BIOPHYTIS

Initiation coverage

A bright future in aging

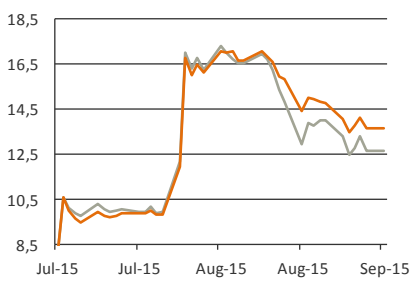
Recommandation	NEUTRAL
Target price	11,9€
Potential	-15%

in € / share	2014	2015e	2016e	2017e
diluted EPS	-0,19	-1,13	-1,13	-0,47
Chg 1 year	*ns*	*ns*	*ns*	*ns*
Revisions	*ns*	*ns*	*ns*	*ns*

ISIN	FR0012816825
Ticker	ALBPS-FR
DJ sector	

Price	€13,9
Nb of shares (m)	6,11
Diluted nb of shares (m)	6,11
Market cap (m€)	85
Float (m€)	31

	1m	3m	1 year
Absolute chg	-6,5%	n.d.	n.d.
Relative chg	-4,3%	n.d.	n.d.



12/31	2014	2015e	2016e	2017e
PE	n.s.	n.s.	n.s.	n.s.
EV/CA	n.s.	n.s.	n.s.	n.s.
EV/EBITDA	n.s.	n.s.	n.s.	n.s.
EV/EBITA	n.s.	n.s.	n.s.	n.s.
FCF yield	n.s.	n.s.	n.s.	n.s.
Yield	n.s.	n.s.	n.s.	n.s.
Net debt/EBITDA	n.s.	n.s.	n.s.	n.s.

In its IPO on Alternext Paris in mid-July 2015, Biophytis issued 1,672,500 new shares at the price of €6 per share, corresponding to an around €10m capital increase. Following this and profiting from the good performance of the share, Biophytis raised additional funds through the issue of 666,700 new shares to a North American investor for a total of €6m. The company has consequently raised €16m, close to the amount that we felt was needed at the time of the IPO. Biophytis therefore has the means to finance its strategy. Our valuation currently equals €11.9 per share, significantly higher than the IPO price due to a WACC of 13.8% vs. 15.3%. We have a NEUTRAL rating while waiting for the authorisation (expected by mid-2016) for the start of the phase II-b studies.

Biophytis' platform is derived from natural molecules to which the organism is already naturally exposed through foods (phytonutrients) and which consequently offer in principle a favourable pharmacological profile. Biophytis targets diseases linked to aging, particularly the degeneration of muscles and the retina. Two products, in dry AMD (age-related macular degeneration) and sarcopenic obesity, should enter into phase IIb clinical trials by mid-2016. These products target the intermediate stages of these diseases for which no treatment currently exists, markets totalling several billion euros. Biophytis' strategy involves the licensing of these products after clinical proof of concept in 2017 and 2018.

The evolution of the world population over the next 20 years will be marked by the continuation of the population aging trend already seen in the past, notably in the core target population for Biophytis (60 years +). This population should grow from 895 million persons in 2015 to 1.542 billion by 2035.

Biophytis' objective is to respond to the needs of patients diagnosed in the intermediate stage, for which there is no treatment. Its business model is based on 2 steps :

1. Bring its 1st generation drugs through clinical proof of concept (Phase IIb), supplemented by the description of the mechanism of action, demonstration of the safety of drug candidates and their characterisation in connection with secondary indications

2. The development in parallel in its two programmes for 2nd generation drugs with improved chemical properties and patent protection, following by the signing of partnerships with drug companies

This strategy has several advantages:

1) Supplying early proof of concept for the 1st generation drug

2) Partially eliminating the risk of each candidate drug, with safety having been established by the fact that: 1) the active ingredient comes from nutrients known by the body; 2) the 2nd generation drug has an identical or analogous structure to the 1st

3) Potential partnership without waiting for the results of the 2nd generation drug

The first drug, in sarcopenic obesity, aims to improve the mobility of older persons. The effectiveness of BIO 101 has been observed in terms of muscle mass and the quantity of proteins, which determines the muscular function and constitutes a major factor in clinical improvement. A phase IIb study of BIO101 involving 180 patients should begin by mid-2016. Results should be announced in 2017, thereby opening the way for the licensing of this product. Our forecasts assume over €600m in revenues.

