biophytis

NEW THERAPEUTICS FOR AGING DISEASES

Annual Report 2016

THE DISEASE OF AGING BIOTECH COMPANY

Société Anonyme [Limited Liability Company] with a Board of Directors with a share capital of € 1,989,282.60
Registered office: 14, avenue de l'Opéra - 75001 PARIS
Trade and Companies Register (RCS) of Paris 492 002 225

2016 REFERENCE DOCUMENT

AMF AUTORITÉ DES MARCHÉS FINANCIERS

This document is a free non- binding translation, for information purposes only, of the French language "Document de Référence 2016" as submitted to the AMF on July 28, 2017. 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, in particular Article 212-13, this reference document has been filed with the French Autorité des marchés financiers (the "**AMF**") on July 28, 2017 under number R. 17-060. 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

What is your assessment of the year 2016?

2016 was another year of major progress for Biophytis, we launched an ambitious clinical program in Europe and the United States creating value for our drug candidates: Sarconeos for sarcopenia and Macuneos for AMD. SARA-PK was successfully completed and produced very promising results for Sarconeos. A network of clinical centres has been set up in Europe and the United States to conduct the phase-2b SARA-INT interventional study. The authorisations necessary to initiate the SARA-OBS pre-recruitment study of sarcopenic patients have been obtained. As for Macuneos, we began production of clinical batches. Finally, we further strengthened our scientific capacity by bringing our teams closer to our partners: The Institute of Biology Paris Seine, the Institute of Myology, and the Institute of Vision. Biophytis presented a total of 6 papers at the ICFSR, SCWD, and ARVO conferences. From early 2017, we strengthened the Company's financial position, in order to focus on this year's goals of carrying out the phase-2b SARA and MACA clinical programmes.

Is Biophytis the only company of its kind operating in the field of age-related diseases?

Biophytis is, to our knowledge, the only biotech specifically targeting degenerative diseases related to ageing. This is probably why the phase-2b SARA and MACA clinical programmes are at the forefront of two increasingly prevalent diseases for which there is no treatment available. For Sarconeos, a first-in-class candidate in sarcopenia, SARA is the first clinical programme to improve mobility. For Macuneos, a first-in-class candidate in dry AMD, MACA is the first program targeting the intermediate form of the disease.

Has Sarconeos confirmed its potential in the treatment of sarcopenia?

Regarding Sarconeos, our drug candidate in sarcopenia, the SARA-PK study has (i) demonstrated a change in pharmacodynamic parameters consistent with the mechanism of action, (ii) confirmed the safety of Sarconeos, (iii) allowed determining the range of doses to be administered in the interventional study (SARA-INT), and (iv) determined Sarconeos pharmacokinetic parameters for the elderly. The SARA-OBS study, which is currently underway, will allow a better characterisation of the sarcopenic patients who will be recruited later in the interventional study (SARA-INT). 300 patients will be monitored for 6 months in 8 clinical centres in the United States and Europe. Patients over the age of 65 are recruited according to the criteria defined by the Foundation for the National Institutes of Health: An appendicular lean mass to body mass index (ALMBMI) ratio under 0.8 for men, and under 0.5 for women, and loss of mobility, determined by a score under 8 in the Short Physical Performance Battery Index (SPPB ≤ 8). The main criteria of the measurements include the 6-minute walking test and the 400-metre test. Finally, the interventional study (SARA-INT) will be conducted in the centres already open for SARA-OBS, as well as in additional centres. SARA-INT will evaluate the efficacy of Sarconeos in 333 sarcopenic patients treated for 6 months.

Do you believe that it will be possible to test Macuneos in patients with AMD by 2018?

Concerning Macuneos, our candidate drug in AMD, a new clinical-regulatory protocol was designed that aims to obtain data of clinical activity by 2018. Consequently, the MACA-INT interventional study is expected to start in the second half of 2018, a year later than was expected in 2016, but it will be based on clinical activity data and on a perfectly characterised patient sample. Preparatory phase 2b includes a pharmacokinetic and safety study in healthy volunteers and elderly patients with intermediate AMD (MACA-PK study). First of all, as part of a SAD scheduled for the second half of 2017, healthy volunteers over 55 years of age receive a series of single ascending doses of Macuneos. Then, the 3 doses will be successively tested in MAD for 28 days in patients with AMD during the first half of 2018. This study includes the assessment of several pharmacodynamic parameters including ERG (Electro-RetinoGram), adaptation to darkness, contrast sensitivity, and visual acuity. Finally, a follow-up period of 2 months will be proposed to the patient groups that have been tested with MAD, subject to approval by the regulatory authorities. It is expected to be completed in the second half of 2018. The advantage of this new MACA-PK clinical design is that it offers the opportunity to evaluate the effects of Macuneos as early as 2018, prior to the launch of the interventional phase on pharmacodynamic parameters in patients with AMD. Another preparatory study, MACA-OBS, will aim to better characterise the target population of patients with intermediate dry AMD, and to reduce recruitment time in major centres in Europe and the United States. The applications for the approval of the MACA-INT interventional study in Europe (IMPD Ph2) and in the United States (IND Ph2) should be submitted in the second half of 2018. MACA-INT will involve approximately twenty clinical investigation centres in Europe and the United States, include 300 patients, and have as its main criterion the progression of the size of the atrophic geometry measured by autofluorescence of the back of the eye.

Would you be interested in co-developing Sarconeos or Macuneos with industrial partners?

Our priority today is to continue developing our drug candidates Sarconeos and Macuneos until their clinical activity in patients is demonstrated for the main targeted indications. We do not plan to market these medicines directly; we will choose the best partners at the right time to co-develop our two drug candidates when we receive our marketing authorisations, once evidence of their clinical activity has been established, in 2018 at the earliest.

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GENERAL COMMENTS

Definitions

In this reference document, 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 reference document:

- The accounts prepared in accordance with International Financial Reporting Standards (IFRS) and the annual financial statements for the year ended 31 December 2015, presented on pages 192 and 288, and the associated Statutory Auditor's report, presented on page Reference Document filed with the AMF on 28 April 2016 under the number R.16-036.

- The accounts prepared in accordance with IFRS standards for the years ended 31 December 2014 and 31 December 2013, presented on page 181, and the associated Statutory Auditor's report, presented on the basic document filed with the AMF on 18 June 2015 under the number I.15-0055.

Warning

This reference document contains information on the Company's activity, as well as on the market within which it operates. This information derives 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 reference document also contains information on the objectives and lines of development of the Company. These indications are sometimes identified by the use of the future or conditional tenses and of terms with a prospective character, 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 reference document could prove erroneous without the Company being subject in any way to an obligation of updating, subject to the applicable regulation, notably the General Regulations of the French Financial Markets Authority (the "**AMF"**).

Investors are also invited to consider the risk factors described in section 4 "Risk factors" of this reference document 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 reference document.

1. RESPONSIBLE PERSONS

1.1. PERSON RESPONSIBLE FOR THE REFERENCE DOCUMENT

Mr. Stanislas Veillet,
Chairman/CEO

1.2. DECLARATION BY THE RESPONSIBLE PERSON

Paris, 28 July 2017

"I hereby certify, having taken all reasonable measures to this effect, that the information contained in this Reference Document 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 Reference Document and have read the whole of the reference Document.

The historical financial information presented in this document has been the subject of the reports of the statutory auditor.
The report on the financial statements prepared in accordance with the IFRS standards, as adopted by the European Union, for the 2016 fiscal year contains an observation." *

1.3. PERSON RESPONSIBLE FOR FINANCIAL INFORMATION

Mr. Jean-Christophe Montigny
Administrative and financial director
Address: UPMC 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 Meeting of Shareholders ruling 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 Meeting of Shareholders ruling 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 Meeting of Shareholders ruling 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 Meeting of Shareholders ruling 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 2016, appearing in section 20.1 "Consolidated financial statements drawn up in accordance with IFRS standards for the financial year ended 31 December 2016" of the Reference Document.

This 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	**31/12/2015**	**31/12/2016**
TOTAL ASSETS	**13,542**	**8,393**
Non-current assets	**2,710**	**2,501**
o/w intangible fixed assets	*2,244*	*2,125*
o/w tangible fixed assets	*194*	*276*
o/w other non-current financial assets	*272*	*99*
Current assets	**10,831**	**5,892**
o/w other receivables	*1,422*	*2,827*
o/w cash and cash equivalents	*9,409*	*3,066*
TOTAL LIABILITIES	**13,542**	**8,393**
Total shareholders' funds	**11,598**	**4,519**
Equity, group's share	*11,629*	*4,549*
Interests not conferring control	*(31)*	*(30)*
Non-current liabilities	**428**	**962**
o/w commitments to staff	*25*	*48*
o/w non-current financial debts	*403*	*913*
Current liabilities	**1,515**	**2,913**
o/w current financial debts	*399*	*176*
o/w supplier debts and associated accounts	*701*	*1,920*
o/w tax and social debts	*361*	*722*
o/w other creditors and miscellaneous debts	*54*	*94*

Simplified income statement in thousands of euros IFRS Standards	**31/12/2015**	**31/12/2016**
Operating income	**532**	**1,667**
o/w net revenues	-	-
Operating expenses	**(5,575)**	**(9,609)**
Net operating profit	**(5,043)**	**(7 942)**
Net profit	**(5 233)**	**(7 954)**
Net earnings per share	*(1,08)*	*(1,28)*

Simplified cash flow statements in thousands of euros IFRS	**31/12/2015**	**31/12/2016**
Cash flows linked to operating activities	**(3 301)**	**(6 633)**
O/w internal financing capacity	*(2,565)*	*(6,848)*
(-) Including change in working capital requirements (WCR)	*736*	*(216)*
Cash flows linked to investment activities	**(6)**	**(129)**
Cash flows linked to financing activities	**12 705**	**407**
Effect of variations in foreign exchange rates	2	12
Change in cash and cash equivalents	**9 400**	**(6 343)**
Opening cash and cash equivalents	9	9,409
Closing cash and cash equivalents	9,409	3,066

Level of net indebtedness in thousands of euros IFRS Standards	**31/12/2015**	**31/12/2016**
+ Non-current financial debts	403	913
+ Current financial debts	399	176
- Cash and cash equivalents	(9 409)	(3 066)
Total net indebtedness	**(8 607)**	**(1 977)**

4. RISK FACTORS

Investors are encouraged to consider all of the information in this reference document, 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 reference document, 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 reference document, 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.
The two product technologies under development involve both types of pathologies: sarcopenia (degeneration of skeletal muscles) and AMD (age-related macular degeneration).

The company has concentrated the essential part of its investments on the development of two products: Sarconeos (sarcopenia) and Macuneos (dry AMD), which are under clinical development. Moreover, the company has extended its research by establishing the second generation of products, BIO103 (sarcopenia) and BIO203 (AMD), which are under preclinical 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 Reference Document, 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 2018, 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 co-contractors 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 will be necessary to obtain the 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 the invoking of 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
4.4.6		Risks relating to loss of or changes to the status of Young Innovative Company

Paragraphs	Types of risk	Risks
4.4.7		Risks linked to changes of accounting methods for the company accounts
4.5	INSURANCE AND RISK COVERAGE	
4.6.1	MARKET RISK	Liquidity risks
4.6.2		Currency risks
4.6.3		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

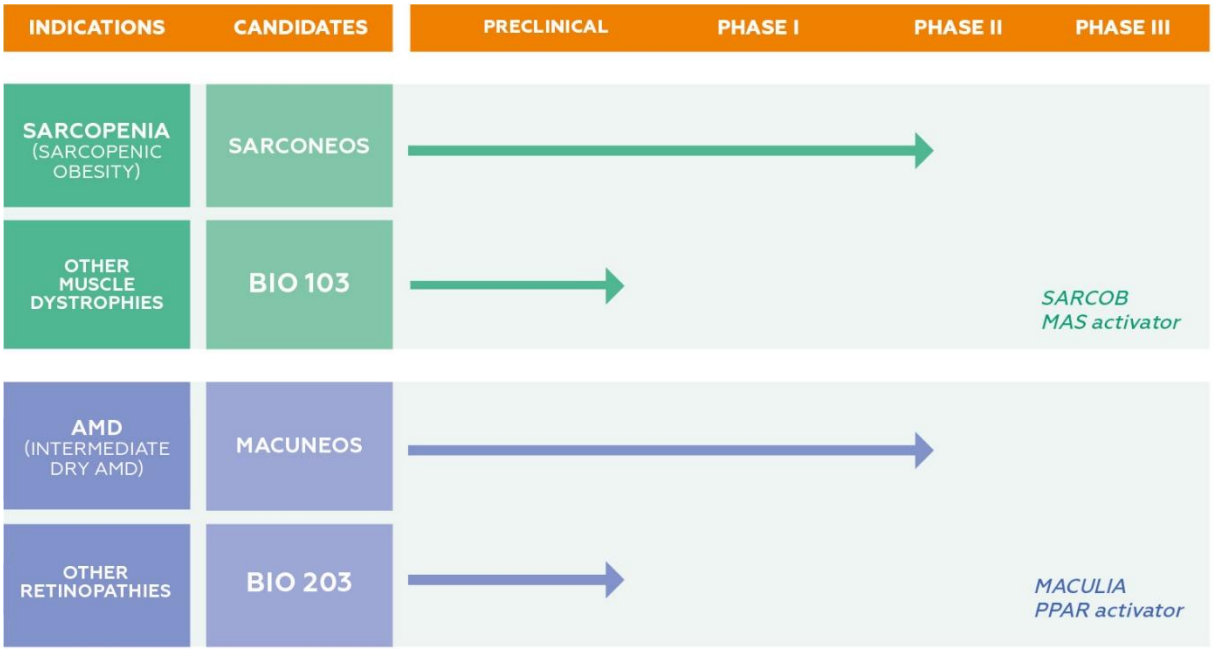
The Company conducts preclinical (BIO103 and BIO203) and clinical (Sarconeos and Macuneos) programs, the principal objective of which is the development and marketing of therapeutic solutions for the treatment of sarcopenia and AMD.

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 on the date of this Reference Document are as follows:



The Company may not be able to obtain 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, the 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 Reference Document.

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 pertaining 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 situation, 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 in 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 Reference Document, 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 development of the Company and its ability to generate revenues will depend on the degree of acceptance of the Company's products by the market, based on several factors, notably including:

- its effectiveness and its therapeutic benefit perceived by prescribers and patients;
- the absence of any side effects and adverse drug interactions;
- ease-of-use of the product, linked notably to its mode of administration;
- the cost of treatment;
- reimbursement policies of governments and other third-party payers;
- the effective implementation of a scientific publication strategy;
- support by 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 reference document 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 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 CMO (Contract Manufacturing Organisations) and CRO (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.

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 director.

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 staff and may not be able to attract or retain them under conditions which are acceptable from an economic 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 operational IT and existing financial and management 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 co-contractors and subcontractors

The Company draws on 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 the aid of 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 establishments 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, the USA and in other countries, regulations are likely:

- to delay and/or significantly increase the cost of development, testing, manufacturing and marketing of products;
- to limit the indications for which the Company is authorised to market its products;

- to impose strict 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 observe 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 operations, 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 will be necessary to obtain the 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 achievement is generally spread 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.

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 lines, 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 shift 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 demands, 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 the UPMC and CNRS (see Chapter 11 of this reference Document).

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 covered, 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, according to conclusion of those challenges could reduce their scope or result in disability. 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 compensation. 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:

- demands 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 issuance 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 programs.

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 Reference Document, 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 its intellectual property rights will not be infringed upon***

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

The Company thus cannot guarantee that it will be able to prevent and secure compensation 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, whatever 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 compensation sought. Competitors with greater resources than the Company could be more capable of bearing the litigation costs.

On the day of registration of this Reference Document, 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 realise, as well as their remuneration 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 desired 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 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 contractors that they undertake to pass on these confidentiality obligations to their own joint contractors.

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 the invoking of liability due to products

The Company is exposed to risks of citing of its liability, in particular liability due to products linked to trials, manufacturing and marketing of therapeutic products in humans. Its liability may also be cited by way of clinical trials within the context of the preparation of 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 actions may include complaints resulting from actions 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 actions which may be brought against it. If its liability or that of its partners, licensees or subcontractors is called into question 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 actions 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 actions, 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 advance.

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 the execution of agreements binding them to 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 by way of these contracts. 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.

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 in connection with the issuance of a tranche of convertible bonds redeemable in either cash or in new or existing shares.

On the date of this reference Document, the full exercise of all of the instruments granting access to the attributed share capital in circulation on the present date would allow the subscription of 1,280,132 new shares, while generating a dilution equal to 12.9 % of the capital base existing on the present date and to 11.4 % 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.
As of the date of this document, 2,412,481 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 dilution in the event of the drawdown of a new tranche of convertible bonds and warrants or in the event of the drawdown of the remaining three tranches of the convertible bonds and warrants at the date of this document. The calculation summarises the potential dilution in the theoretical case of an issue/conversion/exercise of the convertible bonds and warrants 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	0.90	0.91	0.89	0.90
After issuing, converting, and fully exercising the remaining 3 tranches	0.74	0.76	0.74	0.76

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 the month of 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 diseases and aging.

On 31 December 2016, the cumulative losses according to IFRS standards over the last two financial years amounted to a total of € 13,187,000 of which a loss of € 7,954,000 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 "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.

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

On 31 December 2016, after taking into account the net loss realised for the year, the Group had tax losses which could be carried forward amounting to € 20,563,000. These consist of:

- French tax losses which may be carried forward indefinitely of € 20,361,000;

Within France, the attribution 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 € 201,000;

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 € 1,000;

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 attribution 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 2016 CIR is € 41,604.

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 Reference Document (amounts in € '000)	Amount received*	Amount reimbursed	Remaining amount owed
OSEO - QUINOLIA Project – clinical development of a Quinoa extract acting on Metabolic syndrome	229	90	139
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	7	253
BPI France - Project BIO101 - production of clinical batches, preclinical regulatory and clinical phase of BIO101 for the treatment of sarcopenic obesity	600	-	600
TOTAL	**1,126**	**126**	**992**

** Excluding any costs borne by the Company*

*** The balance of the COFACE advance was considered non-due and was recognised in grants in 2015.*

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 Reference Document.

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.

4.4.6. Risks relating to loss of or changes to the status of Young Innovative Company

The Company benefited for the last time in 2013 from the status of Young Innovative Company reserved for small and medium-sized companies incurring research and development costs representing at least 15% of their costs and fulfilling certain conditions, notably regarding staff and revenues.

Until 2013, this status granted it a reduction in employers' social charges on salaries paid to employees participating in the research. Considering the different caps in place, in 2013, this reduction represented an amount of approximately € 50,000. Since the benefit of these privileges is reserved for companies that were created less than eight years ago, the Company ceased to benefit from them on 1 January 2014.

The Company cannot exclude the possibility that social organisations challenge the method of calculating the reductions practiced by the Company until 2013, with the deadline for clawback of social security contributions being three calendar years plus the year in progress, following

the submission of the formal notice. If such a situation were to occur, it could have an adverse effect on the Company's results, financial condition and prospects.

4.5. INSURANCE AND RISK COVERAGE

The amount of expenses paid by the Company for all the aforementioned insurance policies amounted respectively to € 12.982 net of tax and € 57,490 net of tax during the years ended 31 December 2015 and 31 December 2016

The Company believes that these insurance policies adequately cover insurable risks inherent in its activity and that its insurance policy is consistent with practices in its sector of activity. The Company does not envisage 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 fault 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 UPMC: Bâtiment Cassan 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 occupier 9) Amicable or judicial defence 10) Guarantee of materials (electrical	1) 90,000 2) 90,000 3) 90,000 4) 30,000 5) Guaranteed 6) 20,000 7) 20,000 8) Guaranteed 9) Guaranteed	**In progress** Duration of one (1) year [with tacit renewal] Possibility of annual advance termination with observance of a prior notice period of two (2) 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
		damage and breakages)	10) 30,000	
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 fault; bodily injury 6. B/ damage to entrusted assets; 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	<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 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	**In progress** Duration of one (1) year with tacit renewal. Possibility of annual advance termination with observance of a prior notice period of two (3) months before the expiry date, which is the anniversary of the agreement, i.e. 1 January.
Civil Liability for therapeutic tests SARA PK	**HDI**	1. Civil liability for therapeutic tests	1 Per patient: 400,000 Per protocol €3,000,000	August-December 2016

Insurance policy	Insurer	Covered risks	Amount of guarantees	Expiry/Duration
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
Directors' Liability	**AIG**	Professional fault committed while performing the duties of director	€ 1,000,000/insurance period	**In progress** Duration of one (1) year [with tacit renewal] Anniversary expiry date of the agreement: every 19/02,
Key individual (individual accident)	**ALBINGIA**	1. Accident 2. Illness	€ 350 per day/365 days	**In progress** 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	€1,000,000	**In progress** Duration of one (1) year [with tacit renewal] Possibility of advance termination on each payment maturity of the premium, on 19 August of each year.

Insurance policy	Insurer	Covered risks	Amount of guarantees	Expiry/Duration
Machinery breakdown	**AXA**	Agilent spectrometer	€314,927	**In progress** Duration of one (1) year [with tacit renewal] Possibility of advance termination on each payment maturity of the premium, on 1 January.

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. These amounted to € (3,301,000) and € (6,633,000) on 31 December 2015 and 2016 respectively.

On 31 December 2016, the Group had cash and cash equivalents of € 3,066,000. In addition, in April 2017, the Company:

- Carried out a private placement of €3.7 million through the issuance of 1,310,431 new shares at a price of €2.85 per share;
- Set up a credit facility for up to €15 million (see Section 21.1.5 of the Reference Document for more details on the characteristics of this instrument).

On the date of the Reference Document, 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, taking into account the possibility of drawing the remaining three tranches of its line of financing.
In order to meet 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 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.

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 Reference Document, 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.

On 31 December 2016, cash and cash equivalents amounted to € 3,066,000, of which € 2,001,000 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 Annex to the consolidated financial statements prepared in accordance with IFRS in Section 20.1 of this Reference Document).

Given the low level of reference rates, the Company considers that any change of +/-1% would have an insignificant impact (around € 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 Reference Document, been involved in any administrative, criminal, judicial, or arbitration proceedings requiring market disclosure.

To the knowledge of the Company, no event of an exceptional nature arose during the same period entailing a supplementary risk or additional unprovisioned costs.

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 facility of the Company was located at Biocitech Park, 102 Avenue Gaston Roussel, 93230 Romainville until 15 December 2016.

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

Since 15 December 2016, the principal place of business of the Company is located at the Pierre et Marie Curie University – BC 9, Bâtiment A 4ème étage, 4 place Jussieu, 75252 Paris Cedex 05, under a Public Property Occupancy Agreement (see 8.1.1).

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 (UPMC) 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 the UPMC 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 the UPMC).

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).

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

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

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

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 [Institute of Vision] and Iris Pharma, providing entitlement to a subsidy of € 0.8 million, co-financed by the ERDF.

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

Mai 2014: filing of patent application No. 14 54538 for new chemical entities and their therapeutic use (joint ownership with UPMC 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: appointment 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 the UPMC 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 (Doctor of Pharmacy, 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: opening of the subsidiary Biophytis Inc. in Cambridge, USA.

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

March 2016: Appointment of Dr Susanna Del Signore (La Sapienza University, Rome) as Medical Director.

April 2016: Confirmation of Professor Jean Mariani (Institute of Longevity), Professor René Lafont and Professor Jose-Alain Sahel (Institute of Vision); and the appointment of Dr Philippe Guillet, of Professor Roger A. Fielding (Tufts University, Harvard Medical School) and Dr 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 sarcopenic patients 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.

April 2017: Financing of the phase 2 clinical study on sarcopenia (SARA-INT) by (i) carrying out a private placement of €3,734,728.35 and (ii) the setting up of a bond financing in the amount of €15,000,000.00 as follows:

- Capital increase in cash by a nominal amount of €223,489.80 through the issuance of 1,117,449 new common shares at a unit price of €2.85, to qualified investors;
- Allocation of 1,500 convertible bonds with warrants attached, at a nominal value of €10,000, in favour of Bracknor Fund Ltd, an investment fund (Certificate no. SIBA/PIPO/14/5528) having its registered office at Lyntons Financial Services (BVI) Limited, PO. Box 4408 Road Town, Tortola, British Virgin Islands (**Bracknor**); and
- Capital increase in cash in the nominal amount of €38,596.40 through the issuance of 192,982 new common shares at a unit price of €2.85, to the management.

May 2017: The drawdown of the first tranche of the convertible bonds was exercised, giving rise on 15 May 2017 to the issuance of (i) 330 convertible bonds with a value of €10,000 and (ii) 225,225 stock warrants with an exercise price of €3.33.

The CEO noted, in two decisions dated 16 May 2017:

- The conversion of 30 convertible bonds into 122,449 new common shares resulting in an increase in the share capital of the Company by a nominal amount of €24,489.80; and

- The conversion of 45 convertible bonds into 183,673 new common shares resulting in an increase in the share capital of the Company by a nominal amount of €36,734.60.

By a decision dated 27 May 2017, the CEO noted the conversion of 25 convertible bonds into 102,459 new common shares resulting in an increase of the share capital of the Company by a nominal amount of €20,491.80.

By a decision dated 31 May 2017, the CEO noted the conversion of 25 convertible bonds into 104,166 new common shares, resulting in an increase in the share capital of the Company by a nominal amount of €20,833.20.

By a decision dated 2 June 2017, the CEO recognised the conversion of 20 convertible bonds into 85,106 new common shares, resulting in an increase in the share capital of the Company by a nominal amount of €17,021.20.

By a decision dated 07 June 2017, the CEO recognised the conversion of 20 convertible bonds into 85,106 new common shares, resulting in an increase in the share capital of the Company by a nominal amount of €17,021.20.

By a decision dated 09 June 2017, the CEO noted the conversion of 62 convertible bonds into 263,829 new common shares, resulting in an increase in the share capital of the Company by a nominal amount of €52,765.80.

By a decision dated 09 June 2017, the CEO recognised the conversion of 103 convertible bonds into 438,297 new common shares, resulting in an increase in the share capital of the Company by a nominal amount of €87,659.40.

July 2017: The drawdown of the second tranche of the convertible bonds was exercised, giving rise on 07 July 2017 to the issuance of (i) 300 convertible bonds with a value of €10,000 and (ii) 205,959 stock warrants with an exercise price of €3.6415.

By a decision dated 07 July 2017, the CEO noted the conversion of 200 convertible bonds into 684,931 new common shares, resulting in an increase in the share capital of the Company by a nominal amount of €136,986.20.

By a decision dated 10 July 2017, the CEO recognised the conversion of 100 convertible bonds into 342,465 new common shares, resulting in an increase in the share capital of the Company by a nominal amount of €68,493.

The share capital of the Company now stands at €1,989,282.60.

5.2. INVESTMENTS

5.2.1. Principal investments made during the last two financial years

Amounts in thousands of euros	31/12/2015	31/12/2016
Intangible fixed assets	**2,301**	*2*
of which purchased patents	*2,300*	*-*
Tangible fixed assets	**187**	**127**
*of which materials and tools **	*181*	*79*

Including financial leasing

On 4 June 2015, the Company entered into an agreement for the purchase of a stake in a patent from Metabrain for an amount of € 1.5 million net of tax (family 4 patents, 33% - see section 11.2 of the Reference Document). The price was paid in shares upon admission of the shares of the Company to a listing, by offsetting against the receivable for the subscription of the Company's ordinary shares.

On 5 June 2015, the Company entered into an agreement for the purchase of a stake in a patent from Iris Pharma for € 800,000 (family 7 patents, 33% - see section 11.2 of the Reference Document). The price was paid in shares upon admission of the shares of the Company to a listing, by offsetting against the receivable for the subscription of the Company's ordinary shares.

The main investments in financial year 2016 relate to the acquisition of laboratory equipment.

5.2.2. Principal investments in progress

No significant investment has been made since 1 January 2017.

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 founded in 2006, which develops new classes of drugs against degenerative diseases of aging, the medical need for which is not currently satisfied. Biophytis has two drug candidates in clinical phase: *Sarconeos* (BIO101) in the treatment of Age-related Muscular Dystrophy (sarcopenia); and *Macuneos* (BIO201) in the treatment of Age-related Macular Degeneration (AMD). Biophytis is currently preparing phase 2b clinical trials for *Sarconeos* and *Macuneos,* each of which will involve dozens of centres in Europe and the United States.

- *Sarconeos* (BIO 101) is a drug candidate developed in the treatment of sarcopenia (including sarcopenic obesity), a disease that affects approximately 20 million people worldwide and for which there is no available treatment. It is an oral treatment with a mode of action based on the activation of the Mas receptor which stimulates the production of muscle protein. The preclinical results were convincing, showing in particular a regeneration of the physical performances in elderly animals. Furthermore, preliminary clinical studies have confirmed that the product has good bioavailability in elderly volunteers, and have provided data on the activity of the product. The phase 2b program is progressing. The target population's characterisation and pre-selection study (SARA-OBS study) began in the first half of 2017. It is supervised by the world's leading specialists in the disease. The investigation phase of the interventional study (the SARA-INT study) will involve 333 patients recruited in roughly fifteen centres in Europe and in the United States. It will start in the 2nd half of 2017 as soon as the authorisation is obtained from the regulatory bodies.

- *Macuneos* (BIO 201) is an oral treatment for dry AMD, which accounts for 80% of cases of AMD, i.e. a market estimated at nearly $30 billion annually. To date, no effective treatment has been confirmed for this form of the disease. *Macuneos* works through the activation of Peroxisome-Proliferator Activated Receptors (PPAR), which limit the accumulation of A2E (a visual pigment degradation product involved in the process of oxidative stress) and therefore slows retinal degeneration. The phase 2b program is underway. Based on the recommendation of clinicians working alongside Biophytis, the pharmacokinetic study will include patients and not healthy volunteers as originally planned in 2016 (MACA-PK study), and will begin in the second half of 2017. It will allow observing the effects of BIO201 on the pharmacodynamic parameters, and to obtain clinical data as of 2018. The phase 2b interventional study (MACA-INT study) will last 18 months and involve approximately 300 patients recruited in approximately twenty centres in Europe and the United States. It is expected to start in the second half of 2018, a year later than was expected in 2016, but based on clinical activity data and on a perfectly characterised patient sample.

Each of the two programmes presented by Biophytis have the following advantages:

- Two significant markets that are being given priority by the health authorities and pharmaceutical laboratories,
- Two drug candidates that are entering phase 2b,
- Two indications without available treatment,
- Convincing proofs of concept and a mechanism of action in writing,
- Drug candidates that are ideally suited to the specific needs of patients over 65 years of age,
- The partnership with several world class *translational* research institutes,

[1] Words and expressions in italics in the text are explained in the glossary (section)

- A development strategy for an initial technology licensing agreement as early as 2018, upon receipt of clinical data.

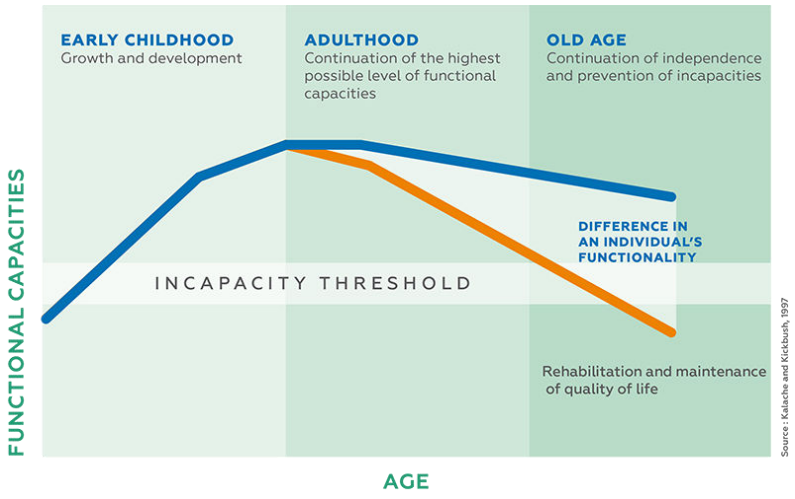
The economic model adopted by Biophytis is advance its programmes as far as the proof of clinical activity of the family of compounds, supplemented by the description of the mechanism of action, the proof of harmless of the candidate molecules and their characterisation for secondary indications. Then, to sign alliances with pharmaceutical companies in order to support the regulatory development as far as commercial launch. Biophytis aims to obtain a first licence agreement as early as 2018.

6.1. POSITIONING: ACTIVE NATURAL MOLECULES AND AGING

6.1.1. The context of degenerative diseases of aging

The aging of the population massively affects Western societies, as well as Japan, China and Russia. The elderly population of these societies already represents several hundreds of millions of people, causing the appearance of rapidly expanding epidemics with particular characteristics (neurodegenerative diseases, *muscular dystrophies*, ARMD, etc.). It should double by 2050, to reach 2 billion individuals, of which 500 million suffering from physical degeneration (sarcopenia, muscular dystrophies, etc.), 400 million from visual degeneration (ARMD) and 135 million from cognitive degeneration (Alzheimer, senile dementia, etc.)[2].These diseases may be extremely debilitating for patients and in the absence of therapeutic treatment, their care represents an economic cost valued in the tens of billions of euros.

Degenerative diseases are diseases in which one or several organs are progressively impaired. The causes may be the accumulation of biological products or *toxins*, as well as the prolonged absence of a biological substance which then entails the progressive degeneration of the organs in question. They are notably influenced by life circumstances: quality of nutrition, physical activity and various forms of stress.



[2] Source OMS – EWGSOP

At present, the only available treatments, since they are heavy and onerous to administer (injections of hormones, *monoclonal antibodies*, etc.), only target the late phases of the pathology, i.e. only 10 to 20% of affected populations. Biophytis' objective is to meet the needs of patients already diagnosed in the so-called intermediate phase, for which no treatment exists. It is by understanding the relationship between *natural active molecules and* mechanisms of degeneration that Biophytis identifies families of active principles present in very small doses within our nutritional environment, capable of acting directly on the mechanism of the disease and potentially permitting its effective and durable slowing.

Moreover, considering the state of progress of these diseases on the day of the diagnosis and at the current state of knowledge, it is unlikely that they can be cured, with this supposing that the patients must follow a *chronic therapy* for several years in order to block or slow the development of the disease. This raises the problem of the acceptability of the treatment both from the perspective of its mode of administration and from that of its potential secondary effects on the organism. By concentrating on candidate families deriving from active principles to which the organism is already naturally exposed by nutrition, Biophytis has identified compounds which a priori offer an extremely favorable pharmacological profile.

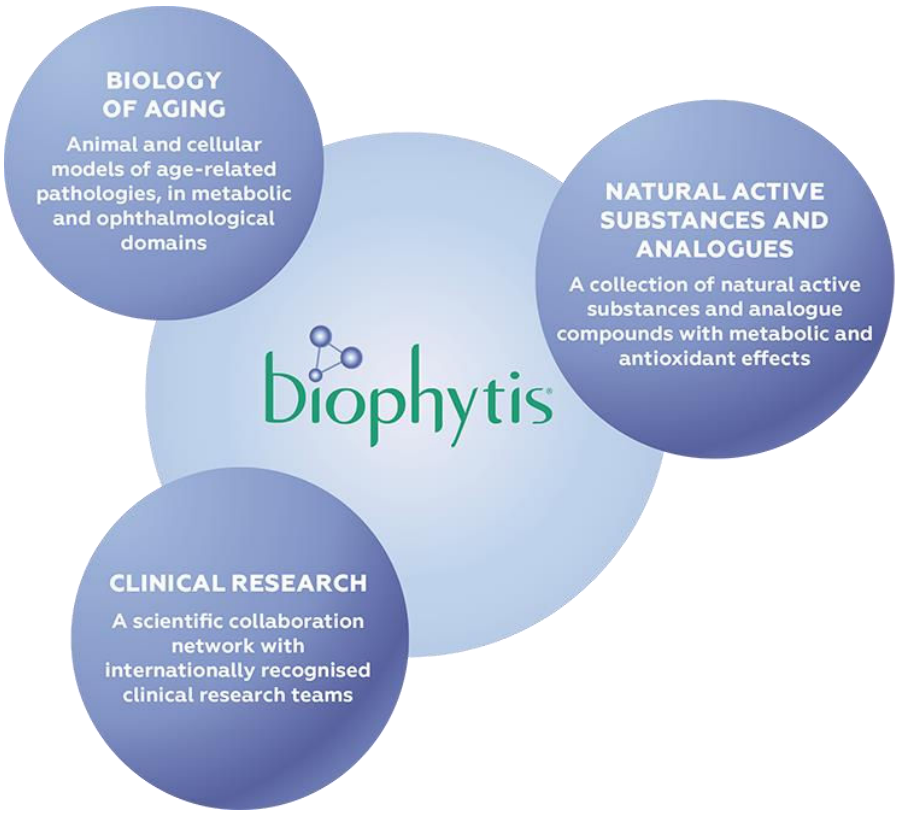
6.1.2. The research platform for candidate medicines

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

The *secondary metabolites* of plants are molecules with a diversity greatly exceeding that generated by synthesis in the *chemical libraries* of the most important small molecules. They derive from defense process of plants against their environment and from co-evolution with different predator species: they are naturally "bioactive". This original property has the consequence that they are still the principal source for the discovery of new medicines: more than 50% of the medicines registered by the FDA in the last 30 years derive from natural active principles (David et al., 2015)[3]. The process of developing new medicines theorized in the 1990s, based on the *screening* of synthetic *chemical libraries* on biological targets, generalized among pharmaceuticals companies, has paradoxically led to a considerable increase in the failure rate for developing candidates (secondary effects, toxicity, ineffectiveness in humans, etc.) and to an explosion of the ratio of R&D costs/registered products.

Natural active molecules have formed the object for some 10 years of academic research in full development, to establish their role in the development of chronic age-related pathologies, in particular degeneration of the eye (notably of the retina), *skeletal muscle*, or 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 (ARMD, AREDS report, 2007[4]). Tens of thousands of other *natural active molecules* are still poorly characterized. There effects on little studied aging processes thus offer a privileged source of "bioactive" molecules with a potential which has still been largely unexploited yet. In partnership with the Institut de Biologie Paris Seine of the University Pierre et Marie Curie (*UPMC*), Biophytis has established a collection of natural active principles belonging to several chemical classes (triterpenoids, polyphenols and *carotenoids*) deriving from food and medicinal plants, in particular tropical ones, by virtue of the establishment of Biophytis in Brazil, in an incubator of innovative companies (CIETEC) within the Federal University of Sao Paulo (USP).

[3] David B, Wolfender JL, Dias DA. 2015. The pharmaceutical industry and natural products: historical status and new trends. *Phytochem Rev*., 14: 299-315.
[4] 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.



The study of the aging process forms the object of intense academic research, with the discovery of molecular and cellular processes, more specific to different organs and pathologies. Numerous theories attempt to explain the results obtained in different models of aging, in particular the theory of calorie restriction, which established that calorie restriction allows life expectancy to be extended and that certain natural active principles, such as resveratrol, which is extracted from grapes, allow this process to be mimicked (Fontana, 2010)[5]; or the theory of *free radicals*, which highlights the role of *oxidative stress*, in particular oxidative stress in the process of cell death (*apoptosis*) of exposed cells, such as certain retinal cells, leading to a proposal to use *antioxidants*, such as Vitamin C and E to treat ARMD with a certain effectiveness (AREDS report, 2007)[6].

Biophytis has decided to concentrate its research efforts on age-linked degeneration of skeletal muscle (sarcopenia) and age-linked degeneration of the retina (ARMD), where the potential of the selected molecules appears most promising, allowing the degeneration processes involved in these pathologies to be blocked or greatly slowed. Moreover, these pathologies are currently without treatment for the targeted indications and are the principal causes of handicap in the population aged over 60.

Biophytis has developed cellular and animal models of age-related pathologies forming the object of its researchers, in collaboration with the biomedical research teams and *translational*

[5] 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.
[6] 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.

research institutions of the UPMC. At the end of 2016, Biophytis moved to the Pierre et Marie Curie University (UPMC), its historical scientific partner. The presence of Biophytis on the Jussieu (Paris) campus has made it possible to establish new scientific collaborations with teams of internationally renowned researchers studying the biology of ageing, and to strengthen its platform for discovering new drugs to treat age-related diseases.

UPMC: The University is a Paris-based university, the heir of the former Sorbonne, specializing in sciences and medicine and located principally between the campus of Jussieu (in the Latin Quarter of Paris) for the sciences, and 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 there with it hosting 100 research laboratories. In the Shanghai 2016 ranking, the UPMC confirmed its position as the leading French research university, ranking 7th in Europe and 39th 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.

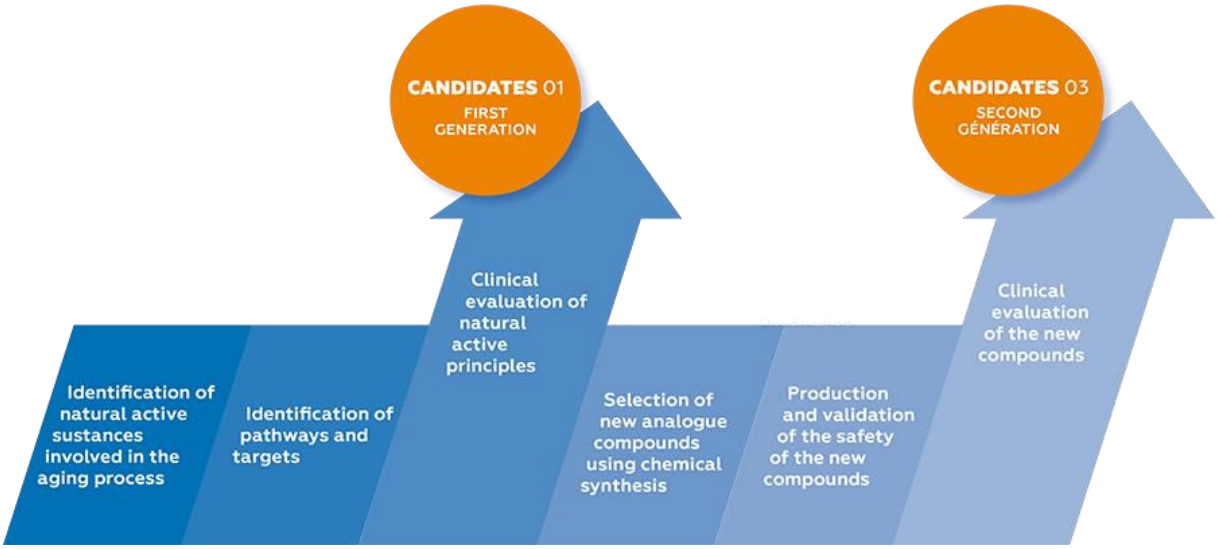
Institut de la Vision /Institute of Vision: established at the heart of the CHNO (Centre Hospitalier National of Ophtalmologie des Quinze-Vingts), the Institute of Vision is one of the most important integrated research centers for diseases of vision in Europe. Designed as a place for meeting and exchanges, it brings together basic, clinical and industrial research on the same site. Since 2010, the MACULIA (ARMD) project has been directed in collaboration with Valérie Fontaine of the UMRS968 of the Institute of Vision.

Institute of Biology Paris Seine: The Institute of Biology Paris-Seine (IBPS - FR3631), established on 1 January 2014, brings together all the research in biology of the Jussieu campus within the Pierre et Marie Curie University (UPMC) where the field 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 the UPMC, with which INSERM has joined forces, the IBPS aims to embody the UPMC'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 stress and their development during ageing.

6.1.3. The development strategy for candidate medicines

The two most advanced programs are oriented towards the development of treatments of two debilitating age-related pathologies, with no medical treatments on the market: sarcopenia, or age-related muscular degeneration, and age-related macular degeneration (ARMD).

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 principle; and second generation candidates (Series BIO-03), based on the development of a proprietary *analogue* of the natural active principle, deriving from the production by chemical synthesis (or hemisynthesis) of the compound.



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 origin allows the *clinical development* of the candidates to be accelerated, due to the nutritional exposure of humans to these substances and their very low toxicity. The discovery of the effects of these substances on the aging process allows their use for the treatment of the targeted pathologies to be patented. Biophytis has thus developed *Sarconeos*, a candidate drug in *clinical development* for treating sarcopenia and *Macuneos*, a candidate drug in *clinical development* for treating ARMD.

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. *Analogue* compounds for natural active principles are synthesized by medical chemistry and selected in previously calibrated cellular models. The synthesis of original compounds will permit the improvement of certain 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. Biophytis has thus developed BIO103, a candidate in *preclinical development* to treat sarcopenia and, potentially, genetic myopathies, and launched the optimisation phase of BIO203, a candidate to treat the AMD.

6.1.4. The pipeline

Biophytis is continuing the clinical and regulatory development of Sarconeos and Macuneos with the intention of launching the phase 2b interventional studies in 2017 and 2018 respectively.

SARA Clinical Programme

The preparation of the phase 2b SARA-INT study initially involved entering into a partnership with the American manufacturer Patheon to launch the production of clinical batches of the drug candidate Sarconeos. Clinical batches currently under production will be used for the interventional study that will be launched in Europe and the United States as soon as the authorisation is obtained from the regulatory bodies, expected by the second half of 2017.

In February 2016, Biophytis presented the clinical and regulatory development plan for Sarconeos to the Federal Agency for Medicines and Health Products (AFMPS, the Belgian regulatory authority), for its scientific approval. In July 2016, the AFMPS granted its authorisation to conduct the SARA-PK pharmacokinetic study in healthy adult and elderly subjects. In the second half of the year, Biophytis was authorised by the French, Belgian, Italian, and American authorities to conduct the SARA-OBS characterisation and pre-selection study of the target population, which is currently underway. Regarding *Sarconeos'* regulatory approval process for phase 2b clinical development, authorisation from regulatory bodies for the SARA-INT interventional study in Europe and the United States, from the EMA (European Medicines Agency, Europe) and the FDA (Food & Drug Administration, USA), is expected in the second half of 2017.

The SARA-PK study will be conducted in Belgium among healthy older volunteers in order to determine the pharmacokinetics and the safe use of *Sarconeos* in that specific population. *Sarconeos* will be administered to approximately 30 healthy elderly volunteers for 14 days, at 3 daily doses (350 mg, 700 mg, and 900 mg per day). This study has (i) confirmed the safety of *Sarconeos*, (ii) allowed determining the range of doses to be administered in the interventional study (SARA-INT), (iii) allowed the pharmacokinetic parameters of *Sarconeos* to be determined for elderly patients and (iv) demonstrated an evolution of pharmacodynamic parameters consistent with its mechanism of action.

The current SARA-OBS study is an observational study consisting of 6 months of research on 300 patients, in which multiple parameters of severity and change in their condition are monitored. The data obtained will allow a better characterisation of the sarcopenic patients who will be subsequently recruited in the interventional study (SARA-INT). 300 patients will be monitored for 6 months in 8 clinical centres in the United States and Europe. Patients over the age of 65 are recruited according to the criteria defined by the Foundation for the National Institutes of Health: An appendicular lean mass to body mass index (ALMBMI) ratio under 0.8 for men, and under 0.5 for women, and loss of mobility, determined by a score under 8 in the Short Physical Performance Battery Index (SPPB ≤ 8). The main criteria of the measurements include the 6-minute walking test and the 400-metre test.

Finally, the interventional study (SARA-INT) will be conducted in the centres already open for SARA-OBS, as well as in additional centres. SARA-INT will evaluate the efficacy of Sarconeos in 333 sarcopenic patients treated for 6 months.

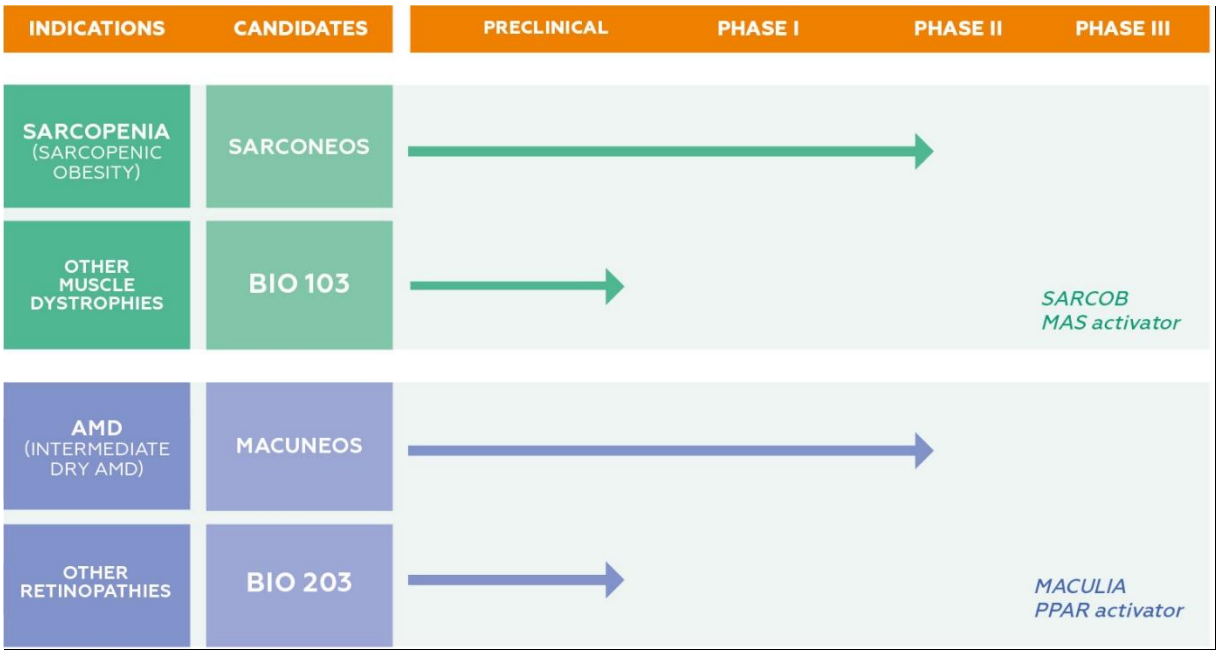
MACA Clinical Programme

The phase 2b MACA programme follows a clinical and regulatory development plan similar to that of the SARA program. In particular, Biophytis successfully completed the industrial scale-up and secured the *Macuneos* production chain with international manufacturing partners.

