 December 2017, all of the warrants$_{T1}$ and warrants$_{T2}$ were outstanding.

The costs related to the issue of notes convertible into shares with share subscription warrants attached are allocated to the debt component, the derivative and the equity instrument in proportion to their respective values.

Note 11: Employee benefit obligation

The employee benefit obligation consist of the provision for retirement allowances, valued on the basis of the provisions of the applicable collective bargaining agreement.

This commitment only applies to employees subject to French law. The principal actuarial assumptions used for the evaluation of the retirement benefits are as follows:

ACTUARIAL ASSUMPTIONS		31/12/2016	31/12/2017
Retirement age		Voluntary departure between 65 and 67	
Collective agreements		Food retailers and wholesalers	Pharmaceutical industry
Discount rate (IBOXX Corporates AA)		1.31%	1.30%
Mortality table		INSEE 2015	INSEE 2017
Wage revaluation rate		2.00%	2.00%
Turnover rate		Mean	Mean
Rate of social charges			
	Executives	44.5%	44.5%
	Non-executive	n/a	N/A

It is specified that the Company has changed its applicable collective bargaining agreement during the 2017 financial year.

The provision for the retirement allowance has evolved as follows:

(Amounts in thousands of euros)	Retirement benefits
At 31 December 2015	**25**
Past service costs	6
Financial Costs	1
Actuarial gains and losses	17
At 31 December 2016	**48**
Past service costs	70
Financial costs	1
Actuarial gains and losses	(5)
At 31 December 2017	**114**

Note 12: Current liabilities

12.1 Trade payables

(amounts in thousands of euros)	31/12/2016	31/12/2017
Research and development suppliers	1,554	2,033
Suppliers – general expenses	366	369
Total trade payables	**1,920**	**2,402**

The increase in the debt with research and development suppliers is consistent with the increase in study and research costs, particularly in connection with the SARA clinical programme and the acceleration of non-clinical studies of the MACA programme.

12.2 Tax and social debts

(amounts in thousands of euros)	31/12/2016	31/12/2017
Personnel and related accounts	242	375
Social security and other social organisations	347	478
Other taxes, duties, and similar payments	133	265
Total taxes and social debts	**722**	**1,118**

12.3 Other creditors and miscellaneous debts

(amounts in thousands of euros)	31/12/2016	31/12/2017
Attendance fees	54	87
Others	40	26
Total other creditors and miscellaneous debts	**94**	**113**

Note 13: Details of expenses and products by function

13.1 Research and development costs

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Staff expenses	(1,789)	(2,104)
Other purchases and external expenses	(4,817)	(7,312)
Other	(182)	(177)
Research and development expenses	**(6,788)**	**(9,593)**
Research tax credit	1,604	2,545
Subsidies	62	5
Subsidies	**1,667**	**2,550**
Net research and development expenses	**(5,121)**	**(7,043)**

Research and development expenses relate to the research on potential new classes of drugs in the treatment of degenerative diseases related to ageing, especially those affecting muscular and visual functions.

13.2 General and administrative expenses

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Staff expenses	(1,145)	(1,257)
Other purchases and external expenses	(1,572)	(1,576)
Other	(103)	(32)
General and administrative expenses	**(2,820)**	**(2,865)**

13.3 Staff expenses

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Salaries and social charges	(1,940)	(2,470)
Share-based payments	(994)	(891)
Staff expenses	**(2,934)**	**(3,361)**

Note 14: Net financial income and expenses

(amounts in thousands of euros)	31/12/2016	31/12/2017
Other financial expenses	(33)	(118)
Amortised cost of bonds (1)	-	(3,145)
Variation in the fair value of derivative liabilities (1)	-	1,756
Other financial income	22	7
Currency gains and (losses)	(1)	0
Total financial income and expenses	**(13)**	**(1,501)**

(1) See Note 10.5 Bonds

Note 15: Income taxes

The total amount of tax losses at 31 December 2017 was estimated at €34,558K, comprising:

- French tax losses which may be carried forward indefinitely of €34,200K
- Tax losses of the US subsidiary of €354K
- Tax losses of the Brazilian subsidiary of €4K

The tax rate applicable to:

- Biophytis is the rate in effect in France, i.e. 33.33%. This rate will gradually decrease starting in 2018 and drop to 25% from 2022.
- Instituto Biophytis Do Brasil is the rate in effect in Brazil, i.e. 34%.
- Biophytic Inc. is the rate in effect in the United States, i.e. 21%.

In application of the principles described in Note 2.19, no deferred tax asset is recorded in the Company's accounts in excess of the deferred tax liabilities.

Reconciliation between theoretical tax and effective tax

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Net profit	(7,954)	(11,409)
Consolidated tax	-	-
Profit or loss before tax	**(7,954)**	**(11,409)**
Current tax rate in France	33.33%	33.33%
Theoretical tax at current rates in France	**2,651**	**3,803**
Permanent differences	530	1,167
Payment in shares	(331)	(297)
Non-activated tax deficit adjusted for deferred taxation	(2,849)	(4,650)
Differences in tax rates	(0)	(23)
Income tax expense/income	**-**	**-**
Effective tax rate	*0.0%*	*0.0%*

The permanent differences include the impact of the research tax credit (non-taxable operating income).

Nature of deferred taxes

(Amounts in thousands of euros)	31/12/2016	31/12/2017
Temporary differences	16	47
Losses carried forward	6,855	11,474
Total deferred tax assets	**6,871**	**11,521**
Temporary differences	(332)	(364)
Total deferred tax liabilities	**(332)**	**(364)**
Net total deferred tax elements	**6,539**	**11,156**
Unrecognised deferred taxes	(6,539)	(11,156)
Net total of deferred taxes	**-**	**-**

Note 16: Earnings per share

	31/12/2016	31/12/2017
Average weighted number of shares circulation	6,202,616	9,188,179
Net profit for the financial year	(7,954)	(11,409)
Basic earnings per share (€/share)	**(1.28)**	**(1.24)**
Diluted earnings per share (€/share)	**(1.28)**	**(1.24)**

Note 17: Related parties

17.1 Remuneration of company officers and management

(amounts in thousands of euros)	31/12/2016	31/12/2017
Fixed remuneration due	719	737
Variable remuneration due	86	174
Benefits in kind	12	20
Attendance fees	54	87
Share-based payments	994	856
Total executive compensation	**1,864**	**1,874**

No post-employment benefit is granted to company officers and management.

17.2 Transactions with Metabrain

Contract research services

The Company signed a contract research agreement with Metabrain on 11 July 2015, the purpose of which is to allow the Company to pursue its research and development activities within the context similar to the one previously provided by the agreement for the provision of the platform. This agreement entered into effect on 1 August 2015 for a period of twelve months. The Company committed to ordering a minimum volume of research services from Metabrain for a value of €250K net of taxes and proceeded to pay this amount on 13 July 2015, in respect of pre-reservation of Metabrain staff for the duration of the agreement. This contract was amended on 1 August 2017 to extend it for an additional period of twelve months, without further order commitments. *

Under this agreement, the Company incurred a charge of €189Kduring the 2016 financial year and €182K during the 2017 financial year.

Note 18: Off-balance-sheet commitments

18.1 Commercial Leases

Property leases

France:

Address	Université Pierre et Marie Curie - 4, place Jussieu - 75005 Paris
Term	15 December 2016 – 15 December 2018, renewable by amendment
Annual fee	€90,700.50 excl. tax

Brazil and United States:

The Company does not currently have a lease agreement in progress.

Commitments

(Amounts in thousands of euros)	Effective start date of the lease	Lease expiry date	Rental expenses at 31/12/2017	Commitment until the next termination period		
				Up to 1 year	1- 5 years	Over 5 years
Paris - UPMC - laboratory and offices	15/12/2016	15/12/2018	78	87	-	-

18.2 Commitments by way of financial debts

Commitments received

Borrowing	Guarantees received	Nominal	Residual amount at 31/12/2017
OSEO seed capital equity loan	- OSEO innovation risk participation for up to 20% of the outstanding loan - OSEO guarantee risk participation as part of the FNG Innovation procedure for 40% of the outstanding loan. - OSEO IDF risk participation for 40% of the outstanding amount of the loan	150	23

Commitments given

Borrowing	Commitments given	Nominal	Residual amount at 31/12/2017
OSEO reimbursable advance - "Quinolia" project	The agreement moreover provides for payment of a reimbursement annuity from 1 January 2009 and until 31 March of each year at the latest, corresponding to: 44% of the proceeds excluding taxes, assignments or granting of licenses, patents or know-how received during the previous calendar year when such transfers or leases related to all or part of the results of the assisted programme and to 44% of the proceeds excluding taxes generated by marketing and in particular, the sale to a third party or use by the beneficiary for the requirements of its own prototypes, pre-series and models, executed within as part of the assisted programme. The due amounts shall be attributed as a priority and for the full amount on the final deadline for payment to OSEO. The application of this mechanism shall not lead the company to pay an amount greater than the aid received.	229	119
BPI France reimbursable advance - "BIO 101"	The agreement moreover provides for payment of a reimbursement annuity from 1 January 2009 and until 31 March of each year at the latest, until 30 September 2023, corresponding to: 35.81 % of the pre-tax proceeds, assignments or granting of licenses, patents or know-how received during the previous calendar year when such transfers or leases related to all or part of the results of the assisted program, and to 35.81 % of the pre-tax proceeds generated by marketing and in particular, the sale to a third party or use by the beneficiary for the requirements of his own prototypes, pre-series, and models, executed within the context of the subsidised program. The due amounts shall be attributed as a priority and for the full amount on the final deadline for payment to BPI. The application of this mechanism shall not lead the company to pay an amount greater than the aid received.	1,100*	600

* Of which €500K will be paid upon completion of the project

Note 19: Management and assessment of financial risks

Biophytis may be exposed to financial risks of different kinds: market risk, liquidity risk and credit risk. Biophytis implements simple resources, commensurate with its size in order to minimise the potentially adverse effects of these risks on its financial performance.
Biophytis' policy is not to subscribe to financial instruments for speculative purposes.

Market risk

Interest rate risk

Interest rate risk represents the Company's exposure to changes in market interest rates.
The Company has subscribed to variable rate debt. An increase/decrease of one point in the basic index would have an impact on financial expenses of less than €1K.
Changes in interest rates could affect returns on cash and term deposits. Nevertheless, this risk is considered insignificant given the current low returns on term deposits held by the Company.

Currency risk
The principal risks linked to foreign as insignificant currency effects impacts are considered not significant due to the low level of activity of its foreign subsidiaries.
At its stage of development, the Group has not contracted any hedges to protect its business against fluctuations in exchange rates. At the same time, the Company cannot exclude the possibility that a significant increase in its activity would entail greater exposure to currency risk. The Company would then envisage use of an appropriate policy to hedge these risks.

Equity risk
The Company holds no investments or investment securities which may be traded on a regulated market.

Credit risk

Credit risk is associated with deposits with banks and financial institutions.
The Company seeks to minimise the risk associated with banks and financial institutions by placing term deposits with first-class financial institutions. The maximum level of credit risk corresponds to the book value of the financial assets. As current receivables mainly consist of research tax credits granted by the French government, the Company does not bear significant credit risk.

Liquidity risk
Since its creation, the Group has financed its growth by strengthening its equity base via successive capital increases (including its IPO in July 2015), recourse to bank loans and bonds, obtaining public aid for innovation and reimbursement of research tax credit receivables.
Significant expenses linked to research and development of candidate drugs have been incurred since the start of the Group’s activity, which to date have generated negative cash flows from operating activities. These amounted to €8,727K and €(6,633K) as at 31 December 2017 and 2016, respectively.
The going concern assumption was adopted by the Board of Directors (see Note 2.1).

The Company will continue to have significant funding needs in the future. The precise extent of the required funding is difficult to estimate accurately and will depend in part on factors that are beyond the Company's control. Areas of significant uncertainty include, but are not limited to:

- The ability to conduct clinical trials, including the ability to recruit patients in a timely manner for these studies;
- Changes in the regulatory environment;
- The approval of other drugs on the market that would potentially reduce the attractiveness of the approach developed by Biophytis.

Should the Company not be able to finance its own growth through partnership agreements, the Company would have to depend on other sources of financing, including the raising of capital or seeking subsidies.

Note 20: Events after the balance sheet date

March 2018:

- Filing of an application for Sarconeos to be designated an Orphan Drug for the treatment of Duchenne muscular dystrophy (DMD), with the European Medicines Agency (EMA) and presentation of MYODA, the new clinical development programme of Sarconeos for DMD.

20.2 PRO FORMA FINANCIAL INFORMATION

Not applicable.

20.3 FINANCIAL STATEMENTS

The annual financial statements of BIOPHYTIS for the financial years ended 31 December 2017 are presented in section 27 of this Annual Report.

20.4 VERIFICATION OF ANNUAL FINANCIAL STATEMENTS

20.4.1 Audit report by the statutory auditors on the consolidated accounts, drawn up pursuant to the IFRS standard - Financial year ended on 31 December 2017

GRANT THORNTON
French member of Grant Thornton International

ERNST & YOUNG AND OTHERS.

Biophytis
Exercice clos le 31 décembre 2017

Rapport des commissaires aux comptes sur les comptes consolidés

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Membre de la compagnie
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Biophytis

Exercice clos le 31 décembre 2017

Rapport des commissaires aux comptes sur les comptes consolidés

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Opinion

In performance of the mission entrusted to us by **your genreal meetings.**, we conducted the audit of the consolidated financial statements related to the financial year ended 31 December 2017 as attached to this report.

We certify that the consolidated financial statements are, with regard to the IFRS standard adopted in the European Union, regular and truthful and provide a faithful image of the assets, financial situation and overall net profit formed by the persons and entities included in the consolidation.

Basis of our opinion

- **Auditing framework**

We have conducted our audit in accordance with professional standards applicable in France. We believe that the elements that we collected form a sufficient and appropriate basis for our opinion.

Our responsibilities under these standards are set out in the "Responsibilities of the statutory auditors relating to audit of the consolidated financial statements" section of this report.

- **Independence**

We conducted our audit mission in compliance with the independence rules that apply to us, for the period from 1 **January 2017.** at the date of issue of our report, and in particular we have not provided services prohibited by the French Code of Ethics for Statutory Auditors.

Observation

The "going concern" paragraph of note 2 to the consolidated financial statements, which sets forth the assumptions underlying the going concern principle,

Justification of assessments

Pursuant to Article L. 823-9 of the Commercial Code relating to the justification of our assessments, we inform you that the assessments which we made related to the appropriate character of the accounting principles applied.

The assessments so made fall within the context of our audit of the financial statements, taken as a whole, and thus contributed to the formation of our opinion expressed in the first part of this report. We have no observations to make on the items in these consolidated financial statements taken individually.

Verification of group information provided in the management report

We have also carried out the specific audit, in accordance with professional standards applicable in France, required by law on the information given in the Group's management report.

We have no observations to make regarding their truthfulness and compliance with the consolidated financial statements.

Responsibilities of the management and the persons making up the corporate governance relating to the consolidated financial statements

It is the responsibility of management to prepare consolidated financial statements that present a true and fair view in accordance with the IFRS as adopted in the European Union, as well as to implement the internal control that it deems necessary for the preparation of consolidated financial statements that are free of material misstatements, whether due to fraud or error.

In preparing the consolidated accounts, it is the responsibility of management to assess the capacity of the company to continue its operations, to present in these accounts, as the case may be, the necessary information relating to the continuity of operations and to apply the accounting policy of going concern, unless it is planned to liquidate the company or to discontinue its activity.

The consolidated financial statements were drawn up by the Board of Directors.

Statutory auditors' report on the consolidated financial statements

It is our responsibility to prepare a report on the consolidated financial statements. Our objective is to obtain reasonable assurance that the consolidated financial statements taken as a whole are free of material misstatements. Reasonable assurance corresponds to a high level of assurance but does not guarantee that an audit performed in accordance with the standards of professional practice can automatically detect any significant misstatement. Such misstatements may arise from fraud or error and are considered material where it can reasonably be expected that they, taken individually or collectively, may influence the economic decisions that the users of the financial statements take based on these.

As stated in article L. 823-10-1 of the French Code of Commerce, our auditing mission is not to guarantee the viability or the quality of the management of your company.

As part of an audit conducted in accordance with the professional standards applicable in France, the statutory auditor exercises its professional judgement throughout this audit. In addition, the statutory auditor:

- identifies and assesses the risks that the consolidated financial statements contain material misstatements, whether due to fraud or error, defines and implements audit procedures to address these risks, and collects information it considers sufficient and appropriate to base its opinion. The risk of not detecting a material misstatement due to fraud is higher than that of a material misstatement resulting from an error, as the fraud may involve collusion, falsification, voluntary omissions, misrepresentation or the circumventing of internal control.

- becomes familiar with the internal control relevant to the audit in order to define audit procedures that are appropriate under the circumstances, and not to express an opinion on the effectiveness of the internal control.

- assesses the appropriateness of accounting policies used and the reasonableness of accounting estimates made by management, as well as the information concerning them provided in the consolidated financial statements.

- assesses the appropriateness of management's application of the going concern accounting policy and, depending on the evidence gathered, whether or not there exists significant uncertainty related to events or circumstances likely to call into question the capacity of the company to continue its operation. This assessment is based on the information gathered up to the date of its report, but it is noted that subsequent circumstances or events could jeopardise the continuity of operations. If it concludes that there is significant uncertainty, it draws the attention of the readers of its report to the information provided in the consolidated financial statements concerning this uncertainty or, if this information is not provided or is not relevant, it certifies the financial statements with reservations, or refuses to certify them.

- assesses the overall presentation of the consolidated financial statements and assesses whether the consolidated financial statements reflect the underlying transactions and events so as to give a true and fair view of them.

- concerning the financial information of the persons or entities included in the scope of consolidation, it collects information that it deems sufficient and appropriate to express an opinion on the consolidated financial statements. The statutory auditor is responsible for the management, supervision and execution of the audit of the consolidated financial statements as well as the opinion expressed on these financial statements.

Neuilly-sur-Seine and Paris-La-Défense., on 25 April 2018

Les Commissaires aux Comptes

GRANT THORNTON
Membre français de Grant Thornton International

Laurent Bouby

ERNST & YOUNG et Autres

Frederic Martineau

20.5 DATE OF THE LATEST FINANCIAL INFORMATION

The date of the latest financial information is 31 December 2017.

20.6 DIVIDEND DISTRIBUTION POLICY

20.6.1 Dividends and reserves distributed by the Company during the last three financial years

Not Applicable.

20.6.2 Distribution policy

There are no plans to introduce a short-term dividend payment policy given the Company's stage of development.

20.7 JUDICIAL AND ARBITRATION PROCEEDINGS

As of the date of this Annual Report, there are no other governmental, judicial, or arbitration proceedings that need be disclosed to the market.

20.8 SIGNIFICANT CHANGE IN THE FINANCIAL OR COMMERCIAL SITUATION OF THE COMPANY

As far as the Company is aware, there have been no significant changes in its financial or commercial position since the latest financial information available on 31 December 2017.

20.9 MANAGEMENT REPORT

The Management Report (as defined in Section 26) must be understood to include all the documents contained in the Annual Report and the information specified below in accordance with the cross-reference table in Section 26.

20.9.1 Activity of the Company during the past financial year

During the year ended 31 December 2017, the Company continued its activity of developing innovative drug candidates to treat age-related degenerative diseases, without treatment, focusing on these Sarconeos and Macuneos candidates.

- **The different stages of the SARA clinical programme continued to follow the programme described in 2016, in particular:**

  - Final results from the SARA-PK clinical study received. Their analysis confirms the good pharmacokinetic profile in healthy elderly subjects, confirms the therapeutic window of the Sarconeos product, and specifies the dosages that will be used in the SARA-INT Phase 2b clinical trial.
  - We also recruited more than 100 patients with sarcopenia in the SARA-OBS observational study, which was carried out in more than 9 clinical centres in the United States, Belgium, France and Italy. The programme includes a sixth-month observational study (SARA-OBS) performed on more than 300 patients with sarcopenia in 11 clinical centres. The mobility and muscle quality of patients are evaluated on the basis of the following criteria: gait speed over 400 meters, walk test of 6 minutes, mobility (SPPB test), muscle strength (grip test), muscle mass and plasma markers of muscle anabolism Data from SARA-OBS will enable us to better define the target population for Sarconeos treatment. After we obtain their consent, we may include patients who participated in the SARA-OBS in the SARA-INT phase 2b study.
  - Authorisation obtained from the US Food and Drug Agency (FDA), then from the Belgian Federal Agency for Medicines and Health Products (FAMHP) to launch the phase 2b interventional study of Sarconeos for sarcopenia (SARA-INT). The objective of SARA-INT is to assess the safety and efficacy of two doses of Sarconeos (175 mg bid and 350 mg bid) administered orally for 26 weeks vs a placebo in a population of men and women over the age of 65 at risk of motor disability, and to estimate the effect of the treatment as concerns the improvement of the physical function and the reduction of the risk of motor disability. The study should include 334 people reporting a loss of physical function in the last 6-12 months and considered at risk of motor disability.

- **A new therapeutic opportunity has been identified for Sarconeos:**

  - The abstract entitled “Sarconeos demonstrates sharp functional improvement and anti-fibrotic properties in an animal model of Duchenne muscular dystrophy" was presented at the World Muscle Society International Congress held in October in Saint Malo, France. These results demonstrate the efficacy of Sarconeos in improving dystrophic muscle function and preventing the appearance of fibrosis. The results open the way to a new therapeutic solution for patients with DMD.
  - As a result, Professor Thomas Voit, a specialist in paediatric diseases, joined the Biophytis Scientific Committee to participate in the design of the MYODA clinical programme in DMD. Dr. Voit is the Director of the centre for Biomedical Research (BRC) at the Great Ormond Street Children's Hospital NHS Foundation Trust and the

Institute of Child Health, University College London. Previously, Professor Voit was Medical and Scientific Director of the Institute of Myology (La Pitié Salpêtrière Hospital).

The implementation of the MACA clinical programme has been accelerated to allow the launch of the first study of the programme: • In 2018:

- All the non-clinical regulatory studies have been completed,
- The definitive formulation has been finalized, and the implementation of the industrial scale-up and the production / supply chain has begun.
- The design of MACA-PK has been finalized: it is a Phase I / IIa clinical study, whose protocol has been optimized to study the safety, pharmacokinetics, and pharmacodynamics of Macuneos, in healthy volunteers in a clinical centre in Belgium (SAD), then in patients with dry AMD recruited in 7 ophthalmic centres in France, Belgium, and Great Britain (MAD).

20.9.2 Information on the Company's activity

The Group has prepared its consolidated financial statements for the years ended 31 December 2015 and 31 December 2017 in accordance with the International Financial Reporting Standards (IFRS), issued by the International Accounting Standards Board (IASB). The term "IFRS" refers to international accounting standards (IAS and IFRS) and interpretative committee interpretations (IFRS Interpretations Committee (IFRS IC) and Standing Interpretations Committee (SIC)) for the year ended on 31 December 2017.

Due to the listing of the Company's shares on Alternext Paris and pursuant to European Regulation No 1606/2002 of 19 July 2002, the Company's financial statements are also prepared in accordance with IFRS adopted by the European Union (EU), at the date of preparation of the financial statements, for all periods presented.

As at 31 December 2017, all IFRS standards issued by the IASB and mandatory are the same as those adopted by the EU and mandatory in the EU, with the exception of:

- IAS 39 - Financial Instruments: Recognition and Measurement (Revised December 2003), or IAS 39, which the EU has partially adopted;
- IFRIC 22 - Foreign Currency Transactions and Advance Consideration, and
- IFRIC 23 - Uncertainty over Income Tax Treatments

The Statutory Auditors of the Company shall inform the Meeting in their reports on the annual and consolidated financial statements, the texts of which will be read to you after this report, on the results of their review of the financial statements presented to you.

Important aspects of the financial accounts are described below:

- **Annex to the financial statements**

The company did not generate sales for the year ended 31 December 2017, as for the year ended 31 December 2016.

The current result before tax for the year ended 31 December 2017 shows a loss of (11,827K) euros compared to a loss of (8,849K) euros for the year ended 31 December 2016.

The financial result for the year ended 31 December 2017 resulted in a deficit of (83K) euros compared with a deficit of (283K) euros for the year ended 31 December 2016.

Operating income for the year ended 31 December 2017 showed a deficit (11,744K) euros against a deficit (8,566K) euros for the year ended 31 December 2016.

Operating expenses for the year ended 31 December 2017 amounted to 11,514K euros against 8,397K euros for the year ended 31 December 2016, including:

- Purchase of raw materials and other supplies: €2,500K
- Other purchases and external expenses €2,500K
- Taxes other and payments: €2,500K
- Salaries and treatments: €2,500K
- Financial expenses €2,500K

The net taxable result for the year ended 31 December 2017 is equal to (9.284K) euros against (7.247K) euros for the previous financial year.

- **Presentation of the consolidated financial statements**

Consolidated net income and income before tax for the year ended 31 December 2017 show a loss of € (11,409K) compared with a loss of € (7,954K) for the year ended 31 December 2016.

The consolidated financial result for the year ended 31 December 2017 resulted in a loss of (1,501K) euros compared to a deficit of (13K) euros for the year ended 31 December 2016.

Consolidated operating income for the year ended 31 December 2017 shows a deficit of (9,908K) euros compared with a deficit of (7,942K) euros for the year ended 31 December 2016.

Research and development expenses for the year ended 31 December 2017 amounted to 7,043K compared to 5,121K euros for the year ended 31 December 2016.

General and administrative expenses for the year ended 31 December 2017 amounted to €2,865K compared to €2,820K for the year ended 31 December 2016.

20.9.3 Progress made or difficulties encountered by the Company

Financing:

A capital increase subscribed by several private investors, including Bracknor Fund, and the management, amounting to €3.7 million, carried out by the issue of 1,310,431 new shares at a unit price of €2.85.

A credit facility is set up with Bracknor Fund for up to €15 million in the form of 5 tranches of €3 million in bonds redeemable in cash or new or existing shares, with warrants ("ORNANEBSA").

In May: drawdown of the first tranche of convertible bonds with a nominal value of €3 million; all bonds were converted into 1,385,085 shares,

In July: drawdown of the second tranche of convertible bonds with a nominal value of €3 million; all bonds were converted into 1,027,396 shares,

10 October: €10.4 million capital increase by private investment and via the issue of 1,989,000 new ordinary shares at a unit price of €2.85 offered to qualified investors

31 October: €7.5 million capital increase by private investment and via the issue of 1,513,000 new ordinary shares at a unit price of €5.00 offered to qualified investors

Human resources:

The Company continued its efforts to develop a complete, multidisciplinary team with a shared ambition in biotech. To this end, the staff has been increased to 23, and 6 new recruits are expected to join the company in the first quarter of 2018. The new hires will mainly work with the research and clinical development teams.