A second product targets dry AMD (>80% of total), which is a slowly developing pathology and can progress into wet AMD (<20% of the market), which is better known and is already addressed by a few blockbusters such as Lucentis ($4.2bn in sales in 2014). A phase IIb study of BIO201 involving 180 patients should begin in 2016. This study will run 24 months, with an intermediate point in 12 months. This product could generate revenues of €800m.

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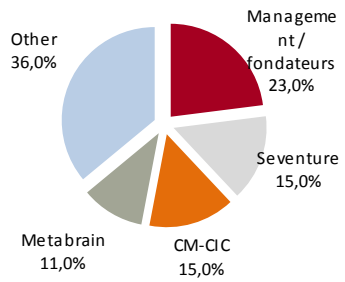
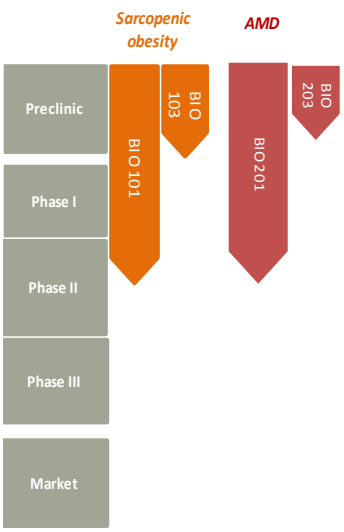
Financial data

Shareholders	
Management/Founders	23%
Seventure	15%
CM-CIC	15%
Metabrain	11%
Float	36%



Pipeline



Next event

Phases IIb in SO + AMD H1 16

Data per share	2012	2013	2014	2015e	2016e	2017e	2018e	2019e	2020e
published EPS	n.s.	-0,14	-0,19	-1,13	-1,13	-0,47	-0,50	-0,50	-0,50
diluted EPS	n.s.	-0,14	-0,19	-1,13	-1,13	-0,47	-0,50	-0,50	-0,50
Var/consensus	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Net asset	n.s.	-0,11	-0,29	1,21	0,08	-0,39	-0,88	-1,38	-1,88
Dividend	n.s.	0,00	0,00	0,00	0,00	0,00	0,00	1,00	2,00

Valuation ratios	2012	2013	2014	2015e	2016e	2017e	2018e	2019e	2020e
P/E	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
VE/Revenue	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
VE/EBITDA	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
VE/EBITA ajusted	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
op. before BFR FCF yield	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
operational FCF yield	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Yield	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

EV (€m)	2012	2013	2014	2015e	2016e	2017e	2018e	2019e	2020e
Share price in €	*n.d.*	*n.d.*	*n.d.*	*13,9*	*13,9*	*13,9*	*13,9*	*13,9*	*13,9*
Capitalization	*n.d.*	*n.d.*	*n.d.*	85	85	85	85	85	85
Net debt	n.d.	n.d.	n.d.	-7,7	-0,8	2,1	5,1	8,1	11,2
Minorities	n.d.	n.d.	n.d.	0,0	0,0	0,0	0,0	1,0	2,0
Provisions	n.d.	n.d.	n.d.	0,0	0,0	0,0	0,0	0,0	0,0
Others	n.d.	n.d.	n.d.	0,0	0,0	0,0	0,0	1,0	2,0
EV	**n.d.**	**n.d.**	**n.d.**	**77**	**84**	**87**	**90**	**95**	**100**

P&L (€m)	2012	2013	2014	2015e	2016e	2017e	2018e	2019e	2020e
Revenue	n.s.	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
chg.	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
EBITDA	n.s.	-0,50	-0,67	-8,00	-8,00	-5,00	-5,00	-5,00	-5,00
EBITA ajusted	**n.s.**	**-0,50**	**-0,67**	**-8,00**	**-8,00**	**-5,00**	**-5,00**	**-5,00**	**-5,00**
chg.	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***	***n.s.***
EBIT	n.s.	-0,50	-0,67	-8,00	-8,00	-5,00	-5,00	-5,00	-5,00
Financial result	n.s.	-0,03	-0,04	0,12	0,12	0,12	-0,04	-0,04	-0,04
Taxes	n.s.	0,00	0,00	1,00	1,00	2,00	2,00	2,00	2,00
Minorities	n.s.	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Net profit	n.s.	-0,52	-0,71	-6,88	-6,88	-2,88	-3,04	-3,04	-3,04
Net profit corrected	**n.s.**	**-0,52**	**-0,71**	**-6,88**	**-6,88**	**-2,88**	**-3,04**	**-3,04**	**-3,04**
chg.	***n.s.***	***ns***	***ns***	***ns***	***ns***	***ns***	***ns***	***ns***	***ns***