The phase 2b interventional study (MACA-INT study) will last 18 months and involve approximately 300 patients recruited in approximately twenty centres in Europe and the United States. The main criterion will be the progression of atrophy geography. It is expected to start in the second half of 2018, one year later than what was expected in 2016, in order to obtain clinical data from patients in the MACA-PK clinical study, which has been extended accordingly, and on a well-characterised sample of patients previously recruited in connection with the MACA-OBS study.

A pharmacokinetic and safety study with elderly healthy volunteers and patients with intermediate AMD (MACA-PK) will be conducted beforehand. The pharmacokinetic study has the advantage of being designed to directly target patients and should allow observing the effects of BIO201 on several pharmacodynamic parameters during a MAD phase (28 days) and a subsequent follow-up phase (60 days). The results should be available in 2018.

An observational study (MACA-OBS) to characterise the target population and to screen patients with dry AMD will be conducted at major recruitment centres in Europe and the United States.



The second-generation drug candidate BIO103 entered the preclinical regulatory phase in the first half of 2017 and will be developed to treat muscular dystrophy.
BIO203 which is undergoing optimisation and development in pharmaceutical form will be able to enter preclinical testing in 2018 and will probably be developed to treat a retinopathy other than AMD.

The Company intends to sign the first licence agreement on using Sarconeos in the treatment of sarcopenia and secondary indications with a global pharmaceutical laboratory that will

continue developing the product in phase 3 and submit an application for a Marketing Authorisation (MA). This agreement could be made at the earliest in 2018, depending on the clinical data that is available.

A second licence agreement on using *Macuneos* in the treatment of AMD and secondary indications is planned with a global pharmaceutical laboratory that will continue developing the product in phase 3 and submit an application for a Marketing Authorisation (MA). This agreement could be made at the earliest in 2018, depending on the clinical data available.

The financial model of Biophytis for all its drug candidates is to ensure projects are carried out through to the proof of clinical activity in patients, and then to license out the technologies to pursue their development in partnership with a pharmaceutical laboratory that could also market the products. The latter will take on the responsibility of obtaining marketing authorisations, therefore Biophytis does not communicate a date for obtaining such authorisations.

6.1.5. The economic model

The objective pursued by Biophytis is to propose two comprehensive and largely risk-free "technological packages" to pharmaceutical laboratories in 2018-2020 in order to sign licence and partnership agreements, taking account of the following factors:

- First generation drug candidate (natural active principle) with proof of clinical efficacy for the principal indication,
- Second generation drug candidate (analogue active principle) which has passed through the regulatory development phases,
- An explored and described mechanism of action,
- Characterisation of the effects in several secondary indications.

Economic potential of Sarconeos
Based on the different studies available on the prevalence of sarcopenia in the American population[7], we obtain the following data on the population that is potentially responsive 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**
% of the US population over 60 years of age suffering from obesity	35%	5.2 million
Number of potential patients in the US for *Sarconeos*		**5.2 million**

Considering there is currently no approved treatment for sarcopenia. We estimate that Sarconeos could achieve a 30% market share. However, if competitors succeed in entering the market before Biophytis, Sarconeos would have a smaller market share, namely 10% of market share in the worst case scenario. The other assumptions selected are as follows:

[7] Baumgartner, R.N. et al., 1998. Epidemiology of sarcopenia among the elderly in New Mexico, American Journal of Epidemiology, 147, pp.755-763.

An annual cost of treatment of €1,000, which is a relatively conservative estimate that takes account of the selling price of comparable products for other diseases
Royalties for Biophytis under a licence agreement set at 10% (mid-point)
Royalties payable by Biophytis to the co-holders of patents set at 10% (maximum rate)

	Scenario 1	Scenario 2	Scenario 3
Patients suffering from sarcopenic obesity	5.2 million		
Market share of Biophytis (peak sales)	10%	20%	30%
Annual cost of the treatment	1,000		
Peak sales	**€520 million**	**€1.04 billion**	**€1.56 billion**
Potential royalties for Biophytis (10%)	€52 million	€104 million	€156 million
Royalties payable to the co-holders of the patents (10%)	€5.2 million	€10.4 million	€15.6 million
Net sales for Biophytis	**€46.8 million**	**€93.6 million**	**€140.4 million**

The potential net sales for Biophytis are estimated between 50 million euros and 140 million euros on the US market based on the selected conservative estimates.
Economic potential of Macuneos
As is the case with *Sarconeos*, the data from the studies on the prevalence of AMD, and in particular dry AMD[8], enable us to evaluate the population that are responsive to *Macuneos* in the USA and worldwide.

	% of individuals	Number of individuals
American population suffering from AMD		3.0 million
Including % dry AMD	90%	2.7 million
Number of potential patients in the US for *Macuneos*		**2.7 million**
Global population suffering AMD		20 million
Including % dry AMD	90%	18 million
Number of potential patients worldwide for *Macuneos*		**18 million**

As is the case with *Sarconeos*, there is no approved treatment for dry AMD at present. We therefore estimate the potential market share of *Macuneos* at 50% on the US market. If a competitor enters the market before Biophytis this could seriously affect this potential with a 25% market share in our worst case scenario. The other assumptions used in our scenarios are as follows:
An annual cost of the treatment of €1,000, a relatively conservative estimate considering the selling price of comparable products for other diseases
Royalties for Biophytis under a licence agreement set at 10% (mid-point)
Royalties payable by Biophytis to the co-holders of the patents set at 11% (maximum rate)

	Scenario 1	Scenario 2	Scenario 3
Patients suffering from dry AMD	2.7 million		
Market share of Biophytis (peak sales)	25%	40%	50%
Annual cost of the treatment	1,000		
Peak sales	**€675 million**	**€1.1 billion**	**€1.35 billion**
Potential royalties for Biophytis (10%)	€67.5 million	€110 million	€135 million

[8] Friedman D.S. et al., 2004. Prevalence of age-related macular degeneration in the United States. Archives of Ophthalmology, 122, pp564–572.

Royalties payable to the co-holders of the patents (11%)	€7.4 million	€12.1 million	€14.9 million
Net sales for Biophytis	**€60.1 million**	**€97.9 million**	**€120.1 million**

If we apply these assumptions to the global population, we will retain a lower market share (worst case scenario 10% and 30% for the best case scenario) as the treatment will not be available in every region of the world.

	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 euros and 480 million euros, a quarter to a third of which are generated in the US.

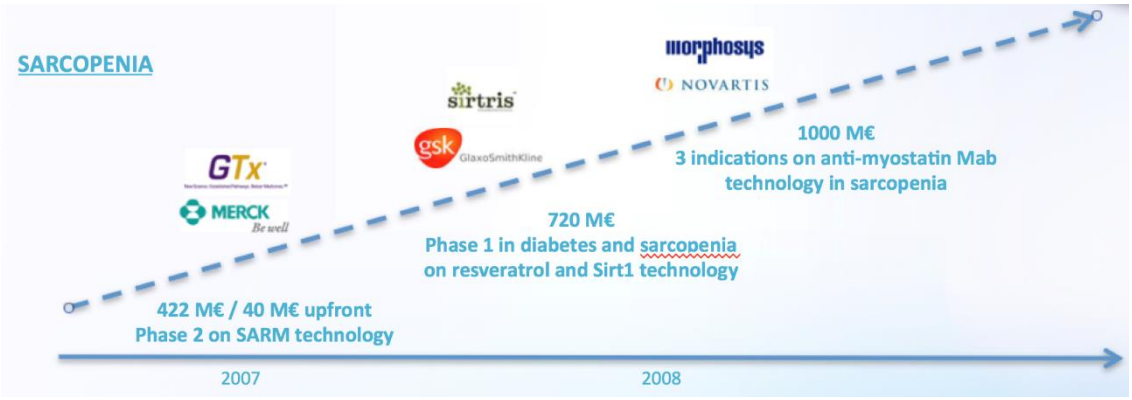
Immediate economic potential

As a consequence of their frequent occurrence and strong growth, sarcopenia and ARMD 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.

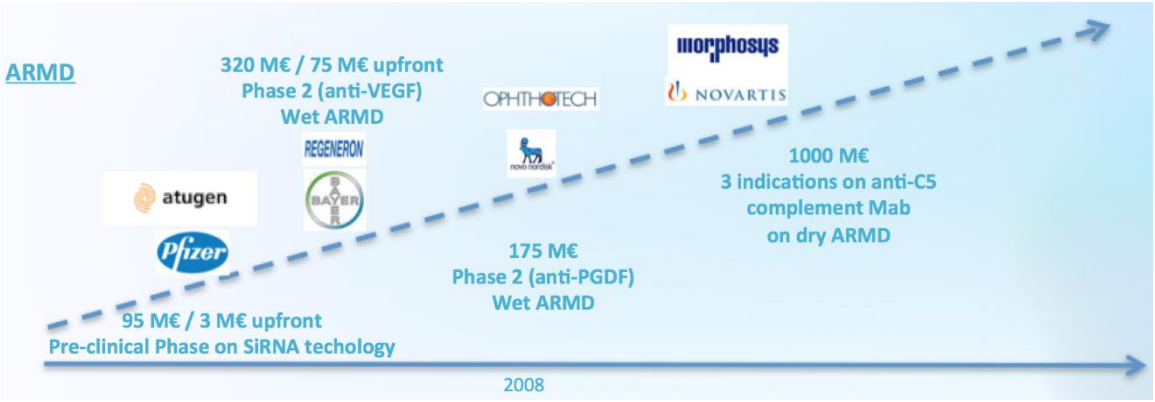
Most of the major pharmaceuticals companies, which have identified these pathologies among their strategic directives for the years 2020-2030, have contributed to this movement, either through their own developments, or by signing technological agreements with biotechnology companies.

As these are new markets without treatment, the first products which shall be marketed offer very high revenue potential, as is illustrated by Novartis/Roche's medicine Lucent is, prescribed to treat exudative ARMD, which currently generates €2 billion of revenues per year.

The licensing agreements already signed are on the scale of this economic potential. The principal agreements drawn up in recent years for products in clinical development for the treatment of sarcopenia and ARMD are presented below.



The licensing agreement between Novartis and Morphosys led to the development of BYM338, currently in phase 2, for sarcopenia in inclusion body myositis and cachexias linked to the treatment of cancer.



The licensing agreement between BAYER and REGENERON led to the marketing of EYLEA in the treatment of wet ARMD.
For these two indications, the value of a license agreement with a global pharmaceuticals company for products in phase 2 is several hundred million euros.

Future economic potential
The domain of degenerative diseases linked to aging has hardly been explored to date. This is a major public health challenge and its scientific exploration will mobilize hundreds of researchers and very significant investments.

Biophytis is one of the first companies to have implemented a platform and a scientific strategy specifically designed to meet this need and which, with the sarcopenia and ARMD programs, is preparing to prove its relevance.

The Company's ambition is to continue to discover and develop new classes of medicines to treat diseases of the aging 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 action mechanism, choice of indication and optimization of candidate drugs;

- Proof of clinical effectiveness and license with a pharmaceutical laboratory.

6.2. PROGRAMME TO COMBAT SARCOPENIA AND OTHER MUSCULAR DYSTROPHIES

6.2.1. Disease and epidemiology

Muscular degeneration or sarcopenia is a natural process which accelerates with age. It is characterised by a loss of muscle mass and function, which is at the origin of a general deterioration in physical condition. The atrophy of muscle fibers, i.e. the reduction in their diameter and number are responsible for this reduction in muscle mass. Obesity aggravates sarcopenia and the degradation of functional capacities. The proportion of obese sarcopenic individuals is nevertheless estimated at 31% of the entire population aged over 60 in the United States.

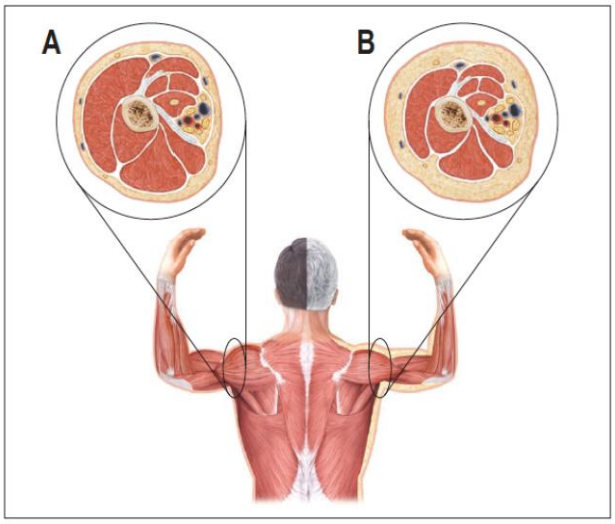
- ***Sarcopenia***

Advancing age is accompanied by a modification of bodily composition. An increase in body fat and a reduction in lean body mass is observed (bony mass, organs, muscle tissue). The term "sarcopenia" was initially defined by Irwin Rosenberg in 1989[9] to describe the reduction in skeletal mass during aging. This word derives from the Greek word sarx for "flesh" and penia for "lack". Since 1989, the purely quantitative definition has evolved to incorporate notions of force and of muscle quality. In 2010, a European working group on sarcopenia in elderly populations (European Working Group on Sarcopenia in Older People[10]) worked on establishing a consensus definition of sarcopenia. 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 performances. In 2016, sarcopenia was finally deemed a disease (code M62.84)[11], which will obviously stimulate the interest of major pharmaceutical groups towards this pathology.

[9] Rosenberg I. 1989. Summary comments: epidemiological and methodological problems in determining nutritional status of older persons. *Am J Clin Nutr*, 50: 1231–1233.

[10] 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.

[11] Anker SD, Morley JE, von Haeling S. 2016. Welcome to the ICD-10 code for sarcopenia. *J Cachexia Sarcopenia* 7: 512-514.



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 the muscles, which are consequences (among other things) of physical and inadequate nutrition. These changes are amplified even further in obese individuals (Benton et al., 2011)[12].

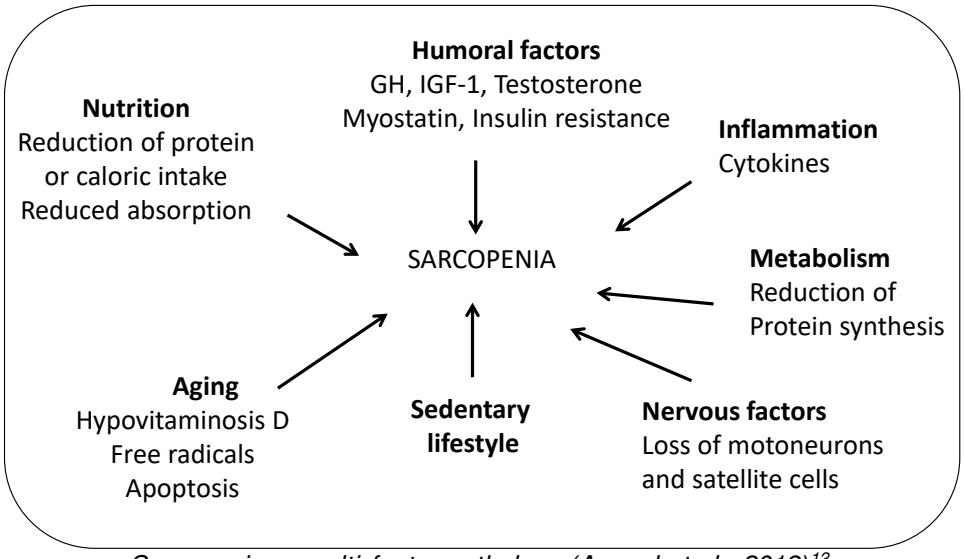
Starting from the age of 30, muscular degeneration is observed at a rate of 3-8% per decade. Muscle tissue is replaced by fibrous and adipose tissue, with this loss accelerating starting from the age of 50. Indeed, the muscle mass declines by approximately 1-2% per year after the age of 50, while force declines by an average of 1.5% per year between 50 and 60 (15%), then at a rate of 3% per year, i.e. with a loss of 30% per decade after the age of 60.

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 both muscle strength and in performance;
- severe sarcopenia, associating the reduction in mass, force and performance.

Sarcopenia is at the origin of a general deterioration in physical condition. It is translated by an increase of the risk of falls, a progressive incapacity to carry out everyday actions, a loss of autonomy and leads fatally to an increase in mortality. Different studies estimate that 25% of individuals aged over 70 and 40% of individuals aged over 80 are sarcopenic.

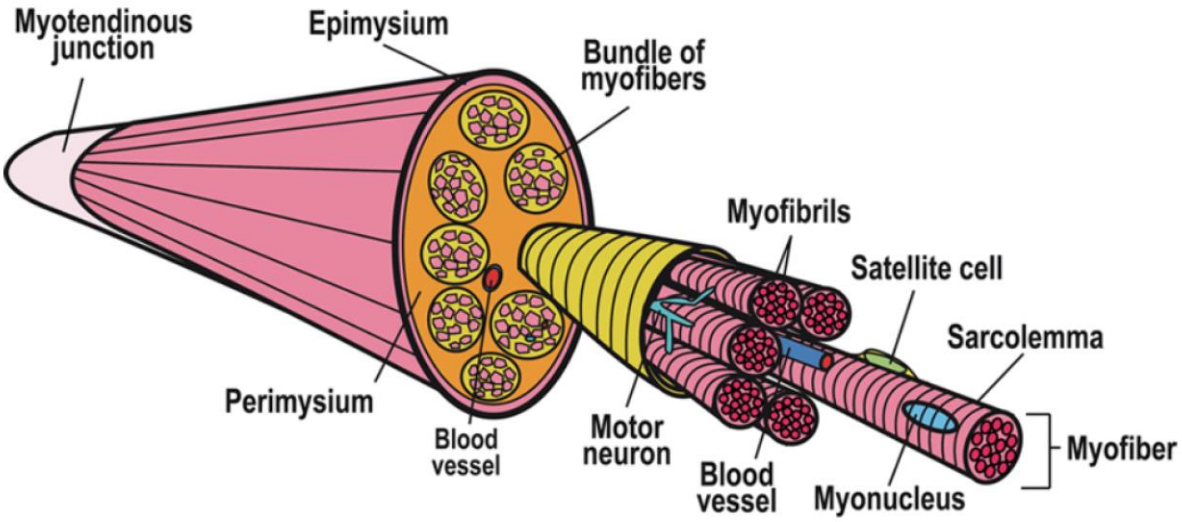
[12] Benton MJ, Whyte MD, Dyal BW. 2011. Sarcopenic obesity : strategies for management. *AJN*, 111: 38-44.



Sarcopenia, a multi-factor pathology (Aussel et al., 2013)[13].

- ***Skeletal muscle***

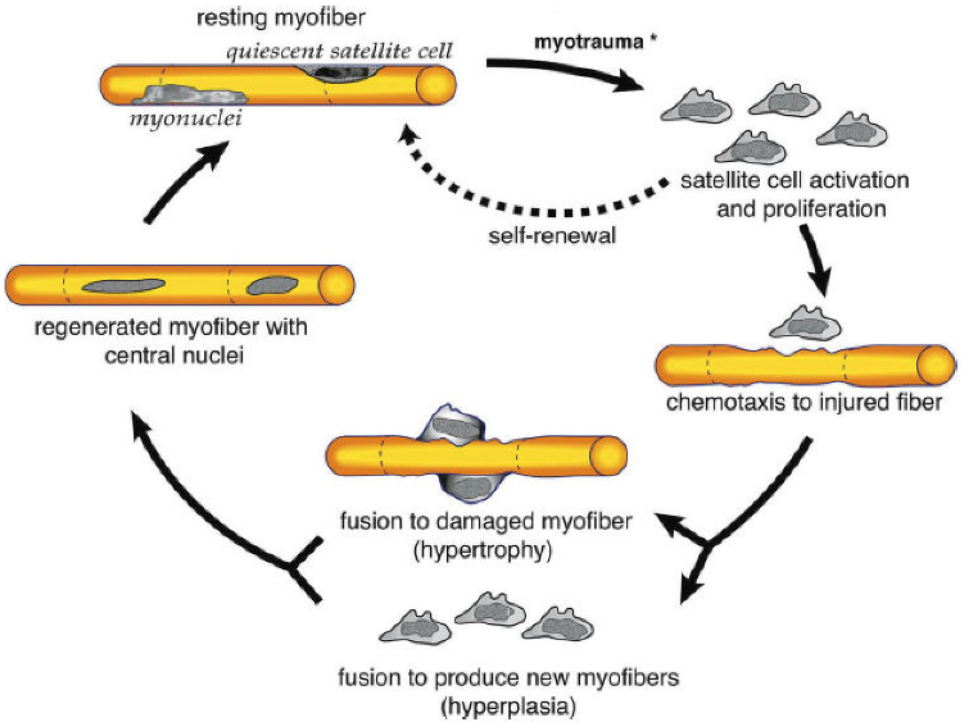
The *skeletal muscles* represent a very significant fraction of body weight and protein mass (28-35% in a healthy adult). They are the source of important renewal, since the organism produces between 250-300 g of muscle protein every day.



Structure of skeletal muscle (Scime et al., 2009)[14]

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

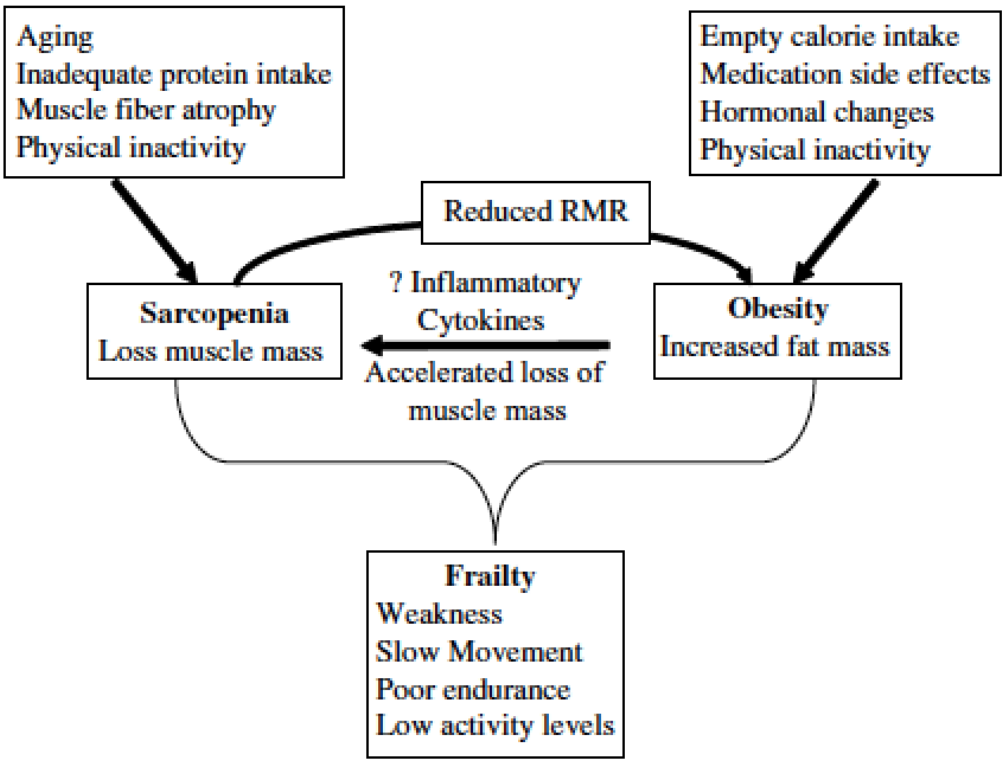
[13] Aussel C, Woelffle E, Lemoigne P, Depailler L, Bouillanne O. 2013. Une nouvelle stratégie nutritionnelle pour lutter contre la dénutrition et la sacopénie : le régime protéique pulsé. *Cahiers Nutrition Diététique*, 48: 33-40.
[14] Scime A, Caron AZ, Grenier G. 2009. Advances in myogenic cell transplantation and skeletal muscle tissue engineering. *Frontiers in Bioscience*, 14: 3012-3023.



The *skeletal muscles* contain several types of *fibers*. Type II fibres are powerful but rapidly fatigued, especially the IIX fibres, while type I fibres are less powerful, but allow prolonged efforts, essentially by consuming fatty acids.

Characteristics	Type I	Type IIA	Type IIX
Contraction Time	Slow	Rapid	Very rapid
Force	Weak	Strong	Very strong
Resistance to fatigue	Strong	Intermediate	Weak
Mitochondria	Abundant	Abundant	Scarce
Oxidative capacity	Strong	Strong	Weak
Source of energy	Lipids	Lipids and Carbohydrates	Carbohydrates

The atrophy of *muscle fibers*, i.e. the reduction in their diameter, is responsible for age-related reduction in muscle mass. This atrophy does not affect all types of *muscle fibers* in a similar way: there are type II fibers which are more affected by advancing age. This atrophy is simultaneously linked to the alteration of the capacity of muscle tissue to synthesize muscle proteins, as well as to exacerbated degradation processes.



The changes leading to sarcopenia are amplified in obese individuals (= sarcopenic obesity) (after Jarosz and Bellar, 2011)[15]

- ***Sarcopenic obesity***

According to a recent study, an obese and sarcopenic individual faces a risk three times higher than a lean sarcopenic individual or a non-sarcopenic obese individual of experiencing a degradation in his functional capacities by the end of an 8-year monitoring period. Sarcopenic obesity is a syndrome affecting a growing number of elderly individuals (10% of those aged over 60) who are overweight or obese and who show an accentuated breakdown of *skeletal muscles* masked by the accumulation of adipose masses within them.
Evidently, the loss of mass and/or of muscle strength increases the risk of a fall and of fractures and leads to a progressive loss of mobility and autonomy. The loss of the metabolic quality of *skeletal muscle*, in particular its capacity to oxidize carbohydrates and lipids and to synthesize proteins, considerably increases the risk of diabetes and of cardiovascular diseases in patients who are often already treated for one or other of these pathologies: arterial hypertension, diabetes and cardiac insufficiency.

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

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

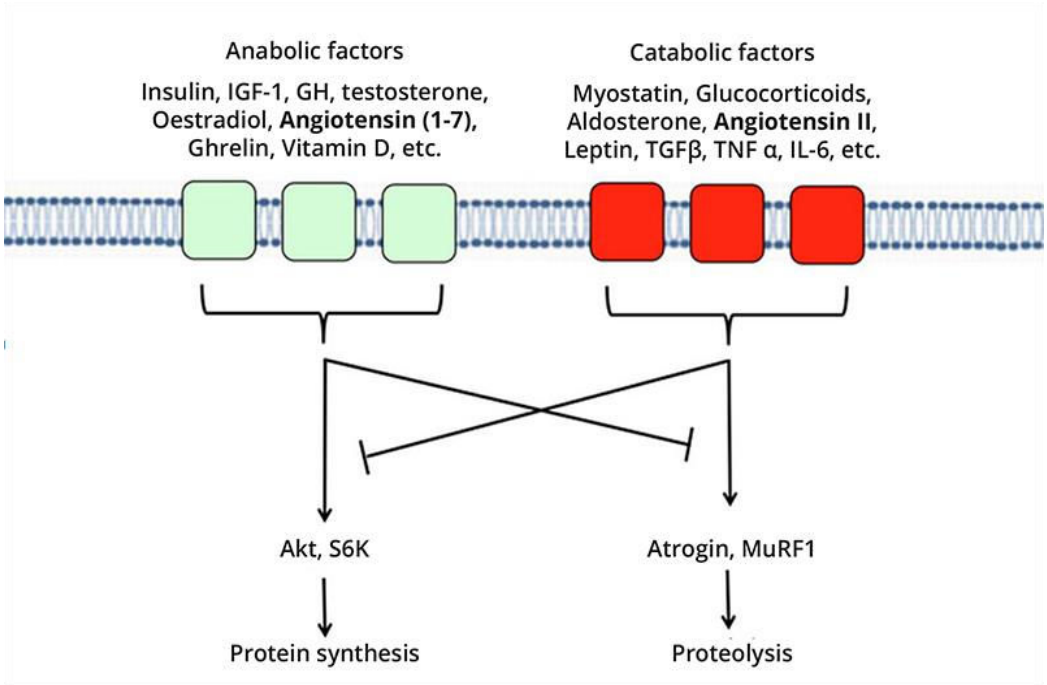
6.2.2. Medical hypothesis

- ***The regeneration of muscle in maintaining muscular functionality***

In simplified fashion, the regeneration of muscle depends on its capacity to synthesize proteins (actin and *myosin*), posing the filaments and to produce new muscle cells (*myoblasts*) which will fuse with the existing *myotubes* (or which fuse among themselves to form new *muscle fibers*). The capacity of the satellite cells to ensure the partial or total renewal of the *muscle fibres* is reduced in the elderly (Snijders et Parise, 2017)[16]. The variations in size of muscles thus depend on those of the size and number of *myotubes*.

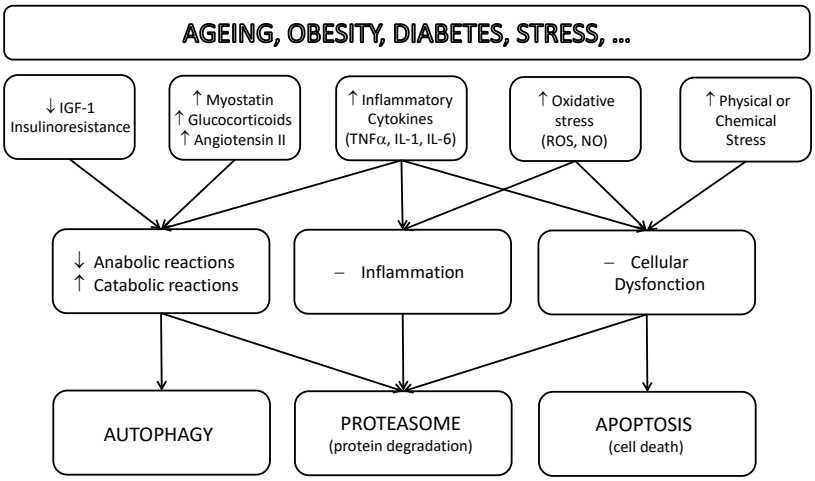
The muscle mass forms the object of a precise multifactor control mechanism, with stimulating factors, such as testosterone *IGF-1* and vitamin D, and inhibiting factors, such as *myostatin*, produced by the muscles themselves in which act in a *autocrine* and *angiotensin II* fashion. On aging, several hormonal changes occur which will shatter this equilibrium and lead to an imbalance between the two types of factors, to the benefit of those favoring muscle degradation. These effects may be magnified by a reduction in physical activity (Rudrappa *et al*., 2016, Gomes *et al*., 2017)[17].

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*).



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

[17] 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 ageing: influence of oxidative stress and physical exercise. *Oncotarget* 8(12): 20428-20440.s



There is also a neurodegenerative component of sarcopenia, linked to a reduction in the number of *motoneurons* and of motor plates, which are essential for muscular activity (Lynch and Ryall, 2008)[18]. Aggravating factors, such as malnutrition, renal insufficiency and diabetes, may influence the intensity and precocity of sarcopenia (Hébuterne, 2003; Pupim et al., 2005; Park et al., 2009; Kim et al., 2010)[19].

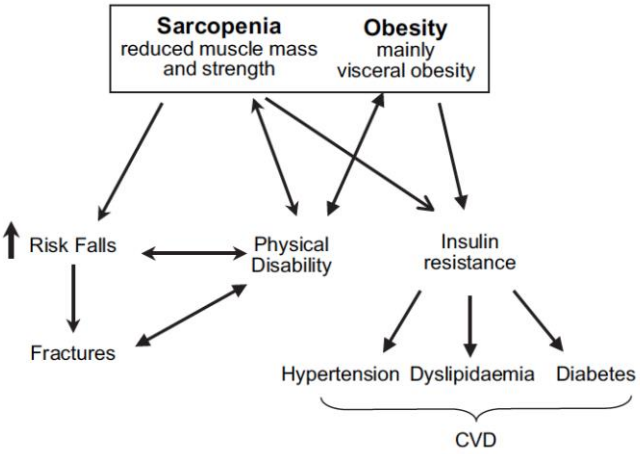
The aging of the muscles is accompanied by a reduction in the size of the *fibers*, as well as by a change in the distribution of the types of *fibers*, to the benefit of type I *fibers* (slow and weak *fibers*). The reduction in the size and number of *myotubes* is not always accompanied by a reduction of the size of the muscles, since following the establishment of inflammatory process and excessive nutritional contributions with regard to the physical activity physique of individuals, these may be infiltrated by *adipocytes*, the multiplication and the development of which will maintain muscle volume constant, 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)[20]. 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 due to the conjunction of several unfavorable factors, the harmful effect of fatty infiltration into the muscles, which reduces their proteosynthetic capacity and amplifies their degeneration and overweight, which limits mobility (Zamboni et al., 2008):

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

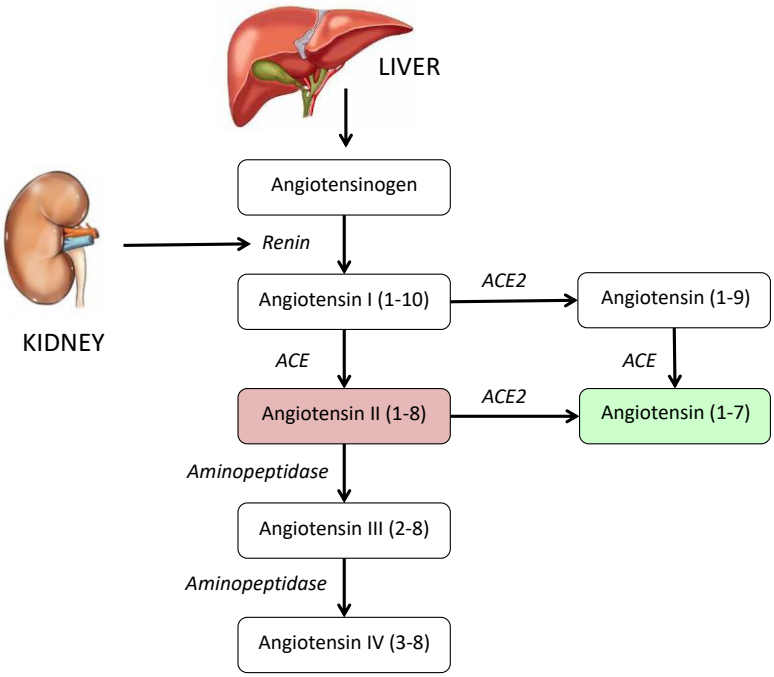
[19] Hébuterne X, Bermon S, Schneider SM. 2001. Ageing and muscle: the effects of malnutrition, re-nutrition, anfd physical exercise. *Curr Opin Clin Nutr Metab* Care, 4(4): 295-300. Pupim LB, Heimbürger O, Qureshi AR, Ikizler TA, Stenvinkel P. Accelerated lean body mass loss in incident chronic dialysis 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.

[20] Walrand S, Boirie Y. 2007. Obésité sarcopénique: "parle à mon gras, mon muscle est malade. *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



- ***The renin-angiotensin system and muscular functionality***

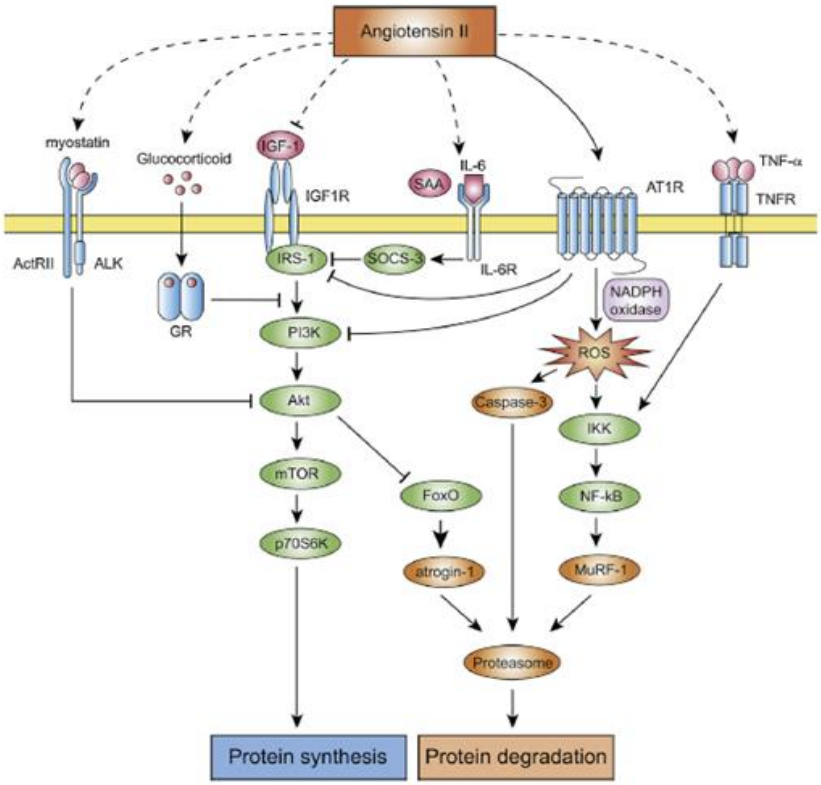
The *renin-angiotensin-aldosterone system* classically refers to a hormonal system, which allows an equilibrium to be maintained between Na^+ (sodium) ions and water, termed sodium and water *homeostasis*. In order to achieve this, renin, an enzyme secreted by the kidney, cleaves the *angiotensinogen*, produced by the liver, to form angiotensin I. This is then cleaved by a "conversion" enzyme (ACE) into angiotensin II, which is a *peptide* with very powerful vasoconstriction 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*:



The physiological roles of all of these compounds are under study. The involvement of the *renin-angiotensin system* (RAS) in the physiopathological process leading to sarcopenia was envisaged in various genetic and *pharmacological* studies on animals and humans (Carter and Groban, 2008)[21].

[21] Carter CS, Groban L. 2008. Role of the renin-angiotensin system in age-related sarcopenia and diastolic dysfunction. *Aging Health*, 4(1): 37-46.

Skeletal muscle cells are the targets of angiotensin II via the AT1R receptor. By virtue of this, it currently appears that angiotensin II is a major player in the appearance of sarcopenia (Yoshida et al. 2013)[22].



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- and IL-6 (Yoshida et al., 2013). These effects may also include a reduction in *autocrine* production of *IGF-1* (Brink et al., 2001)[23].

The study of the physical capacity of elderly patients treated with ACE inhibitors (ACE-I) for arterial hypertension provided a demonstration, in epidemiological or intervention studies, that in certain cases, notably in combination with physical exercise, this treatment could improve the mobility of elderly patients (Buford et al., 2012)[24]. The effect of ACE inhibitors on the physical performance of sports people is moreover well-established by numerous clinical studies, as is the association of an insertion/deletion polymorphism in the ACE gene with the response to resistance or endurance exercises (Ma et al., 2013; Nazarov et al., 2001)[25].

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[22] 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.

[23] 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.

[24] 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 reponses to exercise. *J Am Geriatr Soc*, 60(7): 1244-1252.

[25] 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.

Number of patients	Patients	Compound	Result	Authors
641	Hypertensive Women Aged 77-80	ACE Inhibitor	Lower loss of muscular force and speed of walking over 3 years in the treated group	Onder et al. (2002)[26]
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)[27]
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)[28]
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)[29]
424	Elderly individuals with a muscular function problem 70-89	ACE Inhibitor	Physical activity significantly improved, with an improvement in walking speed in users of ACE inhibitors	Buford et al. (2012)[30]

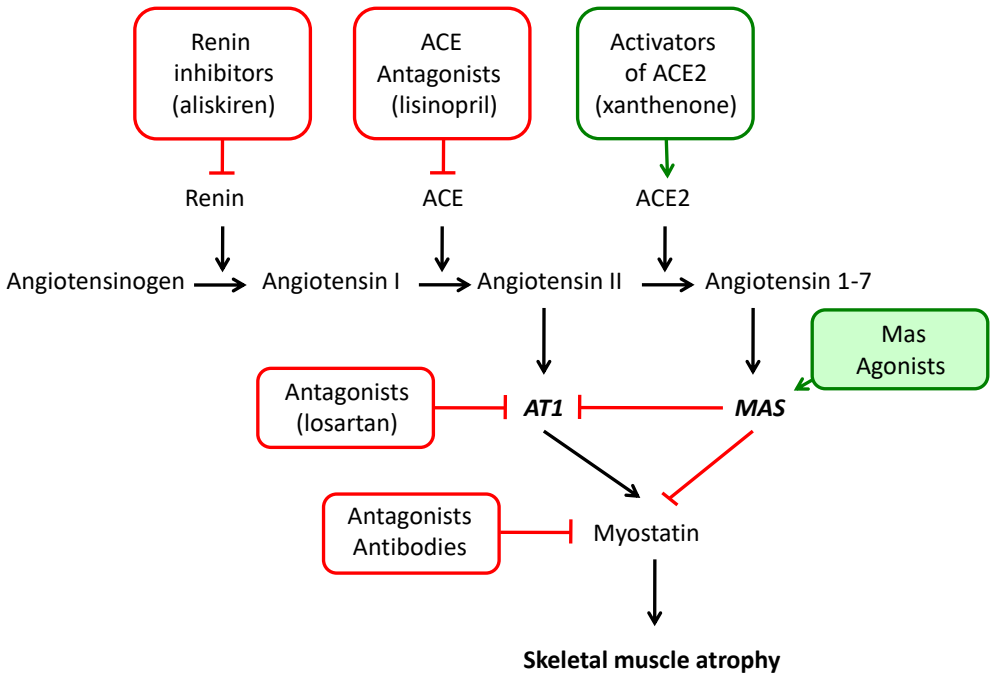
ACE inhibitors were also tested in several clinical studies for treating patients affected by *Duchenne muscular dystrophy*, as a substitute or supplement to *beta blockers*, with very interesting results regarding cardiac insufficiency, delaying the progression of the *cardiomyopathy* (Viollet et al., 2012)[31].

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

Other actors in the RAS system appeared to be able to act on *muscular functionality*. Angiotensin 1-7, formed by an enzyme termed ACE2 and its receptor (Mas) were recently discovered. 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)[32].
Developing *agonists* of the Mas receptor to treat sarcopenic obesity is particularly original, with no product of this type mentioned in the scientific literature for treating this indication. This receptor, which was an orphan until a few years ago, has not, as far as the Company is aware, formed the object of *pharmacological* development. It is likely that the stimulation of Mas will

[26] 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.
[27] 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.
[28] 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.
[29] 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.
[30] 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 reponses to exercise. *J Am Geriatr Soc*, 60(7): 1244-1252.
[31] 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.
[32] 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.

not produce exactly the same effects as the inhibition of the 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 *polypharmacy* by treating not the symptoms but the principle cause of these pathologies in obese sarcopenic elderly individuals by combining physical exercise and pharmaceutical intervention.

6.2.3. Proof of Concept

Biophytis' compounds are the first non-peptide molecules which are agonists of the Mas receptor to form the object of pharmaceutical development. The tests of compounds Sarconeos and BIO103 on muscle cells showed a significant increase in protein synthesis and growth in the diameter of myotubes. Furthermore, in animal models submitted to 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. Finally, 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.

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Biophytis' researchers have directed their interest towards a family of molecules of plant origin, which are *analogues* of insect hormones, and quite surprisingly, present in the medicinal plants

used on various continents (Europe, Africa, the Americas, Asia, and Oceania). In particular, these plants have *anabolizing* and anti-diabetic activities, albeit without it yet being established that these molecules represent active principles.

In this family of almost 400 compounds, a molecule is most frequently encountered and is often the most abundant within a complex cocktail. This is *Sarconeos*. This molecule 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 also sparked research, especially in the United States and Germany. This molecule is very different from mammalian and human hormones and for this reason, does not interfere with their hormone system. It also has a very low toxicity (DL50 oral> 9 g/kg).
It is only quite recently that the molecule has become available with a good degree of purity and in adequate quantities to permit large-scale and unambiguous experimentation regarding the nature of the active molecules used.
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* associated with the *screening* of more than 100 derived molecules. This *screening* had the object of selecting a molecule with improved activity and bioavailability.

Sarconeos was chosen for the following properties:

- this molecule stimulates protein synthesis (*hepatocytes*, myocytes) by stimulating the final phase (translation);
- it has hypoglycaemic effects;
- it has hypolipidaemic effects.

- ***Action mechanism: involvement of Mas***

Biophytis has determined the principal action mechanism of *Sarconeos*, which is responsible for the anabolizing muscular effect, involving the Mas receptor.

With various pharmacological effects arguing in favor of the membrane effect via a *G protein* (Gorelick-Feldman et al., 2010)[33], Biophytis initially prepared conjugates between *Sarconeos* and *serumalbumin*, and observed that the compound bound by the 22-OH remained active, while it was incapable of entering cells, with this confirming a membrane action.

On the basis of the observed effects and an exhaustive bibliographic analysis, around 10 candidate receptors were retained and tested. Ultimately, it was proven that the effects of the 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 the compounds of Biophytis on the cells C2C12, while they were without effect on the *anabolizing* action of *IGF-1*. In the same way, the absence of the Mas receptor following the injection 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)[34]. It nevertheless remains possible that certain effects differ, since it was demonstrated that the Mas receptor

[33] 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.
[34] 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.

could respond differently according to the *peptide/non-peptide* nature of the *ligand* used (Tirupula et al., 2014)[35].