The Company conducted its first election of staff representatives in July 2017.

20.9.4 The Company's research and development activities

The purpose of the Company is to research and develop new drug candidates, the main advances of which have been described in paragraph 1.

The Company has pursued an active policy of communicating the results of its work in scientific conferences where specialists in the Company's therapeutic areas gather:

- April 2017: 4 scientific and clinical works presented at the ICFSR 2017.
- September 2017: Positive results of Sarconeos in a model of Duchenne muscular dystrophy presented at the World Muscle Society International Conference 2017.
- September 2017: Scientific work on Macuneos in the protection of the retina presented at the 2017 Euretina Congress.
- December 2017: Several scientific and clinical works on Sarconeos presented at the SCWD 2017.

The Company also filed two patent applications during the year:

- April 2017: Filing of patent application No. 17 53775 for a new pharmaceutical-grade compound (joint ownership with SORBONNE UNIVERSITY).
- August 2017: Filing of patent application No. 17 58071 for the use of a family of compounds in the treatment of myopathies (joint ownership with SORBONNE UNIVERSITY).

20.9.5 Foreseeable evolution of the Company's position and future prospects

The evolution foreseeable in 2018 concerns three areas:

The continuation of the SARA clinical programme (for sarcopenia), and the conducting of the SARA-INT phase-2b interventional Study: the regulatory authorisations process is underway, and the company plans to include the first patient in the second quarter of 2018. As a result, the administration period could end in the first half of 2019, followed by the publication of preliminary results in the summer of 2019.

The process for obtaining regulatory approval is underway, and the single ascending dose (SAD) phase of the study will be set to begin in the fall of 2018. The results of the SAD phase are expected before the end of 2018.

Preparation of the MYODA clinical programme (in Duchenne Muscular Dystrophy) and launch in the second half of 2018: the clinical plan of Sarconeos in DMD is being developed with clinicians and the CRO; it is planned to begin with a first step of validating the safety and pharmacokinetics of the drug candidate in patients (young people with DMD, from 2 to 18 years old): SARA-PK. MYODA-PK could be launched in the second half of 2018 and MYODA-INT in 2019.

20.9.6 Objective and comprehensive analysis of business developments in terms of the volume and complexity of business

During fiscal year 2017, Mr. Stanislas VEILLET was not granted any founder's warrants.

- The Company's shareholders' equity of the Company amounted to 21,187,000 euros for the year ended 31 December 2017 as against 4,519,000 euros for the year ended 31 December 2016;

- the Company's cash and cash equivalents totalled 20,047,000 for the year ended 31 December 2017 compared to 3,165,000 euros for the year ended 31 December 2016; and

- financial liabilities amount to €1,013,000 (less than 5% of shareholders' equity) for the year ended 31 December 2017, compared to €1,089,000 (less than 25% of shareholders' equity) for the year ended 31 December 2016.

Although it has strengthened its teams, the Company maintains a light structure composed essentially of a small staff of experienced professionals, experts in their respective fields, who coordinate a network of specialized subcontractors contracted to meet the needs of the company. calendar of development programmes, and which lead the research work in partnership with public institutions on the basis of short contracts renewed by endorsements.

The Company is able to finance its business for the coming fiscal year and has the appropriate management team to oversee it.

20.9.7 Description of the main risks and uncertainties

The Company faces several risks more fully developed in the Annual Report. Although the Company does not at this stage have reason to believe that the probability of these risks materializing is high, and that it has taken, on the basis of the information in its possession and the usual practices in the matter for similar companies, the appropriate measures to prevent their materialization, the following risks should nevertheless be mentioned:

- Risks linked to historical losses and forecast losses

In future years, the Group could experience greater operating losses than in the past, as its research and development activities continue, notably on account of:

- the need to conduct new clinical trials in order to approach new market segments, especially for its “Sarcones” and “Macuneos” projects;
- the increase in regulatory requirements governing the manufacture of its products.

The increase in these expenses could have a material adverse effect on the Group’s activity, financial situation, results, growth and prospects.

- Risks linked to the Research Tax Credit

For the CIR, companies must justify on demand the request of the tax authorities for the amount of the CIR and the eligibility of the research work included in the calculation basis of the mechanism. For the purposes of this justification, the Tax Authority recommends that companies draw up a guide containing all of the items necessary for monitoring this tax credit and in particular demonstrating the eligibility for the CIR of the research work carried out. Despite the absence of a formal scientific report, the Company has technical documentation for its research work and is confident of the quality of these documents for justifying the eligibility of the selected projects.

It cannot be excluded that the tax authorities will contest the eligibility for the CIR of projects selected by the Company or the method of calculating eligible expenses applied by the Company, with the right of clawback exercised until the end the third year following the filing of the special declaration provided for calculating the CIR. Furthermore, changes in tax legislation may affect or limit the CIR mechanisms.

- Liquidity risks

Since its creation, the Group has financed its growth by strengthening its equity base via successive capital increases (including on the occasion of its IPO in July 2015), recourse to bank loans and bonds, obtaining public aid for innovation and reimbursement of CIR receivables.

The Group will continue in the future to have significant financing requirements for the development and clinical testing of its candidate drugs. It is possible that the Company will be unable to self-finance its growth, which would lead it to seek other sources of funding, especially through new capital increases.

The level of the Group’s financing needs and their staggering over time depend on elements that are largely beyond its control, such as:

- Higher costs and slower progress than anticipated for its research programs and clinical studies;
- Costs of preparation, filing, defence and maintenance of its patents and other intellectual property rights.

It is possible that the Company may fail to obtain additional capital when it needs it, or that such capital may not be available on acceptable financial terms to the Group. If the necessary funds are not available, the Company may have to delay the clinical trials of its candidate drugs.

20.9.8 Amortisation/depreciation and expenses referred to in article 39.4 of the French General Tax Code

Pursuant to Article 223 quarter of the French General Tax Code, the amount of sumptuary expenses and non-deductible expenses referred to in Article 39-4 of this Code amounts to EUR 0 in respect of the financial statements for the year ended 31 December 2017.

During the year ended 31 December 2017, the Company also did not carry out any tax reinstatement of general expenses referred to in article 39.5 of the French General Tax Code.

20.9.9 Information on payment terms

In accordance with articles L. 441-6-1 and D. 441-4 of the French Commercial Code, and in application of the decree dated 20 March 2017, you will find below, in table form, the breakdown of the payment deadlines for our trade payables showing (i) invoices received not paid as at the balance sheet date, for which the deadline has passed and (ii) invoices received that were paid late during the financial year.

We do not present the breakdown of customer payment periods in the absence of trade receivables in the accounts closed at 31 December 2017.

31/12/2017	0 jour	1 à 30 jours	31 à 60 jours	61 à 90 jours	91 jours et plus	Total (1 jour et plus)	Total
(A) Tranche de retard de paiement							
Nombres de factures concernées	*95*					*56*	
Montant total des factures concernées *(TTC)*	*739,059*	*498,743*	*180,766*	-	*122,802*	802,311	1,541,370
Pourcentage du montant total des achats de l'exercice	*8%*	*5%*	*2%*	-	*1%*	*9%*	
(B) Factures exclues du (A) relatives à des dettes et créances litigieuses ou non comptabilisées							
Nombre de factures exclues	*0*	*0*	*0*	*0*	*0*	*0*	
Montant total des factures exclues	*0*	*0*	*0*	*0*	*0*	*0*	
(C) Délais de paiement de référence utilisés (contractuel ou délai légal - article L. 441-6 ou article L. 443-1 du Code de commerce)							
Délais de paiement utilisés pour le calcul des retards de paiement	- Délais contractuels : (préciser) - Délais légaux (préciser)						

	2017	2016
Achats de matière premières et autres appro.	232,341	231,353
Autres achates et charges externes	8,974,009	6,232,695
	9,206,350	**6,464,048**

31/12/2016	0 jour	1 à 30 jours	31 à 60 jours	61 à 90 jours	91 jours et plus	Total (1 jour et plus)	Total
(A) Tranche de retard de paiement							
Nombres de factures concernées	*71*					*32*	
Montant total des factures concernées (TTC)	*527,749*	*61,908*	*92,962*	*7,068*	*158,545*	320,483	848,232
Pourcentage du montant total des achats de l'exercice	*6%*	*1%*	*1%*	*0%*	*2%*	*3%*	
(B) Factures exclues du (A) relatives à des dettes et créances litigieuses ou non comptabilisées							
Nombre de factures exclues	*0*	*0*	*0*	*0*	*0*	*0*	
Montant total des factures exclues	*0*	*0*	*0*	*0*	*0*	*0*	
(C) Délais de paiement de référence utilisés (contractuel ou délai légal - article L. 441-6 ou article L. 443-1 du Code de commerce)							
Délais de paiement utilisés pour le calcul des retards de paiement	- Délais contractuels : (préciser) - Délais légaux (préciser)						

20.9.10 Table of results

Nature of operations	Financial year 2013	Financial year 2014	Financial year 2015	Financial year 2016	of exercise 2017
Starting date for exercise					
Share capital	753,927	753,927	1,239,100	1,244,700	2,692,682
Number of shares created	753,927	753,927	6,195,501	6,223,501	13,463,413
c) Number of bonds convertible into shares	-	-	-	-	-
II - OPERATIONS AND RESULTS OF THE FINANCIAL YEAR					
a) Turnover excluding taxes	5,976	5,847	7,286	-	-
b) Profit before tax, amortization and provisions	(437,311)	(404,932)	(2,505,507)	(8,481,021)	(11,486,395)
Income taxes	(215,822)	(153,104)	(453,882)	(1,604,291)	(2,544,801)
(d) Income after tax, depreciation and amortization	(394,015)	(536,512)	(2,874,787)	(7,247,084)	(9,283,880)
e) Amount of distributed profits	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable
2.22 Earnings per share					
a) Profit after tax, but before amortization and provisions	(0.31)	(0.36)	(0.33)	(1.36)	(0.66)
b) Profit after tax, depreciation and amortization	(0.52)	(0.71)	(0.46)	(1.16)	(0.69)
c) Dividend paid to each share	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable
IV - PERSONNEL					
Number of patients	8	8	7	13	18
Reduction in body fat	426,560	450,332	730,584	1,202,495	1,431,177
c) Amount of sums paid for social benefits (Social Security, work, etc.)	154,140	205,115	366,902	551,750	645,047

20.9.11 Amount of loans due in less than two years granted outside of its main business activity by the Company to microenterprises, SMEs or to intermediate-sized enterprises with which it has economic ties that justify such loans in accordance with article L. 511-6, 3 bis, paragraph 2 of the French Monetary and Financial Code

Not Applicable.

20.9.12 Injunctions or pecuniary sanctions for anti-competitive practices issued by the French Competition Authority (*Autorité de la concurrence*) in accordance with article L.464-2 of the French Commercial Code

Not Applicable.

20.9.13 Equity investments and takeovers

In accordance with the provisions of Articles L.233-6 and L.247-1 of the French Commercial Code, it is specified that the Company has not taken any significant shareholding or control in companies whose registered office is in France during 2017 fiscal year.

21SUPPLEMENTARY INFORMATION

21.1 SHARE CAPITAL

21.1.1 Amount of the share capital

On the date of this Annual Report, the share capital of the Company amounts to €2,692,682.60, divided into 13.463.413 fully subscribed ordinary shares, with a nominal value of €0.20.

Change in share capital and number of shares outstanding over the period are described in paragraph 20.1 “Consolidated statement of changes in shareholders’ equity” of this Annual Report and note 8 “Capital” of this Annual Report.

BIOPHYTIS BRASIL

On the date of this Annual Report, the share capital of BIOPHYTIS BRASIL is BRL 898,632 (approximately €246,434), divided into 898,632 shares with a nominal value of BRL 1.00 each, divided among the shareholders as follows:

- 850,105 shares held by BIOPHYTIS, fully paid up;
- 48,527 shares held by Wagner Clayton CORREA, fully paid up.

BIOPHYTIS INC.

On the date of this Annual Report, the share capital of BIOPHYTIS INC. is $1,000 (approximately €883.35), divided into 100 shares with a nominal value of $10 each, fully owned by BIOPHYTIS.

21.1.2 Non-equity securities

On the date of this Annual Report, there are no non-equity securities outstanding.

21.1.3 Pledges, guarantees and sureties on the Company’s shares

As far as the Company is aware, on the date of this Annual Report, there is only one pledge on the shares of the Company, namely:

Name of the shareholder	Beneficiary	Starting date of the pledge	Condition for release of the pledge	Number of shares pledged by the issuer	% of pledged share capital of the issuer
Metabrain Research	BNP Paribas, Société Générale, HSBC	18 July 2012	Reimbursement of a bank loan	120,000	1.21%

21.1.4 Acquisition by the Company of its own shares

The Shareholders Meeting of the Company on 16 May 2018 authorised, for a period of 18 months from the date of the shareholders meeting, the Board of Directors to implement a share buyback program of the Company's shares pursuant to the provisions of Article L. 225-209 of the French Commercial Code and in accordance with the General Regulation of the French Financial Markets Authority (AMF) under the conditions described below:

Maximum number of shares to be purchased: 10% of the share capital on the date of buyback of the shares. When shares are purchased in order to increase trading and liquidity of the shares, the number of shares taken into account for calculating the 10% limit defined above is the number of shares purchased, minus the number of shares sold during the authorisation period.

It is stated that the number of shares acquired by the Company with a view to their retention and subsequent delivery as payment or exchange within the context of a merger, demerger or contribution transaction may not exceed 5% of its capital.

Maximum amount of the funds to be devoted to the buyback of shares: €3,500,000.

Objectives of the shares buyback:

- Improving liquidity of transactions and regularity of prices of the Company's securities or avoiding price discrepancies not justified by the market trend, within the context of a liquidity agreement with an investment service provider intervening entirely independently, under the conditions and according to the procedures established by the regulations and recognised market practices, notably the decisions of the Financial Markets Authority (AMF) of 22 March 2005 and 1 October 2008, and in accordance with the AMAFI [French financial markets association] Charter of professional ethics of 8 March 2011, recognised by the decision of the AMF on 21 March 2011;

- To issue shares upon the exercise of rights attached to securities giving access by any means, immediately or in the future, to the share capital of the Company and to carry out any hedging transactions pursuant to the Company's obligations related to these securities, under the conditions provided for by the market authorities and at the times that the Board of Directors may decide,

- To retain shares for subsequent delivery as payment or exchange, in connection with any potential acquisitions in compliance with the market practice accepted by the Financial Markets Authority, particularly in connection with mergers, demergers, or contributions,

- To comply with obligations related to stock option programs, allocation of free shares, employee savings schemes, or other benefits for employees of the Company or of affiliated companies or enterprises, including (i) the implementation of any stock option plan for the purchase of the Company's shares pursuant to Articles L. 225-177 *et seq.* of the Commercial Code, (ii) the allocation of shares to employees by way of participation in the company's profit-sharing and the implementation of any company savings plan under the conditions provided by law, notably Articles L. 3332-1 to L. 3332-8 *et seq.* of the Labour Code or (iii) the allocation of free shares pursuant to Articles L. 225-197-1 *et seq.* of the French Commercial Code;

- Their cancellation and the consequent reduction of capital (notably in order to optimise cash management, profitability or earnings per share),

- To implement any market practice that may be recognised by law or the AMF.

The maximum purchase price per share that the Company may pay for its own shares shall not exceed 300% of the price of the shares offered to the public in connection with the listing of the Company's shares on a US stock exchange, as this price shall be mentioned in the press release regarding the characteristics of the offer of shares of the Company and their admission to trading on an US stock exchange and excluding acquisition costs.

Prior to the implementation of the share buyback program authorised by the Shareholders Meeting of 16 May 2018:

- Publication of a description of the share buyback program (effective and full dissemination by electronic means by a professional broadcaster and posting on the Company's website).

During enforcement of the share buyback program:

- Publication of transactions on D+7 by posting on the Company's website (excluding transactions conducted within the context of a liquidity agreement); and
- Monthly declarations by the Company to the AMF.

Every year:

- Presentation of results of the implementation of the share buyback program and use of shares acquired in the report of the Board of Directors to the Shareholders Meeting.
- On 31 December 2017, the Company held 38,121 own shares within the context of the liquidity agreement concluded with INVEST SECURITIES, complying with the Charter of professional ethics of the French Financial Markets Association, in June 2015. € 300,000 was allocated to the implementation of this liquidity agreement.
- The transactions complying within the share buyback program during the financial year ended 31 December 2017 are as follows (only in connection with the liquidity agreement referred to above):

- Securities purchased	185,510 for 723,729.86 €
Nominal value	0.20
Average price of purchases	€ 3.9013
Number of shares sold	193,722 for 815,281.79 €
Average price of	€ 4.2085
Number of shares registered in the Company's name at the end of the financial year	29,909
Value determined at the average purchase price	29,909 shares at €5.290042, that is €116,683.98

21.1.5 Potential share capital

On the date of this Annual Report, the securities providing access to the share capital were as follows:

Summary table of founder's warrants/warrants

Type of securities	Founder's warrants$_{1-2015}$	Founder's warrants$_{2-2015}$	Warrants$_{2015D}$	Warrants$_{2015}$	Bracknor warrants	Founder's warrants$_{2017}$	Warrants$_{2017}$
Beneficiaries	Stanislas VEILLET, Jean-Christophe MONTIGNY and René LAFONT	Stanislas VEILLET, Jean-Christophe MONTIGNY, René LAFONT, Waly DIOH, Philippe DUPONT, Pierre DILDA and Susanna Del Signore	Former holders of Biophytis bonds$_{2015D}$	Nadine COULM, Marie-Claire JANAILHAC-FRITSCH and Jean-Gérard GALVEZ	Bracknor	Christine BALDUCCI, Louis GUIBOUT, Mathilde LATIL, Marie-Noelle LY, Maria GUETSOVA, Carole BATARD, Sissi ON, Delphine LINARD, Stanislas VEILLET, René LAFONT, Jean-Christophe MONTIGNY, Susanna DEL SIGNORE, Waly DIOH, Philippe DUPONT and Pierre J. DILDA	Jean-Gérard GALVEZ Marie-Claire JANAILHAC-FRITSCH, Nadine COULM and Jean FRANCHI
Date of the Shareholders Meeting	22 May 2015	27 May 2015	27 May 2015	27 May 2015	16 June 2016	16 June 2017	16 June 2017
Date of the Board of Directors	N/A	23 September, 4 December 2015, and 15 March 2016	10 July 2015	04 August 2015	Decision of the Chairman dated 16 May 2017 upon exercise of a delegation granted by the Board of Directors	21 July 2017	21 July 2017

Type of securities	Founder's warrants$_{1-2015}$	Founder's warrants$_{2-2015}$	Warrants$_{2015D}$	Warrants$_{2015}$	Bracknor warrants	Founder's warrants$_{2017}$	Warrants$_{2017}$
					on 3 April 2017		
Nature of the share to subscribe	Ordinary share						
Issuance price	N/A	N/A	€ 0.60	€ 0.80	N/A	N/A	€ 0.30
Unit value under IFRS	N/A	N/A	N.A	€ 8.88	N/A	N/A	€ 2.12
Registered value under IFRS	€ 238 k	€ 1,214k	N/A	€ 480 k	N/A	€ 226 k	€ 143 k
Exercise price per new share subscribed	€2.06	€10.70 for founder's warrants$_{2-2015}$ granted on 23 September and 4 December 2015 and €6.09 for the founder's warrants$_{2-2015}$ granted on 15 March 2016	€ 6	€ 8.40	€ 3.33	€ 3.30	€ 3.30
Parity	1 founder's warrant$_{2015}$ entitles to subscribe to 1 share	1 founder's warrant$_{2-2015}$ entitles to subscribe to 1 share	1 warrant$_{2015D}$ entitles to subscribe to 1 share	1 warrant$_{2015}$ entitles to subscribe to 1 share	1 Bracknor warrant entitles to subscribe to 1 share	1 warrant$_{2017}$ entitles to subscribe to 1 share	1 warrant$_{2017}$ entitles to subscribe to 1 share
Deadline for exercise	Deadline of 4 years from their issuance, i.e. at latest on 22 May 2019, subject to forfeiture	Deadline of 4 years from their issuance, i.e. at latest on 4 December 2019, subject to forfeiture	Deadline of 4 years from their subscription, subject to forfeiture	Deadline of 4 years from their subscription, subject to forfeiture	Deadline of 5 years from their subscription, subject to forfeiture	Deadline of 4 years from their issuance, i.e. at latest on 4 December 2019, subject to forfeiture	Deadline of 4 years from their subscription, subject to forfeiture
General exercise modalities	Being an employee or corporate officer of the Company subject to	Being an employee or corporate officer of the Company subject to	At any time starting from subscription and within the deadline	For (i) 33.33% between subscription date and the first anniversary of	At any time starting from subscription and within the deadline	Being an employee or corporate officer of the Company subject to	For (i) 33.33 % between subscription date and the first anniversary of

Type of securities	Founder's warrants$_{1-2015}$	Founder's warrants$_{2-2015}$	Warrants$_{2015D}$	Warrants$_{2015}$	Bracknor warrants	Founder's warrants$_{2017}$	Warrants$_{2017}$
	the tax regime for employees on the exercise date And At any time	the tax regime for employees on the exercise date And For (i) 33.33% between issuance date and the first anniversary of issuance date, (ii) for 66.66% between the first anniversary of issuance date and the second anniversary of issuance date and (iii) as a whole, starting from the second anniversary of issuance date and at the latest, 4 years after issuance date	for exercise	subscription date, (ii) for 66.66% between the first anniversary of subscription date and the second anniversary of subscription date and (iii) as a whole, starting from the second anniversary of subscription date and at latest, 4 years after subscription date	for exercise	the tax regime for employees on the exercise date And For (i) 33.33% between issuance date and the first anniversary of issuance date, (ii) for 66.66% between the first anniversary of issuance date and the second anniversary of issuance date and (iii) as a whole, starting from the second anniversary of issuance date and at the latest, 4 years after issuance date	subscription date, (ii) for 66.66% between the first anniversary of subscription date and the second anniversary of subscription date and (iii) as a whole, starting from the second anniversary of subscription date and at latest, 4 years after subscription date

Type of securities	Founder's warrants$_{1-2015}$	Founder's warrants$_{2-2015}$	Warrants$_{2015D}$	Warrants$_{2015}$	Bracknor warrants	Founder's warrants$_{2017}$	Warrants$_{2017}$
Number of issued/allocated securities	195,000	483,900	270,414	54,000 (including 48,000 in force to date)	431,184 (225,225 dated 15/05/2017 and 205,959 dated 07/07/2017)	354,000	72,000
Number of warrants exercisable at the date of the Annual Report	152,000	296,133	189,748	48,000	431,184	354,000	72,000
Number of warrants exercised at the date of the Annual Report	43,000	None	80,666	6,000	None	None	None
Number of new shares which may be subscribed	152,000	444,200[1]	189,748	48,000	431,184	354,000	72,000
Total	**152,000**	**444,200[1]**	**189,748**	**48,000**	**431,184**	**354,000**	**72,000**

(1) This total takes into account the nulity of 39,700 founder's warrants$_{2-2015.}$

Summary table of holders of founder's warrants

The following table shows, all of the warrants for subscription of founder's shares (BSA) issued by the Company and in effect to the benefit of its corporate officers and employees on the date of this report.

Holders of founder's warrants$_{2015}$		**Founder's warrants$_{2015}$** Attributed on 22 May 2015	**Founder's warrants$_{2-2015}$** Attributed on 23 September 2015	**Founder's warrants$_{2-2015}$** Attributed on 04 December 2015	**Founder's warrants$_{2-2015}$** Attributed on 15 March 2016	**Founder's warrants$_{2017}$**
Stanislas VEILLET	Chairman and Managing Director	58,500	198,800	N/A	N/A	148,000
René LAFONT	Founder - Employee	58,500	39,700	N/A	N/A	29,000
	Employee	63,000	106,000	N/A	N/A	79,000

Jean-Christophe MONTIGNY						
Philippe GUILLET	Employee	N/A	39,700	N/A	N/A	N/A
Waly DIOH	Employee	N/A	20,000	N/A	N/A	15,000
Philippe DUPONT	Employee	N/A	20,000	N/A	N/A	15,000
Pierre DILDA	Employee	N/A	N/A	20,000	N/A	15,000
Susanna Del Signore	Employee	N/A	N/A	N/A	39,700	29,000
Christine BALDUCCI	Employee	N/A	N/A	N/A	N/A	3,000
Louis GUIBOUT	Employee	N/A	N/A	N/A	N/A	3,000
Mathilde LATIL	Employee	N/A	N/A	N/A	N/A	3,000
Marie-Noelle LY	Employee	N/A	N/A	N/A	N/A	3,000
Maria GUETSOVA	Employee	N/A	N/A	N/A	N/A	3,000
Carole BATARD	Employee	N/A	N/A	N/A	N/A	3,000
Sissi ON	Employee	N/A	N/A	N/A	N/A	3,000
Delphine LINARD	Employee	N/A	N/A	N/A	N/A	3,000
Total granted		**195,000 (including 152,000 in force to date)**	**424,200 (including 384,500 in force to date)**	**20,000**	**39,700**	**354,000**
Founder's warrants$_{2-2015}$ not yet granted (1)		**0**	**0**		**0**	

(1) The Board of Directors will no longer be able to use these different delegations and award new founder's warrants$_{2-2015}$. Indeed, the new delegations of authority decided by the Shareholders Meeting of 16 June 2017 put an end to all previous authorisations with the same purpose, up to the part not yet used.

(2) It is specified that Mr Jean-Christophe MONTIGNY exercised 15,000 founder's warrants$_{1-2015}$ on 27 September 2017 and, as a result, there are 152,000 founder's warrants$_{2017}$ in force at the date of this Annual Report

Summary table of warrant holders

The following table shows, all of the warrants (BSA) issued by the Company and in effect on the date of this report.

Holders of warrants$_{2015}$		**Warrants$_{2015}$** granted on 04 August 2015	**Warrants$_{2015D}$** granted on 10 July 2015	**Bracknor warrants** granted on (i) 15 May 2017 and (ii) 7 July 2017	**Warrants$_{2017}$**
Nadine COULM	Director	18,000	N/A	N/A	18,000
Marie-Claire JANAILHAC-FRITSCH	Director	18,000	N/A	N/A	18,000

Jean-Gérard GALVEZ	Director	18,000	N/A	N/A	18,000
Jean FRANCHI	Director	N/A	N/A	N/A	18,000
Former holders of Biophytis bonds$_{2015D}$		N/A	189,748	N/A	N/A
Bracknor		N/A	N/A	431,184	N/A
Total granted		**54,000 (Including 48,000 in force to date)**	**189,748**	**431,184**	**72,000**
Warrants not yet granted [(1)]		**0**	**0**	**N/A**	**N/A**

(1) The Board of Directors will no longer be able to use these various delegations of authority and grant new warrants$_{2015}$. Indeed, the new delegations of authority decided by the Shareholders Meeting of 16 June 2017 terminated all previous authorisations with the same purpose, up to the part not yet used.