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

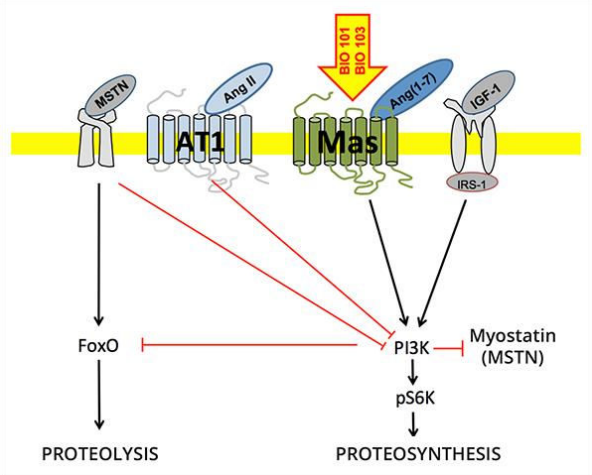
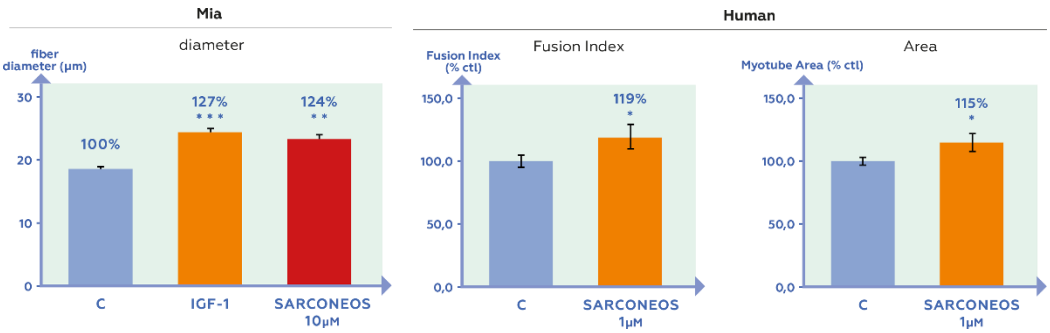


Diagram representing the action mechanism of Sarconeos on muscular anabolism and catabolism

- ***Experiments on muscle cells***

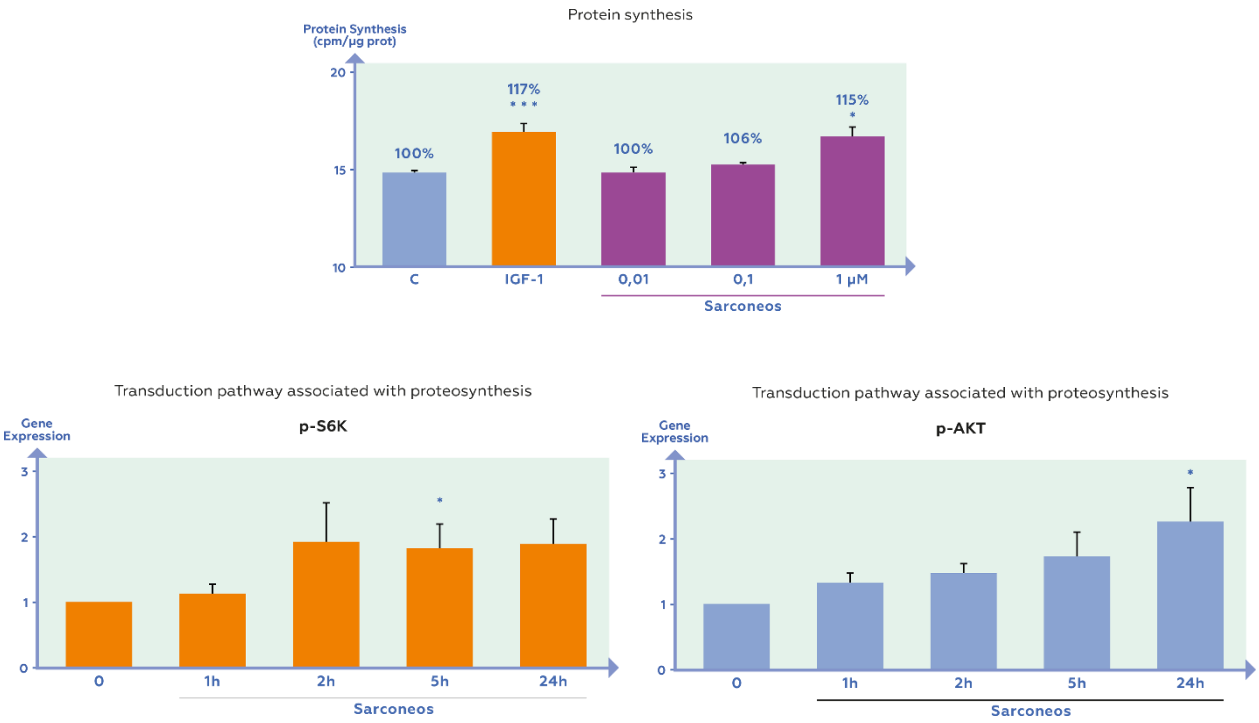
The cells are placed in a medium permitting their proliferation and then their fusion and differentiation into *myotubes*, with the thereby possible of appreciate the effect of molecules to be tested on these two processes. Several markers were used:

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

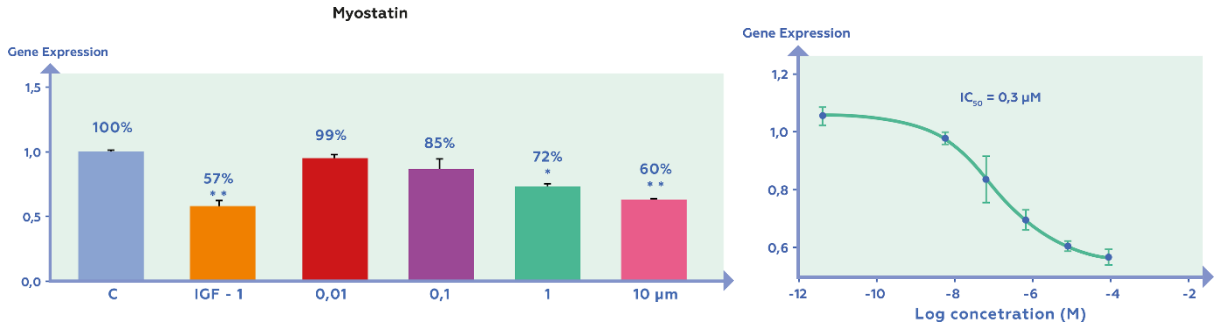


Hypertrophic effect of Sarconeos on murine and human muscle fibres

[35] Tirupula KC, Desnoyer R, Speth RC, Karnik SS. 2014. Atypical signaling and functional desensitization response of mas receptor to peptide ligands. *PLoS ONE*, 9(7): e103520.



Stimulation by Sarconeos of protein synthesis and activation of a transduction pathway involved in proteosynthesis



Dose-dependent inhibition of the expression of myostatin by Sarconeos

The molecules may be tested alone (dose-response effects) or in combination, in order to test *antagonisms* or synergies. The selection of molecules for synthesis was essentially realized on the basis of the measurement of the transcripts.

- ***Experiments conducted in animal models***

Several experiments were carried out to assess the activity of *Sarconeos* in animal models subject to a fat diet, in mice and rats, in particular within a context of obesity and/or aging:

Reference	Animal Model	Results
Foucault et al., 2015, manuscript in preparation	Mouse C57Bl/6J young, fed with a fattening 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[36]	Old and adult C57Bl/6J mice, fed with a fattening diet	Significant improvement in the physical performance of older animals
Foucault et al., 2014[37]	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[38]	Mouse C57Bl/6J 6-8 weeks, fed with a fattening diet, 3-week treatment	Reduction in epididymal and subcutaneous body fat

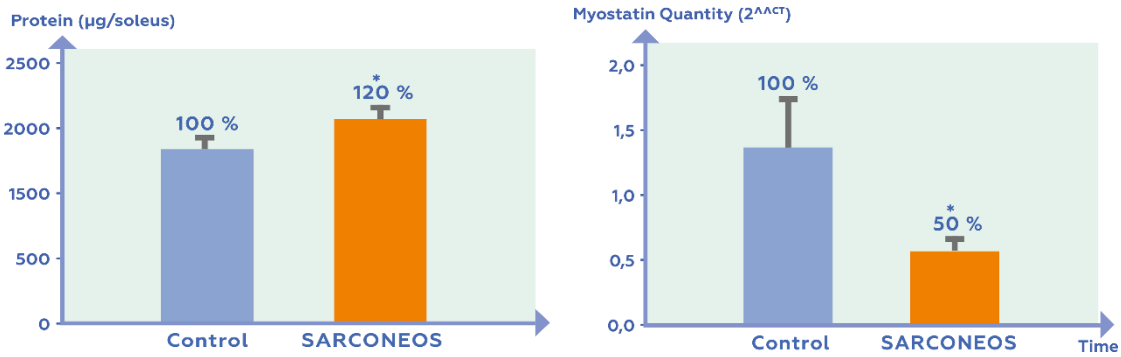
In the case of young animals, the molecules were either incorporated into their feed, or administered orally on a daily basis. We shall consider the principal results obtained here:

- the tested molecules limit the appearance of obesity;
- the muscles are heavier and contain more proteins;
- the expression of the *myostatin* is reduced, while that of the markers of myogenesis (*myogenin*, *myoD*) is increased.

[36] 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.

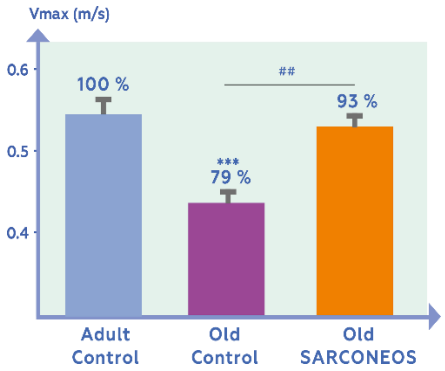
[37] Foucault AS, Even P, Lafont R, Dioh W, Veillet S, Tom. D, Huneau JF, Hermier D, Quignard-Boulangé A. (2014). Quinoa extract enriched in 20-hydroxyecdysone affects energy homeostasis and intestinal fat absorption in mice fed a high-fat diet. *Physiol Behav* 128: 226-231.

[38] 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.



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

A chronic oral treatment with *Sarconeos* is responsible for 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[39].



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

- ***Clinical studies on healthy volunteers***

The effects of *Sarconeos* were evaluated in two clinical studies conducted (1) in a nutritional context: QUINOLIA and (2) as part of a phase 2b study: SARA.

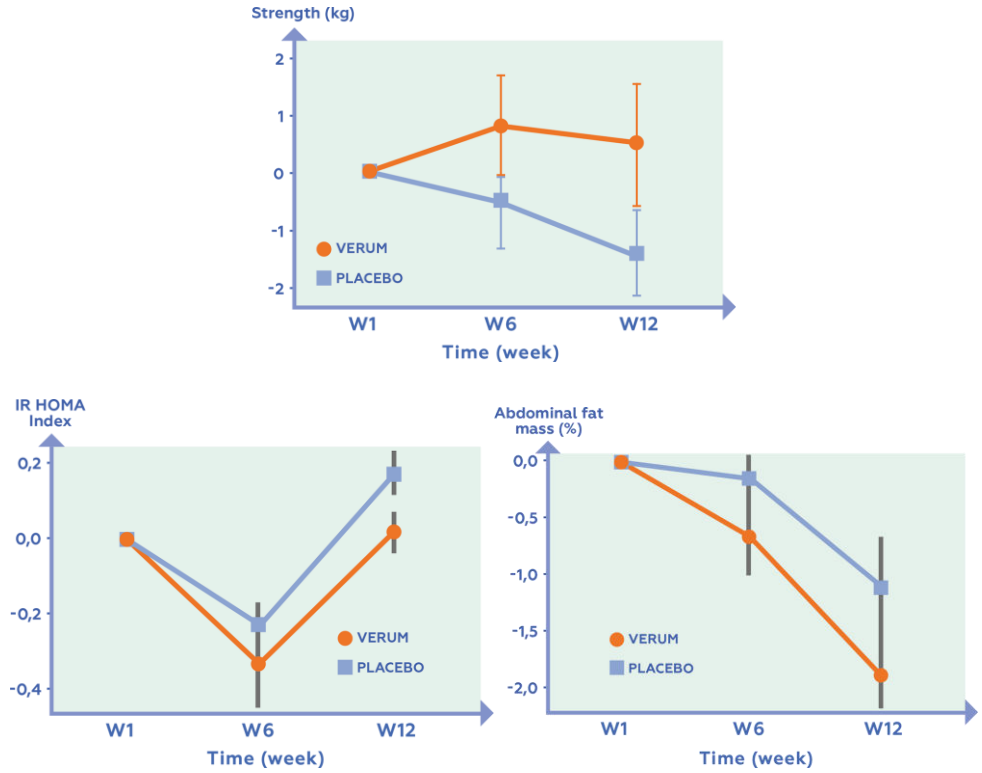
<u>QUINOLIA Study</u>

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). They 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

[39] 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.

mg/ day by the team of Prof. Wuttke of the University of Göttingen (Wuttke and Seidlova-Wuttke, 2013[40]).

Reference	Dosage	Volunteers & Protocol	Results
Foucault *et al.*, 2017, manuscript in preparation	40 mg/day	58 obese volunteers (30 verum, 28 placebo) 18-65 years old 3 months, including 1.5 months under a low-calorie diet	Reduction in abdominal fat Reduction in insulin resistance Stabilisation of weight after the 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 molecule increased their physical capacity (Azizov et al.,1998; Gadhzieva et al., 1995)[41], as well as their muscle mass (+ 6.5%- Simakin

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

[41] 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.

et al., 1988)[42]. The treatment of elderly populations requires a balance to be struck between the benefits of treatment and its impact on their quality of life.

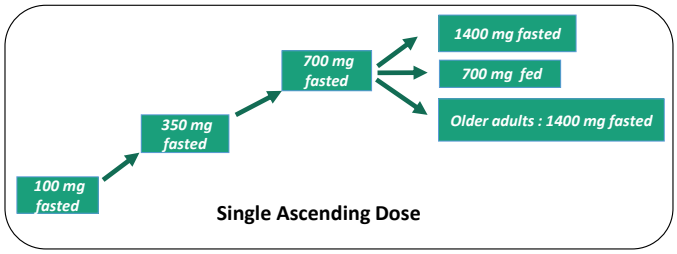
Preparation of Sarconeos clinical batches

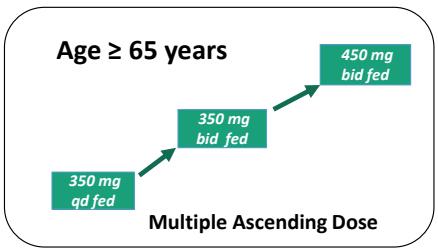
The Active Pharmaceutical Ingredient i.e. API), BIO101, is an extract of *Stemmacantha carthamoides*, a dual-purpose medicinal and food plant cultivated in China and purified for pharmaceutical use (>97% purity of the active molecule) by observing Good Manufacturing Practices for pharmaceutical products (GMP) by Patheon, a global American industrial corporation. The industrial scale-up and production of piloted clinical batches commenced in the third quarter of 2015 and the supply chain has been secured. These batches enabled the SARA-PK study to be carried out. The results of that study are presented below, and another series should be ready for the SARA-INT study.

SARA-PK Clinical Study

As part of the preparation of phase 2b (as described in paragraph 6.1.4 above), a clinical safety, pharmacokinetic, and pharmacodynamic study was conducted by Biophytis between August and November 2016. The SARA-PK clinical study to determine safety and to evaluate pharmacokinetics and pharmacodynamics in healthy, young, and elderly volunteers 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 staggered oral administration of Sarconeos 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.





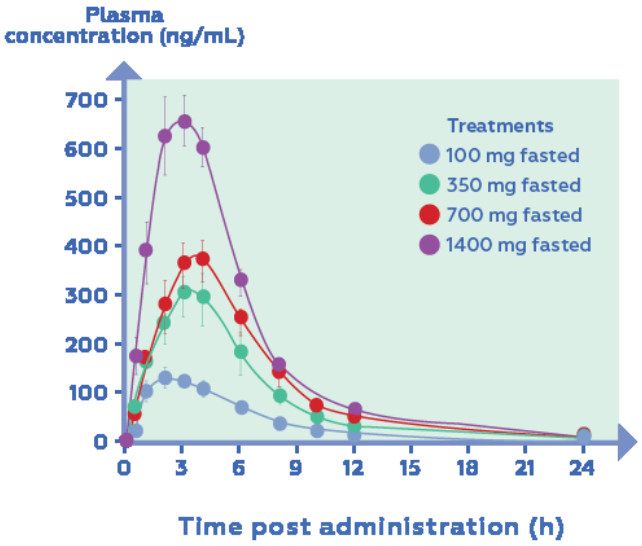
SARA-PK clinical study design SAD (Single Ascending Dose) and MAD (Multiple Ascending Dose).

[42] 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.

The administration of *Sarconeos* in single ascending doses (SAD) of 100, 350, 700, and 1400 mg is well tolerated by healthy young and elderly volunteers. No serious adverse events were noted during this SAD phase. Only mild adverse events were observed. Furthermore, no abnormalities of vital signs or clinical laboratory parameters were observed in these volunteers.

The administration of multiple doses (MAD) for 14 days at 350 mg qd (quaque die, once daily), 350 mg bid (bis in die, twice daily), and 450 mg bid is also well tolerated as attested by the absence of serious adverse events at the doses tested. The adverse events were mild, although there were 3 cases of moderate adverse events at 450 mg bid. The vast majority of adverse events were resolved 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 to reach maximum plasma concentration of between 2 to 3.5 hours depending on the dosages used. The pharmacokinetic parameters (Tmax and AUC) were not significantly modified by the administration of *Sarconeos* under fasting conditions compared to when having taken one meal at 700 mg/day. Similarly, Tmax and AUC are comparable in elderly volunteers and healthy young volunteers at a dose of 1400 mg/day. These factors led to choosing an administration taken along with one meal and two daily intakes for *Sarconeos* in the randomised double-blind SARA-INT clinical trial.
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 MAD (day 14), the steady state is reached on the second day of the Sarconeos administration.

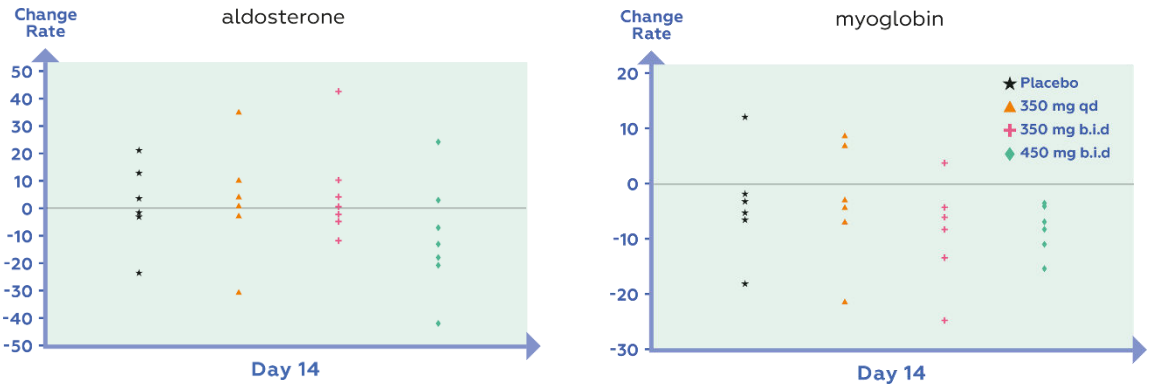


Development of plasma exposure in healthy volunteers under fasting conditions treated with Sarconeos in SAD.

The effects of administering Sarconeos on the development of pharmacodynamic markers were evaluated in MAD in an exploratory framework. Interesting preliminary results showed a tendency to decrease the plasma level of 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 to decrease the level of plasma aldosterone implies that Sarconeos acts 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[43]).

The overall results of the SARA-PK study were orally presented at the International Congress on Frailty and Sarcopenia Research (ICFSR) held in Barcelona on 27-29 April 2017.

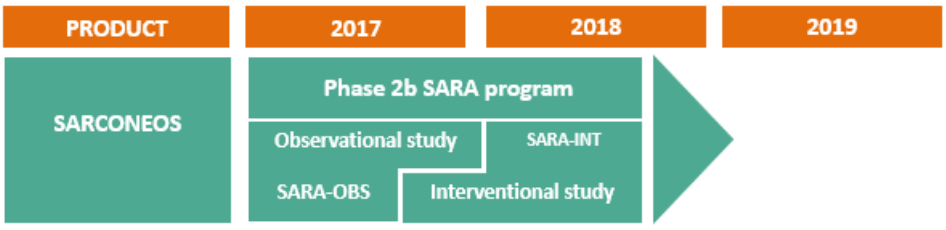


Effect of Sarconeos treatment for 14 days on the development of two pharmacodynamic markers linked to the renin-angiotensin system (aldosterone) and muscle catabolism (myoglobin)

The safety, pharmacokinetic, and pharmacodynamic results of SARA-PK confirm the favourable therapeutic framework of Sarconeos and allow defining 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.

6.2.4. Next stages of development for Sarconeos

The next development stage involves determining the effective therapeutic dose of *Sarconeos* in a phase 2b *clinical study* conducted on 333 sarcopenic patients including sarcopenic obese patients.



- Supervision of SARA clinical studies

Biophytis initiated a pilot study to define the target population and to pre-select patients with sarcopenia (SARA-OBS study) in preparation for the SARA-INT phase 2b study. The supervision of the SARA-OBS study was entrusted to the Contract Research Organisation (CRO) ICON. Biophytis obtained regulatory authorisations to start this study in the target countries and recruitment began in 7 centres located in France, Belgium, Italy, and the United

[43] 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

States. The CRO ICON distinguished itself in recent years by its interest in sarcopenia, notably by developing didactic tools in collaboration with Professor Fielding's centre in Boston, and also by its participation in the Task Force on sarcopenia in addition to the ICFSR congresses in Philadelphia in April 2016 and Barcelona in April 2017.

- SARA-PK Observational Study

To date, several centres have been opened for SARA-OBS: The Gérontopôle in Toulouse with Professor Yves Rolland as principal investigator. Prof. Rolland is also the national coordinator for France. A second French centre was opened at the Hôpital Lyon Sud with Professor Marc Bonnefoy as principal investigator. The Liège University Hospital in Belgium opened with Professor Olivier Bruyère, and the La Sapienza Hospital in Rome, Italy, opened with Professors Donini and Gnessi. In the US, the Gainesville Florida centres with Professor Marco Pahor, and the Tufts University centre in Boston Massachusetts with Professor Roger Fielding have opened. Professor Roger Fielding is the principal investigator of the SARA-OBS study.

The SARA clinical strategy, the SARA-OBS protocol, and their implementation are monitored by the Steering Committee made up of of Professors Roger Fielding, Marco Pahor, Olivier Bruyère, and Yves Rolland.

The criteria used to include the 333 patients are (i) aged ≥ 65 years, (ii) the Foundation for the National Institutes of Health (FNIH) criteria based on a Short Performance Physical Battery (SPPB) score ≤ 8 and an ALM/BMI index of < 0.789 in men and < 0.512 in women. This latter index, calculated from the DEXA (X-ray biphotonic absorptiometry) measurement, is specific to the lean mass of the limbs (Appendicular Lean Mass: ALM) adjusted to the body mass index (Body Mass Index: BMI).

The investigation phase shall last 6 months. It is preceded by a recruitment phase that also lasts 6 months. The main criteria of this study are the measurement of physical performance with the 6-minute walk test and the 400-metre test. Several other secondary criteria such as the grip test or the knee extension test will be evaluated. The evolution of the plasma level of various biomarkers, components of the Renin Angiotensin system involved in muscle metabolism or in inflammation, is also measured. Finally, Patient Reported Outcomes will also be used in this study. They will allow measuring the evolution of the physical state of the patients throughout the 6-month investigation period.

All the data collected in the SARA-OBS framework are hosted on the SARA-data platform[44], which includes various modules along with the electronic case report form of the study, the module containing the body composition data set, and the module for measuring the physical performance of patients with the Adamo actimeter. Finally, one last module that is currently being set up will host data from the biobank.

SARA-OBS should allow the preparation of the SARA-INT interventional study. At the end of the 6-month SARA-OBS investigation period, the baseline data for patients who will be asked participate in the SARA-INT study will be reported.

- SARA-INT Interventional Study

[44] 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

The objective of the clinical study is to assess the effect of the Sarconeos product on muscle function of sarcopenic persons aged over 65 years old, in accordance with criteria proposed by the Foundation for the National Institute of Health (FNIH)[45]. Two *Sarconeos* doses will be compared with placebo: 350 mg in two doses and 700 mg in two doses.
The clinical batches used in the SARA-INT study are being manufactured under the same conditions of Good Manufacturing Practice (GMP) by the American company Patheon and by Amatsi Avogadro as for the SARA-PK study. These clinical batches are available for the start of SARA-INT in the second half of 2017. They come in the form of opaque capsules containing the active ingredient and the excipients.

333 sarcopenic patients will be recruited in roughly fifteen Clinical Investigation Centres in Europe (France, Belgium, and Italy) and the United States. SARA-OBS is a continuation of SARA-OBS and the 8 SARA-OBS Clinical Investigation Centres will be retained, with additional centres added for a total of 15 to 17 centres. We want to remain in the same countries (United States, France, Belgium and Italy) to select these additional centres. The supervision of SARA-INT will be entrusted to the CRO ICON in the same spirit of continuity. Professor Roger Fielding is the principal investigator of SARA-INT and the same Steering Committee as for SARA-OBS has been reappointed.

From a regulatory standpoint, and using data from SARA-PK and SARA-OBS, Biophytis sought the scientific opinion of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). These scientific opinions will make it possible to take into account the comments of the agencies for the submission of the final SARA-INT protocol in the second half of 2017.

It is planned that the same inclusion criteria of SARA-OBS will be used (age ≥ 65 years as well as the Foundation for the National Institutes of Health (FNIH) criteria based on a Short Performance Physical Battery (SPPB) score ≤ 8 and an ALM/BMI ratio of < 0.789 in men and < 0.512 in women.

The main criterion is the 6-minute walk test, which accurately measures the ability to perform everyday tasks. Several secondary criteria including muscle strength, physical performance (SPPB test, Cruz-Jentoft and al. 2010), body composition and plasmatic parameters will be assessed during the study. The investigation phase of this study will take 6 months as recommended by the European Working Group on Sarcopenia[46]. Plasma biomarkers monitored in the SARA-OBS study have also been retained for evaluation in SARA-INT. These are biomarkers related to the Renin-Angiotensin system to inflammation (IL-6, CRP and HsCRP) and to muscle metabolism (PIIINP, Myoglobin, Creatine Kinase MM, and Creatine Kinase MB).

Two Patient Reported Outcomes have been selected from the three used in SARA-OBS and will allow measuring the change of the patient's physical state throughout the investigation period.

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[45] Studenski et al., 2014. The FNIH Sarcopenia Project: Rationale, Study Description, Conference Recommendations, and Final Estimates. *J Gerontol A Biol Sci 2014 May*; 69(5): 547-558
[46] 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.

As for SARA-OBS, data collected during SARA-INT will be hosted on the SARA data platform[47].

This phase-2b study is consistent with the internationalisation strategy of Biophytis and has been designed to meet the regulatory requirements in Europe and the United States in order to reduce the risk of failure, and optimise the potential of *Sarconeos.*

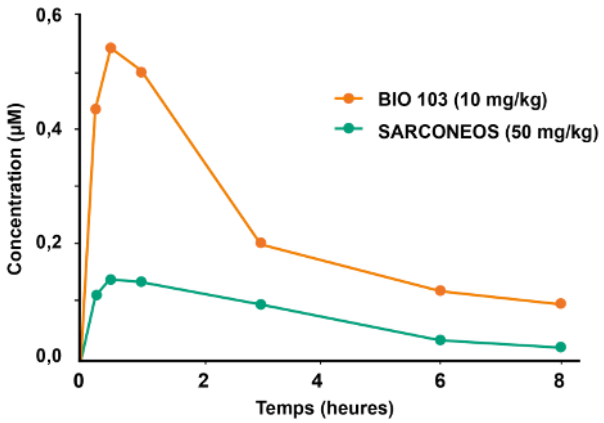
The schedule of this study comprises several phases as follows:

H1 2017:	SARA-OBS Recruitment of patients from the observational phase (late 2017)
H2 2017:	SARA-INT Study: Regulatory filings (AFMPS, ANSM, EMA, AIFA, and the FDA) and start of the clinical research phase.
H2 2018:	SARA-INT Study: Presentation of results

6.2.5. Development of BIO103 for other muscular dystrophies

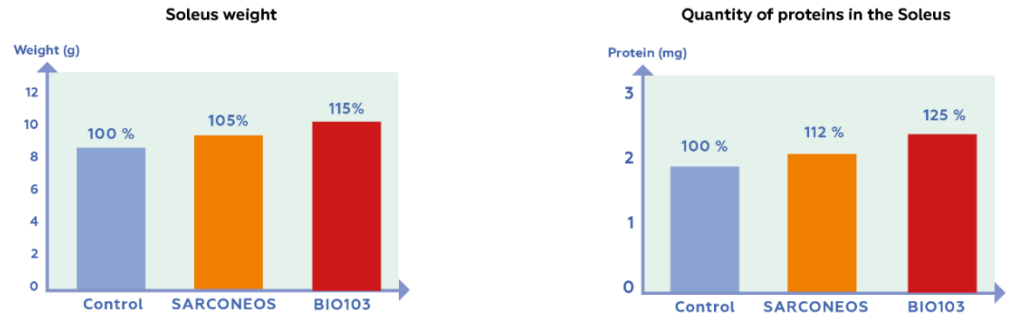
The development of BIO103 involved synthesising more than 150 new chemical molecules, derived through *hemi-synthesis* from *Sarconeos* in more than 5 chemical series, which were assessed in several in vitro tests (notably in the muscular cells C2C12), and in vivo (notably in the obese mouse model).

BIO103 was selected at the end of this process and showed an improved pharmacological profile in relation to *Sarconeos*, with bioavailability 20 times higher than that of *Sarconeos* and improved in vivo activity in the animal model.



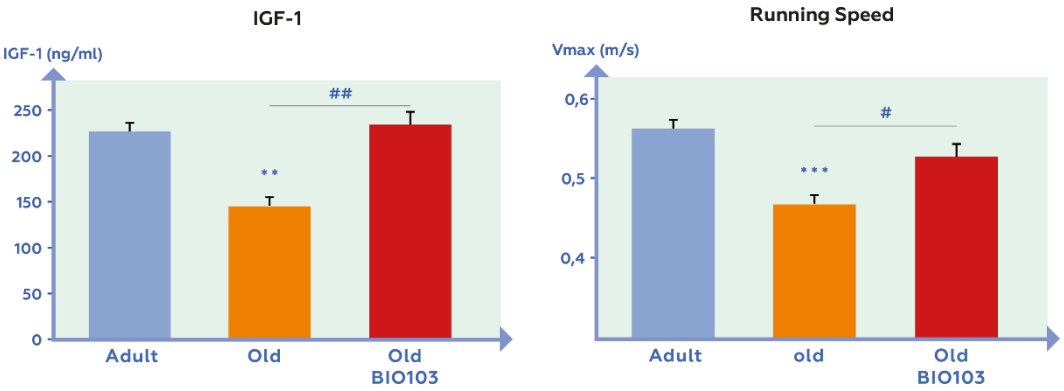
Comparison of BIO103 and Sarconeos plasma levels after oral administration

[47] 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



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. Importantly, and comparably to what we observed in the case of Sarconeos, we 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[48].



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

BIO103 may be developed to treat muscular dystrophies other than sarcopenia. In this regard, Biophytis also intends to assess whether BIO103 is safe to use in animals, by compiling a non-clinical regulatory file, and in humans by subsequently conducting a phase 1 study.

[48] 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

6.2.6. Competition

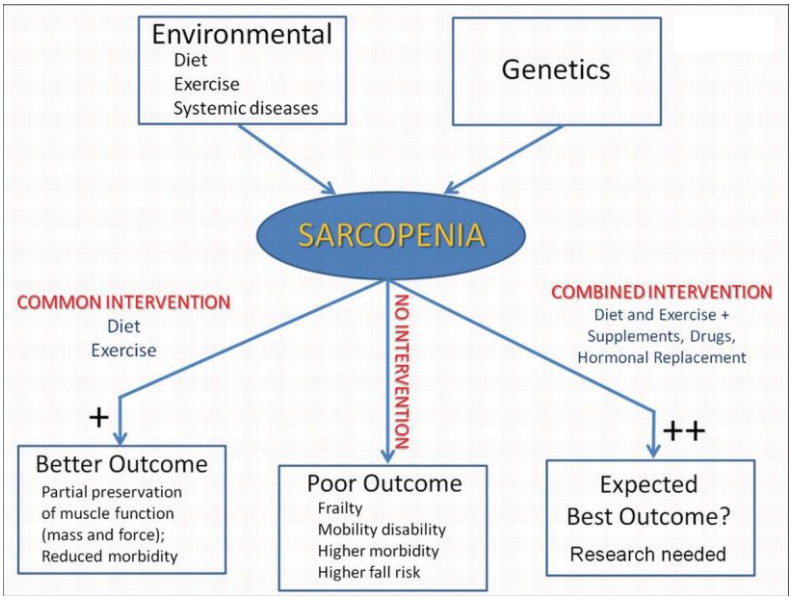
The treatment of elderly populations requires a balance to be struck between the benefits of treatment and its impact on their quality of life.
Physical activity is recommended as a means of combating sarcopenia. It is accordingly advisable to implement a daily 30-minute programme of resistance training that is specifically designed to build up muscle strength and mobility. Physical exercises over an 8-week period may suffice per se to increase muscle strength by 180% and muscle mass by 11% (Fiatarone et al., 1994)[49].

Suitable nutrition is certainly necessary for replenishing the substrates of *protein synthesis*. In fact, in elderly people the digestive tract has a tendency to use amino acids for its own benefit. It is therefore advisable to increase the quantity of proteins ingested so that the *post-prandial* concentration of amino acids is sufficient to stimulate muscular *protein synthesis* (Symons et al., 2007)[50], and even a "pulsed" protein supplement (Aussel et al., 2013)[51]. The *leucine* supplement follows the same logic (Katsanos et al., 2006)[52].

Multinational food corporations, such as Nestlé, Danone and Lactalis, are moreover developing medical nutrition products, based on a supplement of proteins, essential amino acids and Vitamin D, which are marketed in different countries as prescription-only medicines, although their clinical efficacy has yet to be demonstrated in large-scale, multi-centre clinical studies as none of these products have for example obtained a health claim validated by the EFSA (European Food Safety Agency).

Nutraceutical or medicinal treatments aim to increase the efficacy of basic treatments (protein supplements, physical exercises), certainly not to replace them (according to Brotto and Abreu, 2012)[53].

[49] Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, Roberts SB, Kehayias JJ, Lipsitz LA, Evans WJ. 1994. Exercise training and nutritional supplementatino for physical frailty in very elderly people. *J Medicine*, 330(25): 1769-1775.
[50] 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.
[51] 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.
[52] Katsanos CS, Kobayashi H, Sheffield-Moore M, Aarsland A, Wolfe RR. 2006. A high proportion of leucine is required for optimal stimulation of the rate of muscle protein synthesis by essential amino acids in the elderly. *Am J Physiol Endocrinol Metab*, 291: E381-387.
[53] Brotto M, Abreu EL. 2012. Sarcopenia: Pharmacology of today and tomorrow. *J Pharmacol Exp Ther* 343(3): 540-546.



Numerous products belonging to different classes of molecules have been tested on sarcopenic subjects in clinical studies during this last decade. They are:

- Substrate molecules for protein synthesis which are amino acids or their *metabolites* (*leucine*, beta-hydroxy-beta-methyl-butyrate (HMB), citrullin, ornithine), as well as rapidly digestible proteins such as lactoserum.
- Anabolizing hormones such as testosterone or its variants, *SARM*, growth hormone (*GH*), *IGF-1*, vitamin D, ghrelin or progranuline.
- M*yostatin* 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 -adrenergic receptors).
- Various natural substances such as polyphenols (resveratrol, isoflavones), triterpenes (ursolic and oleanolic acids), or phytosteroids (brassinosteroids, phytoecdysones).

Several pharmaceutical laboratories (GSK, Sanofi, Novartis, Eli Lilly, …) have projects to develop drug candidates in phase 1 or 2, based on the use of therapeutic antibodies that inhibit *myostatin*. Several other laboratories (MSD, Pfizer, Servier, Astra Zeneca, Takeda, …) have tested the benefit of different strategies in treating this pathology, in particular the use of testosterone in association with inhibitors of aromatase or Selective Androgen Receptor Modulators (*SARM)*, but the development of these drug candidates was stopped in phase 2 due to side effects and related cancer risks. These technologies were generally developed in cooperation with different biotech companies (Morphosys, GTx, Regeneron, …). Lastly, several centres for clinical research on aging tested the benefit of ACE inhibitors in increasing muscle quality and mobility in elderly patients undergoing treatment for high blood pressure. The results obtained are interesting, but as the primary indicator for ACE inhibitors is high blood pressure and cardiac insufficiency, and as they are generic, no significant private investment has been made with the aim of continuing the *clinical* and regulatory development of these products for this new indication.

Nowadays pharmaceutical laboratories are focusing their efforts on the *clinical development* of *myostatin* inhibitors to treat severe forms of sarcopenia, by also conducting related studies on genetic *muscular dystrophies*, such as *Duchenne myopathy* or clinical situations of *cachexia* (cancer, chronic obstructive bronchopneumopathy). All the projects are in clinical

phase 1 or 2, and the proof of concept of this strategy has yet to be established (Smith and Lin, 2013, Morley and al, 2016)[54].

Clinical studies with myostatin inhibitors and other drug candidates targeting sarcopenia (adapted from Smith and Lin, 2013)[55]

Name	Type	Sponsor	Pathology	Patients	Phase	Stage
LY2495655	Anti-*myostatin antibody*	Lilly	Muscular atrophy	Hip replacement	Phase II	Finished
			Muscle weakness	Frail elderly persons	Phase II	In progress
MYO-029	Anti-*myostatin antibody*	Wyeth	Adult muscular dystrophy	Various muscular dystrophies	Phase II	Stopped
ACE 031	ActRIIb-Fc	Acceleron/Shire	Muscle loss	Menopausal women in good health	Phase Ia	Finished
			Muscular atrophy	Menopausal women in good health	Phase Ib	Stopped
			Duchenne muscular dystrophy	Duchenne muscular dystrophy	Phase II	Stopped
PF-06252616	Anti-*myostatin antibody*	Pfizer	-	Health volunteers	Phase I	Recruitment
BYM338	ActRIIB antibody	Novartis	Inclusion body myositis	Inclusion body myositis	Phase II	Finished
			Skeletal muscle	Sarcopenic adults	Phase II	Finished
			Cachexia	*Cancer-induced cachexia*	Phase II	Finished
			Obesity with type 2 diabetes	Obese persons with type 2 diabetes	Phase II	Recruitment
			Hip fracture	Elderly patients	Phase II	Recruitment
GSK2881078	SARMs	GSK	*Sarcopenia*	Healthy elderly volunteers	Phase I	Finished
CK-2127107	Troponin activator	Astellas/Cytokinetics	*Sarcopenia*	Elderly patients with reduced mobility	Phase Ib	Recruitment

The first published results address the effect of *myostatin inhibitors in* a rare orphan disease: inclusion body myositis, a rare autoimmune disease, in which an increase in mass, muscle strength and mobility has been ascertained.

Nowadays laboratories are focusing their efforts on the *clinical development* of *myostatin* inhibitors to treat the severe forms of sarcopenia by attempting to block its interaction with the activin receptor type IIB (ActRIIB). Some companies such as GSK are still studying Selective Androgen Receptor Modulators (SARM) with drug candidate GSK2881078 and Astellas in collaboration with Cytokinetics is preparing to test its troponin activator product (CK-2127107) on sarcopenia.

Clinical studies with myostatin inhibitors/troponin activator

[54] Morley J. 2016. Pharmacologic options for the treatment of sarcopenia. *J Calf Tissue Int* 98: 319-333.

[55] Smith RC, Lin BK. 2013. Myostatin inhibitors as therapies for muscle wasting associated with cancer and other disorders. *Curr Opin Support Palliat Care*, 7: 352-360.

Company	Product candidate	Target	Stage of development
Biophytis	*Sarconeos*	MAS receptor agonist	Phase 2b Phase 2b ready
Regeneron	REGN1033	Anti-myostatin antibody	Phase II[56]
Novartis	Bimagrumab	Anti-ActRIIB antibody	Phase II[57]
Cytokinetics	CK-2127107	Troponin activator	Phase II[58]

Bimagrumab (BYM338) – Novartis: 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.

REGN1033 – Regeneron: REGN1033 is a human monoclonal human antibody capable of inhibiting *myostatin* activity by targeting GDF8.

CK-2127107 - Cytokinetics in collaboration with Astellas: CK-2127107 is an activator of troponin, a protein located in the sarcomere and sensitive to calcium. Its aims to slow the release of calcium from the regulatory complex involving troponin in fast muscle fibres.

Product candidate	Bimagrumab		CK-2127107	REGN1033
Injection	Intravenous		Subcutaneous	Intravenous
Phase	Phase IIa		Phase I-b	Phase IIa
Structure	Randomized, double blind, placebo control, 40 patients		Randomized, double blind, placebo control, 60 patients	Randomized, double blind, placebo control, 253 patients
Patients	Sarcopenic patients over 65 years of age with reduced mobility		Sarcopenic patients 70-89 years of age	Sarcopenic patients over 70 years of age
Criterion	Variation in thigh muscle volume at 8 weeks	Variation in walking speed at 16 weeks	Variation of the knee extension strength	Variation in lean body mass at 12 weeks
Result product	+8.0%	+0,50m/s		Results are being analysed but the primary criterion has been attained Final results in 2016
Result placebo	+0.35%	+0,35m/s		
Statistically significant	Undetermined	p=0,009		
Clinical trial in progress	Phase II, randomized, double blind, 240 patients over 70 years of age suffering from sarcopenia; result expected in 2017		Beginning of recruitment: Mai 2017:	

In conclusion, there is no drug candidate that specifically targets obesity currently available on the market or in a clinical *trial*. The ideal treatment should certainly combine daily physical exercises to help strengthen muscle mass, proper nutritional advice to prevent protein

[56] https://clinicaltrials.gov/show/NCT01963598
[57] https://clinicaltrials.gov/show/NCT02333331
[58] https://clinicaltrials.gov/ct2/show/ NCT03065959

deficiencies and a drug therapy to stimulate muscle *anabolism* more effectively and limit the related cardiometabolic risk.

	Sarcopenia & Sarcopenic Obesity	Sarcopenia & Cachexia
Standard of care	• **30 min physical exercise / day**	• 30 min physical exercise / day
Products in development	• **SARCONEOS (Phase 2b)**	Anti-myostatin antibodies : • BYM338 (Novartis)
Product attributes	• **Improves mobility** • **Reduces cardiometabolic risk** • **Oral administration**	• Increases muscle mass and strength • No improvement of mobility • Subcutaneous injection

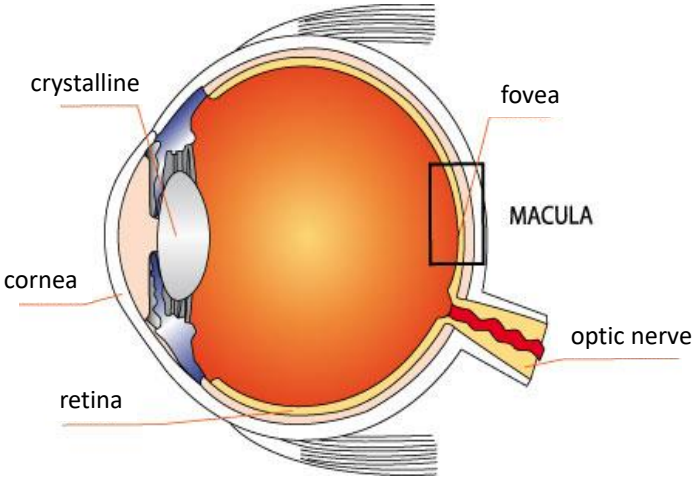
6.3. AGE-RELATED MACULAR DEGENERATION (AMD) PROGRAM

6.3.1. Disease and epidemiology

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. Treatment of the dry form of AMD represents a potential market of €30 billion.

Age-related macular degeneration (AMD) is an irreversible pathology which affects people aged 50 and over. It is characterized by a loss of central vision and gradually leads to blindness. It is a leading cause of irreversible blindness in aging populations, particularly in Europe and North America. The pathology currently affects 30 million people throughout the world. Its prevalence is increasing rapidly and the dry form will represent a potential market of €30 billion in 2023[59]. No treatment is currently available for the dry type of AMD, which is the most common form since it affects more than 80% of patients. A laboratory marketing the drug developed by Biophytis under license 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. Only wet AMD (wet form) is treated with anti-VEGF medications, requiring costly (€12,000 p.a.) and major intervention: daily intravitreal injections.

[59] Visiongain. Macular Degeneration (AMD) and Diabetic Retinopathy (DR): World Drug Market 2013–2023. (2012).



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 characterized by deposits called *drüsen* which only marginally affect vision. The patient gradually notices some deterioration in his central vision, which is then diagnosed by the ophthalmologist; this is the intermediate stage. The final stages comprise two forms of AMD, *geographic atrophy* (dry form) or exudative (wet or neovascular form), whereby the former is far more common than the latter (Smith et al. 2001)[60]. The last stages of these two forms lead to the destruction of the neurosensory retina in the macular region as dry AMD generally progresses very slowly, whereas wet AMD can lead to complete blindness within a few weeks.

Images illustrating the stages of the disease

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)[61]. If left untreated, more than 60 million people throughout the world, including 2 million in France, would be affected in 2050, making AMD a major health concern in 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)[62], 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

[60] 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.
[61] 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.
[62] 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.

develops over time, because the disease tends to become bilateral in 30% - 40% of patients within 5 years.

Serious visual impairment has an enormous impact on the quality of life (Williams et al., 1998)[63]. 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 from emotional distress and depression than other elderly adults (Sahel et al, 2007; Bonastre et al, 2002). 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.

6.3.2. Scientific Hypothesis

Oxidative stress and the resulting inflammation are significant contributory factors to the pathogenesis of AMD. The visual pigment recycling process generates a byproduct called A2E which accumulates in the retinal pigment epithelium, disrupting its function, ultimately causing its death and, consequently, the death of the associated photoreceptors. The research conducted by Biophytis has focused on active ingredients to combat the deleterious effects of A2E.

- ***Causes of AMD***

AMD is a multi-factorial disease, related to aging with associated several risk factors, such as the genetic context, gender, diet, hypertension, smoking and sun exposure. Studies have shown that the later stages of AMD are more frequent in light-skinned individuals than in other groups and that women are more affected than men (Hyman and Neborsky 2002)[64]. Nevertheless, the strongest and most consistent risk factors are smoking and age. Smokers are three to four times more likely to develop AMD and 10 years earlier than non-smokers. However, the current rate of reduction in the prevalence of smoking in the developed countries will not be sufficient to dramatically reduce the incidence of AMD (Marques-Vidal et al. 2003)[65].

Other factors are clearly indicated, particularly genetic factors, which would explain almost 50% of the *phenotypic* variability in several association studies (Priya, 2012)[66]. One of the first genes to be identified as a risk factor for AMD was the ABCA4 gene, which is involved in the *visual pigment* cycle which, when it carries a functional mutation, is responsible for *Stargardt disease*. This association has only been established in a negligible percentage of patients with

[63] Williams RA, Brody BL, Thomas RG, Kaplan RM, Brown SI. 1998. The psychological impact of macular degeneration. *Arch Ophthalmol*, 116: 514-520.
[64] Hyman L, Neborsky R. 2002. Risk factors for age-related macular degeneration : an update. *Curr Opin Ophthalmol*, 13(3): 171-175.
[65] Marques-Vidal P, Ruidavets JB, Cambou JP, Ferrières J. 2003. Changes and determinants in cigarette smoking prevalence in southwester France, 1985-1997. *Eur J Public Health*, 13: 168-170.
[66] 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.

AMD (Fritsche et al., 2012)[67] 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. By adopting different approaches, candidate gene, *linkage* and an association study of increasingly larger cohorts, around twenty genes have been identified and validated, which explains over 50% of genetic variance and is unique for a multifactorial pathology (Priya et al., 2012; The AMD Gene Consortium, 2013[68]). Identification of these genetic factors improves the structuring of patient populations in epidemiological and clinical studies, but the use of these data, combined with environmental factors in order to identify the patients at risk, remains an enormous challenge (Sobrin, 2014)[69].

Aging is the gradual accumulation over time of changes which are associated with (or responsible for) increased susceptibility to disease and death that accompany advancing age (Harman, 1981)[70]. A certain number of degenerative diseases, including glaucoma, *diabetic* retinopathy and AMD, may occur in the retina as a result of aging. Although the specific mechanisms involved in the onset of different types of age-related retinal disorders differ, it is thought that oxidative *stress* and the resultant *inflammation* are significant contributing factors to the pathogenesis.

Theories of the etiology of AMD include hydrodynamic changes in *Bruch's membrane* caused by a gradual accumulation of extracellular material containing lipids and senescence of the *retinal pigment epithelium* (*RPE*). It is thought that this extracellular material originates from the RPE (Feeney-Burns and Eldred, 1983)[71]. *RPE* cells have several different functions in the eyes: the tight junctions between the RPE cells form the *blood-retinal* barrier and these cells are thus responsible for the immune privileged status of the anterior chamber of the eye; they keep the *photoreceptors* alive by supplying them with nutrients and participate in the visual cycle (Marmorstein, 2001; Thompson et Gal, 2003)[72]; they optimize the ionic concentrations in the surrounding tissues and eliminate fluids from the subretinal space (Marmor, 1990)[73]. The current understanding is that a functional impairment of RPE cells is responsible for the development of AMD.