We point out that:

- Marie-Claire JANAILHAC-FRITSCH exercised 6,000 warrants$_{2015}$; as a result, there are 48,000 warrants$_{2015}$ outstanding at the date of this Annual Report;
- In the next warrants issuance for the benefit of directors, the Company will publish items accounting for warrants issuance at fair value.

By a decision of 3 April 2017, the Board of Directors of the Company, upon exercise of the delegation of authority granted by the tenth resolution of the Extraordinary and Ordinary Shareholders Meeting of 10 June 2016, granted to Bracknor Fund, Ltd, a mutual fund (Certificate No. SIBA / PIPO/14/5528) with its registered office at Lyntons Financial Services (BVI), PO Box 4408 Road Town, Tortola, British Virgin Islands, managed by the management company Bracknor Capital Ltd, 1,500 bond warrants redeemable in cash and/or existing and/or new shares with a par value of €10,000 each, divided into five tranches of 300 bonds redeemable in cash or new and existing shares for an amount of €3,000,000.00 each (the "**ORNANE**").

It has been decided that each ORNANE will have a share warrant attached (the "**Bracknor Warrants**" and, with the ORNANE the "**ORNANEBSA**"). It is specified that, on the date of this Annual Report, the number of Bracknor Warrants is not determined but can be determined according to the following formula:

$$n = (r \times Vn) / (125\% \times P)$$

"n" is the number of Bracknor Warrants issued;
"r" is the ratio of Bracknor Warrants issued in relation to the number of ORNANE, i.e. 25%;
"Vn" is the nominal value of the relevant ORNANE tranche; and
"P" is the applicable conversion price.

It is specified that the applicable conversion price depends on the ORNANE tranche to which Bracknor Warrants are attached. The conversion price for the three tranches corresponds to the lowest volume-weighted average price of the Company's shares for the 15 trading days preceding the date of the exercise request of the warrant giving leading to issuance of a new ORNANE tranche from which the Bracknor Warrants are detached.

In theory, the consequences of ORNANEBSA issuance on the shareholding of a shareholder owning 1 % of the Company before the transaction is as follows:

	Undiluted base	Diluted base
Before issuance a new tranche of ORNANEBSA	1.00%	0.89%
After issuance the remaining 3 tranches and conversion of all ORNANE and exercice of all BSA Warrants	0.76%	0.69%

It is specified that the above table has been drafted on the basis of:

- 9,946,413 outstanding shares after completion of:
  - The capital increase decided by the Board of Directors of 3 April 2017, amounting to €223,489.80 by the issuance of 1,117,449 new ordinary shares at a price of €2.85 per share (including issuance premium), premium of €2.65 per share, corresponding to a total subscription amount of €3,184,729.65.
  - The capital increase decided by the Board of Directors of 3 April 2017, amounting to €38,596.40 by the issuance of 192,982 new ordinary shares at a price of €2.85 per share (including issuance premium), premium of €2.65 per share, corresponding to a total subscription amount of €549,998.70.
  - The draw-up of a first tranche of ORNANEBSA decided on 15 May 2017 for an amount of €3,000,000, resulting in issuance of 225,225 warrants and 330 ORNANE, converted between 16 May and 9 June 2017 into 1,385,085 new shares,
  - The draw-up of a second line of ORNANEBSA decided on 7 July 2017 for an amount of €3,000,000, resulting in issuance of 205,959 warrants and 300 convertible ORNANE, converted between 7 July and 11 July 2017 into 1,027,396 new shares,
- Issuance/conversion/exercise on 26 July 2017, i.e. a lower weighted average price for the 15 trading days preceding the relevant date, corresponding to €3.64.

In any event, the maximum number of shares that may be created following the exercise and/or conversion of the convertible bond warrants is limited to the cap set in the tenth resolution of the Extraordinary and Ordinary Shareholders Meeting of 16 June 2017, i.e. 10,000,000 shares on the basis of a nominal value of twenty cents per share.

21.1.6 Authorised share capital

The resolutions related to issuance decided by (i) the Ordinary Shareholders Meeting dated 16 May 2018 ("**OSM**") and (ii) the Extraordinary Shareholders Meeting dated 4 June 2018 (the "**ESM**") are summarized below:

Resolutions	Object of the resolution	Maximum nominal amount in euros	Determination of the issuance price modalities	Duration of the authorisation and expiry	Exercise	Residual amount on the date of this Annual Report
6th Resolution of the ESM	Delegation of powers to be granted to the Board of Directors within the context of the provisions of Article L.225-129-2 of the French Commercial code, to decide issuance of shares and/or securities providing immediate or future access to the share capital or providing entitlement to a receivable, with waiver of the preferential shareholders subscription right, without any beneficiaries and tby an offer to the public.	Nominal amount (capital increases): €3,500,000* (bonds and other receivable granting access to the share capital): €30,000,000**	Note 1	26 months	No	Nominal amount (capital increases): €3,500,000 (bonds and other receivable granting access to the share capital): €40,000,000
7th Resolution of the ESM	Delegation of powers to be granted to the Board of Directors to decide, either issuance of the shares and/or securities granting immediate or future access to the share capital or providing entitlement to a receivable, with the preferential shareholders subscription right, or the incorporation of profits, reserves or premiums into the share capital.	Nominal amount (capital increases): €3,500,000* (bonds and other receivable titles granting access to the share capital: €40,000,000**	-	26 months	No	Nominal amount (capital increases): €3,500,000 (bonds and other receivable titles granting access to the share capital: €40,000,000
8th Resolution of the ESM	Delegation of powers to be granted to the Board of Directors to decide, issuance of shares and/or securities granting immediate or future access to the share capital or providing entitlement to a receivable, with waiver of the preferential shareholders subscription right of the shareholders to the benefit of categories of beneficiaries.****	Nominal amount (capital increases): €3,500,000* (bonds and other receivable titles providing access to the share capital): €40,000,000**	At least equal to 70% of the volume-weighted average of the last ten (10) trading days prior to the date of its determination	18 months	No	Nominal amount (capital increases): € 3,500,000 (bonds and other receivable titles granting access to the share capital): €40,000,000
9th Resolution of the ESM	Delegation of powers to be granted to the Board of Directors to decide, issuance of shares and/or securities granting immediate or future access to the share capital or providing entitlement to a receivable, with waiver of the preferential shareholders subscription right to the benefit of categories of persons ensuring the underwriting of the Company's equity securities that may arise as part of an equity line of financing	Nominal amount (capital increases): €3,500,000* (bonds and other receivable titles providing access to the share capital): €40,000,000**	At least equal to 70% of the volume-weighted average of the last ten (10) trading days prior to the date of its determination	18 months	No	Nominal amount (capital increases): €3,500,000 (bonds and other receivable titles granting access to the share capital): €40,000,000

Resolutions	Object of the resolution	Maximum nominal amount in euros	Determination of the issuance price modalities	Duration of the authorisation and expiry	Exercise	Residual amount on the date of this Annual Report
10th Resolution of the ESM	Delegation of powers to be granted to the Board of Directors to decide on issuance of shares and/or securities granting immediate or future access to the share capital or providing entitlement to a receivable, with waiver of the preferential shareholders subscription to the benefit of categories of persons undertaking to subscribe to a capital increase or any issuance likely to entail a capital increase in the long term.	Nominal amount (capital increases): €3,500,000* (bonds and other receivable titles providing access to the share capital): €40,000,000**	At least equal to 70% of the volume-weighted average of the last ten (10) trading days prior to the date of its determination	18 months	No	Nominal amount (capital increases): €3,500,000 (bonds and other receivable titles granting access to the share capital): €40,000,000
11th Resolution of the ESM	Delegation of powers to be granted to the Board of Directors to decide on issuance of shares and/or securities granting immediate or future access to capital or providing entitlement to a receivable, with waiver of the preferential shareholders subscription right to the benefit of qualified investors or a limited circle of investors within the meaning of paragraph II of Article L.411-2 of the French Monetary and Financial Code (private placement) and within the limit of 20% of share capital per year.	Nominal amount (capital increases): €3,500,000* (bonds and other receivable titles providing access to the share capital): €40,000,000**	At least equal to 70% of the volume-weighted average of the last ten (10) trading days prior to the date of its determination	26 months	No	The following double cap: 20% of the share capital/year (deducting the prior exercise of the delegation) And Nominal amount (capital increases): € 3,500,000 (bonds and other receivable titles granting access to the share capital): €40,000,000
12th Resolution of the ESM	Authorisation to be granted to the Board of Directors to increase the number of shares and/or securities granting immediate or future access to the share capital or providing entitlement to a receivable, issued pursuant to the provisions of Article L.225-135-1 of the Commercial Code, in the event of implementation of the delegations of powers under the preceding six resolutions (9th to 14th) with or without the preferential shareholders subscription rights as appropriate (*Over-allotment option*).	15% of the initial issuance*	Price decided for the initial issuance and up to a cap of 15% of the latter	26 months	No	-
13th Resolution of the ESM	Delegation of powers to be granted to the Board of Directors, in order to decide a capital increase reserved for employees (*rejected*).	Nominal amount €269,268.20	Pursuant to the provisions of articles L.3332-19 and L. 3332-20 of the French Labour Code	18 months	-	-

Resolutions	Object of the resolution	Maximum nominal amount in euros	Determination of the issuance price modalities	Duration of the authorisation and expiry	Exercise	Residual amount on the date of this Annual Report
15th Resolution of the ESM	Authorisation to be granted to the Board of Directors in order for the Company to purchase of its own shares, pursuant to Article L.225-209 of the Commercial Code (*Buyback program*).	10% of the Company's share capital (at any time)	Maximum of 300% of the price of shares offered to the public in connection with the IPO on a US stock exchange of the Company's shares.	18 months	No	10% of the Company's share capital (at any time)
16th Resolution of the ESM	Authorisation granted to the Board of Directors to reduce the Company's share capital by cancellation of shares.	10% of the Company's share capital per twenty-four (24) month period	-	18 months	No	10% of the Company's share capital per twenty-four (24) month period
17th to 20th Resolutions	Delegation of powers and authorisation to be granted to the Board of Directors, in order to decide issuance of warrants$_{2017}$, founder's warrants$_{2017}$, free shares (AGA$_{2017}$), option to subscribe and/or purchase shares (Options$_{2017}$), to the benefit of categories of beneficiaries ****	€ 100,000 for each of the 11th to 14th Resolutions ***	Note 2	18 months	No	€ 400,000 for each of the 11th to 14th resolutions ***

* The nominal amount of the cap for authorised capital increases shall be deducted from the amount of the authorised global cap of €3,500,000 in the 14th Resolution of the ESM.

** The nominal amount of the cap for bonds and other debt securities granting access to the authorised capital shall be deducted from the amount of the authorised global cap of €40,000,000 in the 14th Resolution of the ESM.

*** Exercise of the delegations may result in all of the shares resulting from the exercise of founder's warrants, warrants, options to subscribe or purchase shares and free shares held by the employees, corporate officers and consultants of the Company representing more than 10% of the share capital on a fully diluted basis, provided that this percentage is and will be calculated by taking into account the existing capital, increased by the shares to be issued:

- In connection with exercice of the delegations granted by the 17th to 20rd Resolutions of the ESM
- In connection with exercice of the delegations granted by the 6th to 13th Resolutions of the ESM, and
- In application of any agreement concluded following exercice, prior to the ESM, of any delegation granted by any decision prior to the ESM and whose execution would continue after the ESM.

**** Categories of beneficiaries of the delegations of the 18th Resolution and 17th to 20th Resolutions of the ESM:

Granting of securities (8th Resolution of the ESM) are reserved for:

- Any individual who wishes to invest in a company in order to benefit from a reduction in (i) the wealth tax (in accordance with the provisions of Article 885-0 V bis of the French General Tax Code ("**CGI**") created by Law no. 2007-1223 of 21 August 2007 on labour, employment, and purchasing power (the "TEPA Law"), or any equivalent foreign tax system in the jurisdiction in which the person who wishes to invest would be domiciled for tax purposes, or (ii) income tax (in accordance with the provisions of Article 199 *terdecies-0 A* of the CGI) or any equivalent foreign tax system in the jurisdiction in which the person who wishes to invest would be domiciled for tax purposes, for a minimum individual subscription amount of €10,000 per

transaction (subject to the Company's eligibility for such tax arrangements);

- Any company that ordinarily invests in small and medium-sized companies and wishes to invest in a company in order to enable its shareholders or partners to benefit from a reduction in (i) the wealth tax (in accordance with the provisions of Article 885-0 V bis of the CGI created by the TEPA Law), or any equivalent foreign tax system in the jurisdiction in which the shareholders or partners would be domiciled for tax purposes, or (ii) income tax (in accordance with the provisions of Article 199 *terdecies-0 A* of the CGI) or any equivalent foreign tax system in the jurisdiction in which the shareholders or partners would be domiciled for tax purposes, for a minimum individual subscription in the Company amounting to €20,000 per transaction (subject to the Company's eligibility for such tax arrangements);

- Any investment fund that ordinarily invests in small and medium-sized companies and wishes to invest in a company in order to enable its shareholders or partners to benefit from a reduction in (i) the wealth tax (in accordance with the provisions of Article 885-0 V bis of the CGI created by the TEPA Law), or any equivalent foreign tax system in the jurisdiction in which the subscribers would be domiciled for tax purposes, or (ii) income tax (in accordance with the provisions of Article 199 *terdecies-0 A* of the CGI) or any equivalent foreign tax system in the jurisdiction in which the subscribers would be domiciled for tax purposes, for a minimum individual subscription in the Company amounting to €20,000 per transaction (subject to the Company's eligibility for such tax arrangements);

- any investment companies or investment funds that invest primarily in growth companies (i.e. unlisted companies or companies whose market capitalisation does not exceed €500 million) of any kind, including in particular innovation-focused investment funds ("FCPIs"), venture capital funds ("FCPRs"), whose registered office or that of their management companies is located in the European Union, and local investment funds ("FIPs"), for an individual subscription amount of at least €50,000 (issuance premium included);

- Any legal entity existing under French law or foreign law operating in the health, biotechnology, and/or pharmaceutical sectors that has entered into or is about to enter into a scientific and/or industrial and/or commercial partnership with a significant positive effect on the Company's activities;

- Industrial or commercial companies, investment funds, bodies, institutions or entities of whatever form, French or foreign, that regularly invest in the health, biotechnology, and/or pharmaceutical sectors, for a subscription amount of at least €20,000 (including issuance premium);

- Companies, investment companies, investment funds or saving funds who may invest in French companies listed on the Euronext or Euronext Growth markets or on any other regulated market that specialising in structured bond issues for small and medium-sized companies;

- Any financial institution, public institution, development bank, French or European sovereign fund or any institution attached to the European Union wishing to grant funds to small and medium-sized companies and whose investment conditions may include all or part of an investment in equity and/or in the form of securities granting immediate or future access to the share capital, and

- Corporate officers, directors and/or executive employees of the Company wishing to invest concurrently with beneficiaries covered by the above categories.

Granting of the warrants$_{2017}$ (17th resolution of the ESM) is reserved to natural or legal persons with one of the following characteristics:

(i) member of the Board of Directors or member of any other supervisory, control or study committee or observer within the Company;
(ii) consultants or managers or shareholders of companies providing services to the Company, which have concluded a consultancy or service provision agreement with this latter party at the time of exercice of this delegation by the Board of Directors;
(iii) any employee and/or manager of the Company; or

(iv) any person participating to a significant degree in the scientific and economic development of the company at the time of exercice of this delegation by the Board of Directors.

Granting of the founder's warrants$_{2018}$ (18th resolution of the ESM) is reserved for corporate officers subject to the tax regime of employees and to the employees of the Company and its subsidiaries.

Granting of free shares$_{2018}$ (19th resolution of the ESM) is reserved for employees and corporate officers.

Granting of Options$_{2018}$ (20th resolution of the ESM) is reserved for the benefit of the following beneficiaries:

(i) members or some members of the Company's employees and companies related to it pursuant to the conditions provided for in Article L. 225-180 I of the Commercial Code;

(ii) officers of the Company.

Note 1: The price within the context of a public offer shall be set by the Board of Directors according to the following rules:

- In connection with the capital increase enabling the Company to apply for admission to trading on a US stock market and their first listing: the subscription price of a new share will result from comparing the Company's offering of shares and the subscription applications issued by investors in the so-called "building-up of the order book";
- In the absence of listing, subsequent to or concomitant with the listing and first listing of the Company's shares to trading on a US stock market: equal to 70% of the volume-weighted average of the last ten (10) trading days preceding the date of its determination.

Note 2: (Exercise price of the warrants$_{2018}$, Founder's warrants$_{2018}$, Options$_{2018}$):

1. The exercise price of the warrants$_{2017}$: must be at least equal to the average weighted by the volumes of the last 10 trading days preceding the granting date by the Board (reduced as appropriate by a maximum discount of 20%) for as long as the Company's shares listed to trading on a market or a stock exchange.

2. The exercise price of the founder's warrants$_{2018}$ shall be at least equal to:
   (i) The listing price of the Company's shares on a US stock market as determined by the Board of Directors at the end of the investment period and resulting from comparing the Company's offering of shares and the subscription applications issued by investors in connection with the worldwide offering, in the so-called "building-up of the order book", and this for any granting occurring within six months of the completion of the capital increase enabling the Company to be listed on a US stock market, subject to the provisions set out below under (ii);

   (ii) In the event of completion of one or more capital increases within the six months preceding exercice of this delegation by the Board of Directors, at the subscription price determined during the most recent of the said capital increases assessed on the granting date of each founder's warrant$_{2018}$, provided that the ordinary shares to be issued upon exercise of the founder's warrants$_{2018}$ confer rights equivalent to those issued in connection with the capital increase.
   (iii) For any granting outside of the events provided for in (i) and (ii), at the average of prices weighted by trading volumes of the last 10 trading sessions preceding the granting date of the said founder's warrants$_{2018}$ by the Board of Directors (reduced, as appropriate, by a maximum discount of 20%), for as long as the shares of the Company are listed on a market or a stock exchange.

3. The subscription or purchase price of the shares upon exercise of the Options$_{2018}$: for as long as the shares are listed on a US stock exchange or Euronext Growth, this shall be determined in accordance with article L. 225-177 of the French Commercial Code and shall be set by the Board of Directors on the date on which the options are granted, pursuant to the provisions of articles L. 225-177 and L. 225-179 of the French Commercial Code, it being specified that:

(i) with regard to options to subscribe new shares, the price may not be less than 95% of the average of market prices during the 10 trading days preceding the day on which the option is granted;
(ii) with regard to options to purchase of existing shares, the price may not be less than 95% of the average of market prices during the 10 trading days preceding the day on which the option is granted, or at the average purchase price of shares held by the Company on the date on which the option is granted by way of Articles L. 225-208 and L. 225-209 of the Commercial Code.

21.1.7 Information on the share capital of the Company subject to an option or a conditional or unconditional agreement providing for the issuance of an option

As far as the Company is aware, there are no call or put options or other commitments to its shareholders or commitments granted by these latter parties relating to the Company's shares.

21.1.8 History of the share capital

Issuance date	Nature of transactions	Capital	Issuance premium	Number of issued shares	Number of shares comprising the share capital	Nominal value	Share capital	Issuance premium per share
15 September 2006	Incorporation of the company	63,000	0	630	630	100	63,000	100
30 July 2008	Capital increase	180,000	0	1,800	2,430	100	243,000	100
30 July 2008	Capital increase	24,000	0	240	2,670	100	267,000	100
18 December 2008	Nominal value divded by 100	NA	NA	NA	267,000	1	267,000	NA
18 December 2008	Creation of categories of shares: O and P preference shares	NA	NA	NA	NA	NA	NA	NA
18 December 2008	Capital increase – Issue of P category preference shares	50,859	749,153,07	50,859	317,859	1	317,859	15.73
29 June 2009	Capital increase – Issue of P category preference shares	201,635	2,018,366,35	201,635	519,494	1	519,494	11.01
29 June 2009	Capital increase – Financial year of the right of accretion (P category preference shares have become P bis category	21,804	0	21,804	541,298	1	541,298	1

Issuance date	Nature of transactions	Capital	Issuance premium	Number of issued shares	Number of shares comprising the share capital	Nominal value	Share capital	Issuance premium per share
	preference shares)							
18 July 2012	Creation of categories of preference shares: A and P2	NA	NA	NA	NA	NA	NA	NA
18 July 2012	Capital increase – Conversion of convertible bonds into O shares then conversion into A shares	18,046	180,460	18,046	559,344	1	559,344	11
19 July 2012	Capital increase – Issuance of P2 category preference shares	175,099	1,624,918,72	175,099	734,443	1	734,443	10.28
19 July 2012	Capital increase – Exercise of the accretion right	19,484	0	19,484	753,927	1	753,927	1
22 May 2015	Nominal value divided by 5	NA	NA	NA	3,769,635	0.20	753,927	NA
08 July 2015	Automatic conversion of preference shares into ordinary shares	NA	NA	NA	3,769,635	0.20	753,927	NA
10 July 2015	Capital increase – Listing on Euronext Growth – Issue of ordinary shares	334,500	9.700.500	1,672,500	5,442,135	0.20	1,088,427	6
07 August 2015	Capital increase – Issuance of ordinary shares	133,340	5.866.960	666,700	6,108,835	0.20	1,221,767	9
23 September 2015	Capital increase – Acknowledgment of exercise of warrants	4,583,20	114,580	22,916	6,131,751	0.20	1,226,350,20	6
04 December 2015	Capital increase – Acknowledgment of exercise of warrants	11,550	323,400	57.750	6,189,501	0.20	1,237,900.20	6
26 December 2015	Exercise of warrants	1,200	49,200	6.000	6,195,501	0.20	1,239,100.20	8,40

Issuance date	Nature of transactions	Capital	Issuance premium	Number of issued shares	Number of shares comprising the share capital	Nominal value	Share capital	Issuance premium per share
04 August 2016	Capital increase – Acknowledgment of exercise of warrants	57,680	52,080	28,000	6,223,501	0.20	1,244,700.20	€1.86
03 April 2017	Capital increase – Issuance of ordinary shares	223,489,90	2,961,239.85	1,117,449	7,340,950	0.20	1,.468,190	€2.65
03 April 2017	Capital increase Issue of ordinary shares	38,596.40	511,402.3	192,982	7,533,932	0.20	1,506,78640	€2.65
16 May 2017	Capital increase - Conversion of 30 bond warrants	24,489.80	Total conversion amount: 376,604.08	122,449	7,656,381	0.20	1,531,276.20	Conversion price: €2.45
16 May 2017	Capital increase - Conversion of 45 bond warrants	36,734.60	Total conversion amount: 564,906.12	183,673	7,840,054	0.20	1,568,010.80	Conversion price: €2.45
27 May 2017	Capital increase - Conversion of 25 bond warrants	20,491.80	Conversion amount: 272,264.34	102,459	7,942,513	0.20	1,588,502.60	Conversion price: €2.44
31 May 2017	Capital increase - Conversion of 25 bond warrants	20,833.20	Conversion amount: 268,309.43	104,166	8,046,679	0.20	1,609,335.80	Conversion price: €2.40
02 June 2017	Capital increase - Conversion of 20 bond warrants	17,021.20	Conversion amount: 217,038.30	85,106	8,131,785	0.20	1,626,357	Conversion price: €2.35
07 June 2017	Capital increase - Conversion of 20 bond warrants	17,021.20	Conversion amount: 225,327.66	85,106	8,216,891	0.20	1,643,378.20	Conversion price: €2.35
09 June 2017	Capital increase - Conversion of 62 bond warrants	52,765.80	Conversion amount: 720,545.53	263,829	8,480,720	0.20	1,696,144	Conversion price: €2.35
09 June 2017	Capital increase - Conversion of 103 bond warrants	87,659.40	Conversion amount: 1,291,751.49	438,297	8,919,017	0.20	1,783,803.40	Conversion price: €2.35
07 July 2017	Capital increase - Conversion of	136,986.20	Conversion amount: 3,102,054	684,931	9,603,948	0.20	1,920,789.60	Conversion price: €2.92

Issuance date	Nature of transactions	Capital	Issuance premium	Number of issued shares	Number of shares comprising the share capital	Nominal value	Share capital	Issuance premium per share
	200 bond warrants							
10 July 2017	Capital increase - Conversion of 100 bond warrants	68,493	Conversion amount: 1,369,175	342,465	9,946,413	0.20	1,989,282.60	Conversion price: 2.92
10 October 2017	Capital increase	€397,800	10,044,450	1,989,000	11,935,413	0.20	2,387,082.60	€5.25
26 October 2017	Capital increase – Exercise of 15.000 founder's warrants$_{1\text{-}2015}$	€3,000	27,900	15,000	11,950,413	0.20	2,390,082.60	€2.06
31 October 2017	Capital increase	302,600	7,262,400	1,513,00	13,463,413	0.20	2,692,682.60	5

Changes of the shareholding structure of the Company's share capital over the last 2 financial years (undiluted basis):

	At 26 February 2018		At 31 December 2016	
Shareholders	Number of shares	% of share capital and voting rights	Number of shares	% of share capital and voting rights
Founder (1)	***66,666***	***0.50%***	***66,666***	***0.50%***
Directors (2)	***17,365***	***0.12%***	***17,365***	***0.12%***
Seventure Partners Fund	0	0.00%	482,313	0.00%
CM-CIC Fund	0	0.00%	554,487	0.00%
Subtotal Institutional Investors	**0**	**0.00%**	**1,036,800**	**0.00%**
Stanislas VEILLET - Chairman and Managing Director	1,469,271	10.91%	1,293,833	10.91%

Non-founding employee	42,544	0.32%	25,000	0.32 %
H.M Conseils (3)	11,365	0.084%	11,365	0.084%
METABRAIN RESEARCH	0	0.00%	408,635	0.00%
Treasury stock as at 31 January 2018	34,909	0.26%	38,121	0.26%
Floating shares	11,832,658	74.44%	3,325716	74.44%
TOTAL	***13,463,413***	**100%**	**6,223,501**	**100%**

(1) A founding natural person who is not a corporate officer.
(2) As of 31 December 2015, Marie-Claire JANAILHAC-FRITSCH held 6,000 shares. As of 31 December 2015, Mr Jean-Gérard GALVEZ held, indirectly, by HM Conseils, 11,365 shares.
(3) H.M Conseils is 100% held by Mr Jean-Gérard GALVEZ, director.

The allocation of Company's capital and voting rights on the date of this Annual Report is presented in paragraph 18.1.