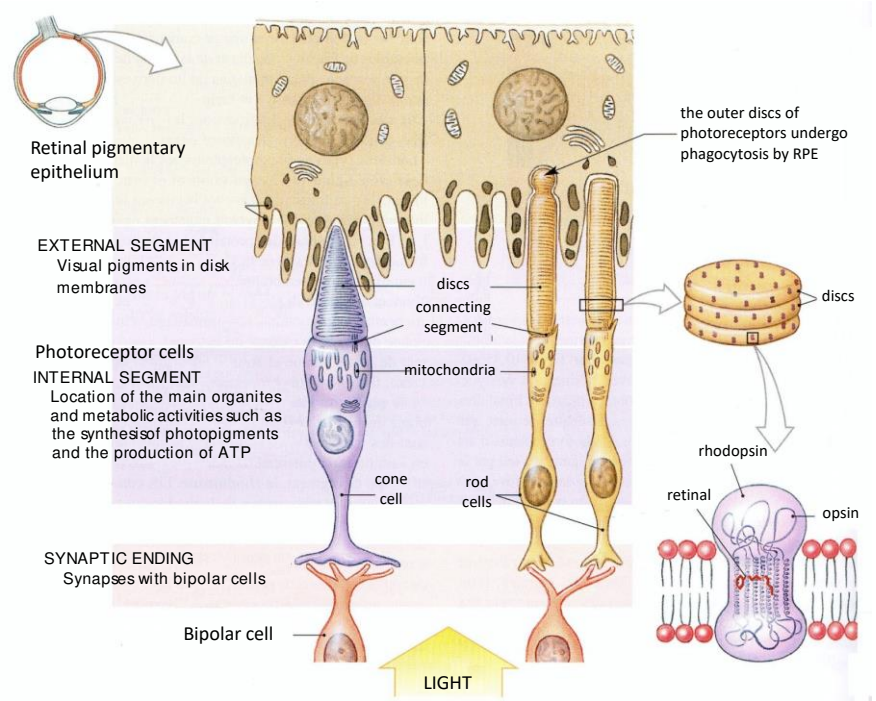
- ***Accumulation of lipofuscin and formation of drüsen***

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

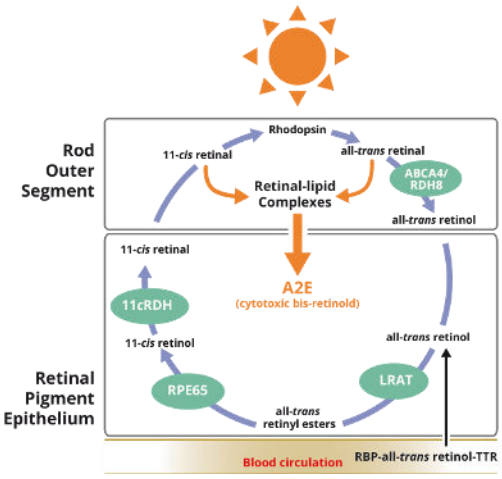
[67] Fritsche LG, Fleckenstein M, Fiebig BS, et al. 2012. A subgroup of age-related macular degeneration is associated with mono-allelic sequence variants in the *ABCA4* gene. *IOVS*, 53: 2112-2118.
[68] Fritsche LG, Chen W, Schu M et al. 2013. Seven new loci associated with age-related macular degeneration. *Nat Genet*, 45(4): 433-439
[69] Sobrin L, Seddon JM. 2014. Nature and nurture - genes and environment - predict onset and progression of macular degeneration. *Progr Retinal Eye Res*, 40: 1-15.
[70] Harman D. 1981. The aging process. *Proc Natl Acad Sci U.S.A.*, 78(11): 7124-7128.
[71] Feeney-Burns L, Eldred GE. 1983. The fate of the phagosome: conversion to 'age pigment' and impact in human retinal pigment epithelium. *Trans Ophthalmol Soc U*K, 103: 416-421.
[72] Marmor MF. 1990. Control of subretinal fluid: experimental and clinical studies. *Eye (Lond)*, 4(Pt 2): 340-344.
[73] Marmor MF. 1990. Control of subretinal fluid: experimental and clinical studies. *Eye (Lond)*, 4(Pt 2): 340-344.

structures (cones and rods). *Rhodopsin*, a complex of the protein opsin and the cis retinal, is responsible for photoreception.

Under the effect of light, the retinal is *isomerized* and detaches from opsin, and the return to its original form, which is indispensable for its activity, triggers a sequence of complex reactions for which the *photoreceptors* and the RPE are jointly responsible.



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)

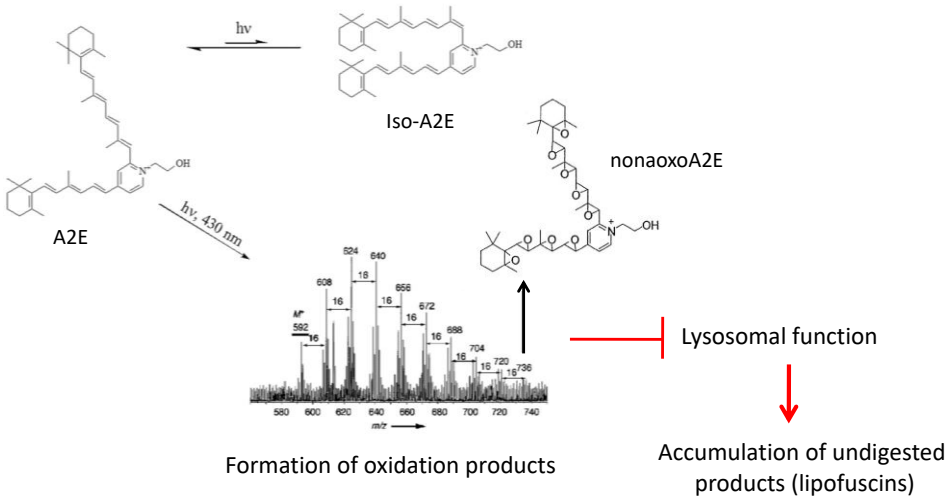


Visual Cycle Modulation: A Novel Therapeutic Approach For Treatment of GA In Dry AMD[74]

[74] MATA et al, 2013 Visual Cycle Modulation: A Novel Therapeutic Approach For Treatment of GA In Dry AMD, Retinal Physician

This protection mechanism nevertheless has a downside, when, as a result of a malfunction of the *visual pigment* cycle (related to age or to genetic faults), A2E accumulates in large quantities in the RPE cells. In fact, this molecule has catatonic *detergent properties*, related to its *ampithatic* structure, which alter the membrane-associated properties. Moreover, in the presence of (blue) light and oxygen, it undergoes oxidation of all or part of its double bonds, and the molecules formed in this process react with various cell components, thereby disrupting RPE activity, particularly its activity of digesting fragments of *photoreceptors* (Sparrow et al, 2000, Bergmann et al., 2004)[75]. As a result, *RPE* cells accumulate waste that they will in part eliminate by exocytosis, a process that causes deposits to form at the basal surface.

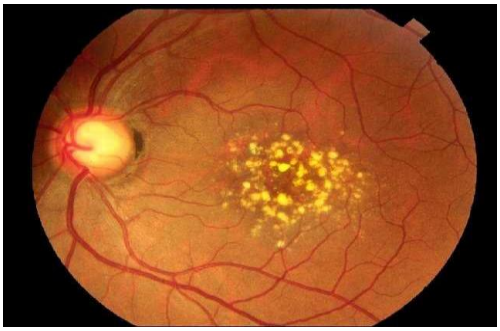
The *drüsen* contain *dendritic cells* from the *choroid* as well as antigen-presenting cells. In addition, complement activation products and complement regulatory proteins are found in the *drüsen*, which indicates the existence of chronic *inflammation* in *Bruch's membrane* (Gehrs et al, 2006)[76]. With age, the *RPE* stores greater amounts of *lipofuscin*. They are composed of lipids and proteins, residues of incomplete *lyosomal* digestion, which have reacted with various factors of the complement. As these deposits contain various forms of A2E they 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.

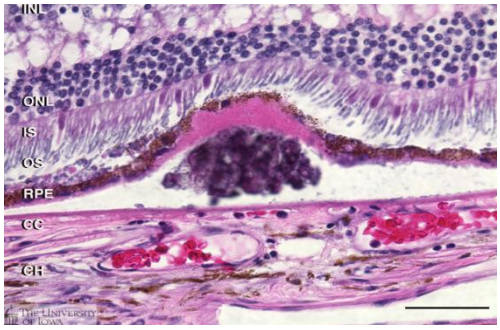


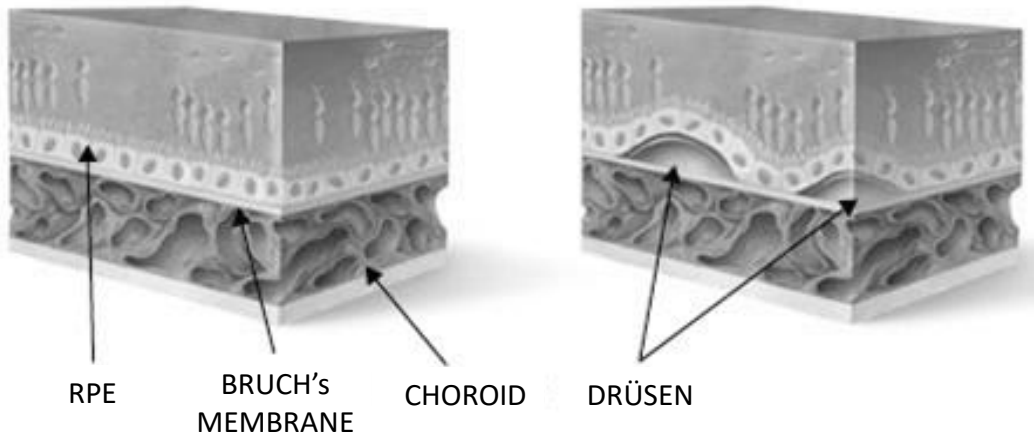
This waste can thus accumulate between the *RPE* cells and their basal membrane (*Bruch membrane*) and form fluorescent deposits called *Drüsen*, which cause deformations of the retina and of perceived images.

[75] Sparrow JR, Nakanishi K, Parish CA. 2000. The lipofuscin fluorophore A2E mediates blue-light-induced damage to retinal pigmented epithelial cells. *IOVS*, 41: 1981-1989. Bergmann M, Schutt F, Holz FG, Kopitz J. 2004. Inhibition of the ATP-driven proton pump in RPE lysosomes by the major lipofuscin fluorophore A2-E may contribute to the pathogenesis of age-related macular degeneration. *FASEB J* 18: 562-564.

[76] Gehrs KM et al. 2006. Age-related macular degeneration: emerging pathogenetic and therapeutic concepts. Ann Med., 38:450-471







- ***Oxidative stress and cell death***

Oxidative stress is considered by many to be the major initial determinant of the different age-related changes in the retina. *Oxidative stress* reflects an imbalance between the production of reactive oxygen species and the ability of the cells to detoxify the reactive intermediaries or to repair the damage caused. Changes in tissue *redox* status can lead to toxic effects due to the production of peroxides and *free radicals* which damage all the cell components, including proteins, lipids and DNA. Certain ROS (reactive oxygen species) can also act as messengers by means of a phenomenon known as redox signaling. Increased *oxidative stress* and the accumulation of molecules damaged by oxidation lead to metabolic disorder and the malfunction of various signaling pathways, which in turn cause the death of the retinal cells or their malfunction. A source of ROS in humans under normal conditions is linked to mitochondrial respiratory activity. Other enzymes that are capable of producing superoxide ions are xanthine oxidase, NADPH oxidase and the cytochrome P450. Hydrogen peroxide is produced by a wide range of enzymes, including several oxidases. The use of Vitamin C and E supplements as *antioxidants* has thus naturally been proposed to treat AMD, where the cells of the retina are subject to intense photo-oxidative stress.

However, the AREDS, conducted for over 10 years in the United States by a consortium financed by the NIH (National Institutes of Health), have established the importance of a supplement based on Zinc and Vitamins C and E, and clarifying the role played by certain nutritional deficiencies, particularly lutein and zeaxanthin, the *visual pigments* which are present throughout the retina (AREDS, 2001[77]). The food supplements that are formulated on the basis of the AREDS recommendations have since been prescribed and marketed globally

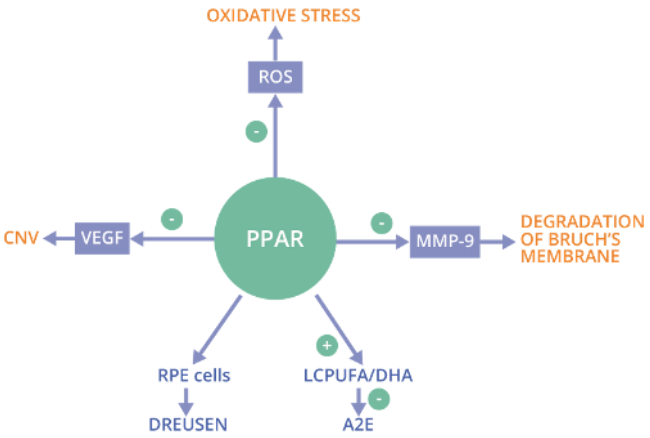
[77] AREDS report N°8, 2001. A Randomized, Placebo-Controlled, Clinical Trial of High-Dose Supplementation With Vitamins C and E, Beta Carotene, and Zinc for Age-Related Macular Degeneration and Vision Loss. *Arch Ophthalmol.*, 119:1417-1436

as the only available treatment, in the hope of slowing down the progression of dry AMD into more severe forms. However, the efficacy of this treatment is poor, and the response appears to vary from patient to patient: the response to the Zinc supplement has thus been associated with the genetic factor ARMS2, whereas the response to the Vitamin C and E supplements has thus been associated with the genetic factor CFH (Awh, 2013[78]). More effective treatments are being developed with the aim of limiting *oxidative stress* or inflammation.

6.3.3. Proof of Concept

Macuneos was selected in a cell test under acute light stress of RPE cells in the presence of A2E.
Macuneos was then administered in two animal models, whose retinal degeneration was induced by blue light, demonstrating significant preservation of the retina. In particular, Macuneos was efficacious after intravitreal and intraperitoneal administration and following oral chronic administration and its dosage was compatible with use in humans.

Biophytis started from the hypothesis that the accumulation of A2E in the retina is responsible for AMD. Biophytis 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.
Macuneos is a Peroxisome Proliferator-Activated Receptor (PPAR) agonist. New studies conducted by Biophytis make it possible to specify that Macuneos is notably a PPARγ agonist but also interacts with PPARβδ with high affinity. Recent data point to the important role played by this class of nuclear receptors - PPAR in providing protection against AMD (Herzlich *et al*., 2008)[79].



Macuneos is an agonist of PPARα, involved in protecting retinal cells

[78] Awh CC et al. 2013. CFH and ARMS2 Genetic Polymorphisms Predict Response to Antioxidants and Zinc in Patients with Age-related Macular Degeneration. *Ophtalmology* 120:2317-2323
[79] Herzlich AA, Tuo J, Chan CC. 2008. Peroxisome proliferator-activated receptor and age-related macular degeneration. *PPAR Research*, article ID 389507.

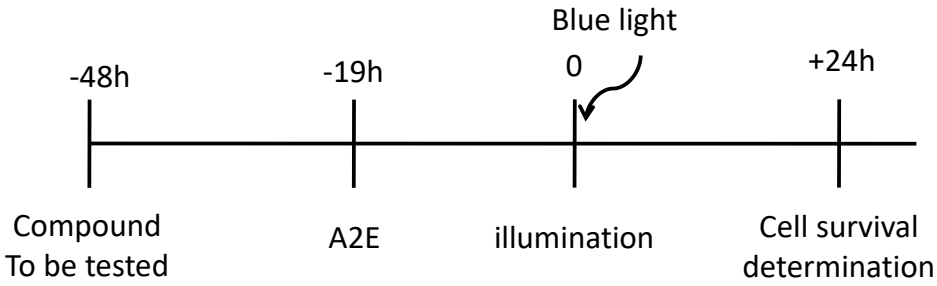
Macuneos provides protection to the A2E-loaded RPE cells in the presence of blue light. The protection conferred by *Macuneos* may be considered at several levels which are mutually compatible:

- *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[80]) or stimulates the *antioxidant* defense enzymes
- *Macuneos* has anti-inflammatory activity and anti-VEGF
- *Macuneos* protects against *apoptosis*

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

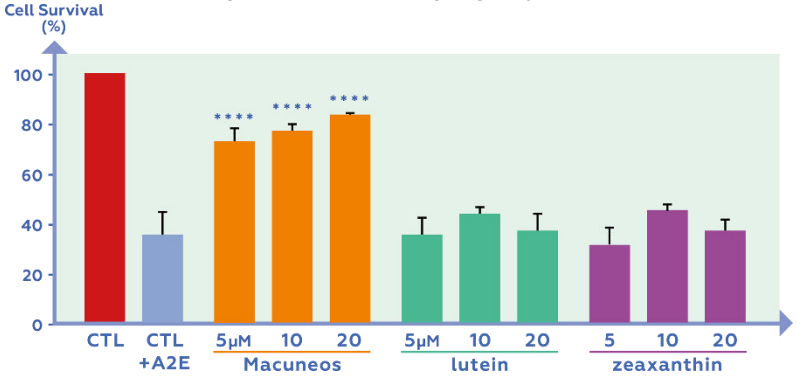
- ***Experiments conducted with retinal cells***

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 were 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 products whose AREDS (lutein and zeaxanthin) studies have shown that their deficiency was linked to a high risk of developing dry AMD.



[80] 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

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

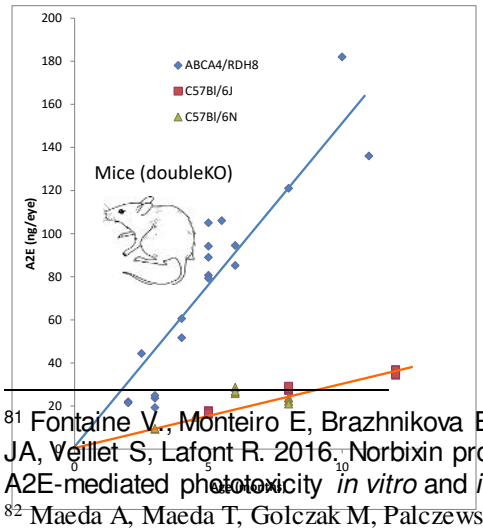
Measuring the survival rates obtained with several doses of the tested substances enables comparisons to be made between the compounds and to select the most active compounds. This approach resulted in the selection of *Macuneos*, a natural active ingredient, and BIO203, a synthetic molecule that is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

- ***Experiments conducted in the animal models for AMD***

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

Reference	Animal Model	Results
Fontaine *et al.*, 2016[81]	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	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	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 coded for 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)[82] and has been used under license.



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

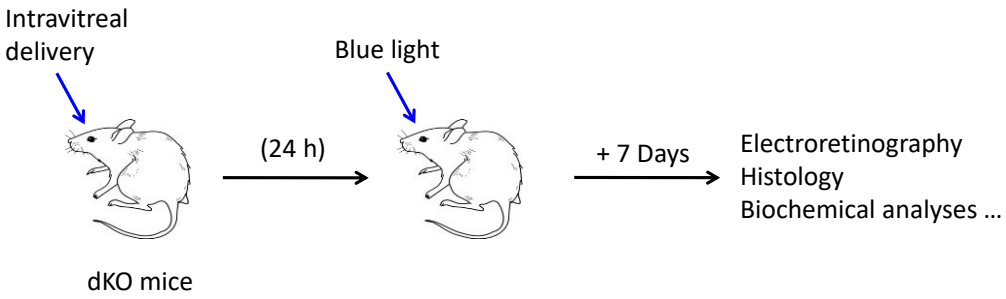
[81] Fontaine V., Monteiro E, Brazhnikova E, Lesage L, Balducci C, Guibout L, Feraille L, Elena PP, Sahel JA, Veillet S, Lafont R. 2016. Norbixin protects retinal pigmented epithelium and photoreceptors against A2E-mediated phototoxicity *in vitro* and *in vivo*. PLoS ONE DOI:10.1371/journal.pone.0167793,

[82] 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

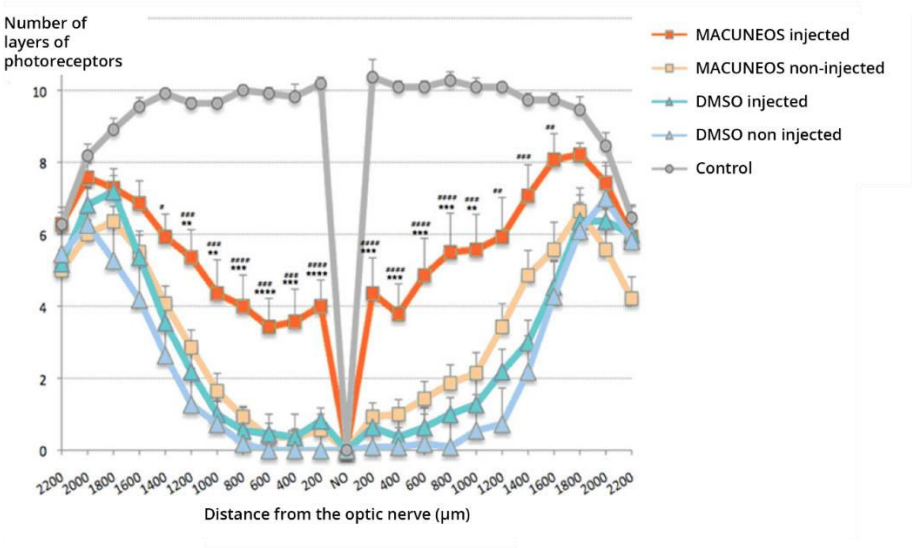
a model for studying AMD in accordance with the scientific hypothesis formulated by Biophytis.

These mice were used in two complementary ways:

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

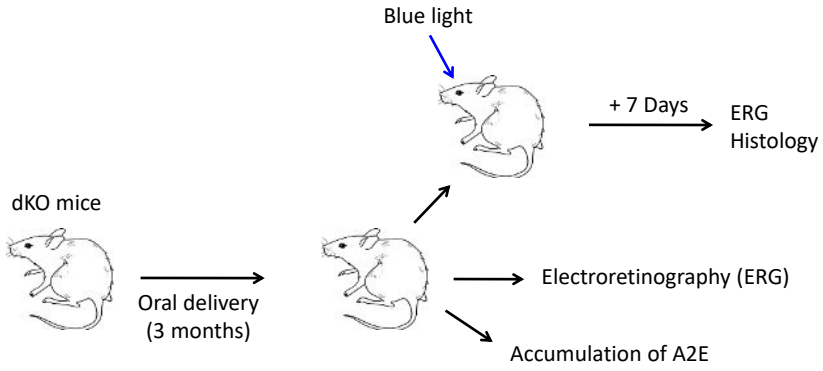


Then, the mice are subjected to intense blue light. Seven days after the irradiation, an electroretinogram is performed, which makes it possible to measure the retinal functionality. In addition, a histological analysis makes it possible to assess the number of residual layers of photoreceptors. In this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



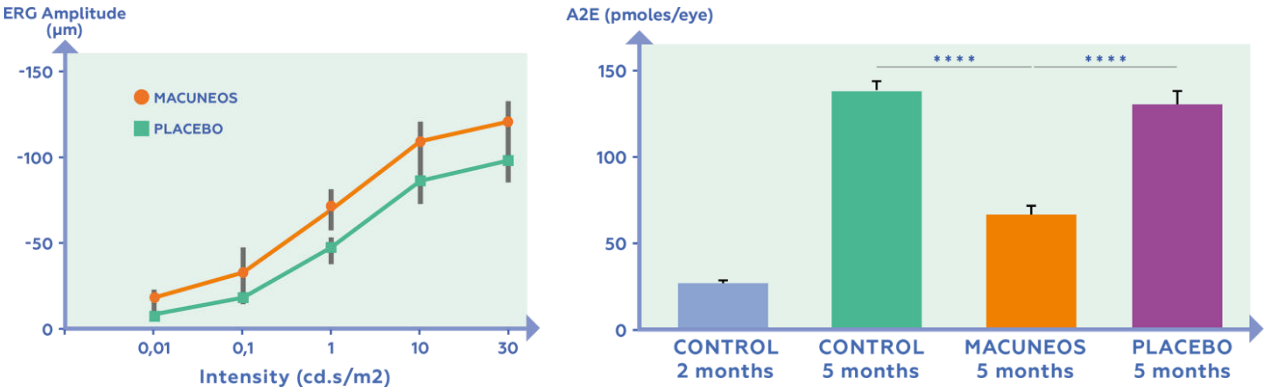
Number of layers of photoreceptors after illumination in mice ABCA4$^{-/-}$ RDH8$^{-/-}$ treated with Macuneos or a control, an intravitreal injection

- ✓ for 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.

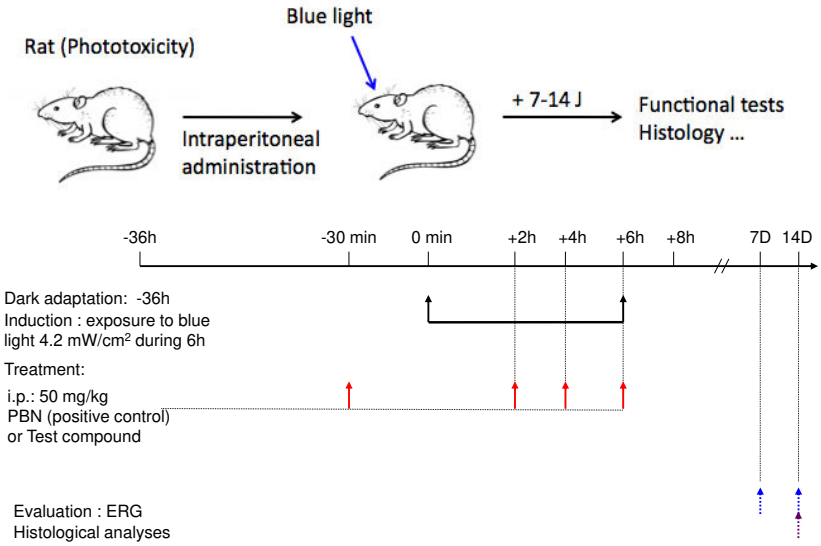
Electroretinogram (A-wave) *A2E accumulation*



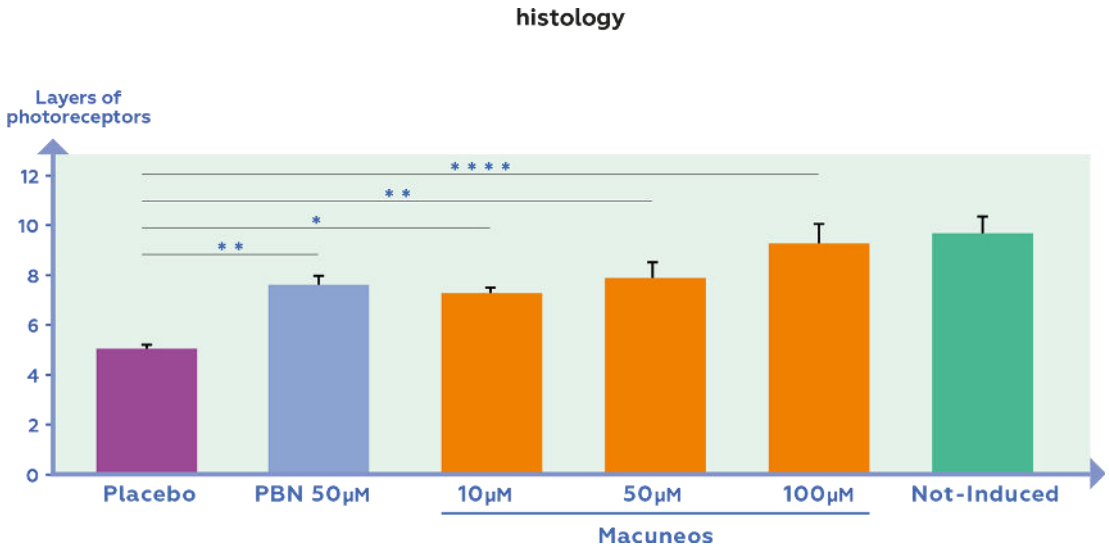
Effects of chronic oral administration of Macuneos on A-Waves of ABCA4$^{-/-}$ RDH8$^{-/-}$ mice and accumulation of A2E in their eyes

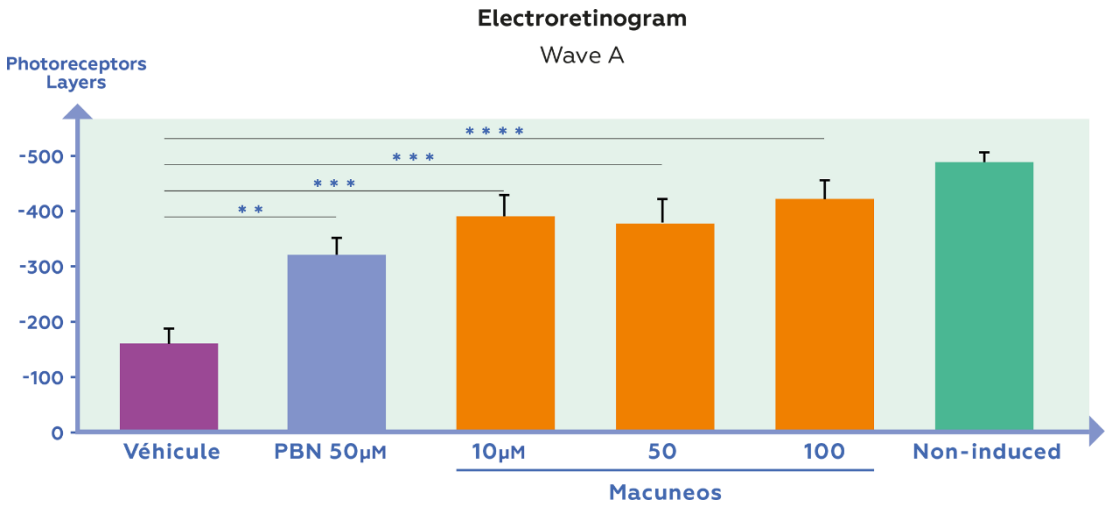
(2)- The second model for AMD was the "blue light" rat model, using normal albino rats in a test for phototoxicity induced by blue light.

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) that results in an improvement in the function of the retina (electroretinogram).





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

Macuneos has thus demonstrated its efficacy in vitro and in vivo and has proved to be more efficacious than the molecules previously described.

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.

- ***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) in the dose-ranging studies (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.

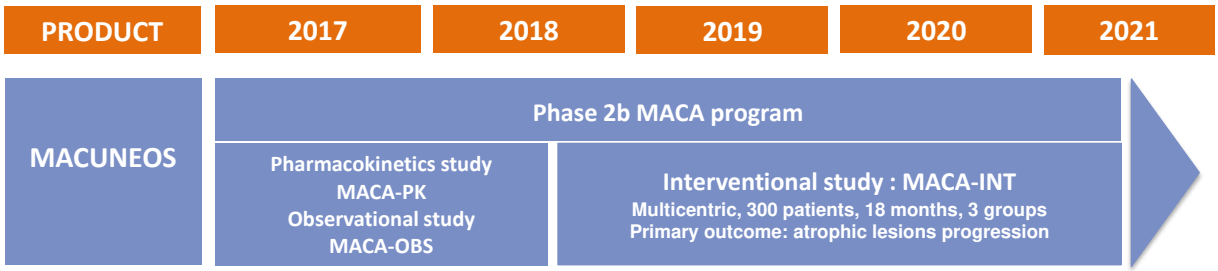
Reference	Dosage	Volunteers & Protocol	Results
Dioh *et al*, owner	35 mg/day	47 healthy volunteers (23 verum, 24 placebo) 20- 50 years 3 months	No serious adverse events *MACUNEOS* is the principal circulating *metabolite*

6.3.4. Next stages of development for Macuneos

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 IIb MACA programme. Prior to the MACA-INT interventional study, two studies will be conducted simultaneously. These preceding studies must begin in the second half of 2017:

- A pharmacokinetic and safety study in healthy volunteers and elderly patients with intermediate-phase AMD (MACA-PK);
- On the other hand, an observational study to characterise the target population and pre-recruit patients (MACA-OBS) will be conducted in Europe and the United States.

This new clinical-regulatory protocol aims 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, and (iii) accurately characterising the population reached before confirming the inclusion criteria of the patients tested.



- MACA-PK Study

This study is expected to produce initial clinical data by 2018. Preparatory phase 2b includes a pharmacokinetic and safety study in healthy volunteers and elderly patients with intermediate AMD (MACA-PK study). Biophytis has called on the CRO SGS (already requested for SARA-PK). The MACA-PK design provides for carrying out the study in three stages in six clinical investigation centres in France and Belgium.

- First of all, as part of an SAD, healthy volunteers over 55 years of age receive a series of single ascending doses of *Macuneos*. The SAD investigation phase is planned for the second half of 2017.
- Then, the three doses with the most advantageous profiles in terms of safety and pharmacokinetics will be successively tested with MAD for 28 days in patients with AMD. The clinical investigation phase with MAD will take place during the first half of 2018. It includes the assessment of several pharmacodynamic parameters including ERG (Electro-RetinoGram), dark adaptation, contrast sensitivity, and visual acuity.
- Finally, a follow-up period of 2 months will be proposed to the patient groups that have been tested with MAD, subject to acceptance by the regulatory authorities. It is expected to be completed towards the end of the second half of 2018.

The advantage of this new MACA-PK clinical design is that it offers the opportunity to evaluate the effects of Macuneos as early as 2018, prior to the launch of the interventional phase on pharmacodynamic parameters in patients with AMD.

- MACA-OBS Study

The second MACA preparatory study aims to better characterise the target population (patients with intermediate dry AMD) and to reduce recruitment time in major centres in Europe and the United States (MACA-OBS study). This study will involve approximately one hundred patients divided amongst seven centres, and will last 12 months. Regulatory approvals for the start-up of MACA-OBS should be obtained in the second half of 2017.

- MACA-INT Study

The objective of this clinical study 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 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 2018. MACA-INT will involve approximately twenty clinical investigation centres in Europe and the United States, include 300 patients, and have as its main criterion the progression of the size of the atrophic geometry measured by autofluorescence of the back of the eye.

Macuneos is supplied as tablets (1 daily), containing 100 mg or 350 mg of Active Pharmaceutical Ingredient (API). The API (BIO201) is a natural active ingredient that is extracted from Bixa orellana cultivated in Peru and purified for pharmaceutical use in accordance with the Good Manufacturing Practices for pharmaceutical products by the Patheon Company on behalf of Biophytis.

300 subjects over 50 years of age and suffering from the intermediate dry form of AMD will be recruited in France in around twenty Clinical Investigation Centers (CIC), including the CIC of the Quinze-Vingt Hospital in Paris, in at least another European country, and in a ten of CICs in the United States, including the Massachusetts Eye and Ear Infirmary (Harvard Medical School) in Boston. They will be randomly assigned to three treatment groups: *Macuneos 100 mg, Macuneos 350 mg* and placebo.

The main criterion is the rate of spread of *geographic atrophy* measured by the autofluorescence images of the back of the eye. This criterion has been selected due to its recognition by European and American regulatory bodies contrary to the accumulation of *lipofuscines* initially planned but invalidated by the FDA. The secondary criteria measured are visual acuity, the accumulation of *lipofuscins* and the change towards severe AMD (geographic atrophy or exudative form).

The provisional schedule of this study which comprises several phases is as follows:

- H2 2017: MACA-PK SAD study (end of H2 2017) and MACA-OBS regulatory filings (end of H2 2018)
- H1 2018: MACA-PK MAD study (end of H1 2018)
- H2 2018: MACA-INT regulatory filings (ANSM, EMA, FDA)
- H2 2018: Start of MACA-INT clinical investigation phase
- H2 2021: MACA-INT: Presentation of results

6.3.5. Development of BIO203

BIO203 is a new molecule selected from synthesised compounds, *similar to the* natural active principles in animal and cellular models of AMD. The candidate is undergoing optimisation of oral administration or intravitreal injection and it must be suitably developed in pharmaceutical form in order to stabilise the activity and bioavailability of BIO203 for over a month.

BIO203 will then be able to enter preclinical testing in 2017, then phase 1 in 2018 to assess whether it is safe for use in humans.

BIO203 will probably be developed to treat retinopathies other than AMD.

6.3.6. Competition

The only drugs that are available on the market are for the treatment of exudative of AMD, i.e. approximately 20% of patients. Laser is effective, but only in around 15% of cases of exudative AMD (Moïsseiev et al. 1995)[83]. The development of vascular endothelial growth factor (VEGF) inhibitors has heralded a new era in the treatment of exudative AMD (Schlingemann & Witmer, 2009)[84]. However, as is the case with many new therapies, there are still unresolved issues, particularly with regard to safety, cost and the frequency of treatments.
The sale of preparations used in the treatment of exudative AMD accounted for around 2 billion dollars in 2014, notably with Lucentis de Roche/Novartis which dominates the market, and more recently with Eylea de Regeneron/Bayer.

Food supplements have been formulated with generic *antioxidant* compounds, namely minerals and vitamins with *antioxidant properties*, for example zinc, vitamins E and C, with real, albeit limited, therapeutic efficacy. The nutraceutic AREDS 1 Formula 1 is considered to be the gold standard 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 joint formula: 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.

No drug exists to treat the dry form of AMD, although a number of agents are being developed in early preclinical and clinical tests.

With regard to the most severe form, *geographic atrophy*, in 2014 Roche launched a Phase 3 clinical study with a therapeutic antibody in an intravitreal injection targeting the complement factors.

Regarding the intermediate stage of the dry form of AMD which is the focus of the studies by Biophytis and which affects the majority of patients: the public health issue and the related economic potential have stimulated investment in research supported by the public authorities: NIH (National Institutes of Health), and biotechs: Acucela, Sirion, Colby, Alexion, Morphosys, Regeneron, which is explained by the ongoing interest on the part of the pharmaceutical laboratories: Novartis, Roche, Bayer, GSK, Novo Nordisk. Various strategies have been adopted either by pre-empting the technologies in the upstream phase or by purchasing post-phase 2 drug candidates or by repositioning the molecules already marketed in order to test them in phase 2. No drug candidates have passed phase 2 to date, presumably due to a lack of understanding of the mechanisms of action and failure to target patient groups.

[83] Moisseiev J, Alhalel A, Masuri R, Treister G. 1995. The impact of the macular photocoagulation study results on the treatment of exudative age-related macular degeneration. *Arch Ophthalmol*, 113(2): 185-189.
[84] Qchlingemann RP, Witmer AN. 2009. Treatment of retinal diseases with VEGF antagonists. *Progr Brain Res*, 175: 253)267

Two main strategies were adopted (Rosenfeld & Legaretta, 2009)[85]: (I) preservation of the *photoreceptors* and *RPE*, with neuroprotector agents, visual cycle inhibitors and vasodilator molecules, (ii) prevention of oxidative *stress*, primarily due to the use of natural *antioxidants*.

Drug	Mechanism of action	Sponsor	Phase	Status
Fenretinide	Visual cycle inhibitor: this *analogue of* retinol inhibits the ability of retinol to bind to RBP (Oral)	Sirion Therapeutics	Phase II	NCT00429936 (Terminated, stopped, problems with night vision)
ACU-4429	Visual cycle inhibitor: this nonretinoid compound inhibits the i*somerisation* of retinol (Oral)	Acucela	Phase II	NCT01002950 (Terminated, stopped)
Tandospirone (AL-8309B)	Neuroprotection: agonist specific receptor 5-HT1A of serotonin) (Topical)	Alcon	Phase 3	NCT00890097 (Terminated, Stopped, treatment ineffective)
NT-501: ciliary neurotrophic factor (CNTF) encapsulated	Neuroprotection: inhibits the degeneration of the (intravitreal) *photoreceptors*	Neurotech Pharmaceuticals	Phase II	NCT00447954 (Terminated)
Brimonidine tartrate	Neuroprotection: Alpha-2 adrenergic receptor agonist (Intravitreal)	Allergan	Phase II	NCT00658619 (Terminated, not very effective)
RN6G	Neuroprotection: fixes and eliminates beta-amyloid (Intravenous)	Pfizer	Phase II	NCT00877032 (Terminated - not published) NCT01003691 (Terminated)
AREDS-2: ± AREDS formulation >/< zinc ± β-carotene ± lutein / zeaxanthin ± omega-3 PUFAs (DHA/EPA)	Antioxidant ± micronutrient supplement (Oral)	NEI – Bausch&Lomb	Phase 3	NCT00345176 (Terminated, not superior to AREDS2 vs. AREDS1)
OT-551	Antioxidant, anti-inflammatory (inhibits nuclear factor kappa B: NF-κB), and antiangiogenic agent (Topical)	Colby Pharmaceuticals	Phase II	NCT00485394 (Stopped) NCT00306488 (terminated)

The development of the majority of candidates listed by Yehoshua, such as Tandospirone or Fenretinide and possibly Brimonidine tartrate or OT-551, has been stopped due to a lack of clinical efficacy of the treatments. The majority of molecules were developed for other pathologies, namely neuroprotective molecules that were developed to treat cerebral neurodegenerative diseases or generic antioxidant molecules. There are different physiopathological mechanisms that cause these strategies to fail.

Although there is no approved treatment for dry AMD, few candidates are currently in the clinical phase.

[85] Rosenfeld PJ, Legaretta J. 2009. Preclinical and phase 1 drugs in development for dry AMD: an overview. *Retinal Physician*, http://www.retinalphysician.com/articleviewer.aspx?articleid=103648

Company	Product candidate	Mechanism	Stage of development	Results
Biophytis	*Macuneos*	PPAR-α agonist	Phase II[86]	2018
Roche Holding AG	Lampalizumab	Anti-factor D	Phase III[87],	~ Oct-2018
Acucela	ACU-4429	RPE65 antagonist	Phase IIb/III[88]	nd
GlaxoSmithKline	GSK933776	Anti-bet amyloid	Phase IIa[89]	~ April-2016
StemCells	HuCNS-SC	Neural stem cells	Phase II[90]	nd
Ocata Therapeutics	MA09-hRPE	RPE cells	Phase II[91]	nd
Ophthotech	Zimura	Anti-C5a receptor	Phase II	nd
Biotime	OpRegen	RPE cells	Phase I/II[92]	nd
US Stem Cell	AdipoCell	Adipocytes	Phase I[93]	nd

Lampalizumab – Roche: Fragment of a humanised monoclonal antibody that binds to the antigen and targets factor D. Factor D is an enzyme involved in activating the complement.

ACU-4429 – Acucela: Small molecule that inhibits the RPE65 enzyme for the treatment of dry AMD.

Product candidate	Lampalizumab		ACU-4429
Administration	Intravitreal		Oral
Phase	2 phases III (SPECTRI and CHROMA)		Phase IIb/III (SEATTLE)
Structure	Randomized, double blind, placebo control, approx. 936 patients per study		Randomized, double blind, placebo control, 480 patients
Patients	Dry AMD in each eye without wet AMD precedent		Over 55 years of age suffering from dry AMD
Criterion	Average variation in the zone of geographic atrophy at 1 year	Evaluation of the patient's vision at 2 years	Average variation in the zone of geographic atrophy at 1 year
Results	Expected mid-2017		Expected Q3 2016 Not yet published

In conclusion, no drug candidate that specifically targets the intermediate dry stage of AMD is available on the market at present, and the two drug candidates currently in phase 3 (Lampalizumab) target a patient population that presents with a severe form of inflammatory geographic atrophy.

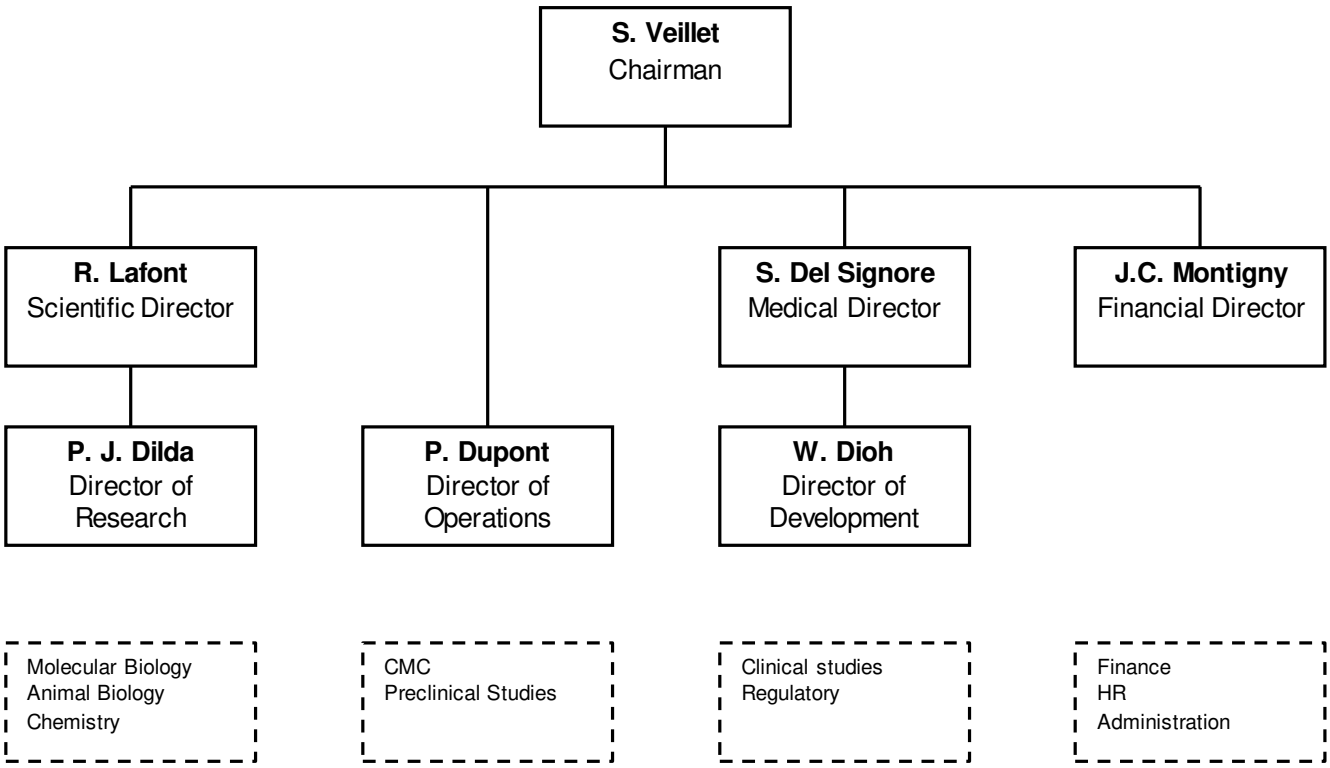
[86] https://clinicaltrials.gov/ct2/show/NCT02247531
[87] https://clinicaltrials.gov/ct2/show/NCT02247479
[88] https://clinicaltrials.gov/ct2/show/NCT01802866
[89] https://clinicaltrials.gov/ct2/show/NCT01342926
[90] https://clinicaltrials.gov/ct2/show/NCT02467634
[91] https://clinicaltrials.gov/ct2/show/NCT02563782
[92] https://clinicaltrials.gov/ct2/show/NCT02286089
[93] https://clinicaltrials.gov/ct2/show/NCT02024269

	Intermediate dry ARMD	Geographic Atrophy	Wet ARMD
Standard of care	• **Zinc + Vitamines C/E (nutraceuticals)**	• None	Anti-VEGF : • Lucentis (Novartis) • Eylea (Bayer)
Products in developement	• **BIO201 (Phase 2b)** • **BI0203 (Pré-clinical)**	Anti-complement factor antibodies : • Lampalizumab (Roche) • LFG316 (Novartis) • Zimura (Ophtotech)	
Product attrbutes	• **Limits A2E accumulation** • **Slows retina degeneration** • **Oral administration**	• Anti-inflammatory • Limits atrophy expansion • Intravitreal injection	• Stops neo-vascularisation • Limits loss of visual acuity • Intravitreal injection

6.4. ORGANIZATION OF THE COMPANY

6.4.1. Organization

Biophytis has an informal and flexible structure and currently employs 14 people, all staff members, who focus on corporate know-how (and value), while covering a wide range of areas of expertise. 8 of them have a doctorate and all of them have a scientific background. The additional scientific resources derive from the cooperation with *translational* research institutes. The development work involved in project ownership is entrusted to recognized providers in the sector under the expert guidance of the R&D Division and the Medical Division.



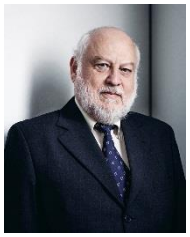
Stanislas VEILLET – Founding President

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 to realise the potential of natural active molecules to in the treatment of chronic age-related diseases. He is the author of some ten patents.

René LAFONT – Director and Scientific Founder



Doctor of Natural Sciences, Emeritus Professor at the University Pierre and Marie Curie

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 studied in particular the effects of the insect moulting hormone, ecdysone, and contributed to the discovery of the effects of this molecule on their development. He managed a laboratory at the *Ecole Normale Supérieure*, then at the UPMC, where he was appointed professor in 1985 and taught Comparative Physiology at the Faculty of Sciences and Cellular Biology at 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 170 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 Susanna DEL SIGNORE – Medical Director

Doctor of Medicine (University La Sapienza, Rome)

Susanna Del Signore manages the BlueCompanion company, which she founded and which specialises in e-health projects and public-private partnerships in the medical field. Before that, she managed the Neuro-degenerative Diseases and Ophthalmology Department of the European Medicines Agency between 2005 and 2009 before joining Sanofi where she was Head of Global Policy of the R&D Department until 2015. She is also an expert in Internal Medicine and Clinical Nutrition.

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 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

Waly 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). Waly joined Biophytis in 2006. He has namely supervised the two clinical studies on the company's products and is currently managing the SARCOB programme.

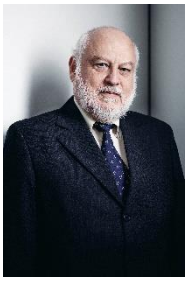
6.4.2. Scientific Committee

Professor Jean MARIANI

Director of the Charles Foix Institute of Longevity; Director of the Neurobiology of Adaptive Processes Laboratory, UMR 7102; hospital doctor at the 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 (Germany) Award; Jaroslav Heyrovsky Medal from the Academy of Sciences in the Czech Republic.

Expert in comparative physiology, analytical methods, phytochemistry; author and co-author of 170 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.

Philippe GUILLET – Medical Director

Doctor of Medicine (*UPMC* – Paris VI)

Philippe GUILLET practised in a hospital environment for over 10 years before joining the pharmaceutical industry in 1985. He held various posts in this industry, at the research clinics of Synthélabo, Rhône Poulenc Rorer, Sanofi-Pasteur, Pierre Fabre, and Exonhit. Philippe contributed to the clinical development and registration, including Stilnox sleeping pills and Rilutek for Amyotrophic Lateral Sclerosis. Before joining Biophytis and then its scientific committee, Philippe managed the "Translational Medicine and External Innovation" Division in the Therapeutic "Ageing Strategies" Unit at Sanofi-Aventis.

Professor Ivana KIM

Professor at Harvard Medical School; Director of the Unit in Massachusetts Eye and Ear; 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 twenty international publications.

Professor Roger A. FIELDING

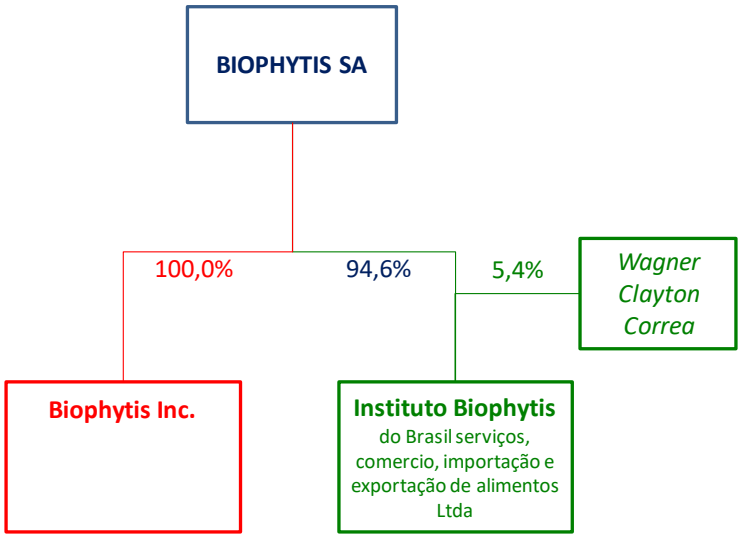
Professor at the Friedman School of Nutrition Science and Policy and at Harvard Medical School; Director of Human Studies at the Jean Mayer USDA Human Nutrition Research Center on Aging

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.

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, the second shareholder of which 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 INVESTMENTS

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 reference document, 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 company governed by Brazilian law (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 reference document, 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.

7.3. GROUP FINANCIAL FLOWS

INSTITUTO BIOPHYTIS DO BRASIL
Financial flows to the Brazilian subsidiary consist of current account contributions, the amounts of which in the last two financial years are detailed below:

- • In 2016: €0
- • In 2015: €23,000

The entire value of the investment, for a gross amount of €295,000 and receivables for a gross amount of €603,000, have been depreciated.

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 2016: €177,000
- • In 2015: €45,000

The entire value of the equity interest for a gross amount of €1,000, and of the current account for a gross amount of €222,000 have been depreciated.

8. PROPERTY, PLANT AND EQUIPMENT

8.1. PROPERTY AND EQUIPMENT

8.1.1. Leased properties

The Company leased the premises where its principal place of business was domiciled, located at Biocitech Park, 102 Avenue Gaston Roussel 93230 Romainville. The lease was concluded for a period from 1 July 2012 to 30 June 2021. In accordance with the possibility given to the tenant of terminating the lease every year on the anniversary of entry into effect of the lease, with a 6-month prior notice period, the Company gave notice to the lessor by a bailiff's instrument notified on 24 December 2015 and entering into effect on 1 July 2016.

The lease was tacitly extended for the period from 1 July 2016 to 31 December 2016.

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) the provision by the University of Pierre and Marie Curie of 274.85 m² of premises located on the 4th floor of Building A, (ii) the provision of certain equipment and materials of the FR3631 Institut Biologie Paris Seine Laboratory and (iii) the housing 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 via rider. This Public Property Occupancy Agreement may be terminated at any time by giving 3 months' prior notice.

The Public Property Occupancy Agreement expressly states that its object covers only the provision of premises and equipment by the Pierre et Marie Curie University. The Public Property Occupancy Agreement does not provide for any collaboration between the Company and the Pierre et Marie Curie University that may produce intellectual property. The Public Property Occupancy Convention specifies that the Company and the Pierre et Marie Curie University will have to conclude a specific collaboration agreement in the hypothetical case of joint research activities.

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.

In respect of the Public Property Occupancy Agreement, the Company incurred a charge of €3,779 during the financial year 2016.

Moreover, its registered office is at 14, Avenue de l'Opéra, pursuant to a commercial domiciliation agreement concluded with SDM on 6 September 2006, by way of which the company pays a rent of € 357 net of tax per quarter. This agreement may be terminated at any time by giving 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 negotiating downwards in view of 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 company is domiciled in an incubator for innovative businesses: within the CIETEC nursery of the Federal University of Sao Paulo (Universidade Federal de Sao Paulo, USP), with 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 "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 CONDITION 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 Reference Document, notably the consolidated financial statements in accordance with IFRS for the year ended 31 December 2016. The reader may consult the Notes to the financial statements, as included in Section 20.1 of the Reference Document.

Comments on the financial statements presented in Sections 9 and 10 of the Reference Document, are established solely on the basis of the consolidated financial statements prepared in accordance with IFRS, included in Section 20.1 of the Reference Document.

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;
- loans from various agencies (OSEO/BPI France, soprano/Sanofi, SODISID/Arcelor in particular);
- reimbursable advances granted by OSEO/BPI France and Coface;
- subsidies granted by the Fonds Unique Interministériel [Single Interministerial Fund] (FUI), the General Council of Seine Saint Denis, and Feder;
- the research tax credit;
- bonds;
- an IPO on the Alternext market in Paris in 2015.

9.2. COMPARISON OF ACCOUNTS FOR THE LAST TWO FINANCIAL YEARS

9.2.1. Formation of operating profit and net profit

(I) <u>of revenue</u>

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 candidate drugs for the treatment of metabolic diseases and aging. In the financial year 2016, it prioritised its efforts on the SARA clinical development programme (Sarconeos drug candidate for the treatment of sarcopenia).

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 regarded 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)	31/12/2015	31/12/2016
Staff expenses	1,613+	1,789+
Other purchases and external expenses	825+	4,817+
Other	62+	182+
Research and development expenses	**2,501+**	**6,788+**
Research tax credit	454	1,604
Subsidies	78	62
Subsidies	**532**	**1,667**
Net research and development expenses	**1,969+**	**5,121+**

Personnel costs, including stock-based payments, for engineers and research personnel amounted to €1,789,000 in 2016, an increase of €176,000 when compared to 2015. This development is due to the combination of:

- A sharp decline in the stock-based payment expense;
- A strengthening of the research team, notably with the recruitment of a Research Director and a Director of Operations at the end of 2015.

Other purchases and external expenses related to the Group's research activity amounted to €4,817,000 in 2016 and were up sharply when compared to the previous year. They comprise approximately 90% of the cost of studies and research related to the Sarconeos project.

The increase in research and development expense was accompanied by an increase in the research tax credit available to the Group in connection with its research activities in France (€1,604,000 in 2016 compared to €454,000 in 2015).

- ***General and administrative expenses***

General and administrative expenses break down as follows during the years presented:

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Staff expenses	2,035+	1,145+
Other purchases and external expenses	1,001+	1,572+
Other	38+	103+
General and administrative expenses	**3,074+**	**2,820+**

Personnel costs, including stock-based payments, for the general management and administrative personnel amounted to €1,145,000 in 2016, a decrease of €890,000 compared to 2015, mainly due to the decrease in stock-based payments.

Other purchases and external expenses amounted to €1,572,000 in 2016, an increase of €571,000, mainly due to an increase in fees.

(III) Net financial income

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Other financial expenses	47+	33+
Interest on bond loans	173+	-
Other financial income	31	22
Currency gains and (losses)	2+	1.
Total financial income and expenses	**190+**	**13+**

Financial net income amounted to -€13,000 at 31 December 2016 - an improvement of €177,000 compared to the previous year. This change is mainly due to a decrease in interest expense, as the 2015 financial year was impacted by interest on the BIOPHYTIS $_{2015C}$ and BIOPHYTIS $_{2015D}$ bonds.

(IV) Corporation tax

The Group did not record any corporation tax.

On 31 December 2016, the Group had tax losses of € 20,563,000, including:

- €20,361 in France
  The attribution 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%.

- € 201,000 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. 34%.

- € 1,000 for the Brazilian subsidiary
  In Brazil, the tax debt follows a declining regime: permitted loss carry-forwards 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) Basic 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.

	31/12/2015	31/12/2016
Average weighted number of shares circulation	4,865,853	6,202,616
Net profit/loss for the financial year	(5 233)	(7 954)
Basic earnings per share (€/share)	**(1,08)**	**(1,28)**
Diluted earnings per share (€/share)	**(1,08)**	**(1,28)**

9.2.2. Balance sheet analysis

(VI) Non-current assets

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Intangible fixed assets	2,244	2,125
Tangible fixed assets	194	276
Other non-current financial assets	272	99
Total non-current assets	**2,710**	**2,501**

Intangible fixed assets consist of quotas of patents acquired during the financial year 2015 from Metabrain and Iris Pharma for € 1,500,000 and € 800,000 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 shares on the Alternext Paris market.

(VII) Current assets

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Other receivables	1,422	2,827
Cash and equivalents	9,409	3,066
Total current assets	**10,831**	**5,892**

Other receivables principally include:

- The Government receivable relating to the Research Tax Credit for a total of €2,058,000 as of 31 December 2016, consisting of:

- The 2015 Research Tax Credit for €454,000 was repaid in January 2017,
- The 2016 Research Tax Credit for €1,604,000 is expected to be repaid in 2017.

- deductible VAT and VAT credits amounting to € 471,000 on 31 December 2016, against € 624,000 on 31 December 2015;

Cash and cash equivalents consist of bank accounts and a 30-day renewable term account.

(VIII) Shareholders' funds

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Capital	1,239	1,245
Issuance and contribution premiums	19,531	19,583
Treasury shares	(50)	(158)
Currency exchange differences	(9)	4
Provisions - attributable to Biophytis shareholders	(3 849)	(8 170)
Net income - attributable to Biophytis shareholders	(5 232)	(7 954)
Shareholders' equity - attributable to Biophytis shareholders	**11,629**	**4,549**
Interests not conferring control	(31)	(30)
Total shareholders' equity	**11,598**	**4,519**

On 31 December 2015, the share capital was set at €1,244,700.20, divided into 6,195,501 fully subscribed and paid-in shares with a nominal value of €0.20.

(IX) Non-current liabilities

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Pension obligation	25	48
Non-current financial debts	403	913
Total non-current liabilities	**428**	**962**

Commitments to staff consist of the provision for retirement allowances.
Non-current financial debts had the following breakdown:

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Reimbursable advances	220	797
Borrowings from and debts with lending institutions	53	23
Financial debts – Lease financing	131	94
Non-current financial debts	**403**	**913**

See section 10 for more information on the financing of the company.

(X) Current liabilities

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Current financial debts	399	176
Trade payables and associated accounts	701	1,920
Tax and social debts	361	722
Other creditors and miscellaneous debts	54	94
Total current liabilities	**1,515**	**2,913**

The increase in trade payables when compared to 31 December 2015 is mainly due to the significant increase in research and development expenses entrusted to third parties.

Current financial debts had the following breakdown:

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Reimbursable advances	73	96
Borrowings from and debts with lending institutions	130	30
Borrowings and miscellaneous financial debts	150	-
Financial debts – Lease financing	43	44
Accrued interest payable	1	0
Current bank liabilities	2	5
Current financial debts	**399**	**176**

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 annexes to the consolidated financial statements prepared in accordance with IFRS in Section 20.1 of the Reference Document.

10.1. INFORMATION ON CAPITAL, LIQUIDITY AND SOURCES OF FINANCING

On 31 December 2016, the net amount of cash and cash equivalents held by the Group (in assets and current bank overdrafts under liabilities) amounted to €3,066,000, compared to €9,409,000 at 31 December 2015.

10.1.1. Capital financing

The Company received a total of € 25,852 (before deduction of expenses linked to capital increases) through contributions from founders, capital increases carried out between 2006 and 2016 and the IPO in 2015.

The following table summarises the principal capital increases by value until the date of this reference document:

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 the 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 placement with a US investor and raising of € 6 million through 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 placement of €3.7 million through the issuance of 1,310,431 new shares at a price of €2.85 per share
2017	376	Conversion of 30 convertible bonds at a conversion price of €2.45.
2017	564	Conversion of 45 convertible bonds at a conversion price of €2.45.
2017	272	Conversion of 25 convertible bonds at a conversion price of €2.44.
2017	268	Conversion of 25 convertible bonds at a conversion price of €2.40.
2017	217	Conversion of 20 convertible bonds at a conversion price of €2.35.
2017	225	Conversion of 20 convertible bonds at a conversion price of €2.35
2017	720	Conversion of 62 convertible bonds at a conversion price of €2.35

Periods	Gross amounts raised in € '000	Transactions
2017	1.291	Conversion of 103 convertible bonds at a conversion price of €2.35
2017	3.102	Conversion of 200 convertible bonds at a conversion price of €2.92
2017	1.369	Conversion of 100 convertible bonds at a conversion price of €2.92
Total	**34.256**	

(1) The IPO of the company on the Alternext Paris market and the private placement with a U.S. investor generated fees of € 1,383,000.
(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 € 1,897,000*
- *dent relating to the acquisition of the quota of ownership of the patents with Metabrain and Iris Pharma for € 1,500,000 and € 800,000 respectively*
  the shareholder current account for € 60,000.

10.1.2. Financing by research tax credit

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Research tax credit	454	1,604

The Company has benefited from the research tax credit since its incorporation. The Research Tax Credit for 2015 was reimbursed in January 2017. The reimbursement of the 2016 CIR is scheduled for 2017.

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 €230,000 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 (€61,000) 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 €180,000 for the "clinical development of Bixilia 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 € 29,000 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 €260,000 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. As of the date of the Reference Document, the Company had received the full amount of €260,000. In 2016, BPI France granted an extension for repayment. If successful, this advance will be repaid in quarterly instalments 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 €1,100,000 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. As of the date of the Reference Document, the Company had received €600,000, on which a registration fee of €33,000 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 Reference Document.

(Amounts in thousands of euros)	OSEO - Quinolia	OSEO – Maculia	OSEO- Sarcob	BPI - BIO 101	Total
At 31 December 2014	**201**	**11**	**-**	**-**	**272**
(+) Collection	-	-	92	-	92
(-) Reimbursement	-	(7)	-	-	(7)
Subsidies	(11)	-	(7)	-	(78)
Financial expenses	11	0	3	-	15
(+/-) Other movements	-	-	-	-	-
On 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
(+/-) Other movements	-	-	-	-	-
At 31 December 2016	**177**	**-**	**188**	**528**	**893**

(XII) Subsidies

Since its inception, the Company has benefited from two main subsidy contracts:

A subsidy of up to €520,000 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 € 475,000 (including € 234,000 from the General Council of Seine-Saint-Denis and € 241,000 from OSEO).

A subsidy of up to €300,000 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 €166,000.

The Company did not obtain any new significant subsidies during the financial year 2015.

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 to the tune of €150,000. 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 € 100,000. This loan was reimbursed in full in January 2016.

Please refer to Note 10.2 to the IFRS consolidated financial statements in Section 20.1 of the Reference Document for further details.

(Amounts in thousands of euros)	OSEO - Equity Loan	BPI - Research Tax Credit prefinancing loan	Total
At 31 December 2014	**83**	**100**	**183**
(+) Collection	-	-	-
(-) Reimbursement	-	-	-
Subsidies	-	-	-
Financial expenses	-	-	-
(+/-) Other movements	-	-	-
On 31 December 2015	**83**	**100**	**183**
(+) Collection	-	-	-
(-) Reimbursement	(30)	(100)	(130)
Subsidies	-	-	-
Financial expenses	-	-	-
(+/-) Other movements	-	-	-
At 31 December 2016	**53**	**-**	**53**

(XIV) Borrowings and miscellaneous financial debts

On 25 July 2014, the Company signed a € 150,000 loan agreement with SODISID within the context of a programme to create 10 jobs. This loan was reimbursed in full in 2016. The capital was reimbursed in full in February 2016.

The Company signed a € 30,000 loan agreement with the UPMC in November 2014, having as object the "partial financing of industrial property costs within the context of 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.

Please refer to Note 10.3 to the IFRS consolidated financial statements in Section 20.1 of the Reference Document for further details.

(Amounts in thousands of euros)	SODISID loan	UPMC loan	Total
At 31 December 2014	**150**	**29**	**179**
(+) Collection	-	-	-
(-) Reimbursement	-	(30)	(30)
Subsidies	-	-	-
Financial expenses	-	1	1
(+/-) Other movements	-	-	-
On 31 December 2015	**150**	**-**	**150**
(+) Collection	-	-	-
(-) Reimbursement	(150)	-	(150)
Subsidies	-	-	-
Financial expenses	-	-	-
(+/-) Other movements	-	-	-
At 31 December 2016	**-**	**-**	**-**

(XV) Convertible bond with the Bracknor Fund

In April 2017, the Company set up a financing line with the Bracknor Fund for up to €15 million in the form of 1,500 convertible bonds with a nominal value of €10,000 each, with warrants attached ("**convertible bonds and warrants**"). Establishing the financing line was decided by the Board of Directors on 3 April, making use of the power of attorney 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 10,000
- Subscription price: at par
- No interest
- Conversion terms: N = Vn/(R x P) where
  - N is the number of shares that may be subscribed
  - Vn corresponds to the nominal value of the convertible bonds, i.e. €10,000
  - R is the conversion ratio i.e. 0.92
  - P is the conversion price, which is the lowest weighted average trading price of the 15 trading days prior to the conversion request date.

On the date of the conversion request, the Company will be able to redeem the convertible bonds in cash according to the following formula: V = Vn/R where V is the amount reimbursed to the bearer.

It is specified that the Company has undertaken to draw the first tranche of convertible bonds in the amount of €3,000,000.00 within a period of 5 to 25 trading days from 7 April 2017.

In addition, under the terms of the convertible bonds and warrants issue agreement, the Company has undertaken to pay Bracknor a commission equal to 2% of the nominal value of all the convertible bonds, i.e. 30 convertible bonds. In a decision dated 15 May 2017, the Company's CEO decided to issue 30 convertible bonds with a nominal value of €10,000 each, with a maturity of 12 months from 3 April 2017.

First tranche

By two decisions dated 15 May 2017, the CEO, in accordance with the delegation of powers granted by the Board of Directors by a decision dated 3 April 2017, making use of the tenth resolution granted by the Combined Shareholders' Meeting of 10 June 2016, noted the issuance of (i) 330 convertible bonds and (ii) 225,225 warrants.

By a decision dated 16 May 2017, the CEO noted (i) the issuance of 122,449 new common shares following Bracknor's conversion request of 30 convertible bonds and (ii) the corresponding increase in the share capital of the Company by a nominal amount of €24,489.80 raising the share capital of the Company from €1,506,786.40 to €1,531,276.20.

By a decision dated 16 May 2017, the CEO noted (i) the issuance of 183,673 new common shares following Bracknor's conversion request of 45 convertible bonds and (ii) the corresponding increase in the share capital of the Company by a nominal amount of €36,734.60 raising the share capital of the Company from €1,531,276.20 to €1,568,010.80.

By a decision dated 27 May 2017, the CEO noted (i) the issuance of 102,459 new common shares following Bracknor's conversion request of 25 convertible bonds and (ii) the corresponding increase in the share capital of the Company by a nominal amount of €20,491.80 raising the share capital of the Company from €1,568,010.80 to €1,588,502.60.

By a decision dated 31 May 2017, the CEO noted (i) the issuance of 104,166 new common shares following Bracknor's conversion request of 25 convertible bonds and (ii) the corresponding increase in the share capital of the Company by a nominal amount of €20,833.20 raising the share capital of the Company from €1,588,502.60 to €1,609,335.80.

By a decision dated 02 June 2017, the CEO noted (i) the issuance of 85,106 new common shares following Bracknor's conversion request of 20 convertible bonds and (ii) the corresponding increase in the share capital of the Company by a nominal amount of €17,021.20 raising the share capital of the Company from €1,609,335.80 to €1,626,357.

By a decision dated 07 June 2017, the CEO noted (i) the issuance of 85,106 new common shares following Bracknor's conversion request of 20 convertible bonds and (ii) the corresponding increase in the share capital of the Company by a nominal amount of €17,021.20 raising the share capital of the Company from €1,626,357 to €1,643,378.20.

By a decision dated 09 June 2017, the CEO noted (i) the issuance of 263,829 new common shares following Bracknor's conversion request of 62 convertible bonds and (ii) the corresponding increase in the share capital of the Company by a nominal amount of €52,765.80 raising the share capital of the Company from €1,643,378.20 to €1,696,144.

By a decision dated 09 June 2017, the CEO noted (i) the issuance of 438,297 new common shares following Bracknor's conversion request of 103 convertible bonds and (ii) the

corresponding increase in the share capital of the Company by a nominal amount of €87,659.40 raising the share capital of the Company from €1,696,144 to €1,783,803.40.

Summary table of the issue and exercise of the first tranche of convertible bonds and warrantss

FR0012816825 - ALBPS

ORNANEBSA

Monitoring of the shares outstanding 07.11.2017

	TOTAL	Round #1	Round #2
Date of issue of ORNANEBSA round		05.15.2017	07.07.2017
Number of ORNANE issued	630 ORNANE issued	330 ORNANE	300 ORNANE
Number of warrants issued	431 184 warrants issued	225 225 warrants	205 959 warrants

**: including 30 ORNANE issued as part of the commitment fees*

	Total shares issued	date	number	issued	date	number	issued
Requests for the conversion of ORNANE	1 385 085 shares	05.16.2017	75	306 122	07.07.2017	200	684 931
		05.26.2017	25	102 459	07.11.2017	100	342 465
		05.31.2017	25	104 166			
		06.02.2017	20	85 106			
		06.08.2017	20	85 106			
		06.09.2017	20	85 106			
		06.09.2017	42	178 723			
		06.09.2017	103	438 297			
Requests to exercice warrants	0 shares		0			0	
ORNANE held by Bracknor Fund Ltd	0 ORNANE		0 ORNANE			0 ORNANE	
Warrants held by Fund Ltd	431 184 warrants		225 225 warrants			205 959 warrants	
Total number of shares issued	2 412 481 shares		1 385 085 shares			1 027 396 shares	

Summary	
Number of shares in 06.09.2017	9 946 413 shares
Number of voting rights in 06.09.2017	9 946 413 voting rights

This board sums up the number of shares outstanding following the implementation of the ORNANEBSA programme (Bonds redeemable for cash and new and existing shares with warrants attached) formulated in the report of 4 April 2017.

Second tranch

By a decision dated 07 July 2017, the CEO, in accordance with the delegation of powers granted by the Board of Directors by a decision dated 3 April 2017, making use of the tenth resolution granted by the Combined Shareholders' Meeting of 10 June 2016, noted the issuance of (i) 300 convertible bonds and (ii) 205,959 warrants.

By a decision dated 07 July 2017, the CEO noted the issuance of 684,931 new common shares following Bracknor's conversion request of 200 convertible bonds and the corresponding increase in the share capital of the Company by a nominal amount of €136,986.20.

By a decision dated 10 July 2017, the CEO noted the issuance of 342,465 new common shares following Bracknor's conversion request of 100 convertible bonds and the corresponding increase in the share capital of the Company by a nominal amount of €68,493.

The entire second tranche of the convertible bonds was exercised.
(See Section 21.1.5 of the Reference Document for more details on the characteristics of this instrument).

In addition, the dilution risk associated with the issue of convertible bonds and warrants is specified in Section 4.4.1 of the Reference Document.

10.1.5. Off-balance-sheet commitments

(XVI) Commitments by way of financial debts

Commitments received

Emprunt	Garanties reçues	Nominal	Montant résiduel au 31/12/2016
Prêt participatif d'amorçage OSEO	-Participation en risque d'OSEO innovation à hauteur de 20% de l'encours du prêt - Participation en risque d'OSEO garantie dans le cadre de la procédure FNG Innovation à hauteur de 40% de l'encours du prêt. - Participation en risque d'OSEO IDF à hauteur de 40% de l'en cours du prêt	150	53

Commitments given

Emprunt	Engagements donnés	Nominal	Montant résiduel au 31/12/2016
Avance remboursable OSEO - projet "Quinolia"	La convention prévoit le paiement d'une annuité de remboursement à compter du 1er janvier 2009 et au plus tard le 31 mars de chaque année correspondant à : 44% du produit hors taxes, des cessions ou concessions de licences, de brevets ou savoir-faire perçu au cours de l'année calendaire précédente lorsque lesdites cessions ou concessions portent sur tout ou partie des résultats du programme aidé et à 44% du produit hors taxes généré par la commercialisation et notamment la vente à un tiers ou l'utilisation par le bénéficiaire pour ses besoins propres des prototypes, pré séries, maquettes, réalisés dans le cadre du programme aidé. Les sommes dues s'imputeront en priorité et à due concurrence sur l'ultime échéance due à OSEO. L'application de ce mécanisme ne conduira pas la société à verser un somme supérieure à l'aide perçue.	229	191
Avance remboursable BPI France – "BIO 101"	La convention prévoit le paiement d'une annuité de remboursement à compter du 1er janvier 2018 et au plus tard le 31 mars de chaque année jusqu'au 30 septembre 2023 correspondant à : 35,81 % du produit hors taxes, des cessions ou concessions de licences, de brevets ou savoir-faire perçu au cours de l'année calendaire précédente lorsque lesdites cessions ou concessions portent sur tout ou partie des résultats du programme aidé et à 35,81 % du produit hors taxes généré par la commercialisation et notamment la vente à un tiers ou l'utilisation par le bénéficiaire pour ses besoins propres des prototypes, pré séries, maquettes, réalisés dans le cadre du programme aidé. Les sommes dues s'imputeront en priorité et à due concurrence sur l'ultime échéance due à BPI. L'application de ce mécanisme ne conduira pas la société à verser un somme supérieure à l'aide perçue.	1 100*	600

* Dont 500 K€ seront versés à l'achèvement du projet

(XVII) Property leases

On 31 December 2016, the amount of future rentals regarding the lease signed with the UPMC was as follows:

(montant en milliers d'euros)	Date de début effectif du bail	Date de fin du bail	Charges de location au 31/12/2016	Engagement jusqu'à la prochaine période de résiliation		
				A 1 an au plus	De 1 à 5 ans	A plus de 5 ans
Paris -UPMC - laboratoire et bureaux	15/12/2016	15/12/2017	4	54	-	

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 2015 and 31 December 2016 respectively amounted to €3,301,000 and €6,633,000.

10.2.2. Cash flows linked to investment activities

Cash usage linked to operating activities for the years ended 31 December 2015 and 31 December 2016 respectively amounted to €6,000 and €129,000.

10.2.3. Cash flow linked to financing activities

Cash flow from financing activities are as follows for the years presented:

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Increase in net capital of subscriptions by offsetting receivables	11,778	-
Expenses associated with capital increases	1,291+	-
Subscription of warrants	205	-
Exercise of warrants & founder's warrants	534	58
Reimbursable advances received, net of repayments	85	634
Collection of subsidies	25	10
Issuance of loans, net of repayments	1,695	280+
Gross financial interest paid	20+	6+
Interest on the investment account	28	24
Reimbursements of lease financing	7+	36+
Change in current accounts	7+	-
Change in current bank overdrafts	20+	4
Other financing flows (liquidity agreement)	300+	-
Cash flows linked to financing operations	**12,705**	**407**

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 Reference Document.

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 founded in 2006, which develops new classes of drugs against degenerative diseases of aging, the medical need for which is not currently satisfied. **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 on these two programs have permitted 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 forming the object of priority attention 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 with 9 individuals with high-level scientific training and more specifically, doctors of medicine, biology and natural sciences (see section 6.4.). Employees working in research and development are each individually linked 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 remuneration, 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 31/12/2014 and 31/12/2015 amounted respectively to €2,501,000 and €6,788,000, consisting mainly of salaries, internal development costs as well as 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 sign alliances with pharmaceutical companies in order to support the regulatory development as far as the 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 research and internal development effort and within the context of exclusive research agreements and collaboration with academic stakeholders (UPMC, 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 dossiers 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 deadline (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. 1 “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 50% jointly owned by the Company with the balance held by public partners, and the company holds the exclusive exploitation rights according to the agreement described in 11.3.2.

- Patent family No. 2 “weight stabilisation”: the invention protected by these patents concerning the use of phytoecdysones in stabilising weight after dieting. The patents are 50% jointly owned by the Company with the balance held by a public partner, and the company holds the exclusive exploitation rights according to the agreement described in 11.3.2.

- Patent family No. 3 “muscular quality”: the invention protected by these patents is the use of phytoecdysones in improving muscular quality in obese and/or sarcopenic mammals. The patents are 33% jointly owned by the Company with the balance held by public partners, and the company holds the exclusive exploitation rights according to the agreement described in 11.3.2.

- Patent family No. 4 “phytoecdysone analogues”: the invention protected by this patent relates to a chemical process for manufacturing phytoecdysones and their use in the preparation of medicines. The patents are 66% jointly owned by the Company with the balance held by a public partner, and with the company holding the exclusive exploitation rights according to the agreement described in 11.3.2.

- Patent Family No. 5 "*Extracts* of 20-hydroxyecdysone": the invention protected by this patent relates to a process for extracting purified 20-hydroxyecdysone and the therapeutic use of these extracts in the improvement of the muscle function or in the treatment of cardiovascular disease. The patents will be held in co-ownership with a public partner.

Patent family		1	2	3	4	5
Application No.		FR 0759478	FR 1160280	FR 1161519	FR 1553547	FR 1753775
SARCOB	Sarconeos	✔	✔	✔		✔
	BIO 103			✔	✔	
	BIO 101					✔

Patents relating to the MACULIA program:

- Patent family No. 5 “Photo-protection”: the invention protected by these patents covers the use of bixin and norbixin to protect the skin against sun damage. The patents are 75% jointly owned by the Company with the balance held by a public partner, and with the company holding the exclusive exploitation rights according to the agreement described in 11.3.2.

- Patent family No. 6 “AMD”: This invention covers the use of bixin and norbixin to protect the eye against AMD. The patents are 50% jointly owned by the Company with the balance held by a public partner, and the company holds the exclusive exploitation rights according to the agreement described in 11.3.2.

- Patent family No. 7 “composition for protecting retinal epithelial cells”: the invention protected by this patent relates to the use of a composition using norbixin for use in the treatment of AMD. The patents are 66% jointly owned by the Company with the balance held by a public partner, and with the company holds the exclusive exploitation rights according to the agreement described in 11.3.2. On 4 June 2015, the Company acquired a quota of ownership of the patents from a private partner who until then held a 33% stake, raising its share of ownership to the 66% mentioned above. The agreement was concluded subject to a termination condition that the Company would be publicly listed on a stock market before 27 May 2016 and that the public partner does not exercise its pre-emptive right, which was removed prior to the registration of this Reference Document.

  Patent family No. 8 “Use of 3-deoxhyanthocyanidins for the treatment of eye diseases”: the invention protected by these patents concerns the use of compounds from the family of flavonoids, anthocyanidins, in particular 3-deoxhyanthocyanidins for the treatment, prevention and/or stabilisation of AMD and/or Stargardt’s disease, pigmentary retinopathy and/or diabetic retinopathy. The patents are jointly owned 50% by the Company and 50% by a public partner, with the company holding sole exploitation rights according to the agreement described in 11.3.2.

Patent family		6	7	8	9
Application No.		FR 0954354	FR 1154172	FR 1553957	FR 1554761
MACULIA	Macuneos	✔	✔	✔	✔
	BIO 203		✔		✔

b) Nature and coverage of patents or patent applications supported by the Company

The Company's patents and applications reflect the research and development efforts implemented to provide innovative solutions for the treatment of AMD (age-related macular degeneration), (MACULIA technology), and the treatment of sarcopenic obesity (SARCOB technology).

(I) SARCOB Program

- ***"Metabolic syndrome" family (Family No. 1)***

The invention protected by this patent covers the use of phytoecdysones in the preparation of a composition to act on metabolic syndrome.

The international patent application (Patent Cooperation Treaty "PCT") "use of phytoecdysones in the preparation of a composition to act on metabolic syndrome" has been filed by the Company, the UPMC, 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 a share equal to 50% of the ownership of these patents, with the remaining 50% held equally by the UPMC and the CNRS.

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	Issued (19/02/2010)
WO	19/11/2008	WO2008FR52088	11/06/2009	WO2009071804	
AU	19/11/2008	AU20080332981	11/06/2009	AU2008332981	Issued (25/09/2014)
BR	19/11/2008	PI0820455	29/09/2015	BR0820455	Review in progress
CA	19/11/2008	CA2008270 6821	11/06/2009	CA2706821	Deemed withdrawn
CN	19/11/2008	CN2008811 8514	02/11/2011	CN102231986	Issued (22/01/2014)
EP	19/11/2008	08856497.6	18/08/2010	EP2217255	Review in progress

Priority					
Country	**Date of application**	**Application No.**	**Date of public'n**	**Public'n No.**	**Status of procedure**
IN	19/11/2008	3976/DELNP/2010	11/11/2011	452011	Review in progress
RU	19/11/2008	RU20100126625	10/01/2012	RU2010126625	Issued (27/08/2013)
US	19/11/2008	US20080745315	10/02/2011	US2011033561	Issued (07/08/2012)

The patent was issued 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 issued 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 issued on the same terms but without any limitation on the dose administered.

- ***"Weight stabilisation" family (Family No. 2)***

The invention protected by these patents covers the use of phytoecdysones in stabilising weight after dieting.

The international patent application (PCT) for "phytoecdysones for use in stabilising weight after dieting" was filed by the Company and the UPMC under the priority of a French patent FR 1160280. The patent application PCT has been extended to China, Europe, Japan, and the United States.

The Company holds a share equal to 50% of the ownership of these patents, with the remaining 50% being held by the UPMC.

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	Issued (27/12/2013)
WO	12/11/2012	WO2012FR52600	16/05/2013	WO2013068704	
CN	12/11/2012	CN201200855214.8	30/07/2014	CN103957727	Issued (14/09/2016)
EP	12/11/2012	12795522.7	17/09/2014	EP2775859	Issued (18/01/2017)
JP	12/11/2012	JP20140540542	11/12/2014	JP2014533256	Review in progress modifications (18/01/2017)

US	12/11/2012	US2012143 56646	16/10/2014	US20140309 203	Abandoned but continued with a new patent below
US01	12/11/2012	US2015359 477			Continuity

They have all been published and requests are under review by the national offices. The patent was issued for Europe and is currently being validated in the various European contracting countries.

The European patent was issued for the use of phytoecdysone to avoid weight recovery in obese mammals after a low-calorie diet.

- ***"Muscular quality" family (Family No. 3)***

The invention protected by these patents cover the use of phytoecdysones in improving muscular quality.

International Patent Application (Patent Cooperation Treaty "PCT") for "phytoecdysones for use in improving the muscular quality of obese and/or sarcopenic mammals" was filed by the Company, the UPMC, 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 a share equal to 33% of the joint ownership of these patents, with 66% held equally by the UPMC (33%) and the INRA (33%).

Priority					
Country	**Date of application**	**Application No.**	**Date of public'n**	**Public'n No.**	**Status of procedure**
FR	13/12/2011	FR1161519	14/06/20 13	FR2983733	Awaiting issuance
WO	13/12/2012	WO2012FR 52931	20/06/20 13	WO2013088 084	
CN	13/12/2012	CN2012866 803	08/10/20 14	CN10409340 9	Awaiting issuance (03/05/2017)
EP	13/12/2012	12813926.8	22/10/20 14	EP2790706	Review in progress (23/09/2016)
US	13/12/2012	US2012143 64249	09/04/20 15	US20150990 22	Abandoned but continued with a new patent below
US01	13/12/2012				Continuity

The patents have not yet been issued either in France or abroad. They have all been published and requests are under review by the national offices.

- ***"Phytoecdysones analogue" family (Family No. 4)***

The invention protected by these patents cover the products derived from 20-hydroxyecdysones and their use in the preparation of medicines.

The international patent application (PCT) for "Products derived from 20-hydroxyecdysones and their use in the preparation of medicines" has been filed by the Company, the UPMC, and Metabrain Research subject to 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 upon issuance of the French patent of a share equal to 66% of the joint ownership of these patents, with the remaining 33% held by the UPMC.

Country	**Date of application**	**Application No.**	**Date of public'n**	**Public'n No.**	**Status of procedure**
FR	20/05/2014	FR1454538			Claims modified after publication (27/11/2015)
WO	20/05/2015	WO2015FR51332	26/11/2015	WI2015177419	
AU	20/05/2015	AU201563121	12/01/2017	AU201563121	
BR	20/05/2015	BR112016027053			
CA	20/05/2015	CA2949649			
CN	20/05/2015				
EP	20/05/2015	15732785.9			Under review
IL	20/05/2015				
IN	20/05/2015				
JP	20/05/2015				
KR	20/05/2015	KR10-2016-7035614			
RU	20/05/2015	RU201649619			
US	20/05/2015	US2015311967			

The patents have not yet been issued either in France or abroad. Apart from the patent published in Australia, reviews by national offices have not yet begun.

The Examiner has given his approval for for several compounds, including BIO103, in the context of the PCT.

- ***"20-hydroxyecdysone extract" family (Family No. 5)***

The invention protected by this patent covers 20-hydroxyecdysone extracts and their use in the preparation of medicines.

The invention was patented on 28 April 2017 under number FR1753775.

The Company will co-own the patent with the UPMC.

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 issued in France and has not yet been extended regionally or internationally.

(II) MACULIA Program

- ***"Photo-protection" family (Family No. 6)***

The invention protected by these patents covers 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 the UPMC under priority of a French patent FR 0954354. A French divisional application FR 1153996 was filed on 10 May 2011 and is awaiting issuance. The PCT patent application was extended to Australia, Brazil, Europe, and the United States.

The Company holds a share equal to 75% of the ownership of these patents, with the remaining 25% held by the UPMC. 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	Issued (27/01/2012)
WO	25/06/2010	WO2010FR51323	29/12/2010	WO2010149942	
BR	25/06/2010	PI1010113-6	15/03/2016	PI1010113	Review in progress (10/01/2017)
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	Issued (16/08/2013)
US	25/06/2010	US201013380768	14/06/2012	US2012149776	Issued 13/11/2015

The patent was issued in the United States. Applications have been published in all other countries except Brazil and are thus under review by the national offices. It was abandoned in Australia.

The US patent has been issued for the use of bixin or norbixin, orally and at a fixed dose, to protect against damage to the skin caused by ultraviolet exposure.

- ***"AMD" family (Family No. 7)***

The invention protected by these patents covers 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 the UPMC under priority of a French patent No. FR 1154172. A French divisional application No. FR 1361229 was filed on 17 November 2013 and is awaiting delivery. The PCT patent application was extended to Brazil, Europe, Japan, and the United States.

The Company holds a share equal to 50% of the ownership of these patents, with the remaining 50% being held by the UPMC.

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	Issued (07/03/2014)
Country	**Date of application**	**Application No.**	**Date of public'n**	**Public'n No.**	**Status of procedure**
WO	14/05/2012	WO2012FR00193	22/11/2012	WO2012156600	
FR (divisional application)	17/11/2013	FR1361229	18/04/2014	FR2996773	Issued (05/08/2016)
BR	14/05/2012	BR11 2013 029318-7	13/05/2014		Under review
EP	14/05/2012	12728639.1	16/04/2014	EP2717891	Issued (14/09/2016)
JP	14/05/2012	JP20140510851	19/06/2014	JP2014514366	Final rejection Completed by a new filing JP01 below
JP01	17/02/2017	JP2017278 51			Divisional application
US	14/05/2012	US201214117461	30/10/2014	US2014322371	Review in progress (26/01/2017)

The patents have all been published and requests are under review by the national offices. It has been issued for Europe and is currently being validated in the various European contracting countries.

In view of the issuance of an initial aspect of the invention in Japan, a divisional application was filed to complete the protection in that country.

- ***"Retinal epithelium" family (Family No. 8)***

The invention protected by this patent covers the use of norbixin for use in the treatment of AMD.

It was filed by the Company, the UPMC and Iris Pharma and was the subject of a PCT extension under the priority of French patent application No. FR1553957. It is being reviewed after publication. Europe was designated in the PCT application.

The Company will hold a share equal to 66% of the ownership of these patents, with the remaining 33% held by the UPMC. 5 June 2015, the Company acquired Iris Pharma's quota of 33%, increasing its share of ownership to the 66% mentioned above. The sale of Iris Pharma to the Company has been registered but does not appear in the databases.

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	Awaiting issuance
WO	30/04/2016	WO2016FR51001	03/11/2016	WO2016174360	

The application is under review in France and at the WIPO level before being considered by the regional or national offices designated in the PCT application.

- ***"3-deoxhyanthocyanidines" family (Family No. 9)***

The invention protected by this patent covers the use of compounds of the family of flavonoids, anthocyanidins, especially 3-deoxhyanthocyanidines, for the treatment, prevention and/or stabilisation of AMD and/or Stargardt disease, pigmentary retinopathy, and/or diabetic retinopathy.

It was filed by the Company and the UPMC and was the subject of a PCT extension under the priority of French patent application No. FR1554761 in the name of the Company, the UPMC, CNRS, and INSERM. It is being reviewed after publication. Europe was designated in the PCT application.

The Company will hold a share equal to 50% of the co-ownership of these patents, with the remaining 50% being held by the UPMC at 30% and the INRA at 20%, following the sale of 20% by the UPMC to INRA. The distribution of patent ownership between the INRA and the UPMC is being published on the public registers. To date, the UMPC appears as the holder of 50% of the patent alongside the Company.

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	Review in progress
WO	27/05/2015	WO2015FR51262	01/12/2016	WO2016189260	Review in progress

The application is under review in France and at the WIPO level before being considered 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 conducted to pursue two ongoing programs, SARCOB, one of the new inventions developed by the Company is expected to be filed in 2016.

11.2.3. Disputes

To date, no litigation, including any opposition proceedings for patents relating to intellectual property rights, has been directed by or against the Company before the courts.

11.3. AGREEMENTS FOR COLLABORATION, RESEARCH, PROVISION OF SERVICES AND LICENSES GRANTED BY THE COMPANY OR GRANTED TO IT

11.3.1. Collaboration, research, service provision and licensing agreements granted by the Company or granted to it

(I) SARCOB consortium agreement

On 22 November 2013, the Company formalised a consortium agreement entering into effect on 1 January 2012 for a period of 24 months starting from this effective date and concluded with Metabrain Research, the UPMC, the NSRF, INSERM, AIM (Myology Institute Association) and the INRA. The patents in families 2, 3, and 4 were developed within the context of this consortium agreement. 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 on patents in the family [t 5], for which the negotiation of co-ownership rules is in progress on a basis similar to the rules made for the patents of families 1, 2, 3, and 4 described below in 11.3.2. . These aspects are developed in 11.3.2.

(II) MACULIA consortium agreement

On 27 July 2012, the Company entered into a consortium agreement with the UPMC 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 lasts 6 months. This agreement has now expired as regards the research and collaboration aspects. It remains in force with regard to the rules governing the transfer of intellectual property rights to research results relating to patents of families [7 to 9]. These aspects are developed in 11.3.2.

(III) MACULIA collaboration agreement

On 20 November 2014, the Company, the UPMC, 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, the UPMC and Iris Pharma. This agreement has a term of six months expiring on 1 April 2015. A first supplementary agreement for renewal 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 supplementary renewal agreement taking effect retroactively on 1 October 2015 was signed on 16 February 2016 and expires on 31 December 2016. A third renewal agreement rider with retroactive effect from 1 January 2017 and expiring on 31 December 2017, was signed on 13 January 2017.

The object of this collaboration agreement is to continue the research undertaken within the context of the two previous agreements. The successive riders also modify the remuneration

paid by the Company to the UPMC, the CNRS, and INSERM to provide for the payment of a five-figure lump sum, one third of which is payable upon signing, with the balance at the expiration 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.

(IV) Inserm research services agreement

On 27 March 2017, the Company, the UPMC, and Inserm Transfert SA entered into 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. Compensation paid to the institutions by the Company is a lump sum of several thousand euros. All results stemming from the present agreement shall be the entire and exclusive property of the Company.

(V) UPMC/CNRS research collaboration agreement

The Company, the UPMC, and CNRS signed a research collaboration agreement on the effects of BIO 101 and BIO 103 on the cachexia associated with the development of cancerous tumours. 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.

(VI) UPMC/CNRS research collaboration agreement

The Company, the UPMC, and CNRS have signed a collaboration agreement concerning the effects of BIO101 and BIO 103 in the prevention of cardiac insufficiency and their role in thermogenesis and energy balance during ageing. 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 a rider dated 22 March 2017 for a period up to 31 July 2017.

The agreements described in (I) to (VII) above are significant agreements of the Company under Section 22 of this Reference Document.

11.3.2. Agreements for the exploitation of industrial property

(I) Joint ownership regulations for family 1 patents

On 9 July 2008, the Company concluded regulations on joint ownership with the UPMC and the CNRS and an operating agreement for the “metabolic syndrome” patent and associated know-how. With regard to the provisions on the rights of exploitation of the Company for the “metabolic syndrome” patent and the associated know-how, the agreement was terminated and replaced by the agreement of 27 May 2015 described in (II) below. It remains applicable as regards the co-ownership provisions that shall remain in force until the expiry or surrender 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 share 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.

(II) SARCOB consortium agreement - SATT Lutech Operating Agreement of 1 January 2016

The Agreement of 22 November 2013 (paragraph 11.3.1) notably provides that the common results arising from the joint and indissociable inventive and/or intellectual contribution of at least two parties are the joint property of the parties which generated it. Joint ownership regulations must be established before any exploitation of 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 4 patents, the Company exercised the exclusive worldwide option from which it benefited by way of the consortium agreement to exploit the joint results of which the Company is joint owner in the field of obesity, sarcopenia, diabetes, and sarcopenic obesity for commercial and industrial purposes. 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 completion on 27 May 2015, of an agreement between the Company and SATT Lutech, acting in the name and on behalf of the UPMC, the CNRS, and the INRA, and also 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 4 patents covered by the consortium agreement, but also covers the family 1 patents covered by the operating agreement described in paragraph 11.3.2 (I) above, and family 2 and 3 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.

(III) MACULIA consortium agreement - SATT Lutech Operating Agreement of 1 January 2016

The Agreement of 27 July 2012 (paragraph 11.3.1) provides that parties who are joint owners of the common results arising from the joint and indissociable inventive and/or intellectual contribution of at least two parties are the joint property of the parties which generated them. Joint ownership regulations must be established before any exploitation of 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 covering not only the family 6 patents but also those of families 7, 8 and 9, 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 the UPMC, 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 products. 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.

(IV) MACULIA collaboration agreement

The collaboration agreement of 20 November 2014 (paragraph 11.3.1) states that the parties are joint owners of the results *ipso jure*, with equal shares. Joint ownership regulations must be established before any exploitation of 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 worldwide 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 pigmented retinopathies, exercisable during the life 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 was still in progress and at this stage had not formed the object of a patent application within six (6) months of the end of the research.

(V) Joint ownership Regulations for family 5 “Photo-protection” patents

On 10 November 2014, the Company and the UPMC concluded a joint ownership agreement for family 6 “Photo-protection” patents. The regulations shall remain in effect until the later of: (i) The expiry or surrender of the last patent, or (ii) until an operating agreement on patents and/or associated know-how is underway or, until the date one of the parties becomes 100% owner of the patents, as the case may be.

By way of application of these regulations, the Company benefits from the exclusive use of patents in the field of foods and medicine for human and animal use, to be formalised through an operating agreement to be concluded. The agreement between the Company and SATT Lutech of 27 May 2015, described in paragraph 11.3.2 (III), constitutes the agreement concluded by way of the regulations.

The ownership of the "Photo-protection" patent 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 share for 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.

(VI) Joint ownership Regulations for family 2 "Weight stabilisation" patents

On 21 March 2016, the Company and the UPMC concluded a joint ownership agreement for family 2 patents with retroactive effect from 10 November 2011. The co-ownership regulations shall remain in force until the last of the patents expires or is abandoned.

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 share 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 this regulation, the Company has the exclusive use of patents in areas specified by the operating agreement concluded between the Company, SATT and the UPMC on 1 January 2016.

(VII) Joint ownership Regulations for family 3 "Muscle quality" patents

The Company, the UPMC, and the French National Institute of Agricultural Research entered into a co-ownership agreement for the partial assignment of a share of the family 3 patent, with retroactive effect from 13 December 2011. The co-ownership regulations shall remain in force until the last of the patents expires or is abandoned.

The ownership of the patents is divided as follows: (i) 50% for the Company, (ii) 30% for the UPMC, 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 share 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 this regulation, the Company has the exclusive use of patents in areas specified by the operating agreement concluded between the Company, SATT and the UPMC on 1 January 2016.