21.2 ARTICLES OF INCORPORATION AND ARTICLES OF ASSOCIATION

21.2.1 Company purpose

The Company's purpose, in France and in all countries is the following:

- creation, operation, leasing, lease management of all business division, factories, establissments, security interests in any company, as well as all attached or connected commercial, financial, industrial, moveable and immoveable transactions, relating directly or indirectly to the activity of research production, distribution and marketing of any product and service beneficial to human or animal health,

- research and development of drug candidates and nutraceuticals, notably in the field of age-related diseases;

- and more generally, all financial, commercial, industrial, civil, moveable and immoveable transactions, which may be associated, directly or indirectly, in whole or in part, with one or other of the purposes specified above or any other similar or related purposes.

21.2.2 Articles of association or other provisions relating to members of the management or governing bodies

(IV) Board of Directors

Article 15 – Board of Directors

The Company is managed by a Board of Directors consisting of at least three (3) and no more than eighteen (18) members, subject to the exception provided by law in the event of a merger.

Article 16 – Appointment and dismissal of directors

I. Appointment/dismissal of directors

During the life of the Company, the directors are appointed by the Ordinary Shareholders Meeting. However, in the event of merger or demerger, appointment may be made by the Extraordinary Shareholders Meeting. The duration of their mandates shall be three (3) years. It expires at the Ordinary Shareholders Meeting of Shareholders approving the accounts for the previous financial year, held in the year in which the mandate of the said administrator expires.

Any retiring director is eligible for re-election indefinitely, subject to the conditions of this article.

The directors may be dismissed and replaced at any time by the Ordinary Shareholders Meeting.

No one over seventy-five (75) may be appointed director, if the proportion of directors who have exceeded this age ismore than a third of the Board members following his/her appointment. If the proportion of one third is exceeded, the oldest director shall be considered to have resigned at the next Shareholders Meeting.

Any director who is a natural person shall, both on appointment and for the duration of his/her mandate, comply with the legal provisions on number directorships held by the same natural person within limited liabilities companies with their headquarters in metropolitan France, with the exceptions provided by law.

An employee of the Company may only be appointed director if his/her employment agreement corresponds to an effectivefunction . The number of employees being members of the Board of Directors cannot exceed one third of the directors in office.

II. Director who is a legal person

Directors may be natural or legal persons. In the latter case, on appointment, the legal person shall designate a permanent representative, who is subject to the same conditions and obligations and who incurs the same civil and criminal liabilities as if he/she were a director in his/her own name, without prejudice to the joint and several liabilities of the legal entity which he/she represents. The permanent representative of a legal person which is a director shall be subject to the age conditions for individual directors.

The mandate of the permanent representative designated by the legal person appointed director is given for the duration of the latter’s mandate.

If the legal entity terminates the mandate of its permanent representative, it shall notify this termination and the identity of its new permanent representative to the Company immediately by registered letter. The same provisions shall apply in the event of death or resignation of the permanent representative.

The appointment of the permanent representative, as well as the termination of his/her mandate are subject to the same registration formalities as if he/she were a director in his/her own name.

III. Vacancy, death, resignation

In the event of vacancy due to death or resignation of one or more directors, the Board of Directors may, between two shareholders meetings, decide on provisional appointments.

When the number of Directors falls below the legal minimum, the remaining directors must immediately cconvene the Ordinary Shareholders Meeting in order to appoint further members of the Board of Directors.

Temporary appointments decided by the Board are subject to approval at the next Ordinary Shareholders Meeting. In the absence of ratification, the deliberations taken and actions previously undertaken by the Board shall nevertheless remain valid.

Article 17 – Organisation and decisions of the Board

I. Chairman

The Board of Directors shall appoint a Chairman among its members whoshall be a natural person, otherwise such appointment shall be void. The Board of Directors shall determine his/her compensation.

The Chairman of the Board of Directors organises and directs the work of the Board and reports to the Shareholders Meeting. He ensures the proper functioning of the Company's bodies, and in particular ensures that the directors are able to fulfil their mission.

A director shall not be appointed Chairman if he is aged seventy-five (75) years or over. If the Chairman has reached this age, he shall be regarded as have resigned at the end of the next meeting of the Board of Directors.

The Chairman is appointed for a period which may not exceed his term as Director. He may be re-elected.

The Board of Directors may dismiss him at any time.

In case of temporary incapacity or death of the Chairman, the Board may delegate the Chairman’s functions to a director.

In the event of temporary incapacity, this delegation of authority shall be granted for a limited period; it is renewable. In the event of death, it shall be valid until appointment of the Chairman.

II. Board meetings

The Board of Directors shall meet as often as the interests of the Company require, upon convening by the Chairman.

Convening shall be made in writing (fax, letter, e-mail) and sent in such a way as to reach

members of the Board no later than 8 days before the Board meeting. Documents necessary for assessment of the decisions or information submitted to the Board shall be attached to these notices. This convening period may be reduced to two (2) days if necessary. Such convening shall be considered null and void if less than one quarter of the Directors are present or represented.

When it has not met for more than three (3) months, at least one third of the members of the Board may request the Chairman to convene it on a given agenda.

The Managing Director may also request the Chairman to convene a meeting of the Board of Directors on a given agenda.

The Chairman is bound by the requests submitted to him/her pursuant to the two preceding paragraphs.

Convening notices shall be made by any means, even verbally.

The Board shall meet at the registered office or at any other location (in France or abroad) indicated in the notice, under the direction of its Chairman or, iabsence abstent, a member designated by the Board to chair the meeting.

Board meetings are chaired by the Chairman of the Board or the Managing Director performing the duties of the Chairman of the Board or, in their absence, by the oldest of the directors attending the meeting or by a director chosen by the Board at the start of the meeting.

The Board may appoint a secretary for each meeting, who need not be one of its members.

They shall be registered, signed by the directors attending the Board meeting.

The directors and any person called to attend meetings of the Board of Directors, are bound to secrecy regarding information of a confidential nature and presented as such by the Chairman.

III. Quorum, majority

The Board may only deliberate validly if at least half of the directors are present or considered to be present, subject to the adjustments made by the internal regulations in the event of videoconference or another means of telecommunication.

Unless otherwise provided in these articles of association and subject to the adjustments made by the internal regulations in the event of videoconference or other means of telecommunications, decisions are taken by majority of votes of members who are present or represented or regarded as present. In the event of a tied vote, the Chairman of the session shall have the casting vote.

For the calculation of the quorum and majority, directors participating in the Board meeting by videoconference or telecommunications media shall be regarded as present under the conditions defined by the internal regulations of the Board of Directors. However, the effective presence or presence by representation shall be necessary for all Board decisions regarding closing of the annual financial statements and consolidated accounts and drawing up of the management report and the report on the management of the group, as well as for decisions regarding dismissal of the Chairman of the Board of Directors, the Managing Director and the Deputy Managing Director.

IV. Representation

Any director may grant a power of attorney in writing to another director to represent him/her at a board meeting.

Each director may only benefit from the powers of attorney received pursuant to the preceding paragraph during each meeting.

These provisions apply to the permanent representative of a legal entity which is a director.

V. Minutes of the decisions

The decisions of the Board of Directors are recorded in minutes drawn up in a special register, numbered and initialled and kept at the registered office in accordance with the internal regulations. These minutes are signed by the Chairman of the meeting and by at least one director. If the Chairman is absent, the minutes shall be signed by at least two directors.

Copies or extracts of the minutes are certified by the Chairman of the Board or by the Managing Director, in the event that general management is not assumed by the Chairman of the Board of Directors, as the option is provided in Article 19 of this Articles of Association, or by a Deputy Managing Director, to whom the functions of Chairman of the Board of Directors have been temporarily delegated or by a proxy duly authorised or this purpose.

VI. Observers

During the life of the company, the Ordinary Shareholders Meeting may appoint observers that may be shareholders or not.

The number of observers may not exceed three (3).

The observers are appointed for a period of three (3) years. Their functions shall cease at the Ordinary Shareholders Meeting approving the financial statements for the past year, held in the year during which their functions expire.

Any observer whose term has expired, may be re-elected subject to meeting the conditions of this article.

Observers may be dismissed and replaced at any time by the Ordinary Shareholders Meeting, without any compensation and even if this dismissal does not appear on the agenda. The functions of observers shall also terminate with the death or incapacity of the individual observer, or the dissolution or bankruptcy of the observer which is a legal person or on resignation.

Observers may be natural or legal persons. When a legal person is appointed observer, it must appoint a permanent representative who is a natural person to represent it at the meetings of the Board of Directors, notifying the Company by any written means. The same provisions shall apply in the event of change of the permanent representative of the legal person.

The observers are responsible for ensuring strict compliance with the articles of association and for submitting their comments at the Board of Directors meetings.

Within the Company, they have a general and permanent advisory and supervisory mission. They study issues that the Board or its Chairman may submit to their examination for an opinion.

Observers shall be convened to each meeting of the Board of Directors, in the same capacity as the directors. Their absence shall not affect the validity of the decisions of the Board of Directors.

In an individual or collective capacity, observers shall only have advisory powers and shall not have voting rights at Board meetings.

Failure to convene the observer or communicate documents to the observer(s) prior to the meeting of the Board of Directors shall in no case constitute grounds for nullity of the decisions of the Board of Directors.

Observers are subject to the same confidentiality obligations as those binding on members of the Board of Directors.

The observers shall not receivced any compensation: they shall not be allocated attendance fees. At the express decision of the Board of Directors, however, observers may be reimbursed for expenses incurred by them as part of their functions. If the Board of Directors grants A special task to the observers or to one of them, it may allocate to them, in addition to a budget for its implementation, fees relating to the importance of the tasks.

Article 18 – Powers of the Board of Directors

The Board of Directors determines the guidelines for Company's activity and ensures their implementation.

Subject to the powers expressly attributed to shareholders' meetings and within the limits of the company's purpose, the Board of Directors considers any issue on the proper functionning of the Company and tby its decisions, settles the issues concerning it.

In its relations with third parties, the Company is bound even by the actions of the Board of Directors which do not relate to the company purpose, unless it can prove that the third party was aware that the act exceeded this purpose or could not have been unaware of it in view of the circumstances. The mere publication of the articles of association shall not constitute such evidence.

The Board of Directors shall carry out controls and inspections that it considers appropriate.

Each director shall receive the information necessary for executing its assignment and may obtain all of the documents which it considers useful from the general management.

The Board of Directors may decide to create study committees responsible for studying issues that the Board or its Chairman submits to it.

(V) General Management

Article 19 – General management - Delegation of powers

I. Principles of organisation

In accordance with the law, the Chairman of the Board of Directors or another individual appointed by the Board of Directors and holding the title of Managing Director, shall manage the Company.

The choice between these two forms of general management is decided by the Board of Directors, which shall inform the shareholders and third parties under regulatory conditions.

The decision of the Board concerning the choice of the form of management is decided by a majority of present or represented directors, present or represented or regarded as present, subject to the specific provisions of Article 17-III, in the event of participation of the directors at the Board Meeting by videoconference or other telecommunications media.

The choice decided by the Board of Directors is valid until expiry of the mandate of the designated Managing Director, regardless of the cause of this expiry, notably including dismissal.

If the Chairman of the Board of Directors manages the Company, the following provisions relating to the Managing Director shall apply to him/her.

II. General management

Managing Director

The Board of Directors decided that either by the Chairman of the Board of Directors or a natural person, who may or may not be a director or shareholder, appointed by the Board of Directors and holding the title of Managing Director, shall manage the Company.

If the Board of Directors decides to separate the functions of Chairman and Managing Director, it shall appoint the Managing Director, set the term of his/her mandate, determine his/her compensation and as appropriate, the limitations on his/her powers.

The duties of the Managing Director shall end automatically on the last day of the calendar quarter during which he reached his sixty fifth birthday. When this age limit is reached while he is in office, the Managing Director shall be regarded as having resigned and a new Managing Director shall be appointed.

The Managing Director may be dismissed at any time by the Board of Directors. When the Managing Director does not assume the functions of Chairman of the Board of Directors, his dismissal, without just cause, may give rise to damages.

The Managing Director has the broadest powers to act in all circumstances on behalf of the Company. He shall exercise these powers within the limits of the company purpose and subject to those which the law expressly attributes to the shareholders and to the Board of Directors.

He shall represent the Company in its relations with third parties. The Company shall be bound by the acts of the Managing Director which do not fall within the corporate purpose, unless it can prove that the third party was aware that the act exceeded this object or could not have been unaware of this in view of the circumstances. The mere publication of the articles of association shall not constitute this proof.

Deputy Managing Directors

Upon proposal of the Managing Director, whether this function is assumed by the Chairman of the Board or by another person, the Board may appoint one or more natural persons as Deputy Managing Director s, who may or may not be directors and shareholders, responsible for assisting the Managing Director. The number of Deputy Managing Director s shall not exceed five. If the Deputy Managing Director is a director, the duration of his duties shall not exceed his term as Director.

The functions of the Deputy Managing Director shall automatically expire on the last day of the calendar quarter during which he reached his sixty fifth birthday. If this age limit is reached while he is in office, the Deputy Managing Director in question shall be regarded as having resigned.

The Deputy Managing Director s may be dismissed at any time by the Board upon proposal of Managing Director. Their dismissal without just cause may give rise to damages.

By agreement with the Managing Director, the Board of Directors shall determine the scope and duration of the powers granted to the Deputy Managing Director s, who shall have the same powers as the Managing Director with regard to third parties. The Deputy Managing Director s have the same powers with respect to third parties as the Managing Director.

If the Managing Director ceases or is unable to perform his duties, the Deputy Managing Director s shall retain their functions and attributions until appointment of the new Managing Director , unless the Board decides otherwise.

The Board of Directors shall determine the compensation of the Deputy Managing Director s.

III. Delegation of powers

The Board of Directors may delegate to the corporate officers, whether they are directors or not, the permanent or temporary assignments which it determines, delegate powers to them and set the compensation for them which it considers appropriate.

Article 20 - Compensation of the Directors

The Shareholders Meeting may allocate to the directors, as compensation for their activities, in the form of attendance fees, a fixed annual sum, determined by such assembly without being bound by previous decisions. Such amount shall be attributed to operating expenses.

The Board of Directors shall freely distribute among its members the global overall amounts allocated to directors in the form of attendance fees; it may notably allocate to the directors who are members of study committees, a higher part than that of the other directors.

The Board of Directors may allocate exceptional compensation for assignments or mandates granted to the directors.

The Board of Directors may authorise reimbursement of travel costs and expenses incurred by the directors in the interest of the Company.

Article 21 – Agreements between the Company and a director, the Managing Director or a Deputy Managing Director

I. Agreements subject to authorisation.

Except for those relating to current operations concluded under normal conditions, any agreement entered into directly or by an intermediary, between the Company and any of its directors and managing director, deputy managing director or with a shareholder holding more than 10% of the voting rights of the company, or in the case of a shareholder being a legal person, the company which controls it pursuant to Article L.233-3 of the Commercial Code, shall be subject to prior authorisation by the Board of Directors.

The same shall apply for agreements in which one of the persons cited in the previous paragraph has an indirect interest.

Agreements between the Company and another company shall also be subject to prior authorisation, if the managing director, one of the managing directors or a director of the Company is the owner, partner with unlimited liability, manager, director, member of the supervisory board or, in general, a corporate officer of the company.

These agreements must be authorised and approved under the legal conditions.

II. Prohibited agreements

It is forbidden for directors other than legal entities to conclude loans in any form with the Company, to be granted a current account or other overdraft by it, as well as to make the Company endorse or guarantee their commitments with regard to third parties. Such agreement shall be considered void.

The same prohibition shall apply to the managing director, the deputy managing directors and to the permanent representatives of directors which are legal persons. It shall also apply to spouses, ascending and descending relatives of the persons cited in this section, as well as to any intermediary.

III. Current agreements

The agreements relating to current operations, concluded under normal operations, are not subject to the legal procedure of authorisation and approval.

21.2.3 Rights, privileges and restrictions attached to the Company's shares

(VI) Voting rights

The voting rights attached to shares or dividend shares is proportional to the amount of capital they represent. Each share is entitled to one vote.
A double voting right has been established for all registered and fully paid-up shares registered in the name of the same beneficiary for at least two years.

(VII) Rights to dividends and profits - Right to liquidation proceeds

Each share provides a right to ownership of the corporate assets, the distribution of profits and to the liquidation proceeds in proportion to the percentage of share capital which it represents.

(VIII) Preferential subscription right

The Company's shares all have a preferential subscription right to capital increases.

(IX) Limitation on voting rights

Not Applicable.

(X) Identifiable bearer shares

The shares are in registered or bearer at the option of the holders, subject to certain legal provisions concerning the form of shares held by certain natural or legal persons. They may only take bearer form after they are paid up in full.

The Company may request at any time, against payment at its expense, within the legal and regulatory conditions, the central depository, the name or denomination, nationality, year of birth or year of incorporation, the address of holders of securities granting immediate or future right to vote at shareholders' meetings and the number of shares held by each of them and, if necessary, restrictions which these securities may be subject.

(XI) Buyback by the Company of its own shares

See paragraph 21.1.4.

21.2.4 Procedures for modifications of shareholder rights

The rights of shareholders, as these appear in the Company's articles of association, may only be amended by the Extraordinary Shareholders Meeting of shareholders of the Company.

21.2.5 Shareholders meetings

Article 24 – Quorum and majority

Shareholders meetings decide under the conditions set by law.

The Ordinary Shareholders Meeting shall take all decisions other than those reserved to the Extraordinary Shareholders Meeting by law and these articles of association. It shall only decide validly at upon first convening if the present or represented shareholders hold at least

one fifth of the shares with voting rights. Upon second convening, no quorum shall be required. It shall rule with a majority of votes of the present or represented shareholders.

The Extraordinary Shareholders Meeting shall amend any provision of the articles of association. It shall only decide validly if the present or represented shareholders hold, upon first convening, at least one quarter and upon second convening, at least one fifth of the shares with voting rights. In the absence of such quorum, the second meeting may be postponed to two (2) months at least after the date on which it had been convended. It shall decide with a majority of two thirds of the votes held by the present or represented shareholders.

In the event of videoconferencing or other telecommunications media permitted by law under the conditions set forth in Article 25 below, shareholders will be considered to be present for the calculation of the quorum and majority who participate in meetings by videoconference or telecommunications media.

Article 25 – Convening of shareholders meetings

Shareholders Meetings shall be convened either by the Board of Directors or the statutory auditors or by a court-appointed representative, under the conditions and with the procedures provided by law or by the majority shareholders in terms of equity or voting rights after a public offer or sale of a controlling stake.

They shall meet at the registered office or at any other location specified in the convening notice.

In the event of listing of the Company's shares on a regulated market or if none of its shares are in registered form, it shall, at least thirty-five (35) days before any Shareholders Meeting to publish a notice in the Bulletin of Mandatory Legal Announcements (BALO) containing the notes required by current legislation.

The convening to Shareholders Meeting is published in a newspaper authorised to receive legal announcements in the department of the registered office, as well as in the Bulletin of Mandatory Legal Announcements (BALO).

However, if all the shares of the Company are in registered form, the announcements provided in the preceding paragraph may be replaced by a convening notice, at the expense of the Company, by ordinary or registered letter to each shareholder. This convening notice may also be forwarded by electronic means of telecommunication implemented under the regulatory conditions.

Any shareholder may also, if the Board of Directors so decides at the time of convening of the meeting, participate in and vote at meetings by videoconference or by any telecommunication media allowing their identification, under the conditions and following the procedure established by the law and decrees.

Any improperly convened meeting may be annulled. The action for nullity shall nevertheless not be admissible when all of the shareholders were present or represented.

Article 26 – Agenda of the meeting

The agenda for meetings is set by the author of the convening notice.

However, one or more shareholders meeting the legal requirements shall be entitled to request, under the conditions provided by law, addition on the agenda of points or draft resolutions. The additionnal requests for draft resolutions is accompanied by the text of the draft resolutions, that may be accompanied by a brief explanatory statement.

These points or these draft resolutions are listed on the agenda of the meeting and brought to the shareholders' attention.

The agenda of the meeting may not decide on an issue that is not listed on the agenda.

Under any circumstances, it may nevertheless dismiss one or several directors and replace them.

The agenda of the meeting may not be amended on the second convening.

When the meeting is convened to deliberate on modifications to the economic or legal organisation of the company on which the works council was consulted pursuant to Article L.2323-6 of the Labour Code, the opinion of this latter party shall be notified to it.

Article 27 – Admission to Shareholders Meetings

Any shareholder may participate in person, by proxy or by correspondence at shareholders meetings of any kind.

The right to participate in general meetings shall be justified:

- for registered shares, by registration in the registered securities accounts held by the Company, on the second business day preceding the meeting at midnight, Paris time;

- for bearer shares, by their registration in the bearer share accounts held by the authorised intermediary, on the second business day preceding the meeting at midnight, Paris time.

The registration or recording of securities in the bearer share accounts held by the authorised intermediary is acknowledged by a certificate of participation issued by this latter party.

The Board of Directors may nevertheless reduce or waive this deadline, provided that it is for the benefit of all shareholders.

Shareholders who have not made the required payments for their shares will not have access to the meeting.

Article 28 – Representation of shareholders and postal voting

I. Representation of Shareholders

A shareholder may be represented by another shareholder, by his/her spouse or partner with whom he/she has entered into a civil solidarity partnership or by any natural or legal person of his/her choice.
Any shareholder may receive powers of attorney issued by other shareholders with a view to being represented at a meeting, without limitations other than those arising from the legal provisions setting the maximum number of votes which the same person may hold both in

his/her own name and as representative.

II. Postal voting

A postal voting form and its annexes shall be forwarded or addressed, at the Company's expense, to any shareholder who requests these in writing as from convening of the Shareholders Meeting.

The Company must comply with any request submitted or received at the registered office no later than six days before the date of the meeting.

Article 29 – Bureau of the shareholders meeting

Shareholders' Meetings are chaired by the Chairman of the Board or, in his absence, by a director delegated for this purpose by the Board. Failing this, the meeting shall appoint its own Chairman.

In the event of convening by the statutory auditors, by a legal representative or by the liquidators, the shareholders meeting shall be chaired by this party or one of those who called the meeting.

The two members of the said meeting with the largest number of votes who accept the position shall act as scrutineers for the shareholders meeting.

The bureau of the meeting shall appoint a secretary, who need not be a shareholder.

Article 30 – Minutes of the decisions

The decisions of shareholders' meetings are recorded in minutes drawn up by the officers and signed by them.

They indicate the date and place of meeting, convening form, agenda, composition of the bureau, number of shares participating in the vote and quorum achieved, documents and reports submitted to the meeting, a summary of the discussions, the text of the resolutions put to the vote and results of the votes.

The minutes are kept in a special register at the registered office under the regulatory conditions.

If, in the absence of a quorum, a meeting cannot regularly deliberate, the bureau of the meeting draws up a report on this.

Article 31 – Right to information and control of shareholders

Before each meeting, the Board of Directors shall make available to shareholders the documents necessary to enable them to decide in full awareness and make an informed judgment on the Company's management and progress of its business.

Any shareholder has the right to submit questions in writing that the Board of Directors shall answer during the meeting as from the above mentioned communication.

At any time, any shareholder shall have the right to obtain documents that the Board of Directors shall, as appropriate, make available to them at the registered office or submit to them in accordance with the laws and regulations in effect.

21.2.6 Mechanisms for delaying, deferring or preventing a change in control

The articles of association of the Company do not contain mechanisms for delaying, postponing or preventing a change of control.

Crossing of thresholds

Any natural or legal person, acting alone or in concert, pursuant to Article L. 233-10 of the French Commercial Code, who comes to hold or ceases to hold a number of shares representing a fraction equal to 5%, 10 %, 15%, 20%, 25%, 30%, 33.33%, 50%, 66.66%, 90% or 95% of the share capital or voting rights, shall inform the Company no later than the close of trading of the fourth trading day following the day of crossing of the aforementioned participation threshold, indicating the number of shares and voting rights held. The person shall specify the number of securities which it holds that provide future access to the share capital and the voting rights attached thereto, as well as any other information required by law.

Moreover, any natural or legal person, acting alone or in concert, who comes to hold or ceases to hold a number of shares representing a fraction of 50% or 95% of the share capital or voting rights is required to inform the AMF at the latest before the close of trading on the fourth trading day following the day of crossing of the aforementioned participation threshold, under the conditions set by the general regulations of the AMF.

If they have not been reported under the above conditions, the shares exceeding the fraction that should have been declared shall be deprived of voting rights, in accordance with the provisions of the French Commercial code.

21.2.7 Public offers

For as long as the securities issued by the Company are admitted to trading on Euronext Growth, any natural person or legal entity, acting alone or in concert, pursuant to article L. 233-10 of the French Commercial Code, who comes to hold, directly or indirectly, over 50% of the capital or of the voting rights of the Company shall be required to file a public offer plan under the legal and regulatory conditions in force.

21.2.8 Specific provisions governing modifications to the share capital

There is no specific provision in the Company's articles of association governing modifications to its share capital which diverges from ordinary company law.

22 SIGNIFICANT AGREEMENTS

The significant agreements to which the Company is a party are the following:

22.1 SERVICE PROVISION AGREEMENTS, RESEARCH AND COLLABORATION AGREEMENTS

22.1.1 Research services agreement

On 5 June 2015, the Company and Metabrain Research (a shareholder of the Company) entered into a framework research services agreement, whose object is to enable the Company to continue its research and development activities and within a context similar to that provided by the agreement for the provision of a technical platform, which expired on 31 October 2015 after renewal by a subsequent amendment agreement signed on 31 October 2013 (the "**Framework Agreement**")

The Framework Agreement allows the Company to benefit from timely access to some of Metabrain Research's equipment and facilities so that the Company may continue its research and development activities.

The Framework Agreement entered into effect on 1 August 2015 for a period of one (1) year. The Framework Agreement was extended by an amendment agreement dated 1 August 2016 for a period of twelve (12) months until 31 July 2017. The Framework Agreement was extended by an amendment agreementdated 1 August 2017 for a period of twelve (12) months until 31 July 2018.

The Framework Agreement expressly provides that no intellectual property right may be claimed by either party on the research and development results carried out by the other party. It also contains a confidentiality clause for information exchanged during execution of the agreement, for the duration of the agreement and for the ten (10) years following its expiry. Fees paid to Metabrain Research are determined transaction by transaction and partially invoiced at the order and then progressively upon performance of the services.

Under the Framework Agreement, the Company incurred a charge of €182,601 during the 2017 financial year.

On 11 July 2015, the parties entered into an initial agreement to apply the Framework Agreement, in order to formalise the terms and conditions of a specific research delivery program (the "**Enforcement Agreement**").

The Enforcement Agreement entered into effect on 1 August 2015, for a twelve- (12) month period. The Enforcement Agreement was extended by an amendment agreement dated 1 August 2016 for a period of twelve (12) months until 31 July 2017.