(VIII) Joint ownership regulations for family 4 "Phytoecdysones analogue" patents

On 18 November 2016, the Company and the UPMC concluded a joint ownership agreement for family 4 patents with effect from 20 May 2014. The co-ownership regulations shall remain in force until the last of the patents expires or is abandoned.

The ownership of the patents is divided as follows: (i) 70% for the Company and (ii) 30% for the UPMC. The Company is in charge of patent management. In the event of an assignment by one party of its share 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 this regulation, the Company has the exclusive use of patents in areas specified by the operating agreement concluded between the Company, SATT and the UPMC on 1 January 2016.

The agreements described in (I) to (VIII) above are significant agreements of the Company under Section 22 of this Reference Document.

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 as a precaution, following opposition proceedings from a third party company.

To date, applications for Brazilian trademarks have all been declined, apart from the BIOPHYTIS trademark No. 830135081 in class 30, which is awaiting the issue decision. The BIOPHYTIS trademark No. 830135090 in class 29 has been registered but is the object of a nullity action which is in progress.

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 form the object of any dispute.

In total, the Company holds the following 24 trademarks or trademark applications:

- French trademarks:

Trademark	Holder	Status	Filing date	Registration or filing number	Renewal date	Classes
MACUNEOS	Institut Biophytis	Registered	26/02/2016	164,252,454	26/02/2026	3 5 42
SARCONEOS	Institut Biophytis	Registered	26/02/2016	164,252,449	26/02/2026	3 5 42
BIOPHYTIS	Institut Biophytis	Registered	05/06/2012	12 3 924 876	30/06/2022	5 29 30
BIOPHYTIS	Institut Biophytis	Registered	06/04/2009	093,642,120	30/04/2019	3
AROLIA	Institut Biophytis	Registered	17/10/2008	083,605,575	31/10/2018	3 5 29 30 32
	Institut Biophytis	Registered	10/10/2008	083,604,077	31/10/2018	3 5 29 30 32 42

Trademark	Holder	Status	Filing date	Registration or filing number	Renewal date	Classes
QUINOLIA	Institut Biophytis	Registered	10/10/2008	083,604,074	31/10/2018	3 5 29 30 32
MONOLIA	Institut Biophytis	Registered	10/10/2008	083,604,081	31/10/2018	3 5 29 30 32
BIXILIA	Institut Biophytis	Registered	10/10/2008	083,604,082	31/10/2018	3 5 29 30 32
ATIBAIA	Institut Biophytis	Registered	27/11/2007	073,539,980	30/11/2017	5 29 30 32 42
BIOPHYTIS	Institut Biophytis	Registered	27/03/2006	063,420,081	30/11/2017	5 29 30 32 42
SARCONEOS	Biophytis	Registered	26/02/2016	164,252,449	26/02/2016	3 5 42
MACUNEOS	Biophytis	Registered	26/02/2016	16 4,252 454	26/02/2016	3 5 42

- EU trademarks[94]:

Trademark	Holder	Status	Priority	Filing date	Registration or filing number	Renewal date	Classes
ATIBAIA	Institut Biophytis	Registered	Under priority of FR 07 3 539980 of 27/11/2007	04/04/2008	6810816	04/04/2018	5 29 30 32 42
BIOPHYTIS	Institut Biophytis	Registered	Under priority of FR 06 3 420081 of 27/03/2006	26/09/2006	5337159	20/09/2016	5 29 30 32 42
BIOPHYTA	Institut Biophytis	Renewed		12/06/2003	3233376	12/06/2013 12/06/2023	3 5 29 30 31

- International trademarks designating the European Union, the United States and China:

Trademark	WO/Country	Holder	Status	Priority	Filing date	Registration or filing number	Renewal date	Classes
BIOPHYTIS	WO	Institut 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

[94] EU: Germany, Austria, Belgium, Bulgaria, Cyprus, Croatia, Denmark, Spain, Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Lithuania, Latvia, Luxembourg, Malta, the Netherlands, Poland, Portugal, the Czech Republic, Romania, the United Kingdom, Slovakia, Slovenia, and Sweden

Trademark	WO/Country	Holder	Status	Priority	Filing date	Registration or filing number	Renewal date	Classes
	WO/EU	Institut Biophytis	Registered					
	WO/USA	Institut Biophytis	Registered			Serial # 79080361 Reg # 3892827		
	Serial # 79080361 Reg # 3892827	Institut Biophytis	Registered					
QUINOLIA	WO	Institut 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	Institut Biophytis	Registered					
	WO/US	Institut Biophytis	Registered			Serial # 79071950 Reg # 3814749		
	Serial # 79080361 Reg # 3892827	Institut Biophytis	Registered					
	WO/JP	Institut Biophytis	Annulled					

- 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	Institut Biophytis	Registered / Nullity action in progress	22/04/2009	830135090	22/11/2021	29
BIOPHYTIS	Institut Biophytis	In progress	22/04/2009	830135081		30

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 filed the following domain name(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

March 2016: The AFMPS (Belgian regulatory authority) issued a favourable opinion on the clinical and regulatory development plan for the phase 2b clinical study of *Sarconeos* in the treatment of sarcopenic obesity. The study will be conducted by the Belgian research organisation, SGS Life Science.

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. DIRECTORS AND MANAGERS

A summary of the main provisions of the Company's articles of association and internal regulations relating to specialised committees appears respectively in paragraphs 21.2 *"Articles of incorporation and of association"* and 16.3 *"Specialised committees - corporate governance"* of this Reference Document.

14.1.1. Composition of the Board of Directors

On the date of this reference document, the Company's Board of Directors had the following composition:

Surname and first name or company name of the member	Mandate/Position held within the Company	Date of Appointment	Year of renewal/Expiry date of the mandate	Duration of mandate
Stanislas VEILLET	Chairman/CEO	1st appointment in the form of a SAS (Chairman): Articles of association of 15 September 2006 1st appointment in the form of a SA (in the capacity of director): Board meeting of 22 May 2015 1st appointment in the form of a SA (in the capacity of Chairman/CEO): Board meeting of 22 May 2015	31 December 2017	3 years old
Jean-Gérard GALVEZ	Director Independent	1st appointment in the form of a SAS: Board meeting of 11 June 2009 1st appointment in the form of a SA: Board meeting of 22 May 2015	31 December 2017	3 years old
Micheline KERGOAT	Director	1st appointment in the form of a SAS: Board meeting of 08 April 2015 1st appointment in the form of a SA: Board meeting of 22 May 2015	31 December 2017	3 years old
Nadine COULM	Director Independent	1st appointment in the form of a SA: Board meeting of 22 May 2015	31 December 2017	3 years old

Surname and first name or company name of the member	Mandate/Position held within the Company	Date of Appointment	Year of renewal/Expiry date of the mandate	Duration of mandate
Marie-Claire JANAILHAC-FRITSCH	Director Independent	1st appointment in the form of a SA: Board meeting of 22 May 2015	31 December 2017	3 years old
Jean M. Franchi	Director	Board meeting of 16 June 2017	31 December 2019	3 years old

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 CEO.

The Independent 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 meet in 2018 to approve the accounts for the year ending 31 December 2017.

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;
- Micheline KERGOAT METABRAIN RESEARCH, 4 avenue de Président François Mitterrand, 91380 Chilly Mazarin;
- Nadine COULM 12 rue Paul Hervieu, 75015 Paris;
- Marie-Claire JANAILHAC-FRITSCH 25, rue du Montparnasse, 75006 Paris;
- Ms Jean M. Franchi: 840 Memorial Drive, 4th Floor, Cambridge, MA 02139.

The expertise and experience of management of these individuals derive from different jobs and management functions, which they have previously held (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 associated in his/her capacity as a director or officer with a bankruptcy, receivership or liquidation;
- - has been the subject of a prohibition on managing;

- - has been the subject of official public incrimination or sanctions pronounced by statutory or regulatory authorities;

- has been prevented by a court from acting 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 mandates in progress 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
Micheline KERGOAT	Not Applicable	Not Applicable
Nadine COULM	Not Applicable	Not Applicable
Marie-Claire JANAILHAC-FRITSCH	Chairman of the Board of Directors Chairman & CEO	Guerbet SA Hellebore SAS
Jean M. Franchi	Director	International Institute of New England

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 Chairman & CEO	Ceprodi SA Columbus Café SA Fastbooking SAS
Micheline KERGOAT	NA	NA

Name	Nature of the mandate	Company
Nadine COULM	Administrator	Femmes Business Angels
Marie-Claire JANAILHAC-FRITSCH	Manager	FJ Immo
Jean M. Franchi	NA	NA

14.1.3. Biographies of the directors

Stanislas VEILLET, Chairman of the Board of Directors and CEO of Biophytis

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 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 author of some ten 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 chairman of subsidiaries and International Vice President, Jean-Gérard joined ActivCard in 1995, a start-up of French origin, as chairman and CEO. 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 has served 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), has a DEA de gestion [at qualifying experience in management] (INP Nancy) and an MBA received from the Stanford Executive Program (California).

Micheline KERGOAT, Director of Biophytis

A Doctor of Human Nutrition and Natural Sciences, Micheline KERGOAT began her career with the pharmaceutical company JANSSEN in Aubervilliers, where she studied the anti-diabetic effects of plant extracts. She then joined the research centre on diabetes of Merck-Serono in Chilly-Mazarin, where she was responsible for studies on isolated organs, particularly the pancreas. She co-founded Metabrain, of which she is the Scientific Director, when Merck-Serono withdrew from diabetes in 2009. She is the author of 45 original publications and some 20 patents

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.

Marie-Claire JANAILHAC-FRITSCH, **Director of Biophytis**

A graduate of HEC, Marie-Claire Janailhac-Fritsch began her career in the pharmaceutical industry with the company **EURORGA**. In 1980, she joined the marketing department of **SMITH KLINE**: while there, she was notably responsible for Tagamet, then the leading medicine in the world by sales.

In 1987, she created **IRIS, Institut de Recherche et d'Innovation Scientifiques** [Institute of Scientific Research and Innovation], specialising in safety and efficacy studies for research centres and cosmetic companies. Within this entity, the creation of the Centre Cosmetovigilance IRIS led her to form an exclusive network of 500 dermatologists/allergists covering the whole of Europe. In 1992, she created **LANATECH, laboratoire Nature et Technique**, which specialises in the design and marketing of active ingredients for cosmetics. In 2013, she sold both companies to **ATRIUM BIOTECHNOLOGIES**.

At the same time, after ten years as President of Friends and Patrons of the Théâtre du Châtelet, she is now the founder and president of the Fondation de la Comédie-Française. She is also a director of the Opéra Comique and a member of the French jury of the Japanese Praemium Imperiale prize, the Nobel Prize equivalent for the Arts, awarded each year by the Emperor of Japan in Tokyo in 5 categories: painting, sculpture, architecture, music, film & theatre.

She is a member of the IFA (French Institute of Directors).

Since 2011, she has been an independent director of Guerbet and since September 2013, Chairwoman of the Board of Directors of the Guerbet Group, the only pharmaceutical group dedicated purely to medical imaging in the international market, listed on NYSE Euronext Paris Compartment B.

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 she brought public 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.

14.1.4. Directors of BIOPHYTIS BRASIL

The management of BIOPHYTIS BRAZIL is conducted 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 the 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 conducted on an exclusive basis by Mr. Stanislas VEILLET (Chairman).

14.2. CONFLICTS OF INTEREST WITHIN THE ADMINISTRATIVE AND GENERAL MANAGEMENT BODIES

The Chairman and CEO, Mr. Stanislas VEILLET, the director Mr. Gérard Jean-GALVEZ, also a shareholder of the company H.M CONSEILS and the directors Nadine COULM and Marie-Claire JANAILHAC-FRITSCH are shareholders, directly or indirectly, of the Company and/or holders of securities convertible into shares of the Company.

The director Mrs Micheline KERGOAT is an employee of METABRAIN RESEARCH, a shareholder of the Company, who entered into a research services agreement with the Company that took effect on 1 August 2015 for a period of twelve months and was renewed by a rider on 1st August 2016 for a further twelve months. The purpose of this agreement is to enable the Company to pursue its research and development activities (see paragraph 22.1.1 of this Reference Document).

At the meeting of the Board of Directors which authorised the conclusion of this agreement between METABRAIN RESEARCH and the Company, the Director, Mrs. Micheline KERGOAT, abstained.

The Company and METABRAIN RESEARCH entered into an initial implementation of the framework agreement on 11 July 2015, which became effective on 1 August 2015 for a period of twelve months and was renewed via a rider on 1 August 2016 for an additional period of twelve months.

Apart from these items, on the date of this reference document 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 for 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 pact or agreement between the major shareholders of the Company, by virtue of 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. HOLDING 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 reference document concerning the sale of their interests in the share capital of the Company, other than that resulting from the holding commitments made to INVEST SECURITIES (in its capacity as Lead Manager and Bookrunner) on admission of the shares to listing on Alternext Paris.

Mr. Stanislas VEILLET and the company H.M CONSEILS have 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 until the expiry of a 24-month period following the date of first listing of the Company's shares on Alternext Paris, until 13 July 2017 inclusive.
During the financing operation 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 common shares on 3 April 2018.

15. REMUNERATION AND BENEFITS IN KIND OF THE OFFICERS AND DIRECTORS

15.1. REMUNERATION OF COMPANY REPRESENTATIVES

The information in this section is established by referring to the code of corporate governance for small and medium companies, as published in December 2016 by MiddleNext and validated as a reference code by the AMF. The tables appearing in the AMF recommendation No. 2014-14 are presented below.

The fixed annual remuneration of Mr Stanislas Veillet is not expected to change for the financial year 2017. His variable annual remuneration targets are set each year by the Board of Directors on the recommendation of the Remuneration Committee.

Table No. 1: Summary table of remuneration and securities attributed to each director and company representative

	Financial year 2016	**Financial year 2015**
Mr. Stanislas VEILLET - Chairman – CEO		
Remuneration due by way of the financial year	186,506	161,311
Value of multi-year remuneration	Not Applicable	Not Applicable
Value of founder's warrants attributed during the financial year	Not Applicable	58,500 founder's warrants$_{2015}$, providing entitlement to 58,500 shares and 198,800 founder's warrants$_{2015}$, providing entitlement to 198,800 shares Total value: €1,452,513
Valuation of bonus shares for the financial year	Not Applicable	Not Applicable
Total	**186,506**	**1.613.824**

Mr. Stanislas VEILLET was attributed:

- by the General Meeting of 22 May 2015, 58,500 founder's warrants$_{2015}$, the conditions of which are detailed in paragraph 21.1.5 of this reference document. Each of the 58,500 founder's warrants$_{2015}$ provide entitlement 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, making use of the authorisation granted by the General Meeting of 27 May 2015, 198,800 founder's warrants$_{2015}$, the conditions of which are detailed in paragraph 21.1.5 of this reference document. Each

of the 198,800 founder's warrants$_{2015}$ provide entitlement to subscribe to one (1) ordinary share with a nominal value of € 0.20 at a subscription price equal to € 0.20 at a subscription price of € 10.70 (with a premium of € 10.50 per share).

- During fiscal year 2016, Mr Stanislas VEILLET was not granted any founder's warrants.

Table No. 2: Summary table of remuneration of each director who is a company officer

The following table shows the remuneration due to company officers who are directors in respect of the financial years ended on 31 December 2016 and 2015 and the remuneration received by these same individuals during these financial years.

The fixed annual gross remuneration of Mr Stanislas Veillet is not expected to change for the financial year 2017. His variable annual remuneration targets are set each year by the Board of Directors on the recommendation of the Remuneration Committee.

	Financial year 2016		**Financial year 2015**	
	Amounts due(1)	Amounts paid(2)	Amounts due(1)	Amounts paid(2)
Mr Stanislas Veillet, Chairman & CEO (since 22 May 2015)				
Fixed remuneration	€150,000	€150,000	117,640	138,961
Variable annual remuneration	€25,000	€35,000	€35,000	0
Variable multi-year remuneration	NA	NA	NA	NA
Extraordinary remuneration	NA	NA	NA	NA
Attendance fees	Not Applicable	Not Applicable	Not Applicable	Not Applicable
Benefits in kind	€11,506	€11,506	8,671	€10,656
Total	**€186,506**	**€196,506**	**€161,311**	**149,617**

(1) by way of the financial year.

(2) during the financial year.

Mr Stanislas VEILLET has received in accordance with the decision of the Board of Directors of 15 March 2016:

(i) A fixed annual remuneration of €150,000 payable over twelve (12) months and variable annual remuneration of up to €50,000, payable within two (2) months of the end of the relevant financial year, depending on the annual targets achieved, based (a) on the authorisation by the Belgian competent authority for the initiation of the phase II clinical studies for the BIO101 drug candidate by the end of 2016, (b) on obtaining the approval of the competent authority in the application relating to the clinical and regulatory development plan for the BIO201 drug candidate before the end of the financial year 2016; (c) on the increase of shareholders' equity: raising at least €10,000,000 and finally (d) on the transfer of all teams to the Pierre et Marie Curie University before June 2016;

(ii) An indemnity in the event of termination for any reason, except for serious misconduct (in the sense of the case law of the Social Chamber of the Court of

Cassation) corresponding to one year of gross fixed remuneration applicable on the date of dismissal.

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 & CEO.

Table No. 3: Attendance fees and other remuneration received by company officers who are not directors

Table of attendance fees and other remuneration received by company officers who are not directors		
Company officers who are not directors	Amounts paid during the financial year 2016	Amounts paid during the financial year 2015
Jean-Gérard GALVEZ		
Attendance fees	€18,000(1)	Not Applicable
Other remuneration	Not Applicable	Not Applicable
Total	**18,000**	**Not Applicable**
Micheline KERGOAT		
Attendance fees	Not Applicable	Not Applicable
Other remuneration	Not Applicable	Not Applicable
Total	**Not Applicable**	**Not Applicable**
Nadine COULM		
Attendance fees	€18,000(2)	Not Applicable
Other remuneration	Not Applicable	Not Applicable
Total	**18,000**	**Not Applicable**
Marie-Claire JANAILHAC-FRITSCH		
Attendance fees	€18,000(3)	Not Applicable
Other remuneration	Not Applicable	Not Applicable
Total	**18,000**	**Not Applicable**

(1) (2) €18,000 is due to him for the financial year 2016.

(2) (2) €18,000 is due to him for the financial year 2016.

(3) (2) €18,000 is due to him for the financial year 2016.

The amount paid to directors in directors' fees within the framework of the general meeting budget, which corresponds to €3,000 per director, is not expected to change in financial year 2017.

Table No. 4: Options for subscription or purchase of shares, founder's warrants or warrants, attributed during the financial years ended 31 December 2016 and 2015 to each director who is a company officer by the issuer and by all group companies

Executive directors	No. and date of the plan	Nature of the options (purchase or subscription)	Valuation of the founder's warrants/warrants according to the method adopted for consolidated accounts *	Number of founder's warrants /warrants awarded during the financial year	Price of exercise	Period of exercise
Stanislas VEILLET Former Chairman of the Company (in the form of an SAS until 22 May 2015)						
2016	N/A	N/A	N/A	N/A	N/A	N/A
2015	Founder's warrants2015 attributed on 22 May 2015	Founder's warrants1-2015	238,309	58.500	€2.06	At any time since 13 July 2015 (admission to Alternext) and until 22 May 2019
	Founder's warrants2-2015 attributed on 23 September 2015	Founder's warrants2015	1.214.204	198.800	€10.70	Exercisable for (i) 33.33% between 23 September 2015 and 23 September 2016, (ii) for 66.66%, between 23 September 2016 and September 2017 and (iii) as a whole, from 23 September 2017 onwards until 23 September 2019

The terms and conditions of individual securities are described in greater detail in paragraph 21.1.5 of this Reference Document.

Table No. 5: Subscription or purchase options for shares, founder's warrants or warrants exercised during the year by each director who is a company officer

Not Applicable

Table No. 6: Bonus shares attributed to each company officer during the financial years ended 31 December 2016 and 2015

Not Applicable

Table No. 7: Bonus shares attributed that have become available for each company officer

Not Applicable

Table No. 8: History of attribution of subscription or purchase options, founder's warrants or warrants - Information on founder's warrants/warrants

Information on valid founder's warrants/warrants issued in favour of company officers			
	Founder's warrants$_{2015}$	Founder's warrants$_{2015}$	Warrants$_{2015}$
Date of the general meeting	22 May 2015	27 May 2015	27 May 2015
Date of the board meeting	N/A	23 September 2015	04 August 2015
Total number of shares which may be subscribed, o/w the number which 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
The Chairman & CEO - Mr. Stanislas VEILLET	58,500	198.800	N/A
The director – Mr. Jean-Gérard GALVEZ	N/A	N/A	18,000
The director – Mrs. Micheline KERGOAT	N/A	N/A	N/A
The director – Mrs. Nadine COULM	N/A	N/A	18,000
The director – Mrs. Marie-Claire JANAILHAC-FRITSCH	N/A	N/A	18,000 (Including 12,000 in force to date)

Starting date for exercise	22 May 2015	23 September 2015	Subscription date
Expiry date	22 May 2019	23 September 2019	At latest, 4 years after the subscription date
Exercise price per new share subscribed	€2.06	€10.70	8.40
Exercise procedures	The Holder(s) may only exercise the founder's warrants$_{2015}$ if, on the Date of the Financial Year, they are employees of the Company or an officer of the Company, subject to the tax regime of employees	The Holder(s) may only exercise the founder's warrants$_{2015}$ if, on the Date of the Financial Year, they are employees of the Company or an officer of the Company, subject to the tax regime of employees	N/A
Number of shares subscribed to date	0	0	6,000
Cumulative number of founder's	0	0	0
Founder's warrants$_{2015}$ or warrants$_{2015}$ outstanding at the end of the financial year	58,500	198,800	48,000

The attribution of founder's warrants/warrants to company officers is detailed in paragraph 21.1.5 of this reference document.

Table No. 9: Subscription or purchase options for shares, founder's warrants or warrants and other securities granted to the first ten employees who are not assignee company officers and options or warrants exercised by this latter parties during the financial years 2015 and 2016

Options granted to the first ten employees who are not assignee company officers and founder's warrants/warrants exercised by these latter parties	Total number of founder's warrants/warrants attributed/ shares subscribed	Weighted average price	2015	2016
Options, founder's warrants, warrants and other financial instruments granted by the Company to the first ten employees who are not assignee Company officers (global information)	381,900 (Of which 39,700 have lapsed due to the departure of an employee)	€7.61	136,500 founder's warrants2015 (GM of 22 May 2015) 225,400 founder's warrants2015 (GM of 27 May 2015 and Board Meeting of 23 September 2015) 20,000 founder's warrants2015 (GM of 27 May 2015 and Board Meeting of 04 December 2015)	39,700 Founder's warrants2-2015 (GM of 27 May 2015 and Board Meeting of 15 March 2016)
Options, founder's warrants, warrants and other financial instruments of the Company held, exercised by the first ten employees who are not assignee Company officers (global information)	28,000	€2.06	Not Applicable	28,000

Table No. 10: History of bonus share issues

Not Applicable

Table No. 11: Details of the conditions of remuneration and other benefits granted to company officers who are directors

Executive directors	Starting date of mandate End date of mandate	Employment agreement	Supplementary pension regime	Indemnities of benefits due or likely to be due on account of the cessation or change n position	Indemnities relating to a non-competition clause
Stanislas VEILLET (Chairman -CEO (in the form of a SA)	Start: 22 May 2015 End: 31 December 2017	No	No	Yes, in cases of dismissal for any reason except for serious misconduct (in the sense of the case law of the Social Chamber of the Court of Cassation), with this indemnity corresponding to one year of gross fixed remuneration applicable on the date of dismissal	No

BIOPHYTIS BRASIL

Mr. Wagner Clayton CORREA, manager of BIOPHYTIS BRAZIL, no longer receives any remuneration.

BIOPHYTIS INC.

Mr. Stanislas VEILLET does not receive any remuneration in his capacity as Chairman 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 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 Chairman of BIOPHYTIS Inc.

15.3. BONUS SHARES, EQUITY WARRANTS (BSA), OPTIONS FOR SUBSCRIPTION OF SHARES OR OTHER SECURITIES ATTRIBUTED TO THE COMPANY OFFICERS

The following table presents, on the date of this reference document, all warrants for founder's shares (BSPCE) issued by the Company in favour of its company officers and directors.

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)
Stanislas VEILLET Chairman – CEO	58,500	198,800	N/A
Jean-Gérard GALVEZ Director	N/A	N/A	18,000
Nadine COULM Director	N/A	N/A	18,000
Marie-Claire JANAILHAC-FRITSCH Director	N/A	N/A	18,000 (Including 12,000 in force to date)
TOTAL	**58,500**	**198,800**	**54,000** (Including 48,000 in force to date)

A detailed description of the characteristics of founder's warrants$_{2015}$ and warrants$_{2015}$ mentioned above appears in paragraph 21.1.5 of this reference document.

On the date of this Reference Document, (i) the exercise of each founder's warrant$_{1\text{-}2015}$ awarded on 22 May 2015 provides entitlement to one new common share of the Company with a nominal value of €0.20 at a subscription price of €2.06 and (ii) the exercise of each founder's warrant$_{2\text{-}2015}$ awarded on 23 September 2015 provides entitlement to one new common share of the Company with a nominal value of €0.20 at a subscription price of €10.70.

On the date of this reference document, the exercise of each warrant$_{2015}$ awarded on 4 August 2015 provides entitlement to one new ordinary share of the Company with a nominal value of € 0.20 at a subscription price of € 8.40.

15.4. ELEMENTS OF REMUNERATION AND BENEFITS DUE OR LIKELY TO BE DUE BY VIRTUE OF OR SUBSEQUENT TO THE CESSATION OF DUTIES OF DIRECTORS OF THE COMPANY

In accordance with statutory provisions, Mr. Stanislas VEILLET may be freely dismissed from his position as Chairman - General Manager by the Board of Directors of the Company.

Mr. Stanislas VEILLET shall receive an indemnity in the event of dismissal for any reason, except for serious misconduct (in the sense of the case law of the Social Chamber of the Court of Cassation) corresponding to one year of gross fixed remuneration applicable to the date of dismissal.

Mr. Stanislas VEILLET benefits from a "GSC" private unemployment insurance policy, the cost of which 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 Limited Liability Company with a Board of Directors. The detailed composition of the Board appears in paragraph 14.1 *"Directors and Officers"*.

The Board of Directors opted during the effective transformation of the Company from a simplified joint stock company into a limited liability company on 22 May 2015, to combine the mandates of Chairman of the Board and CEO.

Mr. Stanislaus VEILLET has been the Chairman & CEO of the Company since 22 May 2015 (with its specified that he had been the Chairman of the Company as a simplified joint stock company since its establishment on 15 September 2006).

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 reference document.

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 form the object of the developments presented in chapter 14 of this reference document.

The General Meeting may allocate to directors, as remuneration for their activity and as a function of their attendance, a fixed annual sum by way of attendance fees, allocated freely among the directors by the Board of Directors.

The internal regulations were adopted by the Board of Directors of 22 May 2015 in order to specify, in particular, the role and composition of the Board, the principles of conduct and the obligations of Board members of the Company As a supplement to the applicable legal and statutory provisions.

The Board of Directors carries out the controls and inspections which it judges appropriate. Each director receives all of the information necessary for performing his/her mission and may request notification of any documents which he/she considers useful.

Each member of the Board of Directors shall undertake to maintain his/her independence of analysis, judgment and action and to participate in the works of the board. He/she shall informs the council of situations of conflict of interest which he/she may face. In addition, the internal

regulations recall the regulations in effect on the dissemination and use of privileged information and specifies that its members must refrain from carrying out transactions on the Company's securities when they hold insider information. Each member of the Board of Directors is required to declare transactions on the Company's shares which he/she executes, whether directly or indirectly, to the Company and to the AMF.

Pursuant to recommendation 1 of the MiddleNext code, the internal regulations of the Company also provide for an obligation of absolute confidentiality and an obligation to observe secrecy of deliberations for the members of the Board of Directors.

The Company considers that it already has, in the persons of Mr Jean Gérard GALVEZ, Mrs Nadine COULM and Mrs Marie-Claire JANAILHAC-FRITSCH, and Mrs Jean M. Franchi, four independent directors, pursuant to the provisions of the Code of Corporate Governance for small and mid-cap stocks, as published in September 2016 by MiddleNext and validated as a code of reference by the AMF, namely who:

- Have not been during the last five years and are not an employee or executive officer of the Company or of any of its affiliates;
- Have not had in the past two years and do not presently 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 form the object of developments presented in Chapter 14 of this reference document.

The CEO holds the broadest powers to act in all circumstances in the name of the Company, subject to the limitations of powers provided in 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 establish committees, setting their composition and attributions and, where applicable, the remuneration of its members.

Each committee has a role of study, analysis and advice on various board decisions relating to its area of competence. It also has the role of studying the issues and/or projects that the Board or its Chairman may submit to its examination. It has no decision-making powers. It issues, within its field of competence, proposals, recommendations and opinions, as appropriate. It has consultative powers and acts under the authority of the Board of Directors, of which it is the emanation and to which it reports.

The Company has a Remuneration and Governance Committee, established on 23 September 2015, a Scientific Committee established on 14 April 2016, and an Audit Committee established on 4 December 2015.

16.3.3. Audit Committee

The Audit Committee meets as often as it considers necessary and at least 4 times a year, of which twice before the meeting of the Board of Directors which draws up the annual and interim financial statements of the Company, at the calling of its Chairman.

- ***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, albeit with it 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 Chairperson of the Audit 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 Audit Committee is three (3) years, ending at the first Board meeting held after the Ordinary General Meeting called to approve the financial statements.

The mandates of the members of the Audit Committee are renewable.

The Audit Committee has consisted, since 4 December 2015, of:

- Nadine COULM, Chairwoman of the Audit Committee, also a director of the Company;

- Marie-Claire JANAILHAC-FRITSCH, also a director and Chairwoman of the Remuneration and Corporate Governance Committee of the Company.

- ***Attributions***

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 financial information provided;

- assessing the existence and relevance of the financial control and internal audit procedures;

- assessing the relevance of the Company's accounting policy;

- examining the 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 substitute auditor, or proposing the appointment of the statutory auditors;

- guaranteeing the 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.

In this capacity, the Audit Committee issues opinions, proposals and recommendations to the Board of Directors and regularly reports to it on its work.

- ***Functioning***

The Audit Committee meets as often as it considers necessary and at least twice a year before the meeting of the Board of Directors, which draws up the annual and interim financial statements of the Company, on calling by its Chairman.

Notices of calling are sent by all written means (notably by e-mail) with a prior notice period of 5 days except in an emergency. The Audit 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, participate by videoconference or telecommunications resources or are represented. As an exception to the above, in the event that the Audit 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 telecommunications resources 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 within the limit of two representation mandates per member.

The Audit Committee reports on its mission to the Board of Directors according to the terms agreed with this latter party. 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 it considers necessary and at least once (1) a year, convened by its Chairman.

- ***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 Chairperson of the Scientific Committee is appointed by the Board of Directors of the Company for the duration of his 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 General Meeting called to approve the financial statements.

The mandates of the members of the Scientific Committee are renewable.

The Scientific Committee has consisted, since 14 April 2016, 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 the UPMC, Scientific Director of Biophytis;

- Professor Philippe Guillet, MD, Geriatrician (UPMC - Paris VI);

- 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 Center on Aging.

- ***Attributions***

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 dossiers 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 it considers necessary and at least once (1) a year, convened by its Chairman.

Notices of calling are addressed by all written means (including by e-mail) with a prior notice period of five (5) days except in an 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 resources, or are represented. As an exception to the above, in the event 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 resources 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 within the limit of two representation mandates per member.

The Scientific Committee reports on its mission to the Board of Directors according to the terms agreed with the latter. It also communicates its recommendations, specifications, and opinions.

A written report of each meeting is drawn up.

16.3.5. Remuneration 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 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 General Meeting called to approve the financial statements.

The mandate of the members of the Compensation and Governance Committee is renewable.

The Remuneration and Governance Committee has consisted, since 23 September 2015, of:

- Marie-Claire JANAILHAC-Fritsch, Chairwoman of the Compensation and Governance Committee, also a director and member of the Company's Audit Committee;

- Jean-Gérard GALVEZ, also a director of the Company.

- ***Attributions***

The Compensation and Governance Committee has the attribution of:

- making recommendations to the Board of Directors (i) on remuneration (fixed and variable) of corporate officers and key executives and notably contributing to the review of remuneration procedures, setting objectives and bonuses for objectives and incentives for the company's officers; (ii) the recruitment, training, development, retention of employees with remuneration programs; and (iii) the shareholder policy and incentive tools for managers and employees, taking into account the objectives of the Company and of individual and collective performances, including the fixing and/or modification of the conditions of attribution or exercise of securities granted to the officers or of the employees, and, where appropriate, the achievement of objectives permitting the exercise of the said securities, as provided under the terms and conditions of the said securities;

- participating in the implementation of the Company's governing bodies;

- identifying, assessing and proposing the appointment of independent directors with a view to the good governance of the Company;

- pronouncing on any other issue relating to human resources which it considers 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 it considers necessary and at least twice (2) a year, on calling by its Chairman.

Notices of calling are addressed by all written means (including by e-mail) with a prior notice period of five (5) days except in an emergency. The Compensation and Governance Committee may also be called verbally. 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 deliberate validly if at least half of its members are present or participating by videoconference or telecommunications media or are represented. As an exception to the above, in the event that the Compensation and Governance Committee consists only of two (2) members, it shall only deliberate validly if the two (2) members in question are present or participating by videoconference or telecommunications media 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 within the limit of two representation mandates per member.

The Remuneration and Governance Committee reports on its mission to the Board of Directors according to the terms agreed with this latter party. It also communicates its recommendations, specifications, and opinions.

A written report of each meeting is drawn up.

16.3.6. Non-voting observers

Article 17.VI of the articles of association provides for the right of the Annual General Meeting to appoint, at its discretion, up to three people, whether natural or legal persons, shareholders or not, for a term of three years expiring at the shareholders' meeting called to approve the accounts for the previous year and held during the year in which their mandates expire. This mandate is renewable indefinitely.

The observers are responsible for ensuring the strict application of the articles of association and for submitting their observations at the sessions of the Board of Directors. Within the Company, they have a general and permanent advisory and supervisory mission. They study the issues that the Board or its Chairman may submit to their examination for an opinion.

Observers shall be called to each meeting of the Board of Directors, in the same capacity as the directors. In an individual or collective capacity, non-voting members shall only have 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 reference document, 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 on the MiddleNext[95] as published in December 2016, insofar as the principles that it contains are compatible with the organisation, size, resources, and shareholding structure of the Company.

The following table details the progress of the Company's reflections on the application 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 presently compliant, with these listed in the table under the heading "To be Adopted".

On this point, the Company considers that on the date of this reference document, 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 2017, 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 & CEO 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 "executive" succession (R 14): The Company considers that it has not complied with the recommendation on the succession of the "executives" in 2016, bearing in mind that this recommendation is the result of the MiddleNext Code amended in September 2016. The Board of Directors intends, in the financial year 2017, to comply with this new recommendation.

[95] http://www.middlenext.com/IMG/pdf/2016_CodeMiddlenext-PDF_Version_Finale.pdf

- Stock options and attribution of bonus shares (R 18): on the present date, the Company has not yet granted stock options or bonus shares; it intends to comply with the recommendation of the MiddleNext Code on this subject as soon as it decides on such an attribution.
- 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 the MiddleNext Code amended in September 2016. The Company intends to submit to its Board of Directors, during the financial year 2017, the points of vigilance provided for by the MiddleNext Code so that the directors may take note and review them.

Recommendations of the Middlenext Code	Adopted	To be adopted
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: Establishment of committees	X	
R 7: Establishment 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: Remuneration of a director	X	
R 11: Establishment of an assessment of work by the Board		X
R 12: Relationship with shareholders	X	
II. Executive power		
R 13: Definition and transparency of the remuneration of executive directors	X	
R 14: Preparation of "executive" succession		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 attribution of bonus shares		X
R 19: Review of vigilance points		X

(I) Internal regulations

On 22 May 2015, the Board of Directors established internal regulations containing the headings recommended by the MiddleNext[96] Corporate Governance Code for listed companies, as published in September 2016, the purpose of which is to define the terms of its organisation and functioning, as a supplement to the legal and statutory provisions.

As the new MiddleNext code, published in September 2016, has extended its recommendations on the content of the internal rules, which should include information on the protection of executive officers and the succession of managers and key persons, the Company intends to amend its rules of procedure in order to incorporate these new recommendations.

[96] http://www.middlenext.com/IMG/pdf/2016_CodeMiddlenext-PDF_Version_Finale.pdf

(II) Accumulation of mandates of the chairman of the board of directors and the CEO

The Board of Directors opted for a combination of the Chairman of the Board and CEO mandates on 22 May 2015

(III) Independent Directors

The Company considers that it already has 4 independent directors, in the persons of Jean-Gérard GALVEZ, Nadine COULM, Jean M. FRANCHI, and Marie-Claire JANAILHAC-FRITSCH, pursuant to the provisions of the MiddleNext Corporate Governance Code for small and mid-Companies, with which the Company intends to comply, namely:

- Not having been, during the last five years, and not being an employee or executive officer of the Company or of any of its affiliates;
- Not having been in the past two years and not having a significant business relationship with the Company or its group (client, supplier, competitor, service provider, creditor, or banker, etc.);
- Not being a leading shareholder of the Company nor holding a significant percentage of voting rights;
- Not having any close family ties with a corporate officer or key shareholder;
- Not having been, during the last six years, a statutory auditor of the company.

Jean-Gérard GALVEZ received no remuneration during the years 2015 and 2016 for his mandate as director. €18,000 were nevertheless paid to him by way of attendance fees for the year 2015 and €18,000 are due to him by way of attendance fees for the year 2016, as described above in Table 3, paragraph 15.1.

Nadine COULM and Marie-Claire JANAILHAC-FRITSCH were appointed directors on 22 May 2015. They received no remuneration during the years 2016 and 2015. €18,000 were nevertheless paid to them by way of attendance fees for the year 2015 and €18,000 are due to them in attendance fees for the year 2016, as described above in Table 3, paragraph 15.1.

Mrs Jean M. Franchi was appointed director on 16 June 2017.

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.

16.5. CHAIRMAN'S REPORT ON INTERNAL CONTROL

The Company has no obligation to draw up a report on its internal control, provided in Article L. 225-37 of the Commercial Code.

On the date of this Reference Document, the Company nevertheless has internal control procedures relating to accounting and financial information, in particular a respect for the separation of tasks:

- The accounting function is performed by the chartered accountant for both the annual and consolidated accounts, persons outside the company who do not have the bank signature,

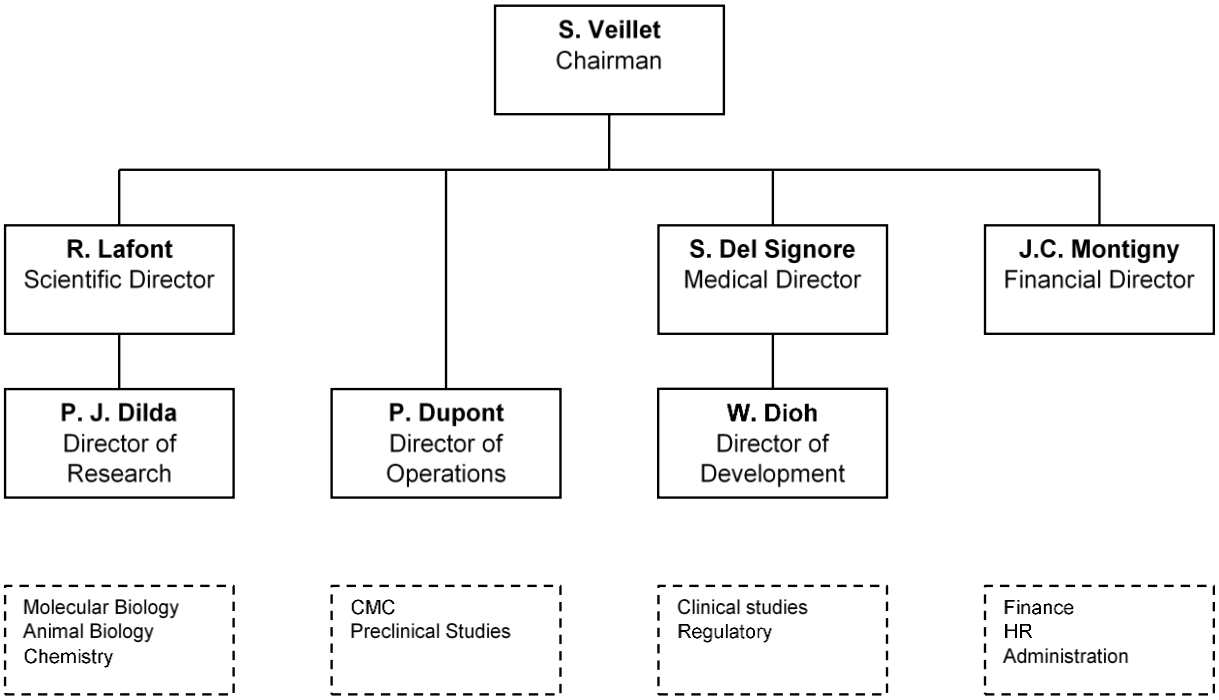
- The Company outsourced the preparation of its payroll to a chartered accountant,

- the Company has established a procedure for delegation of powers and signatures for payments of bills and signing purchase orders.

17. EMPLOYEES

17.1. NUMBER OF EMPLOYEES AND ALLOCATION BY FUNCTION

17.1.1. Operational diagram of organisational structure on the date of registration of this Reference Document



17.1.2. Number and allocation of staff

On the date of submission of this reference document, the Company has 12 employees with indefinite duration employment agreements.

During the financial year, an employee was hired in July 2016 as an administrative assistant and was terminated in November 2016, within the probationary period for employees who agree to said period. The total number of salaried employees of the Company has therefore not changed.

The employees all benefit from "Executive" status.

The Chairman and CEO of the Company, Stanislas VEILLET does not have an employment agreement. In 2009, the Company subscribed a "GSC" private unemployment insurance policy. The payment by the Company of contributions due by way of this insurance is regarded as a benefit in kind, subject to social security contributions and charges.

17.1.3. Collective status

The Company applies the *"Predominantly food retailers and wholesalers"* National Collective Agreement.

There are no collective agreement or internal regulations.

No unilateral commitment or practice is in effect within the Company.

The Company does not have any staff representative.

17.1.4. Clauses of employment agreements

Employment agreements established on the same model notably contain the following clauses:

- - a clause organising the transfer of intellectual property of certain inventions;
- - a confidentiality clause;
- - a non-poaching and non-solicitation clause for a period of 12 months following the cessation by the employee of his/her duties.

No employee of the Company currently has so-called “golden parachute” clause in the event of termination of his/her employment agreement.

17.1.5. Working hours

All employees are subject to a flat-rate pay agreement for the year under the provisions of the “Predominantly food retailers and wholesalers” National Collective Agreement.

17.1.6. Disputes

There has never been a dispute between the Company and one of its employees (past or present).

17.1.7. Remuneration

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;

17.2. HOLDINGS AND STOCK OPTIONS OF THE DIRECTORS

On the date of this reference document, the direct and indirect holdings of the members of senior management (the Chairman and CEO) and the Board of Directors and the number of securities providing access to the Company’s share capital are presented in the following table.

The following table reflects the issuance of 58,500 founder’s warrants$_{2015}$ attributed by the Board meeting of 22 May 2015 to Mr Stanislas VEILLET, Chairman & CEO.

Member of the Board of Directors	Direct holding			Indirect holding			Warrants$_{2015}$/ founder's warrants $_{2015}$
	Shares	Percentage		Shares	Percentage		
		Capital	Voting rights		Capital	Voting rights	
Jean-Gérard GALVEZ(1)	0	0%	0%	11,365	0.11%	0.11%	18,000
Micheline KERGOAT(2)	0	0%	0%	164.631	1.65%	1.65%	0
Stanislas VEILLET (Chairman & CEO)	1,469271	14.77%	14.77%	0	0%	0%	257,300
Marie-Claire JANAILHAC-FRITSCH	6,000	0.06 %	0.06 %	0	0%	0%	12,000
Nadine COULM	0	0%	0%	0	0%	0%	18,000
TOTAL	**1,475271**	**14.83 %**	**14.83 %**	**350,800**	**1.76%**	**1.76%**	**305,300**

(1) Indirectly, through the holding of shares by H.M Conseils, of which Mr. Jean-Gérard GALVEZ is a shareholder and officer.
(2) Indirectly, through the holding of shares by Metabrain Research, of which Mrs Micheline KERGOAT is an employee.

17.3. EMPLOYEE SHARE OWNERSHIP

On the date of this Reference Document, six employees held a total of 109,210 shares, representing 1.10 % of the share capital on an undiluted basis and 353,900 founder's warrants $_{2015}$ (providing entitlement to 353,900 shares), i.e. a total of 4.12% of the share capital on a diluted basis (including the founder's warrants$_{2015}$, the warrants$_{2015}$, the warrants$_{2015D}$, and the warrants$_{bracknor}$).

The Chairman & CEO (non-employee) holds 1,469,271 shares representing 14.77% of the capital and voting rights of the Company on an undiluted basis and 257,300 founder's warrants$_{2015}$ and founder's warrants$_{2-2015}$ (providing entitlement to 257,300 shares), amounting to 15.38% of the share capital on a diluted basis (including the founder's warrants$_{1-2015}$, the founder's warrants$_{2-2015}$,the warrants$_{2015}$, the warrants$_{2015D}$) and the warrants$_{bracknor}$).

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 the date of registration of the Reference Document.

As far as the Company is aware, there is no concerted action between the Company's shareholders.

	Situation on the registration date of the reference document on a non-diluted basis		Situation on the registration date of the reference document on a fully diluted basis (3)	
Shareholders	Number of shares	% of share capital and voting rights	Number of shares and founder's warrants1&2 - 2015/ warrants2015/warrants2015D/warrantsb racknor	% of share capital and voting rights
Founder (1)	***66,666***	***0.67%***	***164,866***	***1.47%***
Directors(2)	***17,365***	***0.17%***	***65,365***	***0.58%***
Seventure Partners Fund	373,562	3.76%	373,562	3.33%
CM-CIC Fund	369,658	3.72%	369,658	3.29%
Subtotal Institutional Investors	***743,220***	***7.48%***	***743,220***	***6.62%***
Stanislas VEILLET - Chairman & CEO	1,469271	14.77%	1,726571	15.38%
METABRAIN RESEARCH	164,631	1.66%	164,631	1.47%
Treasury stock	38,121	0.38%	38,121	0.34%
Free float	7,404595	74.44%	7,835,779(4)	69.80%
Employees (other than founders) and other holders of founder's warrants1 & 2 - 2015	42,544	0.43%	298,244	2.65%

Holders of warrants$_{2015 D}$	0	0.00%	189,748	1.69%
TOTAL	***9,946413***	***100%***	***11,226,545***	***100%***

(1) A founding natural person who is not a corporate officer.
(2) As of the date of this Reference Document, Marie-Claire JANAILHAC-FRITSCH holds 6,000 shares. Mr Jean-Gérard GALVEZ holds, as of the date of this Reference Document, indirectly, through the shareholding of HM Conseils, 11,365 shares.
(3) This table takes account of the 167,000 founder's warrants$_{1-2015}$ allocated by the Board meeting of 22 May 2015 still in force, the 384,500 founder's warrants$_{2-2015}$ issued by the Board of Directors on 23 September 2015, acting on behalf of the General Meeting of 27 May 2015 still in force, the 20,000 founder's warrants$_{2-2015}$ issued by the Board of Directors of 4 December 2015, acting on behalf of the General Meeting of 27 May 2015 still in force, the 39,700 founder's warrants$_{2-2015}$ issued by the Board of Directors of 15 March 2016, acting on behalf of the the General Meeting of 27 May 2015, the 48,000 warrants$_{2-2015}$ issued by the Board of Directors of 4 August 2015, acting on behalf of the the General Meeting of 27 May 2015, and the 189,748 warrants$_{2015D}$ awarded to the benefit of the Biophytis$_{2015D}$ Bondholders by the Board of Directors on 10 July 2015, acting on behalf of the General Meeting of 27 May 2015.
(4) The difference between the number of shares on an undiluted basis and the number of shares on a diluted basis corresponds to the subscription of the warrants$_{bracknor.}$

Principal Shareholders of Biophytis:

Located in Chilly-Mazarin, Metabrain is a Partnering Research Organisation (PRO) specialising in the research of new preventive (nutraceuticals) and therapeutic (drugs) solutions for the treatment of age-related diseases. A spin-off from Merck Serono, Metabrain offers turnkey collaborative research programs to healthcare industries, from concept to development candidate, exploiting the common pathological mechanisms of brain (Alzheimer, Parkinson) and metabolic (diabetes, obesity) diseases. Metabrain has a portfolio of five projects under development and an integrated innovation platform (Chemistry, Biology, Pharmacology, Pharmacokinetics) operating according to industry standards. Metabrain employs over 30 people and generates revenues of approximately € 3 million.
www.metabrainresearch.com

Seventure finances innovation and contributes to the entrepreneurial adventure beside entrepreneurs, sharing their passion. Founded in 1997, Seventure Partners is one of the main venture capital players in Europe, with over € 500 million under management. An active partner of French and European technology companies with strong growth potential, Seventure Partners finances the development of innovative companies in two areas: Information Technology and Communication (ICT) and Life Sciences (SOV), with special leadership in the areas of connected health and the applications of recent discoveries related to the microbiome. Seventure Partners is an AMF-authorised management company and benefits from a truly European dimension. The company is headquartered in Paris and has branch offices in Munich, London, Geneva and Basel.
http://www.seventure.fr

CM-CIC Capital Privé, a subsidiary of CM-CIC Capital Finance, is active in the Venture Capital and Development Capital businesses, investing in SMEs and innovative companies with growth potential that have demonstrated the relevance of their positioning. It places its expertise at the service of directors with medium-term projects and assists them with the development of their company. CM-CIC Capital Privé manages €400 million through its Proximity Investment Funds (PIF) and Mutual Funds for Investment in Innovation (FCPI).
www.cmciccapitalprive.com

Mr. Stanislas VEILLET, Chairman & CEO of the Company.

He co-founded 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

The following significant shareholders are not represented on the Board of Directors:

- The SEVENTURE PARTNERS funds hold 373,562 shares, representing 3.76% of the share capital of the Company on a non-diluted basis;
- The CM-CIC funds hold 369,658 shares, representing 3.72% of the Company's share capital on a non-diluted basis.

18.3. VOTING RIGHTS OF THE PRINCIPAL 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 Shareholders' General Meeting of 16 June 2017 established a double voting right for all registered and fully paid-up shares registered in the name of the same beneficiary for at least two years.

BIOPHYTIS BRASIL

Due to its percentage stake 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 in another form.

BIOPHYTIS INC.

Due to its percentage stake 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 Reference Document, 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 ENTAIL A CHANGE OF CONTROL

As far as the Company is aware, no particular element of the articles of incorporation, articles of association, charter or regulations of the Company could entail 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 reference document, 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. OPERATIONS WITH RELATED PARTIES

During financial year 2015, several regulated agreements were mentioned in the Statutory Auditor's special report presented below.

No regulated agreements were entered into during the year ended 31 December 2016.

19.1. INTRAGROUP AGREEMENTS

a. The subsidiary in Brazil

On the date of this reference document, the Company had a Brazilian subsidiary, the company BIOPHYTIS INSTITUTO 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. The amount owed by BIOPHYTIS BRASIL to the Company in this capacity was 291,621.64 Reais (around € 67,635) on 31 December 2016. 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 take place within the subsidiary, this contract is yet to be implemented.

b. The subsidiary in the United States

On the date of this reference document, the Company also had a subsidiary in the US, BIOPHYTIS INC.

The Company entered into a current account advance agreement with BIOPHYTIS INC to conduct intra-group rebillings by BIOPHYTIS INC. The amount owed by BIOPHYTIS INC. in this capacity on 31 December 2016 was €221,709.06.

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

On 5 June 2015, the Company and METABRAIN RESEARCH, a shareholder in the Company, entered into, with the approval of the Board of Directors of 5 June 2015, a research service agreement, which took effect on 1 August 2015 for a period of twelve months and was renewed on 1 August 2016 for an additional period of twelve months, and whose purpose is to allow the Company to continue its research and development on bases and in a framework similar to an agreement for the provision of a technical platform and services concluded between the Company and METABRAIN RESEARCH on 30 October 2012 and subsequently renewed until 31 July 2015.

With an authorisation of the Board of Directors on 22 May 2015, the Company acquired from METABRAIN RESEARCH the latter party's share (33%) in the joint ownership of the patent (Family No. 4 "Phytoecdysones analogue") relating to the SARCOB project, as described in paragraph 11.2.2 (b) (I) of this reference document.

Within the context of the bond issued by the General Meeting of 27 May 2015 (as also described in paragraph 10.5 of this reference document), the Chairman & CEO Mr. Stanislas VEILLET subscribed to 65,000 Biophytis$_{2015C}$ bonds for an amount of € 125,000. These bonds were, at the request of the Company, fully redeemed in advance by offsetting against the receivable for the subscription of common shares of the Company, issued within the context of the IPO, held by the Company against each of the bondholders, which occurred on the settlement-delivery day of the shares issued in connection with the IPO.

19.3. SPECIAL REPORT OF THE STATUTORY AUDITOR ON THE REGULATED AGREEMENTS, ESTABLISHED FOR THE FINANCIAL YEAR ENDED 31 DECEMBER 2016

Rapport spécial des Commissaires aux Comptes sur les conventions réglementées

Grant Thornton
Commissaire aux Comptes
29, rue du pont
92200 Neuilly-sur-Seine Cedex

BIOPHYTIS
Société Anonyme
au capital de 1 506 786,20 €
14, avenue de l'Opéra
75001 Paris

Ernst & Young et Autres
Commissaire aux Comptes
1 / 2 place des Saisons
92400 Courbevoie – Paris la Défense
Cedex 1

Assemblée générale d'approbation des comptes de l'exercice clos le 31 décembre 2016

Rapport spécial des commissaires aux comptes sur les conventions réglementées

Biophytis
Assemblée générale d'approbation des comptes de l'exercice clos le 31 décembre 2016

Aux actionnaires,

En notre qualité de commissaires aux comptes de votre société, nous vous présentons notre rapport sur les conventions réglementées.

Il nous appartient de vous communiquer, sur la base des informations qui nous ont été données, les caractéristiques, les modalités essentielles ainsi que les motifs justifiant de l'intérêt pour la société des conventions dont nous avons été avisés ou que nous aurions découvertes à l'occasion de notre mission, sans avoir à nous prononcer sur leur utilité et leur bien-fondé ni à rechercher l'existence d'autres conventions. Il vous appartient, selon les termes de l'article R. 225-31 du code de commerce, d'apprécier l'intérêt qui s'attachait à la conclusion de ces conventions en vue de leur approbation.

Par ailleurs, il nous appartient, le cas échéant, de vous communiquer les informations prévues à l'article R. 225-31 du code de commerce relatives à l'exécution, au cours de l'exercice écoulé, des conventions déjà approuvées par l'assemblée générale.

Nous avons mis en œuvre les diligences que nous avons estimé nécessaires au regard de la doctrine professionnelle de la Compagnie nationale des commissaires aux comptes relative à cette mission.

1 Conventions soumises à l'approbation de l'assemblée générale

Nous vous informons qu'il ne nous a été donné avis d'aucune convention autorisée au cours de l'exercice écoulé à soumettre à l'approbation de l'assemblée générale en application des dispositions de l'article L. 225-38 du code de commerce.

2 Conventions déjà approuvées par l'assemblée générale

Nous vous informons qu'il ne nous a été donné avis d'aucune convention déjà approuvée par l'assemblée générale dont l'exécution se serait poursuivie au cours de l'exercice écoulé.

Neuilly-sur-Seine et Paris-La Défense, le 27 avril 2017

Les Commissaires aux comptes

Grant Thornton Membre français de Grant Thornton International	ERNST & YOUNG et Autres
Laurent Bouby Associé	Frédéric Martineau Associé

19.4. REPORTS OF THE STATUTORY AUDITOR ON REGULATED AGREEMENTS, ESTABLISHED BY WAY OF THE FINANCIAL YEAR ENDED 31 DECEMBER 2015

Special report on regulated agreements - Financial Year 2015

Special report of the Statutory Auditor on regulated agreements

BIOPHYTIS
General Meeting to approve the accounts for the financial year ended 31 December 2015

Dear Shareholders,

In our capacity as the Statutory Auditors of your 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 agreements of which we have been notified or which we have discovered on the occasion of our assignment, without having to express an opinion on their utility and well-foundedness or to investigate the existence of other agreements. It is your responsibility, pursuant to the terms of article L. 225-38 of the 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 general 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. This due diligence consisted of verifying the compliance of the information given to us with the basic documents from which it was derived.

1 AGREEMENTS SUBJECT TO THE APPROVAL OF THE GENERAL MEETING

Agreements authorised during the past financial year

By way of application of Article L. 225-40 of the Commercial Code, we have been advised of the following agreements which formed the object of advance authorisation by your Board of Directors.

1.1 BOND ISSUE

Person concerned: Mr. Stanislas Veillet, Chairman & CEO of the Company

Nature and object: Issuance of Biophytis$_{2015C}$ bonds

Terms: The Board of Directors of 26 May 2015 authorised the issuance of a bond loan agreement on 27 May 2015.

Within the context of this bond, the Chairman & CEO of the Company subscribed to 65,000 Biophytis$_{2015C}$ bonds for an amount of € 125,000.

Following the Company's IPO during the financial year 2015, the bonds$_{2015C}$ were repaid, including accrued interest, by offsetting against the receivable for subscription of the common shares of the Company.

1.2 CURRENT ACCOUNT

Person concerned: Mr. Stanislas Veillet, Chairman & CEO of the Company

Nature and object: Reimbursement of the current account

Terms: The Chairman of the Company held a current account receivable against the Company for a principal amount of sixty thousand Euros (€ 60,000), which formed the object of an agreement on 18 July 2012, concluded in the presence of the Company and providing for a reimbursement schedule until 31 July 2017.

The meeting of the Board of Directors of 10 July 2015 authorised the signing of a new agreement for the immediate reimbursement of the current account receivable.

Following the IPO of the Company during the financial year 2015, the current account was reimbursed for an amount of € 60,000, by offsetting with the subscription receivable for the ordinary shares of the Company.

1.3 PATENT ASSIGNEMENT AGREEMENT

Shareholder concerned: Metabrain Research, a shareholder holding more than 10% of the share capital.

Nature and object: The Board of Directors of 28 May 2015 authorised the signing on 4 June 2015 of the agreement to acquire a portion of a patent with Metabrain, for an amount of €1,500,000 net of taxes.

Terms: The purchase price was paid in shares on the admission of shares to trading, by offsetting against receivables for subscription of the ordinary shares of the Company.

1.4

Shareholder concerned: Metabrain Research, a shareholder holding more than 10% of the share capital.

Nature and object: An agreement for the provision of a technical platform and associated services was concluded between Biophytis and Metabrain Research on 31 October 2012.

The said agreement defines Biophytise personnels' access to the installations, equipment, and associated services of Metabrain Research, and defines the general conditions for their availability for Biophytis' scientific experiments.
This agreement was signed for a period of one year and was extended by fourteen subsequent short-term supplementary agreements, expiring on 30 June 2015. At its meeting of 5 June 2015, the Board of Directors authorised a new supplementary agreement to extend the agreement until 31 July 2015 and specified that the agreement was intended to be replaced by a new research agreement, effective from 1 August 2015 onwards.

Terms: As consideration for the provision of the platform for each order Biophytis pays Metabrain Research the agreed remuneration on presentation of an invoice. The amount paid includes remuneration for Metabrain Research's operating costs for the execution of the corresponding order.

By way of this agreement, the Company incurred a charge of € 31,354 during the financial year 2015.

1.5 CONTRACT RESEARCH SERVICES

Shareholder concerned: Metabrain Research, a shareholder holding more than 10% of the share capital.

Nature and object: At its meeting of 5 June 2015, the Board of Directors authorised the signing of a contract research agreement with Metabrain Research on the same date, the object of which is to enable the Company to continue its research and development

activities within a framework similar to the one previously provided by the agreement for provision of the platform.

Terms: This agreement entered into effect on 1 August 2015 and for a period of twelve months. The Company undertook to order a minimum volume of research services from Metabrain Research with a value of € 250,000 net of taxes and paid this amount on 11 July 2015 by way of a pre-reservation of Metabrain Research staff over the life of the agreement.

By way of this agreement, the Company incurred a charge of € 51,409 during the financial year 2015.

Agreements not authorised in advance

Pursuant to Articles L. 225-42 and L. 823-12 of the Commercial Code, we inform you that the following agreements did not form the object of prior authorisation by your Board of Directors.

We are responsible for notifying you of the circumstances under which the authorisation procedure was not followed.

1.6

Shareholder concerned: Metabrain Research, a shareholder holding more than 10% of the share capital.

Nature and object: A supplementary agreement to the agreement for the provision of the technical platform and associated services was concluded between Biophytis and Metabrain Research.

The said agreement defines Biophytise personnels' access to the installations, equipment, and associated services of Metabrain Research, and defines the general conditions for their availability for Biophytis' scientific experiments.

A supplementary agreement to this agreement extending the agreement until 31 October 2015 was concluded under the same terms as the original agreement.

The signing of this amendment was not authorised by your Board of Directors, due to omission.

2 AGREEMENTS ALREADY APPROVED BY THE GENERAL MEETING

We inform you that we have not been notified of any agreement already approved by the general meeting, the execution of which continued during the past year.

Paris, 29 March 2016

The Statutory Auditor
Grant Thornton
French member of Grant Thornton International

Laurent Bouby
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 2016

Consolidated statement of financial position

(Amounts in thousands of euros)	Notes	31/12/2015 *Restated**	31/12/2016
ASSETS			
Patents and software	3	2,244	2,125
Tangible fixed assets	4	194	276
Other non-current financial assets		272	99
Total non-current assets		**2,710**	**2,501**
Other receivables	5	1,422	2,827
Cash and equivalents	6	9,409	3,066
Total current assets		**10,831**	**5,892**
TOTAL ASSETS		**13,542**	**8,393**
LIABILITIES			
Shareholders' funds			
Capital	8	1,239	1,245
Issuance and contribution premiums		19,531	19,583
Treasury shares		(50)	(158)
Currency exchange differences		(9)	4
Reserves - attributable to Biophytis shareholders		(3,849)	(8,170)
Result - attributable to Biophytis shareholders		(5,232)	(7,954)
Shareholders' equity - attributable to Biophytis shareholders		**11,629**	4,549
Interests not conferring control		(31)	(30)
Total shareholders' equity		**11,598**	**4,519**
Liabilities			
Pension obligation		25	48
Non-current financial debts	10	403	913
Total non-current liabilities		**428**	**962**
Current financial debts	10	399	176
Trade payables and associated accounts		701	1,920
Tax and social debts	12.1	361	722
Other creditors and miscellaneous debts		54	94
Total current liabilities		**1,515**	**2,913**
TOTAL LIABILITIES		**13,542**	**8,393**

* *Please refer to Note 2.3 "Corrections to the published financial statements for the year ended 31 December 2015" in the Notes to the IFRS financial statements.*

Consolidated income statement

(In thousands of euros, except for share data)	Notes	31/12/2015 12 months *Restated**	31/12/2016 12 months
Revenue		-	-
Cost of sales		-	-
Gross Margin		**-**	**-**
Net research and development expenses;	13.1	(1,969)	(5,121)
General and administrative expenses	13.2	(3,074)	(2,820)
Net operating profit		**(5,043)**	**(7,942)**
Financial expenses		(222)	(35)
Financial income		31	22
Net financial income	14	**(190)**	**(13)**
Profit or loss before tax		**(5,233)**	**(7,954)**
Tax expense		-	
Net profit (loss)		**(5,233)**	**(7,954)**
Attributable to Biophytis shareholders		*(5,232)*	*(7,954)*
Interests not conferring control		*(1)*	*(0)*
Average weighted number of shares circulation		4,865,853	6,202,616
Basic earnings per share (€/share)	16	**(1.08)**	**(1.28)**
Diluted earnings per share (€/share)	16	**(1.08)**	**1.28)**

** Please refer to Note 2.3 "Corrections to the published financial statements for the year ended 31 December 2015" in the Notes to the IFRS financial statements.*

Consolidated comprehensive income statement

(Amounts in thousands of euros)	31/12/2015 12 months *Restated**	31/12/2016 12 months
Net profit (loss)	**(5,233)**	**(7,954)**
Non-recurring items in net income		
Actuarial gains and losses	4	(17)
Recurring items in net income		
Currency exchange differences	(2)	14
Comprehensive profit (loss)	**(5,231)**	**(7,957)**
Attributable to Biophytis shareholders	*(5,230)*	*(7,958)*
Interests not conferring control	*(1)*	*1*

** Please refer to Note 2.3 "Corrections to the published financial statements for the year ended 31 December 2015" in the Notes to the IFRS financial statements.*

Statement of changes in consolidated 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	Interests not conferring control	Shareholders' equity
At 31 December 2014		*753,927*	**754**	**4,532**	**(6,377)**	**(8)**	**-**	**(1,099)**	**(30)**	**(1,129)**
2015 earnings restated (loss)					(5,232)			(5,232)	(1)	(5,233)
Other elements of the global result					4	(2)		3	(0)	2
Comprehensive result			**-**	**-**	**(5,228)**	**(2)**		**(5,230)**	**(1)**	**(5,231)**
Division of the nominal value	8	*3,015,708*						-		-
Issue of shares	8	*2,339,200*	468	15,567				16,035		16,035
Subscription of warrants				205				205		205
Exercise of warrants		*86,666*	17	517				534		534
Treasury shares acquired					22		(50)	(28)		(28)
Share-based payments	9				2,502			2,502		2,502
Capital increase expenses	8			(1,291)				(1,291)		(1,291)
On 31 December 2015 (restated) *		*6,195,501*	**1,239**	**19,531**	**(9,082)**	**(9)**	**(50)**	**11,629**	**(31)**	**11,598**
2016 Net income					(7,954)			(7,954)	(0)	(7,954)
Other elements of the global result					(17)	14		(3)	1	(3)
Comprehensive result			**-**	**-**	**(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**

* Please refer to Note 2.3 "Corrections to the published financial statements for the year ended 31 December 2015" in the Notes to the IFRS financial statements.

Consolidated cash flow statement

(Amounts in thousands of euros)	Notes	31/12/2015 12 months *Restated**	31/12/2016 12 months
Cash flow generated by operating activities			
Net profit		**(5,233)**	**(7,954)**
Reconciliation of net income with cash flow from operating activities			
Elimination of depreciation of intangible and tangible fixed assets	34	65	167
Provisions, net of reversals		0	6
Share-based payment expense	9	2,502	994
Gross financial interest paid		20	6
Capitalised financial interests		171	(1)
Capital gains or losses on disposal of fixed assets		-	1
Subsidy transferred to result		(61)	(10)
Interest on the investment accounts		(28)	(24)
Discounting/accretion of advances	10.1	1.	(34)
Cash flow from operating activities before changes in working capital requirements		**(2,565)**	**(6,848)**
(-) Change in working capital requirements (net of impairment of trade receivables and inventories)		**736**	**(216)**
Other non-current financial assets		-	1
(Decrease) increase in other receivables		*1,090*	*1,404*
Decrease (increase) in trade receivables and associated accounts		*(323)*	*(1,219)*
Decrease (increase) in tax and social debts		*24*	*(361)*
Decrease (increase) in other accounts payable and other liabilities		(54)	(40)
Cash flow generated by operating activities		**(3,301)**	**(6,633)**
Cash flow generated by investment activities			
Acquisition of intangible and tangible fixed assets	34	(6)	(129)
Cash flow linked to investment operations		**(6)**	**(129)**
Cash flows linked to financing operations			
Increase in net capital of subscriptions by offsetting receivables (1)	8	11,778	-
Expenses associated with capital increases		(1,291)	-
Subscription of warrants	9	205	-
Exercise of warrants & founder's warrants	9	534	58
Reimbursable advances received, net of repayments	10.1	85	634
Collection of subsidies		25	10
Issuance of loans, net of repayments	10.2, 10.3	1,695	(280)
Gross financial interest paid		(20)	(6)
Interest on the investment account		28	24
Reimbursements of lease financing	10.4	(7)	(36)
Change in current accounts		(7)	-
Change in current bank overdrafts	10	(20)	4
Other financing flows (liquidity agreement)		(300)	-
Cash flows linked to financing operations		**12,705**	**407**
Effect of variations in foreign exchange rates		2	12
Increase (Decrease) in cash		**9,400**	**(6,343)**
Opening cash and cash equivalents		9	9,409
Closing cash and cash equivalents		9,409	3,066

* *Please refer to Note 2.3 "Corrections to the published financial statements for the year ended 31 December 2015" in the Notes to the IFRS financial statements.*

(1) Increase in share capital net of subscriptions by offsetting of receivables generated during the Company's IPO, notably

- debts relating to 2015C and 2015D bonds for € 1,897,000;
- the debt relating to the acquisition of the joint ownership quota of the patent with Metabrain and Iris Pharma for € 1,500,000 and € 800,000 respectively (see Notes 27.3 and 17.4),
- the associated current account for € 60,000 (see Note 17.2).

(Unless otherwise stated, amounts in this Annex are in thousands of euros, except for share data)

Note 1: Presentation Note 1: General Information about the Company

Created in September 2006, Biophytis is a biopharmaceutical company that develops potential new classes of drugs in the treatment of degenerative diseases related to ageing, especially those affecting muscular and visual functions.
Biophytis is a limited liability 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 2016 with comparative information for the year ended 31 December 2015.
The consolidated financial statements of Biophytis or the **"Financial Statements"** were prepared under the responsibility of the management of the Company and have been approved and authorised for publication by the Board of Directors on 25 April 2017.

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 prepared its consolidated financial statements for the years ended 31 December 2015 and 31 December 2016 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 2016. Comparative figures are presented for the year ended 31 December 2015.

Due to the listing of the Company's shares on the 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.

On December 31, 2016, all IFRS standards issued by the International Accounting Standards Board (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 that the EU partially adopted;
- IFRS 14 - Regulatory deferral accounts that the EU has not adopted.

Going concern

Despite the loss of €7,954,000 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 over the next twelve months:

- Cash and cash equivalents available on 31 December 2016 were €3.1 million;
- The carrying out of a €3.7 million private placement through the issuance of 1,310,431 new shares at a price of €2.85 per share;
- The possibility of drawing on a line of financing, set up in April 2017, for up to €15 million (see Note 20 Events after the balance sheet date).

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 2016 are the same as those used for the year ended 31 December 2015, with the exception of the new standards, amendments, and interpretations that are mandatory for the Group as of 1 January 2016:

- Amendments to IAS 1 - Presentation of financial statements: “Disclosure Initiative”
- Amendments to IAS 19 - Defined benefit plans: contributions by the staff
- Amendments to IAS 16 and IAS 38 - Clarification on acceptable depreciation methods
- Amendments to IAS 27 - Equity method in individual financial statements
- Amendments to IFRS 11 - Acquisition of a share in a joint activity
- Amendments to IFRS 10, IFRS 12, and IAS 28 - Investment entities: Application of the consolidation exemption
- Improvements to the IFRS (2012 - -2014 cycle)
- Improvements to the IFRS (2010 - -2012 cycle)

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 on 24 July 2014 and in force as of 1 January 2019.
- 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, contingent liabilities on the date of drawing up the financial statements and the amounts reported by way of revenues and expenses for the financial year.

These estimates are based on the assumption that the company is a 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.

- 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 2.24.

2.3 Corrections to the published financial statements for the year ended 31 December 2015

Pursuant to the provisions of IAS 8, a correction of the previously published financial statements for the financial year 2015 has been completed.
As the published financial statements were prepared after the publication of the consolidated financial statements for the year ended 31 December 2015, these financial statements were restated as described below.

Impact on the consolidated income statement

(Amounts in thousands of euros)	31/12/2015 12 months *Published*	Procedures for recognising and spreading the expense of share-based payments (IFRS 2)	Others Corrections	31/12/2015 12 months *Restated*
Gross Margin	**-**	**-**	**-**	**-**
Net research and development expenses	(1,036)	(886)	(47)	(1,969)
General and administrative expenses	(2,070)	(898)	(106)	(3,074)
Other income	7	-	(7)	-
Net operating profit	**(3,099)**	**(1,784)**	**(160)**	**(5,043)**
Net financial income	**(190)**	**-**	**-**	**(190)**
Profit or loss before tax	**(3,289)**	**(1,784)**	**(160)**	**(5,233)**
Net profit (loss)	**(3,289)**	**(1,784)**	**(160)**	**(5,233)**
Attributable to Biophytis shareholders	*(3,288)*	*(1,784)*	*(160)*	*(5,232)*
Interests not conferring control	*(1)*	-	-	*(1)*

The accounting changes that have taken place essentially focus on the recognition of share-based payments. The Company reviewed some of the assumptions used in determining the fair value of the founder's warrants issued in the financial year 2015 and the corresponding expense spreading method.
The overall effect of the accounting changes is an increase in the net loss of €1,911,000. Restated earnings per share amounted to (€1.06), compared with (€0.46) in the consolidated financial statements on 31 December 2015 as published.

Impact on the consolidated statement of financial position

(Amounts in thousands of euros)	31/12/2015 *Published*	Procedures for recognising and spreading the expense of share-based payments (IFRS 2)	Others Corrections	31/12/2015 *Restated*
ASSETS				
Total non-current assets	**2,710**	**-**	**-**	**2,710**
Other receivables	1,397	-	25	1,422
Cash and equivalents	9,409	-	-	9,409
Total current assets	**10,806**	**-**	**25**	**10,831**
TOTAL ASSETS	**13,517**	**-**	**25**	**13,542**
LIABILITIES				
Capital	1,239	-	-	1,239
Issuance and contribution premiums	19,439	-	91	19,531
Treasury shares		-	(50)	(50)
Conversion reserve	(9)	-	-	(9)
Other elements of the global result	0	-	(0)	-
Reserves - attributable to Biophytis shareholders	(5,684)	1,784	50	(3,849)
Result - attributable to Biophytis shareholders	(3,288)	(1,784)	(160)	(5,232)
Shareholders' equity - attributable to Biophytis shareholders	**11,697**	**-**	**(68)**	**11,629**
Interests not conferring control	31+			31+
Total shareholders' funds	**11,666**	**-**	**(68)**	**11,598**
Total non-current liabilities	**428**	**-**	**-**	**428**
Total current liabilities	**1,422**	**-**	**93**	**1,515**
TOTAL LIABILITIES	**13,517**	**-**	**25**	**13,542**

The accounting changes made did not have a significant impact on the Group's total consolidated shareholders' equity on 31 December 2015.

Incidence on the consolidated cash flow statement

The main impact of the corrections was:

- At the level of the cash generated by operating activities:
  - The change in net income for the period -€1,944,000
  - Partially offset by the cancellation of the additional expense related to share-based payments +€1,784,000
- At the level of the change in working capital requirements, a decrease of €68,000.
- At the level of cash flow linked to financing operations, a reduction in capital increase costs of €73,000.

2.4 Consolidation scope and 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.

2.5 Conversion of foreign currencies

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.

2.5.1 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.

2.5.2 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 year-end 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	Year-end rate		Average rate	
(Currency for €1)	31/12/2015	31/12/2016	31/12/2015	31/12/2016
BRL	4.3117	3.4305	3.6916	3.8616
USD	1.0887	1.0541	1.0807	1.1066

2.6 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.

2.7 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 amortised on a straight-line basis over their actual useful lives.
They are amortised 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.

2.8 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.

2.9 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.

2.10 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 the 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.

2.13 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 current bank overdrafts.

2.14 Fair value of financial instruments

Borrowings and financial debts are initially recognised at fair value and subsequently measured at their amortised cost using the effective interest rate 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 their fair value through profit or loss, are term deposits that fall under Level 1.

2.13 Liquidity Agreement

Following its IPO on the Alternext Paris market, the Company signed a liquidity contract with Invest Securities in order to limit the “intra-day” volatility of the Biophytis share price.

In this context, the Company provided €300,000 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”.

2.14 Public Subsidies

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 subsidy 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.

Subsidies are presented in the “Research and Development” category.

These advances are recorded as “Non-current financial debts” and as “Current financial debts” according to 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.

2.15 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.

2.16 Equity

The classification under equity depends on the specific analysis of the characteristics of each issued instrument.

Accessory costs directly attributable to the issuance of shares or options on shares are recorded net of tax, as a deduction from equity.

2.17 Payments in shares

Since its inception, the Company has implemented several remuneration plans settled in equity instruments in the form of "warrants" or "founder's warrants" attributed 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.

2.19 Social commitments

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 as consolidated shareholder's equity under "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.

2.19 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 debts of less than one year is presented under "current borrowings".

Financial liabilities recorded at fair value via the income statement
The Company had no instruments in this category at the end of the financial years presented.

2.20 Corporation 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.

2.21 Sector information

The Company operates in a single activity segment: the development of candidate drugs for the treatment of metabolic diseases and aging.

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.

2.22 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 2014	**-**	**11**	**11**
Acquisition	2,300	1	2,301
Assignment	-	-	-
Transfer	-	-	-
Statement of financial position at 31 December 2015	**2,300**	**12**	**2,312**
Acquisition		2	2
Assignment			-
Transfer			-
Statement of financial position at 31 December 2016	**2,300**	**14**	**2,314**
AMORTISATIONS AND DEPRECIATIONS			
Statement of financial position at 31 December 2014	**-**	**11**	**11**
Increase	57	0	57
Decrease			-
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**

NET BOOK VALUES			
At 31 December 2014	-	-	-
On 31 December 2015	2,243	1	2,244
At 31 December 2016	2,124	1	2,125

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. In July 2015, the Company acquired a joint ownership of these patents held by Metabrain and Iris Pharma for a total amount of €2,300,000 (see Notes 17.3 and 17.4), thus increasing its ownership percentage to 66%.

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 2014	**116**	**-**	**33**	**32**	**4**	**184**
Acquisition	-	181	-	6	-	187
Assignment	-	-	-	-	-	-
Foreign exchange impact	(22)	-	(5)	(1)	(1)	(29)
Transfer	-	-	-	-	-	-
Statement of financial position at 31 December 2015	**93**	**181**	**28**	**36**	**3**	**342**
Acquisition	79	-	32	16	-	127
Assignment	-	-	(2)	-	-	(2)
Foreign exchange impact	17	-	4	1	1	22
Transfer	-	-	-	-	-	-
Statement of financial position at 31 December 2016	**189**	**181**	**62**	**53**	**4**	**489**
AMORTISATIONS AND DEPRECIATIONS						
Statement of financial position at 31 December 2014	**116**	**-**	**18**	**27**	**4**	**165**
Increase	-	5	1	2	-	8
Decrease	-	-	-	-	-	-
Foreign exchange impact	(22)	-	(1)	(1)	(1)	(26)
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**
NET BOOK VALUES						
At 31 December 2014	**-**	**-**	**15**	**5**	**-**	**20**
At 31 December 2015	**-**	**176**	**10**	**8**	**-**	**194**
At 31 December 2016	**69**	**146**	**43**	**17**	**-**	**276**

No losses of value were recorded by way of application of the IAS 36 standard.

Note 5: Other receivables

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Research tax credit (1)	454	2,058
Competitive employment tax credits (CICE)	3	5
Value-added tax	624	471
Prepaid expenses (2)	231	160
Suppliers - advance payments	53	112
Other	57	21
Total other receivables	**1,422**	**2,827**

(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:

- Research Tax Credit 2016: €1,604,000 The Reimbursement of the amount is scheduled to take place during the financial year 2017.
- Research Tax Credit 2015: €454,000 This amount was reimbursed in January 2017.

(2) Prepaid expenses mainly relate to research services provided by an external service provider.

Note 6: Cash and equivalents

The item cash and equivalents had the following breakdown:

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Bank accounts	407	1,065
Term deposits	9,002	2,001
Total cash and cash equivalents	**9,409**	**3,066**

As of December 31, 2016, the Company holds a short-term deposit of €2,000,000 with a maturity of one month.

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)	31/12/2016		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 equivalents	3,066	3,066	2,001	1,065	
Total assets	**5,992**	**5,992**	**2,001**	**3,991**	**-**
Non-current financial debts	913	913			913
Current financial debts	176	176			176
Trade payables and associated accounts	1,920	1,920			1,920
Total liabilities	**3,010**	**3,010**	**-**	**-**	**3,010**

(Amounts in thousands of euros)	31/12/2015		Value - Statement of Financial Position in accordance with IAS 39		
	Value - Statement of Financial Position	Fair value	Financial assets at fair value through the income statement	Loans and receivables	Debts at amortised cost
Non-current financial assets	272	272		272	
Other receivables	1,422	1,422		1,422	
Cash and equivalents	9,409	9,409	9,002	407	
Total assets	**11,103**	**11,103**	**9,002**	**2,101**	-
Non-current financial debts	403	403			403
Current financial debts	399	399			399
Supplier debts and associated accounts	701	701			701
Total liabilities	**1,558**	**1,558**	**-**	**-**	**1,558**

(Amounts in thousands of euros)	31/12/2015		31/12/2016	
	Interest:	Change in fair value	Interest:	Change in fair value
Liabilities				
Liabilities measured at amortised cost: advances	(15)		(19)	

Note 8: Capital

	31/12/2015	31/12/2016
Capital (in thousands of euros)	1,239	1,245
Number of shares, of which	6,195,501	6,223,501
Class O shares	6,195,501	6,223,501
Nominal value (in euros)	0.20	0.20

Share capital

The share capital was set at the amount of €1,244,700.20. It is divided into 6,233,501 shares fully subscribed and paid with a nominal value of €0.20.

Development of the share capital

Financial year 2015

On 22 May 2015, the general meeting decided to divide the nominal value of shares comprising the share capital by five, reducing it from one euro (€ 1) to twenty cents (0.20 €) without modifying the share capital. The historical share data was restated to reflect this transaction.

On 10 July 2015, the Company was listed on the Alternext Paris market. On this occasion, it issued 1,672,500 shares, generating a new capital increase of €335K.

On 4 August 2015, the Company executed a private placement with a US investor by issuing 666,700 new shares, generating a capital increase of €133K.

Moreover, following the exercise of warrants during the year (see Note 9), the share capital was increased by €17K through the issuance of 86,666 new shares with a nominal value of €0.20.

Capital transactions carried out in 2015 can be summarised as follows:

(Amounts in thousands of euros)	Share capital	Issuance and contribution premiums	Subscription by offsetting receivables (1)	Fund raising (gross)	Expenses	Fundraising (net of expenses)
Introduction to Alternext	335	9,701	(4,257)	5,778	(926)	4,852
Private placement with an investor in the US	133	5,867	-	6,000	(365)	5,635
Total	**468**	**15,567**	**(4,257)**	**11,778**	**(1,291)**	**10,487**
Exercise of warrants	17	517	-	534	-	534

(1) See Note (1) in the consolidated cash flow statement

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.

Pbis, P2 and A preferred shares

Within the context of a dissolution or liquidation, these shares provide entitlement to a preferential distribution of the aggregate consideration resulting from such an operation.
These shares lost all their privileges and were automatically converted into ordinary shares on admission to trading of the Company's shares on the Alternext Paris market.

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 2016, by way of this agreement, 38,121 treasury shares were recorded as a deduction from equity and €98K of cash was included among non-current financial assets.

Note 9: Warrants for shares and warrants for founder's shares

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 €162,000. 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	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 attribution	Number of outstanding warrants					Maximum number of shares to be subscribed:
		31/12/2015	Awarded	Exercised	Lapsed	31/12/2016	
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%	**€481,000**

Type	Date of award	Number of outstanding warrants					Maximum number of shares to be subscribed:
		31/12/2015	Awarded	Exercised	Lapsed	31/12/2016	
Warrants$_{2015}$	04/08/2015	48,000	-	-	-	48,000	48,000
Total		**48,000**	**-**	**-**	**-**	**48,000**	**48,000**

The acquisition period for the rights 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

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%	**€794,000**
Founder's warrants$_{2015-2}$	23/09/2015	**424,200**	23/09/2019	€10.70	53.16%	-0.19%	**€2,591,000**
Founder's warrants$_{2015-3}$	04/12/2015	**20,000**	04/12/2019	€10.70	53.79%	-0.22%	**€78,000**
Founder's warrants$_{2015-4}$	15/03/2016	**39,700**	15/03/2019	€6.09	56.74%	-0.41%	**€83,000**

Type	Date of award	Number of outstanding warrants					Maximum number of shares to be subscribed:
		31/12/2015	Awarded	Exercised	Lapsed	31/12/2016	
Founder's warrants$_{2015-1}$	22/05/2015	195,000	-	(28,000)	-	167,000	167,000
Founder's warrants$_{2015-2}$	23/09/2015	424,200	-	-	(39,700)	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
Total		**639,200**	**39,700**	**(28,000)**	**(39,700)**	**611,200**	**611,200**

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

Share-based payment expense recognised for the years shown

Type	31/12/2015				31/12/2016			
	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$_{2015}$	481	-	481	481	481	481	-	481
Founder's warrants$_{2015-1}$	794	-	794	794	794	794	-	794
Founder's warrants$_{2015-2}$	2,591	-	1,191	1,191	2,429	1,191	904	2,095
Founder's warrants$_{2015-3}$	78	-	36	36	78	36	31	67
Founder's warrants$_{2015-4}$	-	-	-	-	83	-	59	59
Total	**3,944**	**-**	**2,502**	**2,502**	**3,866**	**2,502**	**994**	**3,495**

Note 10: Borrowings and financial debts

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Reimbursable advances	220	797
Borrowings from and debts with lending institutions	53	23
Borrowings and miscellaneous financial debts	-	-
Financial debts – Lease financing	131	94
Non-current financial debts	**403**	**913**
Reimbursable advances	73	96
Borrowings from and debts with lending institutions	130	30
Borrowings and miscellaneous financial debts	150	-
Financial debts – Lease financing	43	44
Accrued interest payable	1	0
Shareholder current accounts	-	-
Current bank liabilities	2	5
Current financial debts	**399**	**176**
Total financial debt	**803**	**1,090**

Reconciliation of redemption value/balance sheet value

(Amounts in thousands of euros)	Reimbursement value		Amortised cost	Balance sheet value at 31/12/2016
	31/12/2015	31/12/2016		
Reimbursable advances	333	999	106+	893
Borrowings from and debts with lending institutions	183	53	-	53
Borrowings and miscellaneous financial debts	150	-	-	-
Financial debts – Lease financing	174	138	-	138
Accrued interest payable	1	0	-	0
Current bank liabilities	2	5	-	5
Total financial debt	**842**	**1,196**	**(106)**	**1,090**

Breakdown of financial debts by maturity, in reimbursement value

The maturities of financial debts are broken down as follows:

(Amounts in thousands of euros)	31/12/2016	Current	Non current	
		< 1 year	1- 5 years	> 5 years old
Reimbursable advances	999	112	887	-
Borrowings from and debts with lending institutions	53	30	23	-
Borrowings and miscellaneous financial debts	-	-	-	-
Financial debts – Lease financing	138	44	94	-
Accrued interest payable	0	0	-	-
Current bank liabilities	5	5	-	-
Total financial debt	**1,196**	**192**	**1,004**	**-**

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 2014	**201**	**11**	**-**	**-**	**272**
(+) Collection	-	-	92	-	92
(-) Reimbursement	-	(7)	-	-	(7)
Subsidies	(11)	-	(7)	-	(78)
Financial expenses	11	0	3	-	15
(+/-) Other movements	-	-	-	-	-
On 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
(+/-) Other movements	-	-	-	-	-
At 31 December 2016	**177**	**-**	**188**	**528**	**893**

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 2016	**191**	**208**	**600**	**999**
Share at less than one year	93	20	-	112
Share at 1 year to 5 years	99	189	600	887
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 €230,000 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:

- € 100,000 on the date of signing of the agreement;
- €108,000 on the drawdown of funds;
- The €50,000 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:

- € 12,500/quarter from 31 March 2016 to 31 December 2016 (4 payments)
- € 20,000/quarter from 31 March 2017 to 31 December 2017 (4 payments)
- € 25,000/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 €180,000 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:

- €54,000 on the agreement's signing date;
- €90,000 on the drawdown of funds;
- The €36,000 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 €29,000 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 has reimbursable advance of € 260,000 for the "in vitro, in vivo and pharmacokinetic characterisation of a candidate drug."

Payments were scheduled between the agreement's signing date and the end of the project as follows:

- € 100,000 on the date of signing of the agreement;
- € 108,000 on the call for funds;
- The €52,000 balance upon completion of the project.

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:
  - € 6,500/quarter from 30 June 2017 to 31 March 2018 (4 payments)
  - € 13,000/quarter from 30 June 2018 to 31 March 2021 (12 payments)
  - € 19,500/quarter from 30 June 2021 to 31 March 2022 (4 payments)
- In the event of failure or partial success:
  - € 6,500/quarter from 30 June 2017 to 31 March 2018 (4 payments)
  - € 13,000/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 €1,100,000 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:

- €600,000 on the agreement's signing date;
- The €500,000 balance on completion of the project upon request by the Company.

The contractual reimbursement dates are as follows:

- If successful: €55,000/quarter from 31 December 2018 to 30 September 2023 (20 payments)
- In the event of failure or partial success: €55,000/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 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.

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.

COFACE advance - prospection insurance

The Company signed a COFACE prospection insurance agreement on 15 September 2008, as amended by a supplementary agreement on 22 October 2009. By way of this agreement, the Company received a total of €61,000 in 2009 and 2010.
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 runs from 1 June 2010 to 31 May 2015. The balance of the COFACE advance not used by the Company on 31 May 2015 (€61,000) was deemed as not due and was recorded under subsidies in 2015.

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 2014	**83**	**100**	**183**
(+) Collection	-	-	-
(-) Reimbursement	-	-	-
Subsidies	-	-	-
Financial expenses	-	-	-
(+/-) Other movements	-	-	-
On 31 December 2015	**83**	**100**	**183**
(+) Collection	-	-	-
(-) Reimbursement	(30)	(100)	(130)
Subsidies	-	-	-
Financial expenses	-	-	-
(+/-) Other movements	-	-	-
At 31 December 2016	**53**	**-**	**53**

Change in debts with lending institutions by maturity, in reimbursement value

(Amounts in thousands of euros)	OSEO - Equity Loan
At 31 December 2016	**53**
Share at less than one year	30
Share at 1 year to 5 years	23
Share 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: €150,000
- 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: €100,000
- 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 debts and borrowings

(Amounts in thousands of euros)	SODISID loan	UPMC loan	Total
At 31 December 2014	**150**	**29**	**179**
(+) Collection	-	-	-
(-) Reimbursement	-	(30)	(30)
Subsidies	-	-	-
Financial expenses	-	1	1
(+/-) Other movements	-	-	-
On 31 December 2015	**150**	**-**	**150**
(+) Collection	-	-	-
(-) Reimbursement	(150)	-	(150)
Subsidies	-	-	-
Financial expenses	-	-	-
(+/-) Other movements	-	-	-
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: €150,000
- 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.

Université Pierre & Marie Curie (UPMC) loan

The Company signed a loan agreement with the UPMC in November 2014 having as object "the partial financing of industrial property costs within the context of the application for French patent No. 09 54354, entitled" Food Composition intended for solar protection", filed on 25 June 2009 in the name of the Company.

The main features of the loan are:

- Nominal amount: €30,000
- Duration: 1 year
- Interest-free loan

In this way, the Reimbursement of principal was made during the financial year 2015.
Under the terms of the IFRS standard, the fact that the Company benefited from an interest-free loan is equivalent to considering that the company received a subsidy. 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 = 2.58%) is considered as a subsidy received from the government.

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 2014	**-**	-	-	-
(+) Subscription	181			
(-) Reimbursement	(7)			
On 31 December 2015	**174**	43	131	-
(+) Subscription	-			
(-) Reimbursement	(36)			
At 31 December 2016	**138**	44	94	-

In 2015, the Company entered into a finance lease agreement with a 3-year duration regarding an HPLC system (spectrometer).

Note 11: Pension commitments

The employee benefits consist of the provision for retirement allowances, assessed on the basis of the provisions of the applicable collective agreement, i.e. the Collective Agreement of the "Predominantly food retailers and wholesalers".

This commitment only applies to employees subject to French law. The main actuarial assumptions used for the evaluation of the retirement benefits are as follows:

ACTUARIAL ASSUMPTIONS	31/12/2015	31/12/2016
Retirement age	Voluntary departure between 65 and 67	
Collective agreements	Food retailers and wholesalers	
Discount rate (IBOXX Corporates AA)	2.03%	1.31%
Mortality table	Insee 2014	Insee 2015
Wage revaluation rate	2.00%	2.00%
Turnover rate	Mean	Mean
Rate of social charges		
Executives	45%	44.5%
Non executive	n/a	n/a

The provision for the retirement allowance has evolved as follows:

(Amounts in thousands of euros)	Retirement benefits
At 31 December 2014	**25**
Past service costs	4
Financial costs	0
Actuarial gains and losses	4+
On 31 December 2015	**25**
Past service costs	6
Financial Costs	1
Actuarial gains and losses	17
At 31 December 2016	**48**

Note 12: Current liabilities

12.1 Taxes and social security

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Personnel and related accounts	137	242
Social security and other social organisations	210	347
Other taxes, duties, and similar payments	15	133
Total taxes and social debts	**361**	**722**

Note 13: Details of expenses and products by function

13.1 Research and development costs

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Staff expenses	(1,613)	(1,789)
Other purchases and external expenses	(825)	(4,817)
Other	(62)	(182)
Research and development expenses	**(2,501)**	**(6,788)**
Research tax credit	454	1,604
Subsidies	78	62
Subsidies	**532**	**1,667**
Net research and development costs;	**(1,969)**	**(5,121)**

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)	31/12/2015	31/12/2016
Staff expenses	(2,035)	(1,145)
Other purchases and external expenses	(1,001)	(1,572)
Other	(38)	(103)
General and administrative expenses	**(3,074)**	**(2,820)**

13.3 Staff expenses

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Salaries and social charges	(1,147)	(1,940)
Share-based payments	(2,502)	(994)
Staff expenses	**(3,649)**	**(2,934)**

Note 14: Net financial income and expenses

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Other financial expenses	(47)	(33)
Interest on bond loans	(173)	-
Other financial income	31	22
Currency gains and (losses)	(2)	(1)
Total financial income and expenses	**(190)**	**(13)**

Note 15: Income taxes

The total amount of fiscal deficits on 31 December 2016 was estimated at €20,563, comprising:

- French tax deficits that may be carried forward indefinitely of €20,361;
- Tax deficits of the U.S. subsidiary of €201,000.
- Tax deficits of the Brazilian subsidiary of €1,000;

The tax rate applicable to:

- Biophytis is the rate in effect in France, i.e. 33.33%.
- 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. 34%.

By way of application of the principles described in Note 2.20, 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)	31/12/2015	31/12/2016
Net profit	(5,233)	(7,954)
Consolidated tax	-	-
Profit or loss before tax	**(5,233)**	**(7,954)**
Current tax rate in France	33.33%	33.33%
Theoretical tax at current rates in France	**1,744**	**2,651**
Permanent differences	530	530
Payment in shares	(834)	(331)
Non-activated tax deficit adjusted for deferred taxation	(1,446)	(2,849)
Differences in tax rates	5	(0)
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)	31/12/2015	31/12/2016
Temporary differences	45	16
Losses carried forward	3,860	6,855
Total deferred tax assets	**3,904**	**6,871**
Temporary discrepancies	(372)	(332)
Total deferred tax liabilities	**(372)**	**(332)**
Net total deferred tax elements	**3,533**	**6,539**
Unrecognised deferred taxes	(3,533)	(6,539)
Net total of deferred taxes	**-**	**-**

Note 16: Earnings per share

	31/12/2015	31/12/2016
Average weighted number of shares circulation	4,865,853	6,202,616
Net profit for the financial year	(5,233)	(7,954)
Basic earnings per share (€/share)	**(1.08)**	**(1.28)**
Diluted earnings per share (€/share)	**(1.08)**	**(1.28)**

Note 17: Related parties

17.1 Remuneration of company officers and management

(Amounts in thousands of euros)	31/12/2015	31/12/2016
Fixed remuneration due	388	719
Variable remuneration due	201	86
Benefits in kind	9	12
Attendance fees	54	54
Share-based payments	2,502	994
Total executive compensation	**3,153**	**1,864**

No post-employment benefit is granted to company officers and management.

17.2 Transactions with company officers and management

Biophytis Bonds$_{2015C}$
Within the context of the bond loan agreement issued by the General Meeting of 27 May 2015, the management of the Company subscribed 125,000 Biophytis bonds$_{2015C}$ for an amount of €250,000. Bonds$_{2015C}$ were repaid, including interest earned, by the issuance of Company shares during the IPO in 2015.

Current account
The Company's CEO made advances on the current account. On 10 July 2015, the Company made payable with immediate effect the associated current account held for an amount of €64,000. It was repaid in the amount of €60,000 by issuing shares of the Company at the price of the IPO.

17.3 Transactions with Metabrain

Metabrain is one of the principal shareholders of the Company.

Platform provision agreement
The Company signed a framework agreement with Metabrain on 13 July 2009, in order to formalise the terms of access of Biophytis to Metabrain's facilities and equipment and associated services and define the terms of their availability for Biophytis' scientific experiments. This agreement was signed for a period of one year and was extended by short-term supplementary agreements until 31 October 2015. By way of this agreement, the Company incurred a charge of €31K during the financial year 2015. No charges were incurred during the financial year 2016.

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 €250,000 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 2016 to extend it for an additional period of twelve months. Under this agreement, the Company incurred a charge of €51,000 during the financial year 2015 and of €189,000 during the financial year 2016.