The Enforcement Agreement was not renewed. The Company currently sends Metabrain purchase orders. During the 2017 financial year, the total amount of all the purchase orders amounted to €193,104 for the 2017 financial year.

22.1.2 Research and collaboration agreements

The Company entered into the consortium and collaboration agreements described in 11.3.1 of this Annual Report.

22.1.3 Operating agreements and joint ownership rules

The Company entered into the operating agreements and joint-ownership rules described in 11.3.2 of this Annual Report.

22.1.4 Consultancy agreements

The Company has concluded several consultancy agreements

Scientific advisory agreements - Key opinion leaders

On 9 November 2015, the Company and Dr. Saddek Mohand Saïd, as consultant, entered into a medical cooperation agreement whereby the latter will carry out consultancy missions for the preparation of a clinical phase 2 study within the context of the MACULIA program in defined areas. He also undertakes to perform the role of scientific adviser at meetings with national and international regulatory agencies and to act as scientific guarantor. This agreement entered into effect on 2 November 2015 and for eight (8) months, i.e. until 30 June 2016. The Doctor will receive fixed fees paid in four instalments of € 4,000. This agreement was tacitly renewed for an indefinite period under the same terms and conditions.

Consultancy agreements - SARA Steering Committee

The Company entered into four consultancy agreements between April and July 2016, with (i) Mr Olivier Bruyere, (ii) the University of Florida (Professor Marco Pahor), (iii) Mr Roger Fielding and (iv) Mr Yves Rolland, each for a period of five years from the date of their respective signatures.

The purpose of these agreements is to assist the Company in assessing the SARA clinical trials. Consultants are paid a fixed fee per hour or based on the number of attended meetings. The agreements provide for the transfer of all intellectual property to the Company.

Consultancy agreement - International Pharma - Med Ltd

The Company and International Pharm-Med Ltd. entered into a consultancy agreement dated 6 March 2016 with effect from 1 April 2016. The purpose of this agreement is to assist the Company during the first part of phase II IMPD. An amendment was concluded on 9 November 2016, with effect from 1 November 2016, to extend the consultancy agreement until 30 June 2017. Fees are calculated on a fixed hourly basis and capped on a daily basis.

Consultancy agreements - general mission

The Company entered into three consultancy agreements on 14 April 2016 with (i) Mrs Ivana Kim, (ii) Mr Philippe Guillet and (iii) Mr Roger A. Fielding, each for a period of five years from their respective date of signature. The purpose of these agreements is to assist the Company in assessing clinical trials for all of the Company's products. Consultants are paid a fixed fee per hour or based on the number of attended meetings. The agreements provide for the transfer of all intellectual property to the Company.

Under the above-mentioned consultancy agreements, the Company incurred a charge of €75,745 during the 2017 financial year.

22.1.5 Temporary Public Property Occupancy Agreement

The Public Property Occupancy Agreement (see 8.1.1) defines the access modalities by the Company to certain equipment and materials of the FR 3631 Institut Biologie Paris Seine laboratory and to the new premises occupied within the Pierre et Marie Curie University. Access to equipment and materials enables the Company to continue its missions of researching and developing drug candidates and nutraceuticals.

22.1.6 Agreement for the provision of clinical trials - Icon

The Company and Icon Clinical Research Limited, an Irish limited-liability company with its registered office in South County Business Park, Leopardstown, Dublin 18, Ireland (hereinafter "**Icon**") have entered into a framework agreement for the provision of clinical trial services on 12 December 2016 (the "**Icon Framework Agreement**").

The Icon Framework Agreement entered into effect on 23 November 2016, for a period of five (5) years.

Icon's services to the Company include (i) central and bioanalytical laboratories, (i) preclinical phase 1 (phase 1 CPU), (iii) medical imaging, (iv) interactive IWR technology, (v) medical matters (vi) data, statistics and pharmacokinetics management, (vii) clinical phases II-IV, (viii) clinical and regulatory advice, (ix) marketing advice and notification of results, (x) local partnership services, (xi) use of the Firecrest Clinical solution, (xii) use of the Iconik solution, and (xiii) pharmacovigilance services.

The Icon Framework Agreement also contains a confidentiality clause for the information exchanged during execution of the agreement, for the duration of the Icon Framework Agreement and for the five (5) years following its expiry.

The Icon Framework Agreement expressly provides that the Company will own the concepts, inventions, know-how, analytical framework, and any other intellectual property rights developed by the Company or created by Icon in connection with the provision of services under the Icon Framework Agreement with the exception of any rights owned by Icon prior to the conclusion of the Icon Framework Agreement.

The Icon Framework Agreement provides that each study must be the subject of an enforcement agreement.

Fees paid to Icon shall be determined on a study by study basis for each enforcement agreement within the Framework Contract.

Icon and the Company entered into an initial enfrocement agreement for the Framework Agreement on 23 January 2017, which came into force on 26 July 2016 (the "**Icon Enforcement Agreement**") and will expire on 18 July 2018.

The clinical trials of the Icon Enforcement Agreement focus on the "observational SARA study: characterising sarcopenia and obesity due to sarcopenia in patients over 65 years of age at

risk of reduced mobility". The study covered four (4) countries (Belgium, France, Italy, and the United States) and 428 patients were screened.

Icon's fees will be invoiced monthly to the Company, from the start of the study.

Under the Icon Enforcement Agreement, the Company incurred a charge of €1.557,435 during the 2017 financial year.

22.1.7 Agreement for the provision of clinical trials - SGS

The Company and SGS Belgium NV, SGS Life Sciences, a Belgium company with its registered office located at SGS House, Noorderlaan 87, B-2030, Antwerp, Belgium and registered with the Banque Carrefour des Compagnies [Belgian company database] of Antwerp under number 0404882750 (hereinafter "**SGS**") entered on 16 June 2016 into an agreement for the provision of clinical trial services (the "**SGS Agreement**").

The SGS Agreement took effect on 7 March 2016 and will expire when all services have been performed.

Under the SGS Agreement, SGS provides clinical and bioanalytical testing services for the Sarconeos SARA-PK study.

The SGS Agreement also contains a confidentiality clause for the information exchanged during the execution of the agreement, for the duration of the SGS Agreement and for five (5) years as from its expiry.

The SGS Agreement expressly provides that all data and results generated during the execution of the SGS Agreement shall be the exclusive property of the Company.

The Company and SGS entered into an amendment to the SGS Agreement on 24 November 2016, pursuant to which fees for clinical trials were slightly increased.

Under the SGS agreement, the Company incurred a charge of €686,119 during the 2017 financial year.

It is specified that the Company chose SGS to conduct the MACA-PK clinical study of its drug candidate Macuneos for the treatment of AMD. MACA-PK is intended to study the safety, pharmacokinetics and pharmacodynamics of Macuneos in healthy volunteers in 2017 and in patients with dry AMD in 2018. An agreement in principle has been concluded and a contract is being formalised.

22.1.8 Agreements for the provision of services related to the SARA clinical data platform

a) BlueCompanion SARA DATA agreement

The Company and BlueCompanion Ltd, an English company having its registered office at 2 Floor Street London Street, London W2 1HR, United Kingdom and registered under number 9648211 ("**BlueCompanion**"), entered into on 16 May 2017 an agreement for the provision of services related to the SARA clinical data platform (the "**BlueCompanion SARA DATA Agreement**").

The BlueCompanion SARA DATA Agreement was concluded with retroactive effect from 1 June 2016 and will expire on 31 December 2017.

Under the BlueCompanion SARA DATA Agreement, BlueCompanion assists the Company in the design, development and deployment of a digital platform (SARA-data) as part of the SARA-OBS study enabling it to collect and analyse data required for the development of Sarconeos.

The BlueCompanion SARA DATA Agreement also contains a confidentiality clause for information exchanged during execution of the agreement, for the duration of the BlueCompanion SARA DATA Agreement and for two (2) years as from its expiry.

The BlueCompanion SARA DATA Agreement expressly provides that all intellectual property rights on the developments made by BlueCompanion under the BlueCompanion SARA DATA Agreement will progressively be transferred to Biophytis.

By an amendment agreement dated 22 December 2017, the duration of the BlueCompanion SARA DATA Agreement was extended until 31 December 2018.

b) BlueCompanion SARA-INT Agreement

The Company and BlueCompanion entered into a service agreement for a second digital platform (the "**BlueCompanion SARA-INT Agreement**").

The BlueCompanion SARA-INT Agreement was concluded with retroactive effect from 1 June 2017 and will expire on 30 June 2019.

Under the BlueCompanion SARA-INT Agreement, BlueCompanion assists the Company in the design, development and deployment of a digital platform as part of the SARA-INT study enabling it to collect and analyse data required for the development of Sarconeos.

The BlueCompanion SARA-INT Agreement also contains a confidentiality clause for the information exchanged during execution of the agreement, for the duration of the BlueCompanion SARA-INT Agreement and for two (2) years as from its expiry.

The BlueCompanion SARA-INT Agreement expressly provides that all intellectual property rights on the developments made by BlueCompanion under the BlueCompanion SARA-INT Agreement will be progressively transferred to Biophytis.

Under the BlueCompanion SARA-DATA and BlueCompanion SARA-IN Agreements, the Company incurred a charge of €260,800 during the 2017 financial year.

22.2 SUBSIDIES, ASSISTANCE, AND FINANCING AGREEMENTS

The Company benefits from the following assistance and subsidies:

Name of the lender	Nature	Object	Date of conclusion	Granted amounts	Amounts received/to be received[134]	Maturity date	Bonds related to the transaction
Bpifrance Financement	**Assistance** Reimbursable assistance	Production of clinical batches, preclinical regulatory, and clinical phase of BIO101 for the treatment of sarcopenic obesity	30 November 2016	**1,100,000**	**€600,000** (minusthe amount of the registration fee of €33,000) Up to €1,100,000	**30.09.2023**	Yes **Agreement** of the lender in the event of assignment of securities or a change of control
Bpifrance Financement	**Assistance** Reimbursable assistance	In vitro, in vivo and pharmacokinetic categorisation of a candidate drug	04/02/2015 + Amendment of 7 November 2016	**260,000**	**208,000** In force	**31.03.2022**	Yes **Agreement** of the lender in the event of assignment of securities or a change of control
Bpifrance Financement **(formerly Oseo Innovation)**	**Assistance** Reimbursable assistance	Clinical development of a Quinoa extract acting on Metabolic Syndrome	07/08/2008	**230,000** Revalued at **228,782.82**	**228.782,82** Program expired	**31.122018**	Yes **Agreement** of the lender in the event of assignment of securities or a change of control
Bpifrance Financement **(formerly Oseo Ile de France)**	**Loan** Seed equity loan	Partial financing of the innovation program	04/11/2008	**150,000**	136,500 (Withholding on disbursement, by way of an advance)/ In progress	**30/04/2018**	Yes **Agreement** of the lender in the event of assignment of securities or a change of control

22.3 OTHER AGREEMENTS

On 25 November 2015, the Company entered into an equipment leasing agreement with Bios Analytique SAS. The agreement entered into effect on the signing date for a 36-month period, i.e. until 25 November 2018. The agreement expressly provides that on termination, the Company will have the option of (i) returning the equipment, (ii) extending the term of the contract by one year or (iii) purchasing the equipment (for an amount of € 44,600). The quarterly rent is set at € 13,134. Under the agreement, the Company shall enter into a civil liability insurance within the context of its professional activity or failing this, to entered into an insurance guaranteeing the risks of loss or theft. Moving the equipment outside of the installation premises is subject to prior approval of Bios Analytical. Bios Analytique may terminate the contract for any breach of an obligation with the enforcement of the penalty clause for 10% of the remaining rent.

[134]When the payment of subsidies/loans are provided by tranche or schedule of maturities.

23 INFORMATION DERIVING FROM THIRD PARTIES, DECLARATIONS BY EXPERTS AND DECLARATIONS OF INTEREST

Not Applicable

24 DOCUMENTS ACCESSIBLE TO THE PUBLIC

Copies of this Annual Report are available free of charge at the registered office of the Company located at 14, avenue de l'Opéra, 75001 Paris.

The articles of association, minutes of general meetings and other corporate documents of the Company, as well as the historical financial information and any assessment or declaration by an expert at the request of the Company, which must be made available to shareholders, in accordance with applicable legislation, are available free of charge at the registered office of the Company.

Starting from the listing of the Company's shares on the Euronext Growth market in Paris, regulated information pursuant to the AMF General Regulations will also be available on the Company's website (www.biophytis.com/).

25 INFORMATION ON HOLDINGS

Information regarding the companies in which Biophytis holds a proportion of the share capital likely to have a significant impact on the assessment of its assets, its financial situation or its results are contained in Sections 7 “Organisational Diagram” and 20 “Financial information concerning the assets, financial situation and results of the Company” of the Annual Report.

26 GLOSSARY

Agonists/antagonists

Molecules which, by binding to receptors, will activate or conversely, inactivate them.

Amphipathic

Organic molecules which possess regions with opposing properties (e.g. hydrophilic/hydrophobic). This is a property possessed in particular by detergents.

Anabolism

The process of synthesis of organic molecules by cells.

Analogue (compound)

Substance related to a natural active ingredient and that has related properties.

Monoclonal antibody

An antibody is a molecule specifically directed against another molecule, the antigen. An antibody is termed monoclonal when it has been produced on an industrial scale by a single line of cells (the clone). The purity of monoclonal antibodies allows them to be used for diagnostic purposes in order to identify in vitro the specific antigen sought, but also for therapeutics.

Angiotensinogen

The angiotensinogen is a plasma protein produced by the liver and the precursor of various peptides, such as angiotensin I and angiotensin II, involved in particular in the regulation of blood volume arterial pressure.

Antioxidant

Substance capable of protecting cellular components against oxidizing substances and e.g. capable of “trapping” free radicals.

Apoptosis

This term refers to a process of programmed cell death.

Geographic atrophy

The advanced form of dry ARMD, during which the retinal pigmentary epithelium degenerates from place in place and which is the cause of a significant loss of vision.

Autocrine

A biologically active substance which acts on the same cell which produced it (e.g. myostatin).

Blood-retinal barrier

The set of structures (cell junctions) which prevent the diffusion of proteins between the blood and the eye.

Beta blockers

Molecules capable of blocking the activity of a subcategory (type β) of receptors for noradrenaline, a neurotransmitter.

Cachexia

State of extreme debility of the organism (loss of weight, muscular atrophy) which appears as the consequence of a pathology (e.g. cancer).

Carotenoid

Carotenoids are yellow, orange or red pigments produced by vegetables and which animals may accumulate through their food. Since they are fat-soluble, they are in general easy to assimilate by organisms. They belong to the chemical family of the terpenoids and are formed through the polymerisation of 5 carbon atom units.

Catabolism

The process of breakdown of organic molecules by cells.

Adipose cell

Also termed “adipocytes”, these cells accumulate a large quantity of reserves in the form of lipids (triglycerides).

Dendritic cells

Cells of the immune system, responsible for the “presentation of antigens”, an early stage of specific immune responses.

Multinucleated cell

Cells with several nuclei, also termed syncytium. E.g. striated muscle fibres.

Chemical libraries

A chemical library is a bank of natural or synthetic molecules. Chemical libraries may contain from several dozens to several million chemical compounds.

Choroid

The choroid is one of the layers of the wall of the eye globe, located between the sclera externally and the retina internally. It is a highly vascularized layer, responsible for nourishing the iris and the retinal photoreceptors.

CRO

CROs (Contract Research Organizations) are Contract Research Companies which carry out research and development work necessary for elaborating and marketing pharmaceutical products.

Cytokines

These proteins are agents of intercellular communication and which generally act at a short distance from their place of production (paracrine or autocrine action).

Cationic detergent

An amphipathic molecule with a hydrophobic (lipophilic) region and a hydrophilic region carrying a positive electric charge.

Clinical development

See clinical study.

Drüsen

Deposits of amorphous material in the retina, located between the Bruch’s membrane and the retinal pigmentary epithelium.

Muscular dystrophies

Diseases characterised by a progressive degeneration of the muscles of the body, which may have various origins (genetic, ageing, etc.).

Electroretinogram

The electroretinogram (ERG) is an electrophysiological examination. It is carried out by specialized clinical neurophysiology or ophthalmology departments and allows the electrical activity of the photoreceptors to be measured and certain retinal anomalies to be diagnosed. It is carried out using an electroretinograph during electroretinography.

Vascular endothelium

The innermost layer of the blood vessels (and the only one at the level of the capillaries).

Retinal pigmentary epithelium (RPE)

The external pigmented layer of the retina, consisting of a single cell layer, which constitutes the *blood-retinal barrier* and which maintains a close relationship with the photoreceptors.

Aetiology

In medicine, aetiology is the study of the causes and factors of a disease.

Clinical study

A clinical trial (or clinical study) is a scientific study conducted on humans, providing an assessment of the effectiveness and tolerance of a treatment (in particular of a medicine), of a diagnostic method or more generally of a particular factor (genetic, nutritional, etc.).
Classically, 3 phases are distinguished in the development of a medicine prior to obtaining a Marketing Authorization (AMM).

- *Phase 1:* a phase I study is preliminary to the study of the effectiveness of a medicine. It takes place after the preclinical phase. It consists of assessing the tolerance and absence of undesirable effects in subjects who are most frequently healthy volunteers. This phase also permits the study of the kinetics and metabolism in humans of the substance under study. The studied groups are most frequently of small size (20 to 80 participants).
- *Phase II:* or “pilot study” consists of determining the optimal dose of the medicine and any adverse effects. Eligible population: people with the condition (often less than 500). It is subdivided into two phases: IIa and IIb. Phase IIa estimates the effectiveness of the molecule on a limited number (from 100 to 200) of sufferers, while phase IIb determines the therapeutic dose of the molecule on a broader scale (from 100 to over 300 sufferers).
- *Phase 3:* or “pivot study” is the comparative study of effectiveness strictly speaking. It compares the treatment either to a placebo or to the reference treatment. Groups are of significant size, often numbering several thousand participants. These are extremely onerous programs, which may be financed publicly or privately (pharmaceutical companies).

Muscle fibre

Contractile tissue comprising muscle tissue, also termed myocyte.

Muscular functionality

Expresses the capacity of the muscles to contract and develop sufficient force to ensure movements.

GH

Growth Hormone produced by the pituitary gland, which acts by stimulating the production of IGF-1 by the liver, as well as by other tissues (muscle).

Hemisynthesis

In chemistry, hemisynthesis is the chemical synthesis of a molecule from natural compounds which already contain a part of the target molecule.

Hepatocyte

Base cell of the liver, which secretes bile.

HOMA IR

The HOMA (= Homeostasis Model Assessment) estimates the activity of the beta cells of the pancreas (which produce insulin) and the sensitivity of the tissues to insulin. The HOMA IR more specifically measures insulin resistance and is calculated from plasma concentrations of glucose and insulin. https://www.dtu.ox.ac.uk/homacalculator/

Homeostasis

The set of mechanisms which guarantee the maintenance around a stable value of various parameters of the internal milieu (glycaemia, acid-base equilibrium, etc.).

IGF-1

Insulin-like Growth Factor I, produced in particular (but not exclusively) by the liver under the effect of GH.

Secondary indication

The use of a medicine on a priority basis to treat another pathology (or other symptoms).

Inflammation

Non-specific immune reaction, produced in response to tissue lesions of various origins (physical, chemical, infectious, etc.).

Isomerise/isomerisation

Transformation of a chemical compound into a compound with a different spatial conformation.

Leucine

One of the 20 amino acids which is a component of proteins.

Ligand (endogenous)

Molecule produced by the organism and capable of binding specifically to a receptor.

Linkage

Linkage (genetic linkage) refers to the fact that two or several genes tend to be transmitted jointly by an individual to its descendants.

Lysosomes

Organelles appearing in the form of vesicles filled with various digestive enzymes allowing the digestion of the contents of phagocytosis vesicles.

Macuneos

Commercial or pharmaceutical name corresponding to the molecule BIO 201 developed by Biophytis.

Stargardt disease

Stargardt disease is a rare disease of genetic origin. This pathology associates a reduction in bilateral visual acuity with specific retinal lesions. Most frequently, it relates to hereditary macular retinopathies.

Bruch's membrane

A complex of proteins and glycoproteins (= basal lamina) on which the cells of the retinal pigmentary epithelium rest.

Metabolite

A metabolite is an organic compound which is an intermediary or product of metabolism. This term is generally reserved for small molecules and monomers, as opposed to macromolecules. In this way, glucose is a *metabolite*, unlike glycogen, which is a polysaccharide with a very high molecular weight.
So-called primary metabolites are distinguished from so-called secondary metabolites.
Primary *metabolites* are directly involved in the processes that are essential for the normal development and reproduction of cells. They are, for example, amino acids, carboxylic acids, alcohols, antioxidants, nucleotides, polyols, or even vitamins.
Secondary metabolites do not participate directly in the vital processes of the cell, but nevertheless fulfil important ecological functions. This is the case of e.g. antibiotics and pigments.

Microarrays

These are "DNA chips", sets of DNA molecules fixed on a small matrix, allowing the level of activity of a set of genes within cells or tissues to be assessed.

Microbiota

The set of microorganisms found in a given environment (e.g. in the digestive tract).

Mitochondria

Cellular organelles of globular or extended form, which constitute the power plants of cells, within which, the oxidation of molecules (carbohydrates, lipids) produces the energy necessary for the functioning of cells. A hepatocyte thus contains around a thousand mitochondria.

Morbidity

A term used in epidemiology, expressing the incidence or prevalence of a disease.

Motoneurons

Nerve cells, the cellular body of which is located in the central nervous system (spinal medulla) and which innervate the skeletal muscles, thereby stimulating their contraction.

Skeletal muscles

Consist of multinucleate muscle fibres grouped into bundles and contract in response to a nervous stimulus of central origin.

Myoblasts

Stem cells present in the muscles and capable of generating muscle fibres (= satellite cells).

MyoD

One of the transcription factors specific to muscle, which orient the activity of the genome so that cells evolve into muscle cells.

Myogenin

Growth factor which promotes the fusion of myoblasts to form multinucleate myotubes which subsequently differentiate into muscle fibres.

Myopathy (Duchenne muscular dystrophy, cardiomyopathy)

Neuro-muscular diseases translated by a degeneration of the skeletal or cardiac muscles.

Myosin

Protein present in the form of filaments within muscle fibres and which, in association with actin, permit their contraction.

Myostatin

Myostatin is a protein factor produced by the muscles, which limits their growth. In its absence, the muscles experience very strong growth, even in the absence of physical activity.

Myotubes

Multinucleated cells formed by the fusion of myoblasts and which then differentiate into muscle fibres.

Oxido-reduction

An oxido-reduction reaction is a chemical reaction, during which two substances exchange electrons.

PBN

PBN = Phenyl-*N*-*tert*-Butylnitrone is a molecule with antioxidant properties, used as positive evidence in eye protection tests against damage caused by blue light.

Peptide

Small chain of amino acids interlinked by peptide bonds. Beyond a certain size, the term protein is used.

Phagocytosis

Phagocytosis is the cellular process by which large vesicles are formed (= phagosomes) which are capable of engulfing large particles or even whole cells. The content of these vesicles is then digested by enzymes contributed by the lysosomes.

Pharmacology

A scientific discipline which studies the interactions between active substances and the organism, with the aim of developing medicines.

Phenotypic

In genetics, the phenotype is the set of observable characteristics of an individual. Very often, the use of this term is more restrictive: the phenotype is then considered at the level of a single character, at the cellular or even molecular level.

Photoreceptor

The term photoreceptor designates a light-sensitive sensory neuron found in the posterior layer of the retina. The cones present in the central retina are distinguished from the rods present in the peripheral retina.

Visual pigment

See rhodopsin.

Polypharmacy

Polypharmacy is defined by the World Health Organization as “the simultaneous administration of numerous medicines” or by “the administration of an excessive number of medicines”.

Prandial (post-prandial)

The period following the ingestion of a meal.

Proteasome

Structure formed by the association of specific proteins with the role of breaking down intracellular proteins recognised as “abnormal” and labelled as such.

G Protein

G Protein is a protein which permits the transfer of information within the cell. It thus participates in a mechanism termed signal transduction.
Following the activation of a receptor located on the surface of the cell, G protein, which is bound to this receptor will be able to have an inhibitory or excitatory effect within the cell via a signalling cascade.

Proteolysis

Process of breakdown of proteins by the cutting of peptide bonds between amino acids by enzymes termed proteases or peptidases.

Proteosynthesis

Process of formation of proteins by coupling of the amino acids into chains in a specific sequence.

Free radicals

Atoms or poly-atomic structures with an unpaired electron, which react with neighboring by removing the electron which they lack and may thus cause chain reactions. The principal ones are the superoxide $O_2^{\bullet -}$ radical, the hydroxyl radical $HO^{\bullet}$ and the nitric oxide radical $NO^{\bullet}$.

Translational research

Translational research associates basic research (in a laboratory) and clinical research (on the patient) within the same structure, allowing the execution of all of the research stages, from its fundamental aspects to it application within the patient.

Retinopathy

Retinopathy is a term designated all of the afflictions affecting the retina. It is sometimes used in opposition to the term retinitis to designate those which are not of an infectious nature.

Rhodopsin

Rhodopsin is a photosensitive pigment, present in the photoreceptor cells of the retina. It is formed by the association of a protein, opsin, and of a small molecule, retinal.

SARM

SARM ("Selective Androgen Receptor Modulator") are a new class of ligands of the receptors of male hormones, (androgens) like testosterone.

Sarconeos

Commercial or pharmaceutical name corresponding to the molecule BIO 101 developed by Biophytis.

Screening

Selection process using a test of biological activity, executed on a set of substances.

Serumalbumin

The major protein produced by the liver, present at high concentrations in blood plasma.

siRNA

siRNA are small interfering RNA molecules (ribonucleic acids), which may specifically be associated with certain sequences of messenger RNA and thus prevent the expression of genes from which these RNAs were formed.

SORBONNE UNIVERSITY – Pierre et Marie Curie University (Paris VI)

SORBONNE UNIVERSITY is based in Paris. The heir to the former Sorbonne, it specialises in sciences and medicine. It is located in the Jussieu campus (in the Latin Quarter of Paris) for sciences, and in the hospital campuses of Pitié-Salpêtrière, Saint-Antoine, Trousseau and Tenon for medicine. It accommodates some 32,000 students (21,000 in sciences and 11,000 in medicine). 4,500 lecturers-researchers and researchers work there with it hosting 125 research laboratories. In the Shanghai 2014 ranking, SORBONNE UNIVERSITY confirmed its position as the leading French research university, ranking 6th in Europe and improving slightly at global level to 35th.

Oxidative stress

The oxidative (or oxidizing) stress defines the attacking of the components of the cell by active species of oxygen (ROS = Reactive Oxygen Species).