Agreement for the assignment of shares in patents
On 4 June 2015, the Company entered into an agreement to sell a share of a patent with Metabrain for an amount of €1,500,000 pre-tax. The price was paid in shares upon the Company's market listing, by offsetting against the receivable for the subscription of the Company's common shares.

17.4 Transactions with Iris Pharma

Agreement for the assignment of shares in patents

On 5 June 2015, the Company entered into an agreement to sell a share of a patent with Iris Pharma for an amount of €800,000 pre-tax. The price was paid in shares upon the Company's market listing, by offsetting against the receivable for the subscription of the Company's common shares.

Note 18: Off-balance-sheet commitments

18.1 Commercial Leases

Property leases

France:

The Company relocated during the financial year 2016 and entered into a temporary occupancy agreement for its administrative offices and laboratories:

Address	Université Pierre et Marie Curie - 4, place Jussieu - 75005 Paris
Term	15 December 2016 – 15 December 2017, renewable by amendment
Annual fee	€90,700.50 pre-tax, with compensation for the preparation of the works carried out by the Company for €32,000.

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 charges at 31/12/2016	Commitment until the next termination period		
				Up to 1 year	1- 5 years	Over 5 years
Paris - UPMC - laboratory and offices	15/12/2016	15/12/2017	4	54	-	

18.2 Commitments by way of financial debts

Commitments received

Borrowing	Guarantees received	Nominal	Residual amount at 31/12/2016
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	53

Commitments given

Borrowing	Commitments given	Nominal	Residual amount on 31/12/2016
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 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.	229	191
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 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 €500,000 will be paid upon completion of the project

Note 19: Management and assessment of financial risks

Biophytis may be exposed to various financial risks: 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 expense of +/- €1,000.
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 (€6,633,000) and (€3,301,000) on 31 December 2016 and 2015 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 2017:

- All data from the SARA-PK study was obtained, including pharmacokinetic and pharmacodynamic results. Their analysis has allowed confirming the good pharmacokinetic profile in healthy elderly subjects, the therapeutic window of the Sarconeos product, and to determine the dosages that will be used in the SARA-INT phase 2b clinical trial.

- Opening of the first clinical centres in Europe and the start of recruitment of sarcopenic patients for the SARA-OBS study.

April 2017:

- Carried out a private placement of €3.7 million through the issuance of 1,310,431 new shares at a price of €2.85 per share.

- Setting up of a financing line with Bracknor Fund of up to €15 million in the form of 1,500 bonds redeemable in cash or new or existing shares with a nominal value of €10,000 each, with warrants ("convertible bonds and warrants").

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 2016 are presented in Section 27 of this Reference Document.

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 - Financial years ended on 31 December 2016

GRANT THORNTON
French member of Grant Thornton International

ERNST & YOUNG and Others

Exercice clos le 31 décembre 2016

Rapport des commissaires aux comptes sur les comptes consolidés

GRANT THORNTON
Membre français de Grant Thornton International
29, rue du Pont
92200 Neuilly-sur-Seine Cedex

Commissaire aux Comptes
Membre de la compagnie
régionale de Versailles

ERNST & YOUNG et Autres
1/2, place des Saisons
92400 Courbevoie - Paris-La Défense Cedex 1
S.A.S. à capital variable

Commissaire aux Comptes
Membre de la compagnie
régionale de Versailles

Statutory Auditor's report on the consolidated financial statements

To the Shareholders,

In compliance with the assignment entrusted to us by your General Meeting, we hereby present our report for the year ended 31 December 2016 on:

- - The audit of the consolidated financial statements of BIOPHYTIS, as attached to this report
- - The justification of our assessments,
- - the specific audit required by law.

The consolidated financial statements were prepared by the Board of Directors. It is our responsibility, on the basis of our audit, to express an opinion on these accounts.

Opinion on the consolidated financial statements

We conducted our audit in accordance with professional standards applicable in France; these standards require due diligence providing reasonable assurance that the consolidated financial statements do not contain any significant anomalies. An audit consists of verifying, on a sample basis or using other selection methods, the elements justifying the amounts and appearing in the consolidated financial statement. It also consists of assessing the accounting principles followed, the significant estimates adopted and the overall presentation of the financial statements. We believe that the elements that we collected form a sufficient and appropriate basis for our opinion.

We certify that the consolidated financial statements are, with regard to the IFRS 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.

Without qualifying the opinion expressed above, we draw your attention to:

- The “going concern” paragraph of Note 2.1 to the consolidated financial statements, which sets forth the assumptions underlying the going concern principle,
- Note 2.3 “Corrections to the published financial statements for the year ended 31 December 2015" concerning the corrections made and their impact on the financial statements for 2015.

II. Justification of our assessments

Pursuant to Article L. 823-9 of the Commercial Code relating to the justification of our assessments, we inform you that the assessments we made relate to the appropriate character of the accounting principles applied.

The assessments thus 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.

III. Specific audit

We 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.

Neuilly-sur-Seine and Paris-La Défense, 27 April 2017

The Statutory Auditor

GRANT THORNTON
Membre français de Grant Thornton International

ERNST & YOUNG et Autres

Laurent Bouby

Frédéric Martineau

20.5. DATE OF THE LATEST FINANCIAL INFORMATION

The date of the latest financial information is 31 December 2016.

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 Reference Document, 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 2016.

21. SUPPLEMENTARY INFORMATION

21.1. SHARE CAPITAL

21.1.1. Amount of the share capital

On the date of this Reference Document, the share capital of the Company amounts to €1,989,282.60, divided into 9.946.413 fully subscribed and paid up shares, with a nominal value of €0.20.

BIOPHYTIS BRASIL

On the date of this Reference Document, 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 Wagner Clayton CORREA, fully paid up.

BIOPHYTIS INC.

On the date of this Reference Document, 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 reference document, there are no non-equity securities outstanding.

21.1.3. Status of pledges, guarantees and sureties encumbering the Company's shares

As far as the Company is aware, on the date of this reference document, there is only one pledge on its shares, namely:

Name of the shareholder	Beneficiary	Starting date of the pledge	Condition for lifting the pledge	Number of shares pledged by the issuer	% of share capital of the issuer pledged
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 General Meeting of the Company, which met on 16 June 2017 authorised, for a period of 18 months from the date of the general meeting, the Board of Directors to implement a share

repurchase program of the Company's shares pursuant to the provisions of Article L. 225-209 of the 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 repurchase of the shares. When shares are with the aim of increasing 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 repurchase of shares: €2,000,000

Objectives of the repurchases of shares:

- 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 on account of the Company's obligations tied 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, splits, or contributions,

- Honouring obligations related to stock option programs, attributions of bonus 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 bonus shares pursuant to Articles L. 225-197-1 *et seq.* of the French Commercial Code;

- Their cancellation and the consequent reduction of capital (in particular with a view towards optimising cash management, return on equity 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 repurchase program authorised by the General Meeting of 16 June 2017:

- 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 the execution 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 General Meeting.
- On 31 December 2016, the Company held 38,121 own shares within the context of the liquidity agreement concluded with INVEST SECURITIES, consistent 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 carried out under the share buyback program during the financial year ended 31 December 2016 are as follows (only in connection with the liquidity agreement referred to above):

Securities purchased	294,015 for €1,516,322.10
Nominal value	0.20
Average price of purchases	5,157295
Number of shares sold	260,412 for €1,342,999.18
Average price of	5,157209
Number of shares registered in the Company's name at the end of the financial year	38,121
Value determined at the average purchase price	38,121 shares at €5.290042, or €201,661.69

21.1.5. Potential share capital

On the date of this reference document, the securities providing access to the share capital were as follows:

Summary table of founder's warrants/warrants

Type of securities	Founder's warrants$_{2015}$	Founder's warrants$_{2-2015}$	Warrants$_{2015D}$	Warrants$_{2015}$	Bracknor warrants
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
Date of the General Meeting	22 May 2015	27 May 2015	27 May 2015	27 May 2015	10 June 2016
Date of the board meeting	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 on the use of a power of attorney granted by the Board of Directors on 3 April 2017
Nature of the share to subscribe	Ordinary share				
Exercise price per new share subscribed	€2.06	€10.70 for founder's warrants$_{2-2015}$ Attributed on 23 September and 4 December 2015 and €6.09 for the founder's warrants$_{2-2015}$ Attributed on 15 March 2016	€6	€8.40	€3.33
Parity	1 founder's warrant$_{2015}$ provides	1 founder's warrant$_{2-2015}$ provides	1 warrant$_{2015D}$ provides	1 warrant$_{2015}$ provides	1 Bracknor warrant

Type of securities	Founder's warrants$_{2015}$	Founder's warrants$_{2-2015}$	Warrants$_{2015 D}$	Warrants$_{2015}$	Bracknor warrants
	entitlement to 1 share	entitlement to 1 share	entitlement to 1 share	entitlement to 1 share	provides entitlement to 1 share
Deadline for exercise	Deadline of 4 years from their issuance, i.e. at latest on 22 May 2019, under penalty of forfeiture	Deadline of 4 years from their issuance, i.e. at latest on 4 December 2019, under penalty of forfeiture	Deadline of 4 years from their subscription, under penalty of forfeiture	Deadline of 4 years from their subscription, under penalty of forfeiture	Deadline of 5 years from their subscription, under penalty of forfeiture
General exercise conditions	Being an employee or officer of the Company subject to the tax regime for employees on the exercise date And At any time	Being an employee or officer of the Company subject to the tax regime for employees on the exercise date And For (i) 33.33% between the issue date and the first anniversary of the issue date, (ii) for 66.66% between the first anniversary of the issue date and the second anniversary of the issue date and (iii) as a whole, starting from the second anniversary of the issue date and at the latest, 4	At any time starting from the subscription and within the deadline for exercise	For (i) 33.33% between the subscription date and the first anniversary of the subscription date, (ii) for 66.66% between the first anniversary of the subscription date and the second anniversary of the subscription date and (iii) as a whole, starting from the second anniversary of the subscription date and at latest, 4 years after the subscription date	At any time starting from the subscription and within the deadline for exercise

Type of securities	Founder's warrants$_{2015}$	Founder's warrants$_{2-2015}$	Warrants$_{2015 D}$	Warrants$_{2015}$	Bracknor warrants
		years after the issue date			
Number of securities issued/attributed	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)
Number of warrants exercisable on the current date	167,000	296,133	189,748	30,000	431,184
Number of warrants exercised on the current date	28,000	None	80,666	6,000	None
Number of new shares which may be subscribed	167,000	444. 200(1)	189,748	48,000	431,184
Total	**167,000**	**444. 200(1)**	**189,748**	**48,000**	**431,184**

(1) This total takes into account the lapse 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 company 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
Stanislas VEILLET	Chairman & CEO	58,500	198,800	N/A	N/A
René LAFONT	Founder - Employee	58,500	39,700	N/A	N/A

Jean-Christophe MONTIGNY	Employee	78,000	106,000	N/A	N/A
Philippe GUILLET	Employee	N/A	39,700	N/A	N/A
Waly DIOH	Employee	N/A	20,000	N/A	N/A
Philippe DUPONT	Employee	N/A	20,000	N/A	N/A
Pierre DILDA	Employee	N/A	N/A	20,000	N/A
Susanna Del Signore	Employee	N/A	N/A	N/A	39,700
Total attributed		**195,000 (including 167,000 in force to date)**	**424,200 (including 384,500 in force to date)**	**20,000**	**39,700**
Founder's warrants$_{2\text{-}2015}$ not yet attributed(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$_{2\text{-}2015}$. Indeed, the new delegations of authority decided by the General Meeting of 10 June 2016 put an end to all previous authorisations with the same purpose, up to the unused portion.

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$_{2015}$** Attributed on 04 August 2015	**Warrants$_{2015D}$** Attributed on 10 July 2015	**Bracknor warrants** Attributed on (i) 15 May 2017 and (ii) 7 July 2017
Nadine COULM	Director	18,000	N/A	N/A
Marie-Claire JANAILHAC-FRITSCH	Director	18,000	N/A	N/A
Jean-Gérard GALVEZ	Director	18,000	N/A	N/A
Former holders of Biophytis bonds$_{2015D}$		N/A	189,748	N/A
Bracknor		N/A	N/A	431,184
		54,000	**189,748**	

Total attributed	**(Including 48,000 in force to date)**		**431,184**
Warrants not yet attributed(1)	**0**	**0**	**N/A**

(1) The Board of Directors will no longer be able to use these various delegations and award new warrants$_{2015}$. Indeed, the new delegations of authority decided by the General Meeting of 10 June 2016 put an end to all previous authorisations with the same purpose, up to the unused portion.

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 Reference Document

By a decision dated 3 April 2017, the Board of Directors of the Company, using the delegation granted by the tenth resolution of the Combined General Meeting of 10 June 2016, awarded Bracknor Fund, Ltd, a mutual fund (Certificate No. SIBA / PIPO/14/5528) having 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 convertible bonds for an amount of €3,000,000.00 each (the "**convertible bonds**").

It has been decided that each convertible bond will have a share warrant attached (the "**Bracknor warrants**" and, with the convertible bonds the "**convertible bond warrants**"). It is specified that, on the date of this Reference Document, 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 convertible bonds, i.e. 25%;
“Vn" is the nominal value of the relevant convertible bonds tranche; and
“P" is the applicable conversion price.

It is specified that the applicable conversion price depends on the convertible bond 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 rise to the issue of a new tranche of convertible bonds from which the Bracknor warrants are detached.

In theory, the impact of the issue on the stake of a shareholder owning 1% of the Company before the transaction is as follows:

	Undiluted base	Diluted base
Before issuing a new tranche of convertible bonds warrants	1.00%	0.89%
After issuing the remaining 3 tranches and converting all of the convertible bonds and exercising all of the Bracknor warrants.	0.76%	0.69%

It is specified that the above table has been produced 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 through the issuance of 1,117,449 new common shares at a price of €2.85 per share (including issue premium), an issue 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 through the issuance of 192,982 new common shares at a price of €2.85 per share (including issue premium), an issue premium of €2.65 per share, corresponding to a total subscription amount of €549,998.70.
  - The draw of a first line of convertible bond warrants decided on 15 May 2017 in the amount of €3,000,000, resulting in the issuance of 225,225 warrants and 300 convertible bonds, converted between 16 May and 9 June 2017 into 1,385,085 new shares,
  - The draw of a second line of convertible bond warrants decided on 7 July 2017 in the amount of €3,000,000, resulting in the issuance of 205,959 warrants and 300 convertible bonds, themselves converted between 7 July and 11 July 2017 into 1,027,396 new shares,
- An issue/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 Combined General 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 issuance resolutions approved by the General Meeting of 16 June 2017 ruling on an extraordinary basis are summarised below:

Resolutions of the GM of 16 June 2017	Object of the resolution	Maximum nominal amount in euros	Procedures for determination of the issue price	Duration of the authorisation and expiry	Use	Residual amount on the date of this reference document
9th Resolution	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 Commercial Code, for the purpose of deciding on the issuance of shares and/or securities providing immediate or future access to the share capital or providing entitlement to a receivable, with the suppression of the preferential subscription right, without an indication of the beneficiaries and through an offer to the public.	Nominal amount (capital increases): €2,500,000* (bonds and other receivable titles providing access to the share capital): €30,000,000**	Note 1	26 months	No	Nominal amount (capital increases): €2,500,000 (bonds and other receivable titles providing access to the share capital): €30,000,000

Resolutions of the GM of 16 June 2017	Object of the resolution	Maximum nominal amount in euros	Procedures for determination of the issue price	Duration of the authorisation and expiry	Use	Residual amount on the date of this reference document
10th Resolution	Delegation of powers to be granted to the Board of Directors to decide, either on the issuance of the shares and/or securities providing immediate or future access to the share capital or providing entitlement to a receivable, with the maintenance of the pre-emptive subscription right, or the incorporation of profits, reserves or premiums into the share capital.	Nominal amount (capital increases): €2,500,000* (bonds and other receivable titles providing access to the share capital: €30,000,000**	-	26 months	No	Nominal amount (capital increases): €2,500,000 (bonds and other receivable titles providing access to the share capital: €30,000,000
11th Resolution	Delegation of powers to be granted to the Board of Directors to decide, on the issuance of shares and/or securities providing immediate or future access to the share capital or providing entitlement to a receivable, with the suppression of the preferential subscription right of the shareholders in favour of categories of beneficiaries.****	Nominal amount (capital increases): €2,500,000* (bonds and other receivable titles providing access to the share capital): €30,000,000**	At least equal to 70% of the volume-weighted average of the last ten (10) trading days prior to the date of its fixing	18 months	No	Nominal amount (capital increases): €2,500,000 * (bonds and other receivable titles providing access to the share capital): €30,000,000
12th Resolution	Delegation of powers to be granted to the Board of Directors to decide, on the issuance of shares and/or securities providing immediate or future access to the share capital or providing entitlement to a receivable, with the suppression of the preferential subscription right in favour 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): €2,500,000* (bonds and other receivable titles providing access to the share capital): €30,000,000**	At least equal to 70% of the volume-weighted average of the last ten (10) trading days prior to the date of its fixing	18 months	No	Nominal amount (capital increases): €2,500,000 (bonds and other receivable titles providing access to the share capital): €30,000,000

Resolutions of the GM of 16 June 2017	Object of the resolution	Maximum nominal amount in euros	Procedures for determination of the issue price	Duration of the authorisation and expiry	Use	Residual amount on the date of this reference document
13th Resolution	Delegation of powers to be granted to the Board of Directors to decide on the issuance of shares and/or securities providing immediate or future access to the share capital or providing entitlement to a receivable, with the suppression of the preferential subscription right of the shareholders in favour of categories of persons undertaking to guarantee the completion of a capital increase or any issuance likely to entail a capital increase in the long term.	Nominal amount (capital increases): €2,500,000* (bonds and other receivable titles providing access to the share capital): €30,000,000**	At least equal to 70% of the volume-weighted average of the last ten (10) trading days prior to the date of its fixing	18 months	No	Nominal amount (capital increases): €2,500,000 (bonds and other receivable titles providing access to the share capital): €30,000,000
14th Resolution	Delegation of powers to be granted to the Board of Directors to decide on the issuance of shares and/or securities providing immediate or future access to capital or providing entitlement to a receivable, with the suppression of the preferential subscription right in favour 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): €2,500,000* (bonds and other receivable titles providing access to the share capital): €30,000,000**	At least equal to 70% of the volume-weighted average of the last ten (10) trading days prior to the date of its fixing	26 months	No	The following double ceiling: 20% of the share capital/year (deducting the prior uses of the delegation) And Nominal amount (capital increases): €2,500,000 * (bonds and other receivable titles providing access to the share capital): €30,000,000
15th Resolution	Authorisation to be given to the Board of Directors to increase the number of shares and/or securities providing 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 cited in the preceding six resolutions (9th to 14th) with the maintenance or suppression of the preferential subscription rights as appropriate (*Overallocation option*).	15% of the initial issue*	Price retained for the initial issue and up to a cap of 15% of the latter	26 months	No	-

Resolutions of the GM of 16 June 2017	Object of the resolution	Maximum nominal amount in euros	Procedures for determination of the issue price	Duration of the authorisation and expiry	Use	Residual amount on the date of this reference document
16th Resolution	Delegation of powers to be granted to the Board of Directors, for the purpose of deciding on a capital increase reserved for employees (*rejected*).	Nominal amount €45,203	Pursuant to the provisions of articles L.3332-19 and L. 3332-20 of the Labour Code	18 months	-	-
18th Resolution	Authorisation to be granted to the Board of Directors with a view to the purchase by the Company 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)
19th Resolution	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
20th to 23st Resolutions	Delegation of powers and authorisation to be granted to the Board of Directors, in order to decide on the issuance of warrants$_{2017}$, founder's warrants$_{2017}$, bonus shares (AGA$_{2017}$), subscription and/or purchase of shares (Options$_{2017}$), to the benefit of categories of beneficiaries ****	€ 166,000 for each of the 20th to 23st Resolutions ***	Note 2	Warrants$_{2017}$ Founder's warrants 2017: 18 months AGA $_{2017}$ Options $_{2017}$: 38 months	No	€166,000 for each of the 20th to 23rd Resolutions

* The nominal amount of the ceiling for authorised capital increases shall be deducted from the amount of the authorised global ceiling of €2,500,000 in the Seventeenth Resolution of the General Meeting of 16 June 2017.

** The nominal amount of the cap for bonds and other debt securities giving access to the authorised capital shall be deducted from the amount of the authorised global ceiling of €30,000,000 in the Seventeenth Resolution of the General Meeting of 16 June 2017.

*** The use of the delegations may not entail that all of the shares resulting from the exercise of founder's warrants, warrants, stock options for subscription or purchase of shares and bonus shares held by the employees, officers and consultants of the Company represent 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 the use of the delegations granted by the 20th to 23rd Resolutions
- In connection with the use of the delegations granted by the 9th to 15th Resolutions, and
- In application of any agreement concluded following the use, prior to the General Meeting, of any delegation granted by any decision prior to the General Meeting and whose execution would continue after the General Meeting.

**** Categories of beneficiaries of the delegations of the 11th resolution and 20th to 23rd resolutions:

Allotment of securities (11th resolution) 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 created by Act no. 2007-1223 of 21 August 2007 on labour, employment, and purchasing power (the "TEPA Act"), 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 Tax Code) 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 enterprises 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 French General Tax Code created by the TEPA Act), 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 Tax Code) 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 enterprises 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 French General Tax Code created by the TEPA Act), 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 Tax Code) 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 who primarily invest in companies known as growth companies (i.e. unlisted companies or companies whose market capitalization does not exceed €500 million) of any kind, including in particular innovation-focused investment funds ("FCPI"), risk investment funds ("FCPR), whose registered office or that of their management companies is located in the European Union, and local investment funds ("FIP"), 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 the issue premium);

- Companies, investment companies, investment funds, or mutual fund managers who may invest in French companies listed on the Euronext or Alternext markets or on any other regulated market specialising in structured bond issues for small and medium-sized enterprises;

- Any financial institution, public institution, development bank, French or European sovereign fund, or any institution attached to the European Union wishing to raise funds for small and medium-sized enterprises and whose investment conditions may include all or part of an investment in equity and/or in the form of securities giving immediate or future access to the share capital; and

- Officers, directors and/or executive employees of the Company wishing to invest concurrently with beneficiaries covered by the above categories.

The allocation of the warrants$_{2017}$ (20th resolution) is reserved for the benefit of natural or legal persons having one of the following characteristics:

(i) holders of an executive mandate or a member of any other supervisory, control or study committee or carrying out the duties of observe the within the Company;
(ii) consultants or directors 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 use of this delegation by the Board of Directors;
(iii) any employee and/or officer 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 use of this delegation by the Board of Directors.

The allocation of the founder's warrants$_{2017}$ (21th resolution) is reserved for officers subject to the tax regime of employees and to the employees of the Company and its subsidiaries.

The allocation of bonus shares$_{2017}$ (22th resolution) is reserved for employees and corporate officers.

The allocation of Options$_{2017}$ (23st resolution) is reserved for the benefit of the following beneficiaries:

(i) members or some members of the Company's staff and companies tied to it under the conditions cited 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 admission, subsequent to or concomitant with the admission 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 fixing.

Note 2: (Exercise price of the warrants$_{2017}$, Founder's warrants$_{2017}$, Options$_{2017}$):

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 date of attribution by the Board (reduced as appropriate by a maximum discount of 20%) for as long as the Company's shares of the Company are admitted to trading on a market or a stock exchange.

2. The exercise price of the founder's warrants$_{2015}$ shall be at least equal to:
   (i) The introduction price of the Company's shares being traded 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 attribution occurring within six months of the completion of the capital increase permitting the Company to be admitted to a US stock market, subject to the provisions set out below under:

   (ii) (ii) In the event one or more capital increases are carried out during the six months preceding the implementation 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 date of attribution of each founder's warrant$_{2017}$, provided that the common shares to be issued in the exercise of the founder's warrants$_{2017}$ confer rights equivalent to those issued in connection with the capital increase.
   (iii) For any attribution occurring outside of the scenarios cited in (i) and (ii), at the average of prices weighted by trading volumes of the last 10 trading sessions preceding the date of attribution of the said founder's warrants$_{2017}$ by the Board of Directors (reduced, as

appropriate, by a maximum discount of 20%), for as long as the shares of the Company are traded on a market or a stock exchange.

3. The subscription or purchase price of the shares through the exercise of the Options$_{2017}$: for as long as the shares are traded on a US stock exchange or Alternext, this shall be determined in accordance with Article L. 225-177 of the 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 Commercial Code, it being specified that:
   (i) with regard to options for the subscription of 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 for the 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

Date of issues	Nature of operations	Capital	Issue premium	Number of shares created	Number of shares comprising the share capital	Nominal value	Share capital	Issue 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	Division by 100 of the nominal value	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	201,635	2,018,366,35	201,635	519,494	1	519,494	11.01

Date of issues	Nature of operations	Capital	Issue premium	Number of shares created	Number of shares comprising the share capital	Nominal value	Share capital	Issue premium per share
	preference shares							
29 June 2009	Capital increase – Financial year of the right of accretion (P category preference shares have become P bis category preference shares)	21,804	0	21,804	541,298	1	541,298	1
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	Division by 5 of the nominal value	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 – Admission to Alternext – Issuance 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 – Confirmation of	4,583,20	114,580	22,916	6,131,751	0.20	1.226.350,20	6

Date of issues	Nature of operations	Capital	Issue premium	Number of shares created	Number of shares comprising the share capital	Nominal value	Share capital	Issue premium per share
	exercise of warrants							
04 December 2015	Capital increase – Confirmation 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
04 August 2016	Capital increase – Confirmation 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 common shares	38.596,40	511.402,3	192,982	7,533,932	0.20	1.506.786,40	€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	52.765,80	Conversion amount: 720.545,53	263,829	8,480,720	0.20	1,696,144	Conversion price: €2.35

Date of issues	Nature of operations	Capital	Issue premium	Number of shares created	Number of shares comprising the share capital	Nominal value	Share capital	Issue premium per share
	62 bond warrants							
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 200 bond warrants	136.986,20	Conversion amount: 3.102.054	684,931	9,603,948	0.20	1,920,789.60	Conversion price: €2.92
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

Changes in the distribution of the Company's share capital over the last 2 financial years (undiluted basis):

	At 31 December 2016		On 31 December 2015	
Shareholders	Number of shares	% of share capital and voting rights	Number of shares	% of share capital and voting rights
Founder (1)	***66,666***	***1.07%***	***80,301***	***1.30%***
Directors(2)	***17,365***	***0.28%***	***17,365***	***0.28%***
Seventure Partners Fund	482,313	7.75%	933,875	15.07%
CM-CIC Fund	554,487	8.91%	924,145	14.92%
Subtotal Institutional Investors	**1,036,800**	**16.66%**	***1,858,020***	***29.99%***

Stanislas VEILLET - Chairman & CEO	1,293,833	20.79%	1,293,833	20.88%
Non-founding employee	25,000	0.40%	0%	0%
H.M Conseils (3)	11,365	0.18%	2,273	0.30%
METABRAIN RESEARCH	408,635	6.57%	603,385	9.74%
Treasury stock	38,121	0.61%	4,518	0.07%
Free float	3,325716	53.44%	2,326,714	37.55%
TOTAL	**6,223,501**	**100%**	**6,195,501**	**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, through the shareholding of HM Conseils, 11,365 shares.
(3) H.M Conseils is 100% held by Mr Jean-Gérard GALVEZ, director.

The allocation of capital and the Company's voting rights on the date of this Reference Document is presented in paragraph 18.1.

21.2. ARTICLES OF INCORPORATION AND ARTICLES OF ASSOCIATION

21.2.1. Company object

The Company has as its object, in France and in all countries:

- the creation, operation, leasing, lease management of all operating assets, factories, institutions, the taking of stakes in any company, as well as all attached or connected commercial, financial, industrial, securities and property operations, relating directly or indirectly to the activity of research production, distribution and marketing of any product and service beneficial to human or animal health

- the research and development of drug candidates and nutraceuticals, notably in the field of age-related diseases;

- and more generally, all financial, commercial, industrial, civil, securities or property operations, 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. Statutory or other provisions relating to members of the management or governing bodies

(I) 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 General Meeting. However, in the event of merger or demerger, the appointment may be made by the Extraordinary General Meeting. The duration of their mandates shall be three (3) years. These end at the end of the Ordinary General Meeting of Shareholders which has approved 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 satisfying the conditions of this article.

The directors may be dismissed and replaced at any time by the Ordinary General Meeting.

No person may be appointed a director if, having exceeded the age of seventy five (75), his appointment has the effect of raising the proportion of directors who have exceeded this age to more than a third of the Board members. If the proportion of one third is exceeded, the oldest director shall be considered to have resigned at the end of the next General Meeting.

Any director who is a natural person shall, both on appointment and for the duration of his mandate, comply with the legal provisions on multiple directorships that the same natural person may hold within limited liabilities companies having 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 effective job. The number of directors bound to the Company by an employment agreement 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 be obliged to 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 own name, without prejudice to the joint and several liability 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 revokes the mandate of its permanent representative, it shall be obliged to notify this revocation and the identity of its new permanent representative to the Company immediately by registered letter. The same shall hold in the event of death or resignation of the permanent representative.

The appointment of the permanent representative, as well as the cessation 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 general meetings, make provisional appointments.

When the number of Directors falls below the legal minimum, the remaining directors must immediately call the Ordinary General Meeting in order to make up the numbers of the board.

Temporary appointments made by the Board are subject to ratification at the next Ordinary General Meeting. In the absence of ratification, the deliberations taken and actions previously concluded by the Board shall nevertheless remain valid.

Article 17 – Organisation and decisions of the Board

I. Chairman

The Board of Directors shall elect a Chairman from among its members who, under penalty of nullity of the appointment, shall be a natural person. The Board of Directors shall determine his/her remuneration.

The Chairman of the Board of Directors organises and directs the work of the Board and reports to the General 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 may 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 shall be granted for a limited period; it is renewable. In the event of death, it shall be valid until the election of the new Chairman.

II. Board meetings

The Board of Directors shall meet as often as the interests of the Company require, on calling by the Chairman.

The calling 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, with these notices of calling to be accompanied by the documents necessary for assessment of the decisions or

information submitted to the Board. This period for calling may be reduced to two (2) days if necessary, with this calling 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 ask the Chairman to call it on a given agenda.

The CEO may also ask the Chairman to call a meeting of the Board of Directors on a given agenda.

The Chairman is bound by the demands at submitted to him by virtue of the two preceding paragraphs.

Notices of calling shall be made by any means, even verbally.

The Board shall meet at the headquarters or at any other location (in France or abroad) designated in the notice, under the direction of its Chairman or, in his absence, a member designated by the Board to chair the meeting.

Board meetings are chaired by the Chairman of the Board or the CEO 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.

A register shall be maintained, 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 use of videoconferencing 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 use of videoconferencing 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 deciding 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 the drafting of the annual financial statements and consolidated accounts and the drawing up of the management report and the report on the management of the group, as well as for decisions regarding the dismissal of the Chairman of the Board of Directors, the CEO and the Deputy CEO.

IV. Representation

Any director may give a mandate in writing to another director to represent him/her at a board meeting.

Each director may only hold one of 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 proceedings

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 regulations. These minutes are signed by the Chairman of the meeting and by at least one director. In the absence of the Chairman of the meeting, 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 CEO, 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 Constitution, or by a Deputy CEO, 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. Non-voting observers

During the life of the company, the Ordinary General Meeting may appoint observers chosen from among the shareholders or outside them.

The number of observers may not exceed three (3).

The observers are appointed for a period of three (3) years. Their duties shall cease at the end of the Ordinary General Meeting of Shareholders called to approve the financial statements for the past year, held in the year during which their functions expire.

Any outgoing observe the may be re-elected subject to meeting the conditions of this article.

Observers may be dismissed and replaced at any time by the Ordinary General Meeting, without any compensation due them and even if this dismissal does not appear on the agenda. The duties of observers shall also end with the death or incapacity of for the individual observer, or the dissolution or bankruptcy for the observer which is a legal person or on resignation.

Observers may be natural or legal persons. When a legal person is appointed observe, 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 of the same by any written means. The same shall hold in the event of change of the permanent representative of the legal person.

The observers are responsible for ensuring the strict application of the articles of association and for submitting their observations at the sessions of the Board of Directors.

Within the Company, they have a general and permanent advisory and supervisory mission. They study the issues that the Board or its Chairman may submit to their examination for an opinion.

Observers shall be called to each meeting of the Board of Directors, in the same capacity as the directors, albeit without their absence able to affect the validity of the decisions of the Board of Directors.

In an individual or collective capacity, non-voting members shall only have advisory powers and shall not have voting rights at Board meetings.

Failure to call the observer or forward 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 duties of observers are performed free of charge: these latter parties shall not be allocated attendance fees. At the express decision of the Board, however, observers may be reimbursed for expenses incurred by them as part of their assignment. If the Council entrusts a particular mission to the observers or to one of them, it may allocate to them, in addition to a budget for its implementation, remuneration relating to the importance of the entrusted assignment.

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 general meetings of shareholders and within the limits of the company object, the Board of Directors considers any issue concerning the smooth running of the Company and through its decisions, settles the issues concerning it.

In its relations with third parties, the Company is committed even by the actions of the Board of Directors which do not relate to the company object, unless it can prove that the third party was aware that the act exceeded this object or could not have been unaware of it in view of the circumstances, it being excluded that the mere publication of the articles of association shall not constitute such evidence.

The Board of Directors shall carry out the controls and inspections that it considers appropriate.

Each director shall 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.

(II) General Management

Article 19 – General management - Delegation of powers

I. Principles of organisation

In accordance with the law, the General Management of the Company is assumed at his liability, either by the Chairman of the Board of Directors or by another individual appointed by the Board of Directors and holding the title of CEO.

The choice between these two forms of execution of general management is made by the Board of Directors, which shall inform the shareholders and third parties of the same under regulatory conditions.

The decision of the Board concerning the choice of the form of exercise of general management is taken 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 a participation of the directors at the Board Meeting by videoconference or other telecommunications media.

The choice so made by the Board of Directors is valid until the expiry of the mandate of the designated CEO, regardless of the cause of this expiry, notably including dismissal.

When the general management of the Company is assumed by the Chairman of the Board of Directors, the following provisions relating to the CEO shall apply to him.

II. General Management

Chief Executive Officer

As a function of the choice made by the Board in accordance with the provisions of the above paragraph, the general management of the Company is assumed either by the Chairman of the Board of Directors or by a natural person, who may or may not be a director or shareholder, appointed by the Board of Directors and holding the title of CEO.

When the Board of Directors chooses to separate the functions of Chairman and CEO, he shall appoint the CEO, set the term of his mandate, determine his remuneration and as appropriate, the limitations on his powers.

The duties of the CEO 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 CEO shall be regarded as having resigned and a new CEO shall be appointed.

The CEO may be dismissed at any time by the Board of Directors. When the CEO does not assume the duties of Chairman of the Board of Directors, his dismissal may give rise to damages if this is decided without just cause.

The CEO holds the broadest powers to act in all circumstances on behalf of the Company. He shall exercise these powers within the limits of the company object 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 actions of the CEO 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, albeit with it excluded that the sole publication of the articles of association shall not constitute this proof.

Deputy CEOs

At the proposal of the CEO, whether this role is assumed by the Chairman of the Board or by another person, the Board may appoint one or more natural persons as Deputy CEOs, who may or may not be directors and shareholders, responsible for assisting the CEO. The number of Deputy CEOs shall not exceed five. If the Deputy CEO is a director, the duration of his duties shall not exceed his term as Director.

The duties of the Deputy CEO shall 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 Deputy CEO in question shall be regarded as having resigned.

The Deputy CEOs may be dismissed at any time by the Board at the proposal of CEO. Their dismissal without just cause may give rise to damages.

By agreement with the CEO, the Board of Directors shall determines the scope and duration of the powers granted to the Deputy CEOs, who shall have the same powers as the CEO with regard to third parties. The Deputy CEOs have the same powers with respect to third parties as the CEO.

If the CEO ceases or is unable to perform his duties, the Deputy CEOs shall retain their functions and attributions until appointment of the new CEO, unless the Board decides otherwise.

The Board of Directors shall determine the remuneration of the Deputy CEOs.

III. Delegation of powers

The Board of Directors may delegate to the officers, whether they are directors or not, the permanent or temporary assignments which it determines, delegate powers to them and set the remuneration for them which it considers appropriate.

Article 20 - Remuneration of the Directors

The General Meeting may allocate to the directors, as remuneration for their activities, by way of Attendance fees, a fixed annual sum, which this meeting shall determine without being bound by previous decisions. The amount of the same 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 share than that of the other directors.

The Board of Directors may allocate exceptional remuneration for assignments or mandates entrusted to the directors.

The Board of Directors may authorise the 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 CEO or a Deputy CEO

I. Conventions subject to authorisation.

Except for those relating to current operations concluded under normal conditions, any agreement entered into directly or through an intermediary, between the Company and any of its directors and CEO or with a shareholder holding more than 10% of the voting rights of the company, or in the case of a corporate shareholder, 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 CEO, one of the CEOs or a Director of the Company is the owner, partner with unlimited liability, manager, director, member of the supervisory board or, in general, a director of the company.

These agreements must be authorised and approved under the legal conditions.

II. Prohibited agreements

On penalty of nullity of the contract, it is prohibited for directors other than legal persons to contract loans in any form from the Company, to be granted a current account or other overdraft by it, as well as to arrange for it to guarantee or endorse their commitments with regard to third parties.

The same prohibition shall apply to the CEO, the deputy CEOs 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

(III) 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.

(IV) 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.

(V) Preferential subscription right

The Company's shares all have a preferential subscription right to capital increases.

(VI) Limitation on voting rights

Not Applicable.

(VII) 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.

(VIII) Buyback by the Company of its own shares

See paragraph 21.1.3.

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 General Meeting of shareholders of the Company.

21.2.5. General meetings of shareholders

Article 24 – Quorum and majority

General meetings decide under the conditions set by law.

The Ordinary General Meeting shall take all decisions other than those reserved to the competence of the Extraordinary General Meeting by law and these articles of association. It shall only decide validly at the first calling if the present or represented shareholders hold at least one fifth of the shares with voting rights. On the second calling, no quorum shall be required. It shall rule with a majority of votes of the present or represented shareholders.

The Extraordinary General Meeting shall be the sole party authorised to amend the articles of association in all of their provisions. It shall only decide validly if the present or represented shareholders hold, at the first calling, at least one quarter and on the second calling, at least one fifth of the shares with voting rights. In the absence of this latter quorum, the second meeting may be postponed to a date at most two (2) months after the one on which it had been called. It shall decide with a majority of two thirds of the votes held by the present or represented shareholders.

If use is made 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 – Calling of general meetings

General Meetings shall be called 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 by 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 notice of calling.

When the shares of the Company are admitted to trading on a regulated market or if none of its shares are in registered form, it shall be obliged, at least thirty five (35) days before any General Meeting to publish a notice in the Bulletin of Mandatory Legal Announcements (BALO) containing the notes required by current legislation.

The convening of General Meetings is realised by its placement 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 notice of calling, at the expense of the Company, made by ordinary or registered letter to each shareholder. This notice of calling may also be forwarded by electronic means of telecommunication implemented under the regulatory conditions.

Any shareholder may also, if the Council so decides at the time of calling 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 notice of calling.

However, one or more shareholders meeting the legal requirements shall be entitled to request, under the conditions provided by law, the inclusion on the agenda of points or draft resolutions. The request for inclusion of 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.

At 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 calling.

When the meeting is called 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 Meetings

Any shareholder may participate in person, by proxy or by correspondence at general 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 understated by a certificate of participation issued by this latter party.

The Board of Directors may nevertheless shorten or remove 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

Starting from the calling of the meeting, 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.

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 general 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 elect its own chairman.

In the event of calling by the statutory auditors, by a legal representative or by the liquidators, the general 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 general meeting.

The bureau of the meeting shall appoint a secretary, who need not be a shareholder.

Article 30 – Minutes of the decisions

The proceedings of shareholders' meetings are recorded in minutes drawn up by the officers and signed by them.

They indicate the date and place of meeting, the form of calling, the agenda, the composition of the bureau, the number of shares participating in the vote and the quorum achieved, the documents and reports submitted to the meeting, a summary of the discussions, the text of the resolutions put to the vote and the results of the votes.

The minutes are entered in a special register kept at the registered office under the regulatory conditions.

If, in the absence of a quorum, a meeting cannot deliberate in regular fashion, 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.

Starting from the notification provided above, any shareholder has the right to submit questions in writing that the Board of Directors shall be obliged to answer during the meeting.

At any time, any shareholder shall have the right to obtain the documents that the Board of Directors is obliged, as appropriate, to 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, is obliged to 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 obliged to make the aforementioned notification 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 of the same 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 Commercial Cod.

21.2.7. Public offers

For as long as the securities issued by the Company are admitted to trading on Alternext, any natural or legal person, acting alone or in concert, pursuant to Article L. 233-10 of the 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 effect.

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 as follows:

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 in the Company) entered into a framework research services agreement, the object of which is to enable the Company to continue its research and development 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 rider 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 agreement entered into effect on 1 August 2015 for a period of one (1) year. The Framework Agreement was extended by an amendment dated 1 August 2016 for a period of twelve (12) months until 31 July 2017.

This 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 with the information exchanged during the execution of the agreement, for the duration of the agreement and for the ten years following its expiry. The remuneration paid to Metabrain Research is determined transaction by transaction and partially invoiced in the order and then progressively, as the service is executed.

Under this Framework Agreement, the Company incurred a charge of €186,040 during the financial year 2016.

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 programme (the "**Application Agreement**").

This Application Agreement entered into effect from 1 August 2015 onwards, for a twelve- (12) month period. The Application Agreement was extended by a rider dated 1 August 2016 for a period of twelve (12) months until 31 July 2017.

22.1.2. Research and collaboration agreements

The Company entered into the consortium and collaboration agreements described in 11.3.1 of this Reference Document.

22.1.3. Operating agreements and joint ownership regulations

The Company entered into the operating agreements and joint-ownership regulations described in 11.3.2 of this Reference Document.

22.1.4. Scientific advisory agreements - Key opinion leaders

On 9 November 2015, the Company and Dr. Saddek Mohand Saïd, in his capacity as consultant, signed 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 has a duration of eight (8) months, i.e. until 30 June 2016. It may be extended by an amendment after the prior written agreement of the parties. The Doctor will receive fixed remuneration paid in four instalments of € 4,000. This contract was tacitly renewed for an indefinite period under the same terms and conditions.

22.1.5. Consultancy agreements - SARA Steering Committee

The Company concluded 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 the evaluation of the SARA clinical trials. Consultants are paid a fixed fee per hour or their compensation is calculated based on the number of meetings they attend. The agreements provide for the transfer of all intellectual property to the Company.

22.1.6. 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 contract is ensure assistance for the Company in 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. Remuneration is calculated on a fixed hourly basis and capped on a daily basis.

22.1.7. It is specified that the said consultancy agreement has been tacitly renewed under the same terms and conditions. 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 the evaluation of clinical trials for all of the Company's products. Consultants are paid a fixed fee per hour or their compensation is calculated based on the number of meetings they attend. The agreements provide for the transfer of all intellectual property to the Company.

22.1.8. Temporary Public Property Occupancy Agreement

The Public Property Occupancy Agreement (see 8.1.1) defines the terms of access 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 pursue its missions of researching and developing drug candidates and nutraceuticals.

22.1.9. 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 as of 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 affairs (vi) management of data, statistics and pharmacokinetics, (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 with the information exchanged during the 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 application agreement.

The remuneration paid to Icon shall be determined on a study by study basis for each application agreement within the Framework Contract.

Icon and the Company entered into an initial application agreement for the Framework Agreement on 23 January 2017, which came into force on 26 July 2016 (the "**Icon Application Agreement**"), and will expire on 18 July 2018.

The clinical trials of the Icon Application 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 remuneration will be invoiced monthly to the Company, from the start of the study.

Under this Icon Application Agreement, the Company incurred a charge of €203,115 during the financial year 2016.

22.1.10. Agreement for the provision of clinical trials - SGS

The Company and SGS Belgium NV, SGS Life Sciences, a Belgian 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**") have, as of 16 June 2016, entered into an agreement for the provision of clinical trial services (the "**SGS Agreement**").

The SGS Agreement took effect on 7 March 2016 and will end 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 with the information exchanged during the execution of the agreement, for the duration of the agreement and for the five (5) years following 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 concluded an amendment to the SGS Agreement on 24 November 2016, pursuant to which the compensation for clinical trials was slightly increased.

By way of this agreement, the Company incurred a charge of €1,373,448 during the financial year 2016.

22.1.11. Agreement for the provision of services related to the SARA Clinical Data Platform

On 16 May 2017, 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 an agreement for the provision services related to the SARA Clinical Data Platform (the "**BlueCompanion Agreement**").

The BlueCompanion Agreement was concluded with effect from 1 June 2016 and will end on 31 December 2017.

Under the BlueCompanion 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 development of Sarconeos.

The SGS Agreement also contains a confidentiality clause with the information exchanged during the execution of the agreement, for the duration of the agreement and for the two (2) years following its expiry.

The BlueCompanion Agreement expressly provides that all intellectual property rights of the developments made by BlueCompanion under the BlueCompanion Agreement will be transferred to Biophytis as and when they arise.

Under this agreement, the Company incurred a charge of €56,000 during the financial year 2016.

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	Amounts Granted	Amounts Received/receivable[97]	Maturity date	Bonds linked to the operation
Bpifrance Financement	**Aid** Reimbursable aid	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** (less the 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	**Aid** Reimbursable aid	In vitro, in vivo and pharmacokinetic categorisation of a candidate drug	04/02/2015 + Amendment of 7 November 2016	**260,000**	**208,000** In progress	**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)**	**Aid** Reimbursable aid	Clinical development of a Quinoa extract acting on Metabolic Syndrome	07/08/2008	**230,000** Revalued at **228,782.82**	**228.782,82** Program closed	**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** (Withheld on disbursement, by way of an advance)/[98] In progress	**30/04/2018**	Yes **Agreement** of the lender in the event of assignment of securities or a change of control

[97] When the payment of subsidies/loans are provided by tranche or schedule of maturities.

Name of the lender	Nature	Object	Date of conclusion	Amounts Granted	Amounts Received/receivable[97]	Maturity date	Bonds linked to the operation
Bpifrance Financement **(formerly Oseo Ile de France)**	**Aid** Reimbursable aid	Clinical development of Bixilia with the aim of obtaining a health claim	30/08/2010	**180,000**	**54,000**/ N/A Program closed	**30/06/2016**	Yes **Agreement** of the lender in the event of assignment of securities or a change of control
Bpifrance Financement	**Loan** CIR prefinancing	Reearch and development costs for the year 2013, eligible for the Research Tax Credit	31/12/2013	**100,000**	**100,000**/ Closed/ Repaid	**30/01/2016**	Yes **Agreement** of the lender in the event of assignment of securities or a change of control
FEDER	**Subsidy**	Maculia project	17/01/2013	**300,000** Revalued at **284.945**	**168,014**/ N/A Programme closed	N/A	Yes **Notification** of modifications in the status of the beneficiary
Bpifrance Financement **(formerly Oseo Innovation)**	**Subsidy** Aid with maturation (AIMA)	Galenic feasibility study for improving bioavailability and stability of compounds for the treatment of AMD	04/11/2014	**25,000**	**22,891**/ Programme closed	N/A	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 concluded 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. The agreement obliges the Company to contract civil liability insurance within the context of its professional activity or failing this, to contract insurance guaranteeing the risks of loss or theft. Moving the equipment outside of the installation premises is subject to the 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.

23. INFORMATION DERIVING FROM THIRD PARTIES, DECLARATIONS BY EXPERTS AND DECLARATIONS OF INTEREST

Not Applicable

24. DOCUMENTS ACCESSIBLE TO THE PUBLIC

Copies of this Reference Document are available free of charge at the registered office of the Company located at 14, avenue de l'Opéra, 75001 Paris.

This Reference Document is also available on the Company's website (www.biophytis.com/) and on the AMF website (www.amf-france.org).

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 Alternext Paris market, 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 Reference Document.

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)

Substances related to a natural active principle and which possesses 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 fibers.

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 characterized by a progressive degeneration of the muscles of the body, which may be of various origins (genetic, aging, 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 (EPR)

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 the 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 2:* or "pilot study" consists of determining the optimal dose of the medicine and any undesirable effects. Eligible population: sufferers (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 fibers (= 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 fibers.

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 fibers.

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 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

The 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 signaling 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.

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 "lifelong" or long-term treatment.

University –University Pierre and Marie Curie (Paris VI) (UPMC)

The University is a Paris-based university, the heir of the former Sorbonne, specializing in sciences and medicine and located principally between the campus of Jussieu (in the Latin Quarter of Paris) for the sciences, and 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, the University confirmed its position as the leading French research university, ranking 6th in Europe and improving slightly at the global level to 35th.

27. APPENDICES

27.1. 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 afont 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/[99] - 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

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	

[99] In the process of referencing

Food composition										
France									In the process of being drafted	

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