Renin-angiotensin system

The renin-angiotensin system (RAS), also termed the renin-angiotensin-aldosterone (RAAS) system, and is a complex system, governing BP and hydro-mineral equilibrium. It has recently been shown that it possesses other functions.

Adipose tissue

Tissue constituted by cells rich in lipids or adipocytes. A distinction is drawn in particular between the peripheral sub-epidemic adipose tissue and the visceral adipose tissue (intra-abdominal).

Toxin

Substance likely to injure or kill cells or the organism, which may have various origins: formed by the organism (waste), deriving from food or produced by pathogenic microorganisms, etc.

Digestive tract

The set of organs used to ingest, digest and absorb food.

Chronic therapy

Long-term. Said of a “lifelong” or long-term treatment.

27 APPENDICES

27.1 COMPANY ACCOUNTS FOR THE FINANCIAL YEAR ENDED 31 DECEMBER 2017

Balance sheet – Assets

BIOPHYTIS Balance sheet—Assets in €000s	Notes	31/12/2017 Amount	Deprec. & amort. Prov.	Net book values	31/12/2016 Net book values
Subscribed capital—uncalled					
INTANGIBLE FIXED ASSETS					
Preliminary and formation expenses					
Development costs					
Concessions, patents and similar rights	3.1	2 406	397	2 009	2 125
Other intangible fixed assets					
TANGIBLE FIXED ASSETS					
Land					
Buildings					
Industrial fixtures, fittings, plant machinery	3.1	185	55	130	69
Other tangible fixed assets	3.1	102	38	64	49
Fixed assets under construction					
Advances and prepayments					
FINANCIAL FIXED ASSETS					
Other holdings in subsidiaries and affiliates	3.2	296	296	-	-
Receivables related to shares in subsidiaries	3.2	603	603	-	-
Other long-term investments	3.2	0		0	0
TOTAL FIXED ASSETS		**3 592**	**1 390**	**2 202**	**2 244**
INVENTORIES OF PRODUCTS AND WORK IN PROGRESS					
Raw materials, supplies					
Intermediate products and finished goods					
Merchandise					
Advances and prepayments paid on orders		-	-	-	112
ACCOUNTS RECEIVABLE					
Trade accounts receivable					
Other receivables	4	3 693	372	3 321	2 581
Subscribed capital—called up, unpaid					
OTHER CURRENT ASSETS					
Marketable securities	6	138	-	138	147
Cash	6	20 026	-	20 026	3 134
ACCRUAL ACCOUNTS					
Prepaid expenses	7	235	-	235	144
TOTAL CURRENT ASSETS		**24 092**	**372**	**23 720**	**6 118**
Bond redemption premiums					
Unrealised exchange loss		25	-	25	
TOTAL ASSETS		**27 709**	**1 761**	**25 947**	**8 362**

Balance sheet – Liabilities

BIOPHYTIS Balance sheet—Liabilities in €000s	Notes	31/12/2017	31/12/2016
EQUITY			
Share capital or proprietorship account	8	2 693	1 245
Premiums arising from share issues, mergers, assets brou	8	43 727	19 123
Revaluation reserves		-	-
Legal reserve		-	-
Statutory or contractual reserves		-	-
Regulated reserves		-	-
Other reserves		-	-
Carry forward		(15 840)	(8 592)
PROFIT OR LOSS FOR THE YEAR		**(9 284)**	**(7 247)**
Investment grants		-	-
Regulated provisions		-	-
NET EQUITY		**21 296**	**4 528**
OTHER LIABLE EQUITY			
Proceeds of issues of participating stock		-	-
Contingent advances	11	966	999
TOTAL OTHER LIABLE EQUITY		**966**	**999**
PROVISIONS FOR LIABILITIES AND CHARGES			
Provisions for liabilities	10	25	-
Provisions for charges		-	-
TOTAL PROVISIONS		**25**	**-**
LIABILITIES			
Convertible bonds payable	12		
Other bonds payable			
Borrowings from and debts with lending institutions	13	23	53
Current bank liabilities		7	5
Borrowings and miscellaneous financial debts		0	0
Advances and prepayments received on orders in progress			
Trade accounts payable	14	2 401	1 918
Tax and social debts	14	1 117	721
Trade accounts payable—fixed assets	14	-	40
Other payables	14	87	54
ACCRUAL ACCOUNTS			
Deferred income	7	26	32
TOTAL LIABILITIES		**3 661**	**2 823**
Unrealised exchange profit		-	11
TOTAL LIABILITIES		**25 947**	**8 362**

Income statement

BIOPHYTIS Profit & loss statement (in €000s)	Notes	31/12/2017 12 months	31/12/2016 12 months
OPERATING INCOME			
Sale of merchandise		-	-
Production sold		-	-
NET SALES		**-**	**-**
Change in stock of finished goods and work in progress		-	-
Operating subsidies		-	10
Reversals on amortisations and provisions; expense transfers		20	12
Other income		5	0
TOTAL OPERATING INCOME		**25**	**21**
OPERATING EXPENSES			
Purchases of goods for resale		-	-
Change in inventory (merchandise)		-	-
Purchases of raw materials, supplies and other consumables		232	231
Change in inventory (raw materials and supplies)		-	-
Other purchases and external expenses		8 974	6 233
Taxes, duties, and similar levies		232	179
Salaries and appointments		1 431	1 202
Social contributions		645	552
OPERATING CHARGES			
Amortisation expense for fixed assets		167	136
Provisions on current assets		-	-
Allocations to provisions for contingencies and charges		-	-
Other charges		87	54
TOTAL OPERATING COSTS		**11 769**	**8 587**
OPERATING PROFIT OR LOSS		**(11 744)**	**(8 566)**
Financial income	17	134	59
Financial expenses	17	217	342
NET FINANCIAL INCOME		**(83)**	**(283)**
OPERATING PROFIT OR LOSS BEFORE TAX		**(11 827)**	**(8 849)**
Extraordinary income		-	-
Extraordinary expenses	18	2	2
EXTRAORDINARY NET INCOME		**(2)**	**(2)**
Employee profit-sharing			
Income taxes	19	(2 545)	(1 604)
PROFIT OR LOSS FOR THE YEAR		**(9 284)**	**(7 247)**

Notes to the financial statements

(Unless otherwise indicated, the amounts mentioned in this Annex are in euros)

Note 1: Presentation of the activity and major events

The following information constitutes the notes to the annual financial statements, which form an integral part of the annual financial statements for the financial year ended on 31 December 2017.

Each of the years presented had a duration of twelve months, covering the period from 1 January to 31 December.

The annual financial statements of Biophytis at 31 December 2017 were approved by the Board of Directors on 26 March 2018.

1.1 Information on the Company and its activity

Created in September 2006, Biophytis develops potential new classes of drugs in the treatment of degenerative diseases related to ageing, especially those affecting muscular and visual functions.

Biophytis' research focuses on the development of candidate drugs for the treatment of metabolic and age-related diseases.

Address of the registered office: 14, Avenue de l'Opéra - 75001 PARIS

Trade and Companies Register Number: 492 002 225 RCS PARIS

Form of company: joint stock company

Biophytis is referred to hereinafter as the "Company"

1.2 Significant Events

January 2017

- Grouping of the entire staff of the Company on the Jussieu campus of the Pierre and Marie Curie University (UPMC), the very first scientific partner of the Company.

March 2017

- The Company confirms the excellent pharmacokinetic profile in healthy elderly subjects, the therapeutic window of the Sarconeos product, and determines the dosages that will be used in the SARA-INT phase 2b clinical trial.

- Opening of the first clinical centres as part of the SARA-OBS observational study in Europe and start of patient recruitment.

April 2017

- Carried out a private investment of €3.7 million via the issue of 1,310,431 new shares at a price of €2.85 per share.

- Setting up of a credit facility with Bracknor Fund of up to €15 million in the form of 1,500 notes convertible into shares with share subscription warrants attached (French acronym "ORNANEBSA") with a nominal value of €10,000 each.

Mai 2017:

- Authorisation granted by US regulatory authorities to open two clinical centres and start recruitment of patients with sarcopenia in the United States.

- Issue of an initial tranche of 300 notes convertible into shares with share subscription warrants attached and 30 convertible bonds in respect of the commitment fee in favour of Bracknor Fund. Convertible bonds are accompanied by the issue of 225,225 warrants.
  These 330 bonds were fully repaid by the issue of 1,385,085 shares.

July 2017

- Issue of a second tranche of 300 convertible bonds, with a total nominal value of €3.0 million, accompanied by the issue of 205,959 warrants in favour of Bracknor Fund.
  These 300 bonds were fully repaid by the issue of 1,027,396 shares.

October 2017

- Private investment of €10.4 million with institutional investors in Europe and the United States via the issue of 1,989,000 new shares at a price of €5.25 per share.

- Authorisation obtained from the US Food and Drug Agency (FDA), to launch the phase 2b interventional study of Sarconeos for sarcopenia (SARA-INT) in the United States.

- Private investment of €7.5 million via the issue of 1,513 000 new shares at a price of €5 per share.

December 2017

- Authorisation obtained from the Belgian Federal Agency for Medicines and Health Products (FAMHP), to launch the phase 2b interventional study of the Sarconeos drug candidate for sarcopenia (SARA-INT) in Belgium.

1.3 Events subsequent to the end of the financial year

March 2018:

- Filing of an application for Sarconeos to be designated an Orphan Drug for the treatment of Duchenne muscular dystrophy (DMD), with the European Medicines Agency (EMA) and presentation of MYODA, the new clinical development programme of Sarconeos for DMD.

Note 2: Accounting principles, rules and methods

2.1 Principles for preparing the financial statements

The financial statements of BIOPHYTIS have been prepared in accordance with the standards and interpretations of the Commercial Code (Articles L123-12 to L123-28) and the general rules for preparation and presentation of financial statements (French Accounting Standards Authority (ANC) 2014-03, as amended by regulations subsequently issued by the Accounting Regulations Committee).

The basic method used to value items recorded in the accounts is the historical cost method.

The general accounting conventions were applied in observance of the principle of prudence, in accordance with the following assumptions:

- going concern basis;
- consistency of accounting methods from one financial year to another;

- independence of financial years.

For a better understanding of the financial statements presented, the major forms and methods of valuation are specified below, including when:

- a choice is offered by the law;
- an exception provided by law is used
- the application of an accounting requirement is not sufficient to give a true picture;
- there is a departure from the accounting requirements.

Going concern

Despite the loss of €9,284K for the financial year, the Board of Directors approved the accounts under the going concern assumption, taking into account the following elements to cover the future cash requirements of the Company during the next twelve months:

- Cash amounting to €20 million
- The possible use of the credit facility set up with Bracknor Fund Limited and which could give rise to additional financing of €9 million.

In order to meet its needs after that date, the Company intends to continue its search for the most appropriate financing.

2.2 Intangible fixed assets

Intangible assets consist primarily of purchased patents and trademarks.

Intangible assets are stated at their acquisition or production cost.

Fixed assets with a finite life are amortised using the straight-line method over their useful life by the Company, i.e.:

Items	Depreciation period
Purchased patents	Estimated useful life of patents (20 years) – Straight line
Software	3 to 5 years – Straight line

The value of intangible assets is tested as soon as a risk of impairment is identified. The test consists of reconciling the net book value of these assets with the future cash flows based on medium-term plans. When the net book value exceeds the value of the discounted cash flows, an impairment loss is recognised, corresponding to the difference between the sum of these flows and the net book value.

Expenditures related to the registration of patents and the research and development of products are recorded as expenses.

2.3 Tangible fixed assets

Tangible assets are valued at their acquisition cost (purchase price and accessory costs) or at their cost of production by the company.

The elements of the assets form the object of amortisation plans determined according to the actual duration of use of the asset.

The depreciation periods and methods adopted are principally the following ones:

Items	Depreciation period
Laboratory material	3 to 5 years - Straight line
Installations and fixtures	3 to 5 years - Straight line
Office and computer equipment	3 years – Straight line
Office furniture	3 to 5 years – Straight line

2.4 Financial fixed assets

Equity securities are recorded at their acquisition cost. Their value is reviewed annually by reference to their utility value, which takes account notably of the current and projected profitability of the subsidiary in question and the equity stake held. As appropriate, impairment is recorded as a provision, if the utility value falls below the acquisition cost.

Loans and receivables are assessed at their nominal value. These elements are, if necessary, written down through provisions to adjust them to their utility value on the closing date of the financial year.

2.5 Receivables

Receivables are valued at their nominal value. They are, as appropriate, written down on a case by case basis, via a provision to take account of the difficulties of recovery to which they are likely to give rise.

Other receivables include the nominal value of the research tax credit recorded in the assets for the financial year of acquisition, corresponding to the financial year during which eligible expenditures giving rise to the tax credit were generated.

Research tax credit

Research tax credits are granted to companies by the French state in order to encourage them to carry out research of a technical and scientific character. Firms whose expenditures meet the required criteria receive a tax credit that (i) may be deducted from income tax for the year in which it was granted and for the three following years, or (i) in certain circumstances, the positive difference between the tax credit and due tax may also be repaid to the Company.
If a company meets certain criteria concerning revenue, workforce, or assets that allow it to be considered as a small or medium-sized enterprise as defined by the European Union, it may request the immediate repayment of the research tax credit. Biophytis meets these criteria.

The research tax credit is presented in the income statement as a credit to the “income tax” line.

Employment Competitiveness Tax Credit

According to the ANC information note of 28 February 2013, the Employment Competitiveness Tax Credit (CICE) is recorded as a reduction in staff costs. The excess tax credit constitutes a receivable against the State which can be used for payment of the tax due for the following three years. Following the same rules as the research tax credit, the competitive employment tax credits (CICE) may be used for payment of corporation tax due for the year of realisation of expenses and for the following three years or, if appropriate, be reimbursed for its excess part.

The Company used this tax credit through its research and development efforts.

Subsidies

The subsidies received are recorded as soon as the corresponding receivable becomes certain, considering the conditions imposed by the grant.

Subsidies are registered as revenue by taking into account, as appropriate, the rythm of corresponding expenditures, in such a way as to respect the principle of matching expenses with revenues.

2.6 Marketable securities

Securities are reported among the assets at their acquisition value.
Provisions for potential impairment is determined by comparing the acquisition cost and the likely realisation value.

Liquidity Agreement
Own shares acquired within the context of the liquidity agreement implemented by the Company in July 2015 are valued at purchase price. They are compared to their likely market value and written down if necessary.

2.7 Foreign currency transactions

Expenses and foreign currencies are recorded at their current value on the transaction date.

Receivables and liabilities in foreign currencies existing on the closing date of the financial year are translated at the exchange rate in effect on that date.

The difference resulting from the conversion of foreign currency debts and receivables at this last rate is recorded in the balance under the item negative and positive “translation differences”. Negative foreign exchange differences form the object of a provision for risks and charges for an equivalent amount.

2.8 Capital increase expenses

Capital increase and contribution expenses are directly charged to the amount of the issue and contribution premiums. It is specified that the costs relating to convertible bonds are maintained as expenses (see note 2.11).

2.9 Provisions for risks and expenses

These provisions, recorded in accordance with CRC Regulation 2000-06, are intended to cover the risks and expenses that events in progress or arising render probable, the amount of which is quantifiable regarding their object, but for which the execution, maturity, or amount are uncertain.

2.10 Retirement allowance

The amount of future payments corresponding to benefits granted to employees are evaluated on an actuarial basis, adopting hypotheses about the evolution of salaries, retirement age, mortality, and then adjusting these valuations to their present value.

These commitments do not form the object of provisions but are recorded in off-balance sheet commitments.

2.11 Borrowings

Loans are stated at their nominal value.
Issuance costs for loans are immediately expensed.
Accrued interest are recorded in liabilities, at the interest rate stipulated in the agreement.

2.12 Financial Instruments - Convertible bonds

A financial instrument that does not meet the definition of shareholders' equity is classified in an intermediate heading between shareholders' equity and debt, provided that in accordance with the terms of the contract and the economic conditions of the issue, redemption of the instrument is under the exclusive control of the issuer.
Each tranche of convertible bonds is recognised at the date of issue as other equity. Issuance costs for this financial instrument are immediately expensed.

2.13 Conditional advances

Advances received from public bodies to finance research activities of the Company or for territorial commercial prospecting, for which the reimbursements are conditional, are recorded as liabilities under the heading "Conditional advances" and their characteristics are detailed in Note 11.

The operation may be resolved:

- by a success of the project resulting in the reimbursement of advances obtained according to a schedule specified in the agreement;
- or by a failure of the project, entailing a total or partial abandonment of the receivables by the body that granted this reimbursable advance. In this case, the abandonment of the receivable granted will constitute a subsidy.

In the event of a default, the agreed write-off of the receivable is recorded as a subsidy.

2.14 Research and development expenses

Research and development costs are recorded as expenses in the period in which they are incurred.

2.15 Net financial income

Net financial income principally includes:

- depreciation charges on current accounts
- interest charges linked to borrowings;
- interest received by way of term accounts;
- Gains and losses on assignments of treasury shares.

Note 3: Intangible, tangible and financial fixed assets

3.1 Intangible and tangible fixed assets

FIXED ASSETS AMORTISATION AND IMPAIRMENT (Amounts in €000s)	31/12/2016	Acquisition	Disposal	31/12/2017
Other intangible fixed assets	2 414	4	(12)	2 406
Total intangible fixed assets	**2 414**	**4**	**(12)**	**2 406**
Industrial fixtures, fittings, plant machinery and equipment	107	82	(4)	185
General installations, fixtures and fittings	45	12	(12)	44
Office, IT equipment, and furniture	47	30	(19)	58
Total tangible fixed assets	**199**	**124**	**(35)**	**287**
TOTAL	**2 613**	**128**	**(47)**	**2 693**

FIXED ASSETS AMORTISATION AND IMPAIRMENT (Amounts in €000s)	31/12/2016	Provision	Reversals	31/12/2017	Net values 31/12/2017
Other intangible fixed assets	289	120	(12)	397	2 009
Total intangible fixed assets	**289**	**120**	**(12)**	**397**	**2 009**
Industrial fixtures, fittings, plant machinery and equipment	37	22	(4)	55	130
General installations, fixtures and fittings	13	14	(12)	15	29
Office, IT equipment, and furniture	31	11	(18)	24	34
Total tangible fixed assets	**81**	**47**	**(34)**	**94**	**193**
TOTAL	**369**	**167**	**(46)**	**491**	**2 202**

3.2 Financial fixed assets

GROSS VALUE OF FIXED ASSETS (Amounts in €000s)	31/12/2016	Increases	Decreases	31/12/2017
Other holdings in subsidiaries and affiliates	296	-	-	296
Receivables related to shares in subsidiaries and affiliates	603	-	-	603
Other long-term investments	0	-	-	0
Total financial fixed assets	**899**	**-**	**-**	**899**

FIXED ASSETS AMORTISATION AND IMPAIRMENT (Amounts in €000s)	31/12/2016	Provision	Reversals	31/12/2017	Net values 31/12/2017
Other holdings in subsidiaries and affiliates	296	-	-	296	-
Receivables related to shares in subsidiaries and affiliates	603	-	-	603	-
Other long-term investments	-	-	-	-	0
Total financial fixed assets	**899**	**-**	**-**	**899**	**0**

Financial fixed assets consist of:

- equity securities and related receivables of the subsidiary Instituto Biophytis do Brasil for €295K and €603K respectively, fully depreciated in view of the lack of activity of this subsidiary since 2010;
- equity securities of the subsidiary Biophytis Inc., created in September 2015, for € 919 and fully depreciated.

Note 4: Other receivables

The tables below detail the components of “Receivables” items at 31 December 2017 and their breakdowns for maturity of up to one year or more than one year:

STATEMENTS OF RECEIVABLES (Amounts in €000s)	31/12/2017		
	Gross amount	Up to 1 year	More than 1 year
Of fixed assets			
Receivables related to shares in subsidiaries and affiliates (1)	603	-	603
Total fixed assets	**603**	**-**	**603**
Of current assets			
Government – Research Tax Credit (5)	2 549	2 549	-
Government – Business Competitiveness Tax Credit (2)	9	9	-
Value-added tax (3)	709	709	-
Group (4)	367	-	367
Accrued income	4	4	-
Other receivables	5	5	-
Accounts receivable from suppliers	49	49	-
Total current assets	**3 693**	**3 326**	**367**
Prepaid expenses	235	235	-
Overall total	**4 531**	**3 561**	**970**

(1) Receivables associated with investments correspond to receivables held against the subsidiary Biophytis Brasil

(2) In the absence of taxable income and considering its status as a Community Small and Medium-Sized Company, the Company may apply for the reimbursement of the Employment Competitiveness Tax Credit (“CICE”) in the year following its recording:

(3) VAT receivables relate mainly to deductible VAT.

(4) Group receivables relate to the subsidiary Biophytis Inc.

(5) In the absence of taxable income and considering its status as a Community Small and Medium-Sized Company, the Company may apply for the reimbursement of the Employment Competitiveness Tax Credit (“CICE”) in the year following its recording: Debt assets with respect to the Government relating to the Research Tax Credit ("CIR") consist of 2017 CIR of €2,549K which is expected to be reimbursed in 2018.

Note 5: Details of receivables

BREAKDOWN OF ACCRUED INCOME (Amounts in €000s)	31/12/2017	31/12/2016
Other receivables		
Other accrued income	4	33
Total other receivables	**4**	**33**
Overall total	**4**	**33**

Note 6: Investment securities and cash

The following table shows a detailed statement of investment securities and cash:

INVESTMENT SECURITIES AND CASH (Amounts in €000s)	31/12/2017	31/12/2016
Liquidity agreement	327	245
Term accounts	10 001	2 001
Bank accounts and cash	9 835	1 035
Total investment securities and cash	**20 163**	**3 281**

The liquidity agreement consists of:

- a cash reserve of €190K
- treasury shares for €137K.

At 31 December 2017, the Company held two term deposits maturing in January 2018, with nominal values of €7,000K and €3,000K respectively.

Liquidity Agreement

Following its IPO on the Euronext Growth market (formerly Alternext Paris), the Company signed a liquidity contract with Banque Invest Securities in order to limit the "intra-day" volatility of the Biophytis share price.
In this context, the Company provided €300K to this institution to take long and short positions on the Company's shares.

Note 7: Adjustment accounts

The amount of prepaid expenses by nature has the following breakdown:

PREPAID EXPENSES (Amounts in €000s)	31/12/2017	31/12/2016
Research services	182	100
Equipment leasing	2	2
Fees	19	18
Travel expenses	5	13
Insurance	25	7
Other	2	3
Total prepaid expenses	**235**	**144**

The amount of prepaid expenses relates only to operating expenses.

Prepaid income amounted to €26K at 31 December 2017 and consisted of the costs of fitting out UPMC premises by the Company and paid for by UPMC under the terms of the public property occupancy agreement. This revenue will be recognised in the income statement at the same rate as the amortisation of the corresponding fixed assets.

Note 8: Shareholders' equity

8.1 Change in shareholders' equity

The change in shareholders' equity for the 2016 and 2017 financial years is as follows:

BIOPHYTIS Change in shareholders' equity Amount in €000s	Capital *Number of shares*	Capital	Share premiums	Carry forward	Result	Total shareholders' equity
At 31 December 2016	***6 223 501***	**1 245**	**19 123**	**(8 592)**	**(7 247)**	**4 528**
Allocation of results 2016				(7 247)	7 247	-
Net income 2017					(9 284)	(9 284)
Capital increase	*4 812 431*	962	20 779			21 742
Conversion of bonds	*2 412 481*	482	5 818			6 300
Exercise of founder's warrants	*15 000*	3	28			31
Subscription of warrants			22			22
Expenses associated with capital increases			(2 043)			(2 043)
At 31 December 2017	***13 463 413***	**2 693**	**43 727**	**(15 840)**	**(9 284)**	**21 296**

The Company made several private investments generating a capital increase of €962K and an issue premium of €20,779K, broken down as follows:

- In April 2017:
  - Private investment of €3.2 million via the issue of 1,117,449 new shares at a price of €2.85 per share. This transaction generated a capital increase of €223K and an issue premium of €2,961K.
  - Capital increase subscribed by the management of the Company, amounting to €550K, via the issue of 192,982 new shares at a unit price of €2.85. This transaction generated a capital increase of €39K and an issue premium of €511K.

- October 2017:
  - Private placement of €10.4 million via the issue of 1,989,000 new shares at a price of €5.25 per share. This transaction generated a capital increase of €398K and an issue premium of €10,044K.
  - Private investment of €7.6 million via the issue of 1,513,000 new shares at a price of €5 per share. This transaction generated a capital increase of €303K and an issue premium of €7,262K.

In addition, 630 bonds held by Bracknor Fund Limited (see note 12) were repaid in new shares, generating the issue of 2,412,481 shares with a nominal value of €0.20, representing a capital increase of €482K and an issue premium of €5,818K.

Lastly, following the exercise of founder's warrants during the year, the share capital was increased by €3K via the issue of 15,000 new shares with a nominal value of €0.20.

8.2 Composition of the share capital and detail by categories of shares

SHARE CAPITAL COMPOSITION	31/12/2017	31/12/2016
Capital (in €000s)	2 693	1 245
Number of shares	13 463 413	6 223 501
of which Ordinary shares	13 463 413	6 223 501
Nominal value (in €000s)	0,20 €	0,20 €

Share capital was set at the amount of €2,692,682.60. It is divided into 13,463,413, shares fully subscribed and paid up, with a nominal value of €0.20.

This number is understood as excluding warrants for the subscription of shares ("BSA") and "warrants for founder's shares" ("BSPCE") granted to certain investors and to certain natural persons, whether or not employees of the Company and not yet exercised.

Capital management

The Group's policy is to maintain a solid capital base in order to preserve the confidence of investors and creditors and to sustain the future development of its activity.

In this capacity, a liquidity agreement was signed with Invest Securities. On 31 December 2017, the Company held 29,909 of its own shares.

8.3 Distribution of dividends

The Company did not distribute any dividends during the presented financial years.

Note 9: Equity instruments

9.1 Warrants for shares issued to the benefit of financial investors

Type	Date of award	Characteristics of the plans		
		Total number of warrants awarded	Date of maturity	Exercise price
Warrants$_{2015D}$	10/07/2015	**270 414**	10/07/2019	6,00 €

Type	Date of award	31/12/2016	Awarded	Exercised	Lapsed	31/12/2017	Maximum number of shares to be subscribed:
Warrants$_{2015D}$	10/07/2015	189 748				189 748	189 748
Total		**189 748**	-	-	-	**189 748**	**189 748**

9.2 Warrants

Type	Date of award	Characteristics of the plans		
		Total number of warrants awarded	Date of maturity	Exercise price
Warrants$_{2015}$	04/08/2015	**54 000**	04/08/2019	8,40 €
Warrants$_{2017}$	21/07/2017	**72 000**	21/07/2021	3,30 €

Type	Date of award	31/12/2016	Awarded	Exercised	Lapsed	31/12/2017	Maximum number of shares to be subscribed:
Warrants$_{2015}$	04/08/2015	48 000				48 000	48 000
Warrants$_{2017}$	21/07/2017		72 000			72 000	72 000 *
Total		**48 000**	**72 000**	-	-	**120 000**	**120 000**

** It being specified that these warrants are in the process of acquiring rights*

The vesting period for the issued plan is as follows:

Type	Vesting period		
Warrants$_{2015}$	1/3 to 04/08/2015	1/3 to 04/08/2016	1/3 to 04/08/2017
Warrants$_{2017}$	1/3 to 21/07/2017	1/3 to 21/07/2018	1/3 to 21/07/2019

9.3 Warrants for founder's shares

Type	Date d'attribution	Caractéristiques des plans		
		Nombre total de bons attribués	Date de maturité	Prix d'exercice
BSPCE$_{2015\text{-}1}$	22/05/2015	**195 000**	22/05/2019	2,06 €
BSPCE$_{2015\text{-}2}$	23/09/2015	**424 200**	23/09/2019	10,70 €
BSPCE$_{2015\text{-}3}$	04/12/2015	**20 000**	04/12/2019	10,70 €
BSPCE$_{2015\text{-}4}$	15/03/2016	**39 700**	15/03/2020	6,09 €
BSPCE$_{2017\text{-}1}$	21/07/2017	**227 000**	21/07/2021	3,30 €
BSPCE$_{2017\text{-}2}$	21/07/2017	**127 000**	21/07/2021	3,30 €

Type	Date of award	31/12/2016	Awarded	Exercised	Lapsed	31/12/2017	Maximum number of shares to be subscribed:
Founder's warrants$_{2015\text{-}1}$	22/05/2015	167 000		(15 000)		152 000	152 000
Founder's warrants$_{2015\text{-}2}$	23/09/2015	384 500				384 500	384 500
Founder's warrants$_{2015\text{-}3}$	04/12/2015	20 000				20 000	20 000
Founder's warrants$_{2015\text{-}4}$	15/03/2016	39 700				39 700	39 700 *
Founder's warrants$_{2017\text{-}1}$	21/07/2017		227 000			227 000	227 000 *
Founder's warrants$_{2017\text{-}2}$	21/07/2017		127 000			127 000	127 000 *
Total		**611 200**	**354 000**	**(15 000)**	-	**950 200**	**950 200**

** It being specified that certain warrants are in the process of acquiring rights*

The vesting period for the issued plans is as follows:

Type	Vesting period		
Founder's warrants$_{2015-1}$	Fully vested at the grant date		
Founder's warrants$_{2015-2}$	1/3 to 23/09/2015	1/3 to 23/09/2016	1/3 to 23/09/2017
Founder's warrants$_{2015-3}$	1/3 to 04/12/2015	1/3 to 04/12/2016	1/3 to 04/12/2017
Founder's warrants$_{2015-3}$	1/3 to 15/03/2016	1/3 to 15/03/2017	1/3 to 15/03/2018
Founder's warrants$_{2017-1}$	1/3 to 21/07/2017	1/3 to 21/07/2018	1/3 to 21/07/2019
Founder's warrants$_{2017-2}$	1/3 to 21/07/2017	1/3 to 21/07/2018	1/3 to 21/07/2019

9.4 Equity instruments awarded to directors

	Issuance and award decision	Type	Issues awarded and subscribed	Awarded and likely to be subscribed	Exercised	Exercisable at closing 31/12/2017	Exercisable under conditions	Lapsed
Stanislas VEILLET	22/05/2015	Founder's warrants	58 500			58 500	-	
	23/09/2015	Founder's warrants	198 800			198 800	-	
	21/07/2017	Founder's warrants	148 000			49 333	98 667	
	TOTAL		405 300	-	-	306 633	98 667	-
Nadine COULM	04/08/2015	Warrants	18 000			18 000	-	
	21/07/2017	Warrants	18 000			6 000	12 000	
	TOTAL		36 000	-	-	24 000	12 000	-
Marie Claire JANAILHAC FRITSCH	04/08/2015	Warrants	18 000		6 000	12 000	-	
	21/07/2017	Warrants	18 000			6 000	12 000	
	TOTAL		36 000	-	6 000	18 000	12 000	-
Jean Gérard GALVEZ	04/08/2015	Warrants	18 000			18 000	-	
	21/07/2017	Warrants	18 000			6 000	12 000	
	TOTAL		36 000	-	-	24 000	12 000	-
Jean M. FRANCHI	21/07/2017	Warrants	18 000			6 000	12 000	
	TOTAL		18 000	-	-	6 000	12 000	-

Note 10: Provisions for risks and charges

PROVISIONS (amount in €000s)	31/12/2017				
	Amount at the beginning of the year	Provision	Reversals w/ objects	Reversals w/o objects	Amount at year-end
Provision for exchange losses	-	25			25
Total provisions for risks and charges	-	25	-	-	25

Disputes and liabilities

The Company may be involved in legal, administrative or regulatory proceedings in the normal course of its activity. A provision is recorded by the Company when there is a sufficient probability that such disputes will entail costs borne by the Company.

Note 11: Contingent advances

CONTINGENT ADVANCES (Amounts in €000s)	OSEO Quinolia	OSEO Sarcob	BPI BIO 101	TOTAL
At 31 December 2016	**191**	**208**	**600**	**999**
(+) Collection		52	-	52
(-) Reimbursement	(73)	(13)	-	(86)
At 31 December 2017	**119**	**247**	**600**	**966**

OSEO reimbursable advance - "Quinolia" project

On 7 August 2008, the Company received from OSEO a non-interest-bearing reimbursable advance of €230K for the "clinical development of an extract of Quinoa active on metabolic syndrome".
Payments were scheduled between the date of signing of the agreement and the end of the project as follows:

- € 100Kon the date of signing of the agreement;
- €108K on the drawdown of funds;
- The €50K balance on completion of the project.

Since the signing of this agreement, several amendments were signed to postpone the end of the program and the reimbursement maturities:
Following the confirmation of the success of the program, an amendment was signed on 8 July 2013, relating to the fixing of the definitive amount of the aid.
Since the deferral of repayments granted by BPI France (formerly OSEO) on 30 April 2015, repayment terms are as follows:

- € 12.5K/quarter from 31 March 2016 to 31 December 2016 (4 payments)
- € 20K/quarter from 31 March 2017 to 31 December 2017 (4 payments)
- € 25K/quarter from 31 March 2018 to 31 December 2018 (4 payments)

The agreement moreover provides for payment of a reimbursement annuity starting from 1 January 2009 and at latest on 31 March of each year, corresponding to: 44% of the pre-tax proceeds, assignments or granting of licenses, patents or know-how received during the previous calendar year when such transfers or leases related to all or part of the results of the assisted program, and to 44% of the pre-tax proceeds generated by marketing and in particular, the sale to a third party or use by the beneficiary for the requirements of his own prototypes, pre-series, and models, executed within the context of the subsidised program.
The due amounts shall be attributed as a priority and for the full amount on the final deadline for payment to OSEO. The application of this mechanism shall not lead the company to pay an amount greater than the aid received.

BPI France reimbursable advance - "Sarcob" project

On 4 February 2015, Biophytis obtained from BPI France a reimbursable advance of €260K for the "in vitro, in vivo and pharmacokinetic characterisation of a drug candidate".

Payments were scheduled between the date of signing of the agreement and the end of the project as follows:

- € 100K on the date of signing of the agreement;
- € 108K on the call for funds;
- The €52K balance on completion of the project, on 26 June 2017.

Since the signing of this agreement, an amendment was signed in 2016 to postpone the end of the program and the reimbursement maturities:

Since the deferral of repayments granted by BPI France (formerly OSEO) on 07 November 2016, repayment terms are as follows:

- If successful:
  - € 6.5K/quarter from 30 June 2017 to 31 March 2018 (4 payments)
  - € 13K/quarter from 30 June 2018 to 31 March 2021 (12 payments)
  - € 19.5K/quarter from 30 June 2021 to 31 March 2022 (4 payments)
- In the event of failure or partial success:
  - € 6.5K/quarter from 30 June 2017 to 31 March 2018 (4 payments)
  - € 13K/quarter from 30 June 2018 to 30 September 2019 (6 payments)

The agreement, moreover, provides for payment of a reimbursement annuity starting from 1 January 2009 and at the latest on 31 March of each year, corresponding to: 40 % of the pre-tax proceeds, assignments or granting of licenses, patents or know-how received during the previous calendar year when such transfers or leases related to all or part of the results of the assisted program, and to 40 % of the pre-tax proceeds generated by marketing and in particular, the sale to a third party or use by the beneficiary for the requirements of his own prototypes, pre-series, and models, executed within the context of the subsidised program.
The due amounts shall be attributed as a priority and for the full amount on the final deadline for payment to BPI. The application of this mechanism shall not lead the company to pay an amount greater than the aid received.

BPI France reimbursable advance - "BIO 101" project

In July 2016, the Company received BPI France's consent for a non-interest-bearing reimbursable advance of €1,100K for the "production of clinical batches, in the preclinical regulatory phase and clinical phase 1 of BIO101, for the treatment of sarcopenic obesity".
Payments were scheduled between the date of signing of the agreement and the end of the project as follows:

- €600K on the agreement's signing date; The funds were received by the Company on 1 December 2016, net of registration expenses of €33K.
- The €500K balance on completion of the project upon request by the Company.

The contractual reimbursement dates are as follows:

- If successful: €55K/quarter from 31 December 2018 to 30 September 2023 (20 payments)
- In the event of failure or partial success: € 55K/quarter from 31 December 2018 to 30 September 2020 (8 payments)

The agreement moreover provides for payment of a reimbursement annuity starting from 1 January 2018 and at latest on 31 March of each year until 30 September 2023, corresponding to: 35.81% of the proceeds excluding taxes, assignments or granting of licenses, patents or know-how received during the previous calendar year when such transfers or leases related to all or part of the results of the assisted programme and to 35.81% of the proceeds excluding taxes generated by marketing and in particular, the sale to a third party or use by the beneficiary for the requirements of its own prototypes, pre-series and models, executed within as part of the assisted programme.
The amounts due shall be attributed first and for the full amount on the final deadline for payment to BPI. The application of this mechanism shall not lead the company to pay an amount greater than the aid received.

Note 12: Bond issues - Convertible bonds and warrants

CHANGE IN BOND LOANS (amount in €000s)	Notes convertible into shares with share subscription warrants attached
At 31 December 2016	**-**
(+) Collection	6 000
(+) Commitment fee	300
(-) Conversion	(6 300)
At 31 December 2017	**-**

On April 3, 2017, the Company signed an agreement with Bracknor Fund Limited for the issue of notes convertible into shares with share subscription warrants attached allowing a potential €15 million of funds to be raised at the discretion of the Company.

The Board of Directors shall decide on the issue of:

- An initial tranche of 300 notes convertible into shares with share subscription warrants attached and 30 convertible bonds in respect of the commitment fee on 15 May 2017
- A second tranche of 300 notes convertible into shares with share subscription warrants attached on 7 July 2017.

These tranches were fully repaid in shares during the year.

The Company may issue 900 additional warrants in favour of Bracknor Fund Limited, which may give rise to a bond issue for an additional maximum amount of €9 million provided that the previous tranche issued is fully repaid.

The convertible bonds (French acronym: ORNANE) have the following characteristics:

- Nominal value: €10K
- Maturity: 12 months
- No interest
- Conversion terms as follows: N = CA / CP where
    - N is the number of shares that can be subscribed;
    - CA is the nominal value of the convertible bonds;
    - CP is 92% (i.e., 8% discount) of the lowest of the 10 volume-weighted average daily quoted prices of the Company's stock immediately preceding the conversion request date and at least equal to the face value of the action (0.20 €).

It is also specified that the Company may repay in cash according to the following formula: (CA/CP) x Weighted average quoted price on the conversion date.
These bonds were repaid in ordinary shares during the year (see Note 8.1).

Note 13: Loans from lending institutions

CHANGE IN BORROWINGS FROM LENDING INSTITUTIONS (amount in €000s)	OSEO - Equity Loan
At 31 December 2016	**53**
(+) Collection	-
(-) Reimbursement	(30)
At 31 December 2017	**23**

OSEO - Equity Loan

On 4 November 2008, the Company obtained an equity loan from OSEO with the object of the partial financing of the innovation program.

The main features of this equity loan are:

- Nominal amount: €150K
- Duration: 8 years, of which 3 years of deferral of amortisation of principal
- Interest rate:
  - During the deferred period: Average 3-month Euribor + 3.20%/year
  - During the amortisation: Average Euribor 3-month + 5%/year
- Interest paid quarterly in arrears

Amendments were signed with the object of extending the loan and an allowance in additional capital. Since 30 April 2015, the Company has reimbursed principal as follows: €7,500/quarter from 29 February 2016 to 31 August 2018.

Note 14: Debt maturities at the end of the financial year

STATEMENTS OF LIABILITIES	31/12/2017			
(Amounts in €000s)	Gross amount	Up to 1 year	1- 5 years	Over 5 years
Contingent advances				
Contingent advances	966	226	740	-
Total contingent advances	**966**	**226**	**740**	**-**
Financial debt				
Current bank liabilities	7	7	-	-
Loans from lending institutions	23	23	-	-
Borrowings and miscellaneous financial debts	0	0	-	-
Total financial debt	**30**	**30**	**-**	**-**
Accounts payable				
Trade accounts payable	2 401	2 401	-	-
Personnel and related accounts	375	375	-	-
Social security and other social organisations	477	477	-	-
Value-added tax	192	192	-	-
Other taxes, duties, and similar payments	72	72	-	-
Other payables	87	87	-	-
Total accounts payable	**3 605**	**3 605**	**-**	**-**
Overall total	**4 600**	**3 860**	**740**	**-**

Note 15: Details of expenses payable

Expenses payable had the following breakdown for the two financial years presented:

BREAKDOWN OF ACCRUED EXPENSES (Amounts in €000s)	31/12/2017	31/12/2016
Loans from lending institutions		
Accrued interest payable	0	0
Total loans from lending institutions	**0**	**0**
Current bank liabilities		
Fees payable	7	5
Total current bank liabilities	**7**	**5**
Trade accounts payable		
Trade accounts (suppliers)—accrued invoices	859	1 070
Total trade accounts payable	**859**	**1 070**
Tax and social debts		
Personnel – Provision for paid leave	152	128
Other accrued expenses	220	112
Accrued social contributions	211	134
Government—Accrued expenses	53	30
Total taxes and social debts	**637**	**404**
Other payables	87	54
Total other payables	**87**	**54**
Overall total	**1 591**	**1 534**

Note 16: Transfer of expenses

TRANSFERS OF CHARGE (Amounts in €000s)	31/12/2017	31/12/2016
Benefits in kind granted to employees	20	12
Total transfers of charges	**20**	**12**

Note 17: Financial income and expenses

FINANCIAL INCOME (Amounts in €000s)	31/12/2017	31/12/2016
Income from interest	10	24
Proceeds on sale of treasury shares	106	35
Exchange gains	7	0
Reversal of treasury share impairment	11	-
Total financial income	**134**	**59**

FINANCIAL EXPENSES (Amounts in €000s)	31/12/2017	31/12/2016
Costs on sale of treasury shares	35	100
Provision for exchange losses	25	-
Provision for treasury share impairment	-	11
Provision for financial fixed asset impairment	-	1
Provision for current account impairment	150	222
Interest expenses	2	5
Exchange losses	4	3
Total financial expenses	**217**	**342**

Note 18: Extraordinary income and expenses

EXTRAORDINARY EXPENSES (Amounts in €000s)	31/12/2017	31/12/2016
Penalties, fines, donations	-	1
Net book value of assets sold	2	1
Total extraordinary expenses	**2**	**2**

Note 19: Income taxes

The amount recorded in the income statement under corporation tax for the 2017 financial year refers to income relating to the Research Tax Credit (CIR) and amounts to €2,545K.

The amount of the tax losses carried forward indefinitely available to the Company amounted to €34,200K at 31 December 2017.

The tax rate applicable to Biophytis is the effective rate within France, i.e. 33.33%. This rate will gradually decrease starting in 2018 and drop to 25% from 2022.

Note 20: Related parties

20.1 Remuneration of the directors (excluding equity instruments awarded)

Pursuant to Article 531-3 of the General Accounting Plan, the officers of a limited liability company with a Board of Directors are considered to be the Chairman of the Board of Directors, the CEOs and the directors who are natural or legal persons (and their permanent representatives).

No post-employment benefit is granted to members of the Board of Directors.

The remuneration due to Biophytis' officers for the financial years shown was as follows:

EXECUTIVE REMUNERATION (Amounts in €000s)	Function	31/12/2017				
		Fixed remuneration	Variable remuneration	Benefits in kind	Attendance fees	Total
Stanislas VEILLET	Chairman and Chief Executive Officer since 22 May 2015	150	50	20	-	220
Jean-Gérard GALVEZ	Member of the Board of Directors	-	-	-	24	24
Micheline KERGOAT	Member of the Board of Directors	-	-	-	-	-
Nadine COULM	Member of the Board of Directors	-	-	-	24	24
Marie-Claire JANAILHAC-FRITSCH	Member of the Board of Directors	-	-	-	24	24
Jean M. FRANCHI	Member of the Board of Directors	-	-	-	15	15
Total executive remuneration		**150**	**50**	**20**	**87**	**307**

The procedures for allocation of the variable portions are established as a function of performance criteria. For awards of equity instruments to executives, see Note 9.4.
Variable remuneration and attendance fees are paid in the year following their recognition.

20.2 Transactions with Metabrain

Metabrain is one of the principal shareholders of the Company.

Contract research services

The Company signed a contract research agreement with Metabrain on 11 July 2015, the purpose of which is to allow the Company to pursue its research and development activities within the context similar to the one previously provided by the agreement for the provision of the platform. This agreement entered into effect on 1 August 2015 for a period of twelve months. The Company committed to ordering a minimum volume of research services from Metabrain for a value of €250K net of taxes and proceeded to pay this amount on 13 July 2015, by way of a pre-reservation of Metabrain staff for the duration of the agreement. This contract was amended on 1 August 2017 to extend it for an additional period of twelve months, without further order commitments.

Under this agreement, the Company incurred a charge of €189K during the 2016 financial year and €182K during the 2017 financial year.

Note 21: Off–balance sheet commitments

21.1 Retirement allowance

Calculation methodology

The aim of the actuarial valuation is an estimate of the present value of Biophytis' commitments to severance pay for retirement provided by the collective agreements.

These allowances are not recorded as a provision in the Company's accounts of the Company but constitutes an off–balance sheet commitment.

This amount is determined on the different end dates on the basis of an actuarial valuation based on the use of the method of the projected unit credit method, taking into account staff turnover and mortality probabilities.

Actuarial hypotheses

The principal actuarial assumptions used for the evaluation of the retirement benefits are as follows:

ACTUARIAL ASSUMPTIONS	31/12/2017	31/12/2016
	Management	Management
Retirement age	Voluntary departure between 65 and 67	
Collective agreements	Pharmaceutical industry	Food retailers and wholesalers
Discount rate (IBOXX Corporates AA)	1,30%	1,31%
Mortality table	INSEE 2017	INSEE 2015
Wage revaluation rate	2%	2%
Turnover rate	Mean	Mean
Social contribution rate	45%	45%

Calculated commitments

The commitments calculated for retirement allowances had the following breakdown:

RETIREMENT BENEFITS (Amounts in €000s)	31/12/2017	31/12/2016
Amount of commitments	114	48

21.2 Commercial Leases

Property leases

Address Université Pierre et Marie Curie - 4, place Jussieu - 75005 Paris
Term 15 December 2016 – 15 December 2018, renewable by amendment
Annual fee €90,700.50 excl. tax

Expenses and commitments

Location	Real estate rental contracts	Effective start date of the lease	Lease expiry date	Rental expenses net of costs at 31/12/2017	Commitment until the next termination period		
					Up to 1 year	1- 5 years	Over 5 years
Paris	Pierre and Marie Curie University - laboratory and offices	15/12/2016	15/12/2018	78	87	-	-

21.3 Commitments by way of financial debts

Commitments received (in thousands of €)

Borrowing	Guarantees received	Nominal	Residual amount at 31/12/2017
OSEO seed capital equity loan	- OSEO innovation risk participation for up to 20% of the outstanding loan - OSEO guarantee risk participation as part of the FNG Innovation procedure for 40% of the outstanding loan. - OSEO IDF risk participation for 40% of the outstanding amount of the loan	150	23

Commitments given (in thousands of €)

Borrowing	Commitments given	Nominal	Residual amount at 31/12/2017
OSEO reimbursable advance - “Quinolia” project	The agreement provides for the payment of a reimbursement annuity starting from 1 January 2009 and at the latest on 31 March of each year, corresponding to: 44% of the proceeds excluding taxes, assignments or granting of licenses, patents or know-how received during the previous calendar year when such transfers or leases related to all or part of the results of the assisted programme and to 44% of the proceeds excluding taxes generated by marketing and in particular, the sale to a third party or use by the beneficiary for the requirements of its own prototypes, pre-series and models, executed within as part of the assissted programme. The due amounts shall be attributed as a priority and for the full amount on the final deadline for payment to OSEO. The application of this mechanism shall not lead the company to pay an amount greater than the aid received.	229	119
BPI France reimbursable advance - "BIO 101"	The agreement provides for the payment of a reimbursement annuity starting from 1 January 2018 and at the latest on 31 March of each year, until 30 September 2023, corresponding to: 35.81 % of the proceeds net of taxes, assignments or granting of licenses, patents or know-how received during the previous calendar year when such transfers or leases related to all or part of the results of the assisted program and to 35.81 % of the pre-tax proceeds generated by marketing and in particular, the sale to a third party or use by the beneficiary for the requirements of its own prototypes, pre-series and models, executed within the context of the subsidised program. The due amounts shall be attributed as a priority and for the full amount on the final deadline for payment to BPI. The application of this mechanism shall not lead the company to pay an amount greater than the aid received.	1,100*	600

* Of which €500,000 will be paid upon completion of the project

21.4 Lease financing

LEASE CREDIT (Amounts in €000s)	31/12/2017	31/12/2016
Historical cost	181	181
Amortisation:		
- aggregate amt from previous years	35	5
- amortisation during the year	36	30
Total	**71**	**35**
Royalties paid		
- aggregate amt from previous years	53	13
- royalties the year	53	39
Total	**105**	**53**
Remaining royalties to be paid		
- Within one year	53	53
- In more than one year within five years	-	53
- In more than five years	-	-
Total	**53**	**105**
Residual value		
- Within one year	45	-
- In more than one year within five years	-	45
- In more than five years	-	-
Total	**45**	**45**
Amount borne in the year	**53**	43

The lease financing agreement relates to laboratory equipment.

Note 22: Staff

Biophytis' average staff numbers during the last two financial years were as follows:

AVERAGE WORKFORCE	Financial year 2017	Financial year 2016
Management	14,4	12,1
Total average workforce	**14,4**	**12,1**

Note 23: Table of subsidiaries and holdings

TABLE OF SUBSIDIARIES AND HOLDINGS (Amounts in €000s)	Capital	Reserves and carry forward (before allocation of the profit or loss)	Share of capital held	Book value of securities held		Loans and advances made by the company (gross amount)	Profit or loss for the last financial year ended	Dividends	Observations
				Gross	Net				
INSTITUTO BIOPHYTIS DO BRASIL (Brazil)	226	(268)	94,6%	295	-	603	(3)	-	Impairment of shares in subsidiaries and affiliates: €295K Impairment on related receivables: €603K Closing rate: 3.9729 Average rate: 3.6043
BIOPHYTIS INC (United States)	0	(176)	100%	1	-	372	(189)	-	Impairment of shares in subsidiaries and affiliates: €1K Impairment of current account: €372K Closing rate: 1.1993 Average rate: 1.1294

Amount in €000s excl. tax	31/12/2017		31/12/2016	
	GRANT THORNTON	ERNST & YOUNG	GRANT THORNTON	ERNST & YOUNG
Statutory audit mission	43	45	36	38
Services other than account certification	17	17	25	261
Subtotal	**60**	**62**	**60**	**299**
Other services rendered				
- Tax	-	-	-	-
- Other	-	-	-	-
Subtotal	**-**	**-**	**-**	**-**
Total	**60**	**62**	**60**	**299**

27.2 STATUTORY AUDITOR'S REPORT ON THE 2017 ANNUAL FINANCIAL STATEMENTS

Rapport des commissaires aux comptes sur les comptes annuels

BIOPHYTIS

Exercice clos le 31 décembre 2017

At the General Assembly of Biophytis,

OPINION

In performance of the mission entrusted to us by your General Meeting, we conducted the audit of the annual financial statements or **BIOPHYTIS** for the year ended 31 December 2017, as attached to this report.

We certify that the annual financial statements provide, with regard to French accounting rules and principles, a true and fair view of the operations of the past financial year and of the financial position and assets at year end of the company.

BASIS OF OUR OPINION

Auditing framework

We have conducted our audit in accordance with professional standards applicable in France. We believe that the elements that we collected form a sufficient and appropriate basis for our opinion.

Our responsibilities under these standards are set out in the “Responsibilities of the statutory auditors relating to audit of the annual financial statements” section of this report.

Independence

We conducted our audit mission in compliance with the independence rules that apply to us, for the period from 1 January 2017 to the date of issue of our report, and in particular we have not provided services prohibited by the French Code of Ethics for Statutory Auditors.

Observation

Without calling into question the opinion expressed above, we draw your attention to: the “Going concern” paragraph presented in note 2.1, which sets forth the assumptions underlying the going concern principle.

JUSTIFICATION OF ASSESSMENTS

Pursuant to articles L. 823-9 and R. 823-7 of the French Commercial Code relating to the justification of our assessments, we inform you that the most important assessments that we have made, in our professional judgement, relate to the appropriateness of the accounting principles applied, the reasonableness of the significant estimates used and the overall presentation of the financial statements.

The assessments so made fall within the context of our audit of the annual financial statements, taken as a whole, have thus shaped our opinion expressed above. We have no observations to make on the items in these annual financial statements taken individually.

VERIFICATION OF THE MANAGEMENT REPORT AND OTHER DOCUMENTS ADDRESSED TO SHAREHOLDERS

We have also carried out the specific audits required by law, in accordance with professional standards applicable in France.

Information provided in the management report and in other documents addressed to the shareholders on the financial position and the annual financial statements

We have no observations to make as to the fair presentation and the consistency with the financial statements of the information given in the management report of the board of directors and in the other documents addressed to the shareholders on the financial position and the annual financial statements.

Information on corporate governance

We certify that the report of the Board of Directors on corporate governance contains the information required by article L. 225-37-4 of the French Commercial Code.

Other information

In application of the law, we have made sure that the information relating to the identity of the holders of the capital or the voting rights have been communicated to you in the management report.

RESPONSIBILITIES OF THE MANAGEMENT AND THE PERSONS MAKING UP THE CORPORATE GOVERNANCE RELATING TO THE ANNUAL FINANCIAL STATEMENTS

It is the responsibility of management to prepare annual financial statements that present a true and fair view in accordance with the French accounting rules and principles, as well as to implement the internal control that it deems necessary for the preparation of annual financial statements that are free of material misstatements, whether due to fraud or error.

In preparing the annual accounts, it is the responsibility of management to assess the capacity of the company to continue its operations, to present in these accounts, as the case may be, the necessary information relating to the continuity of operations and to apply the accounting policy of going concern, unless it is planned to liquidate the company or to discontinue its activity.

The annual financial statements were approved by the Board of Directors.

RESPONSIBILITIES OF THE STATUTORY AUDITORS RELATING TO THE AUDIT OF THE ANNUAL FINANCIAL STATEMENTS

It is our responsibility to prepare a report on the annual financial statements. Our objective is to obtain reasonable assurance that the annual financial statements taken as a whole are free of material misstatements. Reasonable assurance corresponds to a high level of assurance but does not guarantee that an audit performed in accordance with the standards of professional practice can automatically detect any significant misstatement. Such misstatements may arise from fraud or error and are considered material where it can reasonably be expected that they, taken individually or collectively, may influence the economic decisions that the users of the financial statements take based on these.

As stated in article L. 823-10-1 of the French Commercial Code, our auditing mission is not to guarantee the viability or the quality of the management of your company.

As part of an audit conducted in accordance with the professional standards applicable in France, the statutory auditor exercises its professional judgement throughout this audit. In addition, the statutory auditor:

- identifies and assesses the risks that the annual financial statements contain material misstatements, whether due to fraud or error, defines and implements audit procedures to address these risks, and collects information it considers sufficient and appropriate to base

its opinion. The risk of not detecting a material misstatement due to fraud is higher than that of a material misstatement resulting from an error, as the fraud may involve collusion, falsification, voluntary omissions, misrepresentation or the circumventing of internal control.

- becomes familiar with the internal control relevant to the audit in order to define audit procedures that are appropriate under the circumstances, and not to express an opinion on the effectiveness of the internal control.

- assesses the appropriateness of accounting policies used and the reasonableness of accounting estimates made by management, as well as the information concerning them provided in the annual financial statements.

- assesses the appropriateness of management's application of the going concern accounting policy and, depending on the evidence gathered, whether or not there exists significant uncertainty related to events or circumstances likely to call into question the capacity of the company to continue its operation. This assessment is based on the information gathered up to the date of its report, but it is noted that subsequent circumstances or events could jeopardise the continuity of operations. If it concludes that there is significant uncertainty, it draws the attention of the readers of its report to the information provided in the annual financial statements concerning this uncertainty or, if this information is not provided or is not relevant, it certifies the financial statements with reservations, or refuses to certify them.

- assesses the overall presentation of the annual financial statements and assesses whether the annual financial statements reflect the underlying transactions and events so as to give a true and fair view of them.

Neuilly-sur-Seine and Paris-La Défense, 25 April 2017

Les commissaires aux comptes

Grant Thornton Membre français de Grant Thornton International	Ernst & Young et Autres
Laurent Bouby Associé	Frédéric Martineau Associé

27.3 INTELLECTUAL PROPERTY

Patents

Country	Patent	Applicant/Holder	Inventor(s)	Date of application	Application No.	Date of public'n	Public'n No.	Priority date	Status	Comments
FR478/15869 - Use of phytoecdysones in the preparation of a composition to act on metabolic syndrome (Patent Family No. 1)										
FR	Use of phytoecdysones in the preparation of a composition to act on the metabolic syndrome.	Institut Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René	30/11/2007	FR0759478	05/06/2009	FR2924346		Issued (19/02/2010)	Claims modified after publication 10th annuity paid Next annuity 30/11/2017 Registration of change of name and address BIOPHYTIS 23/11/2016
WO	Use of phytoecdysones in the preparation of a composition to act on the metabolic syndrome	Institut Biophytis Pierre et Marie Curie University Veillet Stanislas Lafont René	Veillet Stanislas Lafont René	19/11/2008	WO2008FR52088	11/06/2009	WO2009071804	30/11/2007		Entered the national phase (AU, BR, CA, CN, EP, IN, JP, RU, and US)
AU	Use of phytoecdysones in the preparation of a composition to act on the metabolic syndrome	Institut Biophytis Pierre et Marie Curie University CNRS	Veillet Stanislas Lafont René	19/11/2008	AU20080332981	11/06/2009	AU2008332981	30/11/2007	Issued (25/09/2014)	9th annuity paid Next annuity 19/11/2017 Registration of change of name and address BIOPHYTIS 07/10/2016
BR	Use of phytoecdysones in the preparation of a composition to act on the metabolic syndrome	Institut Biophytis Pierre et Marie Curie University CNRS	Veillet Stanislas Lafont René Dioh Waly	19/11/2008	PI 200820455-1	29/09/2015	PI 0820455	25/06/2009	Review in progress	Information provided by the SC Firm - 9th annuity paid Next annuity 18/12/2017
CA	Use of phytoecdysones in the preparation of a composition to act on metabolic syndrome	Institut Biophytis Pierre et Marie Curie University CNRS	Veillet Stanislas Lafont René	19/11/2008	CA20082706821	11/06/2009	CA2706821	30/11/2007	Deemed as of (July 2016)	Information provided by the SC Firm
CN	Use of phytoecdysones in the preparation of a composition to act on the metabolic syndrome	Institut Biophytis Pierre et Marie Curie University CNRS	Veillet Stanislas Lafont René	19/11/2008	CN20088118514	02/11/2011	CN102231986	30/11/2007	Issued (22/01/2014)	Information provided by the SC Firm - 9th annuity paid Next annuity 19/11/2017 Registration of change of name and address BIOPHYTIS 09/11/2016
EP	Use of phytoecdysones in the preparation of a	Institut Biophytis	Veillet Stanislas Lafont René	19/11/2008	08856497.6	18/08/2010	EP2217255	30/11/2007	Review in progress,	Information provided by the SC Firm 8th annuity

Country	Patent	Applicant/Holder	Inventor(s)	Date of application	Application No.	Date of public'n	Public'n No.	Priority date	Status	Comments
	composition to act on the metabolic syndrome.	Pierre et Marie Curie University CNRS							reply to notification	paid Next annuity 19/11/2017 Registration of change of name and address BIOPHYTIS 16/11/2016
IN	Use of phytoecdysones in the preparation of a composition to act on the metabolic syndrome	Institut Biophytis Pierre et Marie Curie University CNRS	Veillet Stanislas Lafont René Dioh Waly	19/11/2008	3976/DELNP/2010	11/11/2011	452011	30/11/2007	Review in progress (15/12/2016)	Information provided by the SC Firm Annuities paid on issue
JP	Use of phytoecdysones in the preparation of a composition to act on the metabolic syndrome.			19/11/2008	JP20100535430	17/02/2011	JP2011504921	30/11/2007	Decision to reject (17/02/2014)	
RU	Using phytoecdysones and preparing compositions for treating the metabolic syndrome	Institut Biophytis Pierre et Marie Curie University CNRS	Veillet Stanislas Lafont René	19/11/2008	RU20100126625	10/01/2012	RU2010126625	30/11/2007	Issued (27/08/2013)	Information provided by the SC Firm 8th Annuity Paid Next Annuity 19/11/2016 Not verifiable
US	Use of phytoecdysones in the preparation of a composition for acting on the metabolic syndrome	Institut Biophytis Pierre et Marie Curie University CNRS	Veillet Stanislas Lafont René	19/11/2008	US20080745315	10/02/2011	US2011033561	30/11/2007	Issued (07/08/2012)	Information provided by the SC Firm Annuity paid Next annuity between 03/11/2018 and 07/08/2019 Registration of change of name and address BIOPHYTIS 06/09/2016
FR280/24498 – Phytoecdysones for use in weight stabilisation after a weight-loss diet (Patent Family No. 2)										
FR	Phytoecdysones for use in weight stabilisation after a weight-loss diet	Institut Biophytis	Lafont René Clement Karine Rizkalla Salwa Veillet Stanislas Foucault Anne-Sophie Dioh Waly	10/11/2011	FR1160280	17/05/2013	FR2982489		Issued (27/12/2013)	6th Annuity Paid Next Annuity 30/11/2017 Pending assignment document to register the joint ownership with the UPMC Registration of change of name and address BIOPHYTIS 23/11/2016

Country	Patent	Applicant/Holder	Inventor(s)	Date of application	Application No.	Date of public'n	Public'n No.	Priority date	Status	Comments
WO	Phytoecdysones for use in weight stabilisation after a weight-loss diet	Institut Biophytis Pierre et Marie Curie University	Lafont René Clement Karine Rizkalla Salwa Veillet Stanislas Foucault Anne-Sophie Dioh Waly	12/11/2012	WO2012FR52600	16/05/2013	WO2013068704	10/11/2012		Entered the national phase (AU, BR, CA, CN, EP, IN, JP, RU, and US)
CN	Phytoecdysones for use in weight stabilisation after a weight-loss diet	Institut Biophytis Pierre et Marie Curie University	Lafont René Clement Karine Rizkalla Salwa Veillet Stanislas Foucault Anne-Sophie Dioh Waly	12/11/2012	CN201200855214.8	30/07/2014	CN103957727	10/11/2012	Issued (14/09/2016)	Information provided by the SC Firm - Annuities paid on issue
EP	Phytoecdysones for use in weight stabilisation after a weight-loss diet	Institut Biophytis Pierre et Marie Curie University	Lafont René Clement Karine Rizkalla Salwa Veillet Stanislas Foucault Anne-Sophie Dioh Waly	12/11/2012	12795522.7	17/09/2014	EP2775859	10/11/2012	Issued (18/01/2017) Designation of European contracting countries	5th Annuity Paid Next Annuity 30/11/2017 Registration of change of name and address BIOPHYTIS 16/11/2016
JP	Phytoecdysones for use in weight stabilisation after a weight-loss diet			12/11/2012	JP2014-540542	11/12/2014	JP2014-533256	10/11/2012	Modifications (23/01/2017)	Information provided by the SC Firm - Annuities paid on issue
US	Phytoecdysones for use in weight stabilisation after a weight-loss diet	Institut Biophytis Pierre et Marie Curie University	Lafont René Clement Karine Rizkalla Salwa Veillet Stanislas Foucault Anne-Sophie Dioh Waly	12/11/2012	US201214356646	16/10/2014	US20140309203	10/11/2012	Non-final action mailed (18/08/2016)	Information provided by the SC Firm - surrendered but continued with new US01 patent below
US01	Phytoecdysones for use in weight stabilisation after a weight-loss diet	Institut Biophytis Pierre et Marie Curie University	Lafont René Clement Karine Rizkalla Salwa Veillet Stanislas Foucault Anne-Sophie Dioh Waly	12/11/2012	US2015359477			US01	Continuation	Information provided by the SC Firm - Annuities paid on issue
FR519 / 24479 - Phytoecdysones for use in improving the muscle quality of obese and/or sarcopenic mammals (Patent Family No. 3)										
FR	Phytoecdysones for use in improving the muscle quality	Institut Biophytis	Veillet Stanislas Lafont René	13/12/2011	FR1161519	14/06/2013	FR2983733		Awaiting issuance	Amended claims after publication 6th annuity

Country	Patent	Applicant/Holder	Inventor(s)	Date of application	Application No.	Date of public'n	Public'n No.	Priority date	Status	Comments
	of obese and/or sarcopenic mammals		Foucault Anne-Sophie Dioh Waly Quigniart-Boulange Annie							paid Next annuity 02/01/2018 Registration of change of name and address BIOPHYTIS 23/11/2016
WO	Phytoecdysones for use in improving the muscle quality of obese and/or sarcopenic mammals	Institut Biophytis Pierre et Marie Curie University National Institute of Agricultural Research	Veillet Stanislas Lafont René Foucault Anne-Sophie Dioh Waly Quigniart-Boulange Annie	13/12/2012	WO2012FR52931	20/06/2013	WO2013088084	13/12/2011		Entered the national phase (BR CN EP US)
BR	Phytoecdysones for use in improving the muscle quality of obese and/or sarcopenic mammals	Institut Biophytis Pierre et Marie Curie University National Institute of Agricultural Research	Veillet Stanislas Lafont René Foucault Anne-Sophie Dioh Waly Quigniart-Boulange Annie	13/12/2012	BR 112014014520	19/08/2014				Patent application managed by the Ariboni firm
CN	Phytoecdysones for use in improving the muscle quality of obese and/or sarcopenic mammals	Institut Biophytis Pierre et Marie Curie University National Institute of Agricultural Research	Veillet Stanislas Lafont René Foucault Anne-Sophie Dioh Waly Quigniart-Boulange Annie	13/12/2012	CN201280066803	08/10/2014	CN104093409	13/12/2011	Awaiting issuance (03/05/2017)	Information provided by the SC Firm - Annuities paid on issue Registration of change of name and address BIOPHYTIS 09/11/2016
EP	Phytoecdysones for use in improving the muscle quality of obese and/or sarcopenic mammals	Institut Biophytis Pierre et Marie Curie University National Institute of Agricultural Research	Veillet Stanislas Lafont René Foucault Anne-Sophie Dioh Waly Quigniart-Boulange Annie	13/12/2012	12813926.8	22/10/2014	EP2790706	13/12/2011	Examination report sent Observations by a third party (23/09/2016)	5th Annuity Paid Next Annuity 02/01/2018 Registration of change of name and address BIOPHYTIS 16/11/2016
US	Phytoecdysones for use in improving the muscle quality of obese and/or sarcopenic mammals	Institut Biophytis Pierre et Marie Curie University National Institute of Agricultural Research	Veillet Stanislas Lafont René Foucault Anne-Sophie Dioh Waly Quigniart-Boulange Annie	13/12/2012	US201214364249	09/04/2015	US2015099022	13/12/2011	Non-final action mailed (03/10/2016)	Information provided by the SC Firm – but continued with new US01 patent below

Country	Patent	Applicant/Holder	Inventor(s)	Date of application	Application No.	Date of public'n	Public'n No.	Priority date	Status	Comments
US01	Phytoecdysones for use in improving the muscle quality of obese and/or sarcopenic mammals	Institut Biophytis Pierre et Marie Curie University National Institute of Agricultural Research	Veillet Stanislas Lafont René Foucault Anne-Sophie Dioh Waly Quigniart-Boulange Annie						Continuation	Information provided by the SC Firm - Annuities paid on issue
FR538/30588 - Products derived from 20-hydroxyecdysones and their use in the preparation of medicines (Patent Family No. 4)										
FR	Products derived from 20-hydroxyecdysones and their use in the preparation of medicines	Institut Biophytis	Veillet Stanislas Lafont René Raynal Sophie Lepifre Franck Durand Jean-Denis Dioh Waly	20/05/2014	FR1454538	27/11/2015	FR3021318		Publication of the research report (27/11/2015)	3th Annuity Paid Next Annuity 31/05/2017 Registration in the RNB of the sale of Metabrain Research and the UPMC to Biophytis (08/02/2016 No. 0209914 BOPI 16/11) Registration of change of name and address BIOPHYTIS 23/11/2016
WO	Chemical compounds and use thereof for improving muscular quality	Institut Biophytis	Veillet Stanislas Lafont René Raynal Sophie Lepifre Franck Durand Jean-Denis Dioh Waly	20/05/2015	WO2015FR51332	26/11/2015	WO2015177469	20/05/2014		Registration in the RIB of the sale of Metabrain Research to Biophytis in progress (December 2015) Entered the national phase: AU, BR, CA, EP (IL tbc)
AU	Chemical compounds and use thereof for improving muscular quality	Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Raynal Sophie Lepifre Franck Durand Jean-Denis Dioh Waly	20/05/2015	AU201563121	12/01/2017	AU201563121	20/05/2014	Submitted	3rd Annuity Paid Next Annuity 20/05/2019
BR	Chemical compounds and use thereof for improving muscular quality	Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Raynal Sophie Lepifre Franck	20/05/2015	BR112016027053			20/05/2014	Submitted	3rd Annuity Paid Next Annuity 17/01/2018 Awaiting signed powers - Information provided by SC

Country	Patent	Applicant/Holder	Inventor(s)	Date of application	Application No.	Date of public'n	Public'n No.	Priority date	Status	Comments
			Durand Jean-Denis Dioh Waly							
CA	Chemical compounds and use thereof for improving muscular quality	Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Raynal Sophie Lepifre Franck Durand Jean-Denis Dioh Waly	20/05/2015	CA2949649			20/05/2014	Submitted	2nd Annuity Paid Next Annuity 23/05/2017
CN	Chemical compounds and use thereof for improving muscular quality	Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Raynal Sophie Lepifre Franck Durand Jean-Denis Dioh Waly	20/05/2015				20/05/2014	Submitted	Awaiting signed powers - Information provided by SC
EP	Chemical compounds and their use for improving muscular quality	Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Raynal Sophie Lepifre Franck Durand Jean-Denis Dioh Waly	20/05/2015	15732785.9			20/05/2014	Under review (14/03/2017)	Basic taxes paid
IL	Chemical compounds and use thereof for improving muscular quality	Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Raynal Sophie Lepifre Franck Durand Jean-Denis Dioh Waly	20/05/2015						Awaiting signed powers - Information provided by SC
IN	Chemical compounds and use thereof for improving muscular quality	Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Raynal Sophie Lepifre Franck Durand Jean-Denis Dioh Waly	20/05/2015					Examination to be requested on 20/05/2018	Awaiting signed powers - Information provided by SC

Country	Patent	Applicant/Holder	Inventor(s)	Date of application	Application No.	Date of public'n	Public'n No.	Priority date	Status	Comments
JP	Chemical compounds and use thereof for improving muscular quality	Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Raynal Sophie Lepifre Franck Durand Jean-Denis Dioh Waly	20/05/2015					Examination to be requested on 20/05/2018	Awaiting signed powers - Information provided by SC
KR	Chemical compounds and use thereof for improving muscular quality	Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Raynal Sophie Lepifre Franck Durand Jean-Denis Dioh Waly	20/05/2015	10 -2016 -7035614				Examination to be requested on 20/05/2020	Awaiting signed powers - Information provided by SC
RU	Chemical compounds and use thereof for improving muscular quality	Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Raynal Sophie Lepifre Franck Durand Jean-Denis Dioh Waly	20/05/2015	201649619				Examination to be requested on 20/05/2018	Awaiting signed powers - Information provided by SC
US	Chemical compounds and use thereof for improving muscular quality	Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Raynal Sophie Lepifre Franck Durand Jean-Denis Dioh Waly	20/05/2015	2015311967				Examination to be requested on 20/05/2018	Awaiting signed powers - Information provided by SC
FR775/32484 - Pharmaceutical grade 20-hydroxyecdysone extract, its use and preparation (Patent Family No. 5)										
FR	Pharmaceutical grade 20-hydroxyecdysone extract, its use and preparation	Biophytis	Lafont René Dilda Pierre Dioh Waly Dupont Philippe Del Signore Susanna Veillet Stanislas	28/04/2017	FR1753775					Information provided by the IPSIDE firm
FR354 / 22990 - Food composition for protection from the sun (Patent Family No. 6)										
FR	Food composition for protection from the sun	Institut Biophytis	Veillet Stanislas Lafont René Dioh Waly	25/06/2009	FR0954354	31/12/2010	FR2947173		Issued (27/01/2012)	8th Annuity Paid Next Annuity 30/06/2017

Country	Patent	Applicant/Holder	Inventor(s)	Date of application	Application No.	Date of public'n	Public'n No.	Priority date	Status	Comments
										Registration of change of name and address BIOPHYTIS 23/11/2016
FR (divisional application)	Food composition for protection from the sun	Institut Biophytis	Veillet Stanislas Lafont René Dioh Waly	10/05/2011	FR1153996	05/08/2011	FR2955767	25/06/2009	Issued (16/08/2013)	8th Annuity Paid Next Annuity 30/06/2017 Registration of change of name and address BIOPHYTIS 23/11/2016
WO	Composition for protection from the sun	Institut Biophytis Veillet Stanislas Lafont René Dioh Waly	Veillet Stanislas Lafont René Dioh Waly	25/06/2010	WO2010FR51323	29/12/2010	WO2010149942	25/06/2009		Entered the national phase (AU, EP, US)
AU	Composition for protection from the sun	Institut Biophytis	Veillet Stanislas Lafont René Dioh Waly	25/06/2010	AU20100264314	23/02/2012	AU2010264314	25/06/2009	Surrendered (19/02/2015)	
BR	Composition for protection from the sun		Veillet Stanislas Lafont René Dioh Waly	25/06/2010	PI 201010113-6	15/03/2016	PI1010113-6	25/06/2009	Under review (10/01/2017)	Information provided by the SC Firm - 7th annuity paid Next annuity 22/07/2016
EP	Composition for protection from the sun	Institut Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Dioh Waly	25/06/2010	10745340.9	02/05/2012	EP2445476	25/06/2009	Review in progress (17/02/2017)	7th Annuity Paid Next Annuity 25/06/2017 Registration of change of name and address BIOPHYTIS 16/11/2016
US	Preparation for sun protection	Institut Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Dioh Waly	25/06/2010	US201013380768	14/06/2012	US2012149776	25/06/2009	Issued (03/11/2015)	Information provided by the SC Firm Annuity paid Next annuity between 03/11/2018 and 04/05/2019 Registration of change of name and address BIOPHYTIS 30/11/2016
FR172/25506 - Use of compounds and composition for the treatment of age-related macular degeneration (AMD) (Patent Family No. 7)										
FR	Use of compounds and composition for the treatment of age-related macular degeneration (AMD)	Institut Biophytis	Veillet Stanislas Lafont René Fontaine Valérie Sahel José-Alain	13/05/2011	FR1154172	16/11/2012	FR2975008		Issued (07/03/2014)	Claims modified after publication 6th Annuity Paid Next Annuity 31/05/2017 Registration of change of name and address BIOPHYTIS 23/11/2016

Country	Patent	Applicant/Holder	Inventor(s)	Date of application	Application No.	Date of public'n	Public'n No.	Priority date	Status	Comments
FR (divisional application)	Use of compounds and composition for the treatment of age-related macular degeneration (AMD)	Institut Biophytis	Veillet Stanislas Lafont René Fontaine Valérie Sahel José-Alain	15/11/2013	FR1361229	18/04/2014	FR2996773		Issued (05/08/2016)	6th Annuity Paid Next Annuity 31/05/2017 Registration of legal form and name BIOPHYTIS 23/11/2016
WO	Bixa Orellana composition for treating macular degeneration	Institut Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Fontaine Valérie Sahel José-Alain	14/05/2012	WO2012FR00193	22/11/2012	WO2012156600	13/05/2011		Entered the national phase (BR, EP, JP, US)
BR	Bixa Orellana composition for treating macular degeneration	Institut Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Fontaine Valérie Sahel José-Alain	14/05/2012	BR 112013029318-7	13/05/2014		13/05/2011	Awaiting review	Information provided by the SC Firm - 5th annuity paid Next annuity 10/06/2017
EP	Bixa Orellana composition for treating macular degeneration	Institut Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Fontaine Valérie Sahel José-Alain	14/05/2012	12728639.1	16/04/2014	EP2717891	13/05/2011	Issued (14/09/2016) AT BE CH CZ EE ES FI FR GB HR HU IT LU NL NO PT SK TR	5th Annuity Paid Next Annuity 31/05/2017 Registration of change of name and address BIOPHYTIS 23/11/2016
JP	Use of compounds and composition for the treatment of age-related macular degeneration (AMD)	Institut Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Fontaine Valérie Sahel José-Alain	14/05/2012	JP20140510851	19/06/2014	JP2014514366	13/05/2011	Final rejection (20/02/2017)	Information provided by the SC Firm - Completed by divisional application below
JP01	Use of compounds and composition for the treatment of age-related macular degeneration (AMD)	Institut Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Fontaine Valérie Sahel José-Alain	17/02/2017	JP201727851					Information provided by the SC Firm - Annuities paid on issue
US	Bixa Orellana composition for treating macular degeneration	Institut Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Fontaine Valérie Sahel José-Alain	14/05/2012	US201214117461	30/10/2014	US20140322371	13/05/2011	Decision to reject (03/05/2017)	Information provided by the SC Firm - Annuities paid on issue Registration of change of name and address BIOPHYTIS 06/09/2016
FR397 / 30891 - Composition for protecting cells of the retinal pigment epithelium (Patent Family No. 8)										

Country	Patent	Applicant/Holder	Inventor(s)	Date of application	Application No.	Date of public'n	Public'n No.	Priority date	Status	Comments
FR	Composition for protecting cells of the retinal pigment epithelium	Institut Biophytis Pierre et Marie Curie University Iris Pharma	Veillet Stanislas Lafont René Sahel José-Alain Fontaine Valérie Elena Pierre-Paul	30/04/2015	FR1553957	04/11/2016	FR3035589		Awaiting issuance	Information provided by the SC Firm - 2nd annuity paid Next annuity 02/05/2017 Registration in the RNB of the sale of Iris Pharma 22/12/2016
WO	Composition containing Norbixin for protecting cells of the retinal pigment epithelium	Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Sahel José-Alain Fontaine Valérie Elena Pierre-Paul	28/04/2016	WO2016FR51001	03/11/2016	WO2016174360	30/04/2015	Application published	EP designated
FR761/[135] - Use of 3-deoxhyanthocyanidins for treating ocular diseases (Patent Family No. 9)										
FR	Use of 3-deoxhyanthocyanidins for treating ocular diseases	Biophytis Pierre et Marie Curie University	Veillet Stanislas Lafont René Sahel José-Alain Fontaine Valérie	27/05/2015	FR1554761	02/12/2016	FR3036620		Issue in progress	Information provided by the firm ICOSA 3rd Annuity Paid Next Annuity 31/05/2018
WO	Use of 3-deoxhyanthocyanidins for treating ocular diseases	Biophytis Pierre et Marie Curie University CNRS INSERM	Veillet Stanislas Lafont René Sahel José-Alain Fontaine Valérie	27/05/2016	WO2016FR51262	01/12/2016	WO2016189260	27/05/2016	Application published	EP designated (due date: 27/11/2017

[135] In the process of referencing

INVENTIONS IN PROGRESS – KNOW-HOW

Country	Patent	Applicant	Inventor(s)	Date of application	Application No.	Date of public'n	Public'n No.	Priority date	Status	Comments
Anthocyanidin derivatives										
France									In the process of being drafted	
Food composition										
France									In the process of being drafted	

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