Cash flow statement (€m)	2012	2013	2014	2015e	2016e	2017e	2018e	2019e	2020e
EBITDA	n.s.	-0,50	-0,67	-8,00	-8,00	-5,00	-5,00	-5,00	-5,00
Taxes/EBITA	n.s.	0,00	0,00	0,00	0,00	0,00	0,00	1,00	2,00
Capex	n.s.	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
op. before BFR FCF	**n.s.**	**-0,87**	**-0,92**	**-6,88**	**-6,88**	**-2,88**	**-3,04**	**-3,04**	**-3,04**
Change in WCR	**n.s.**	**0,07**	**0,27**	**-0,26**	**0,00**	**0,00**	**0,00**	**0,00**	**0,00**
operational FCF	**n.s.**	**-0,80**	**-0,65**	**-7,14**	**-6,88**	**-2,88**	**-3,04**	**-3,04**	**-3,04**
Acquisitions/cessions	n.s.	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Capital change	n.s.	0,00	0,00	15,36	0,00	0,00	0,00	0,00	0,00
Dividends	n.s.	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Others	n.s.	-0,21	0,36	0,19	0,00	0,00	0,00	0,00	0,00
published FCF	**n.s.**	**-1,01**	**-0,29**	**8,41**	**-6,88**	**-2,88**	**-3,04**	**-3,04**	**-3,04**

Balance sheet (€m)	2012	2013	2014	2015e	2016e	2017e	2018e	2019e	2020e
Current assets	n.d.	0,03	0,02	-0,16	-0,16	-0,16	-0,16	-0,16	-0,16
WCR	n.d.	0,00	-0,40	-0,14	-0,14	-0,14	-0,14	-0,14	-0,14
Total equity	n.d.	-0,41	-1,10	7,39	0,51	-2,37	-5,40	-8,44	-11,47
Minorities	n.d.	0,00	-0,03	0,00	0,00	0,00	0,00	0,00	0,00
Provisions	n.d.	0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
Net debt	**n.d.**	**0,42**	**0,72**	**-7,69**	**-0,82**	**2,06**	**5,10**	**8,13**	**11,17**
incl. cash	***n.d.***	***0,04***	***0,01***	***8,42***	***1,54***	***-1,33***	***-4,37***	***-7,40***	***-10,44***

Financial ratios (%)	2012	2013	2014	2015e	2016e	2017e	2018e	2019e	2020e
EBITDA/Revenue	n.d.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
EBITA/Revenue	n.d.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
NR corrected/Revenue	n.d.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
WCR /Revenue	n.d.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
ROCE excl. Incorp/ GW	n.d.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
ROE corrected	n.d.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Net debt/Total equity	n.d.	n.s.	n.s.	-104%	-160%	-87%	-94%	-96%	-97%
Net debt/EBITDA (en x)	n.d.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

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1 – Focus on age-related disorders

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1 – Focus on age-related disorders

There are several definitions of old age. The WHO uses the criterion of 65 years and older. A social definition uses the age of retirement, which is obviously variable. In the calculation of the rate of equipment and services destined for older persons, the age of 75 years is pertinent. Finally, the average age seen in geriatric institutions is around 85 years old.

The evolution of the world population over the next 20 years should be marked by the continuation of the population aging trend already seen in the past, notably in the age groups that interest us here, i.e. persons over 60 years old who are particularly concerned by the diseases targeted by Biophytis.

For example, the population of France rose from 45.5 million to 63.5 million persons between 1950 and 2012, an increase of nearly 40%. At the same time, the number of senior citizens over 60 years old more than doubled, rising from 6.7 million to 15 million.

The population pyramid in Europe is tending to swell on the high end

In Europe, the population pyramid will tend to swell on the high end to reflect the aging of the population between 2008 and 2060 according to Eurostat forecasts:

Population pyramid, EU-27, 2008 to 2060 (thousands)

(*) 2010, provisional; 2060 data are projections (EUROPOP2010 convergence scenario).

Source: Eurostat (online data codes: demo_pjangroup and proj_10c2150p)

Source: Eurostat

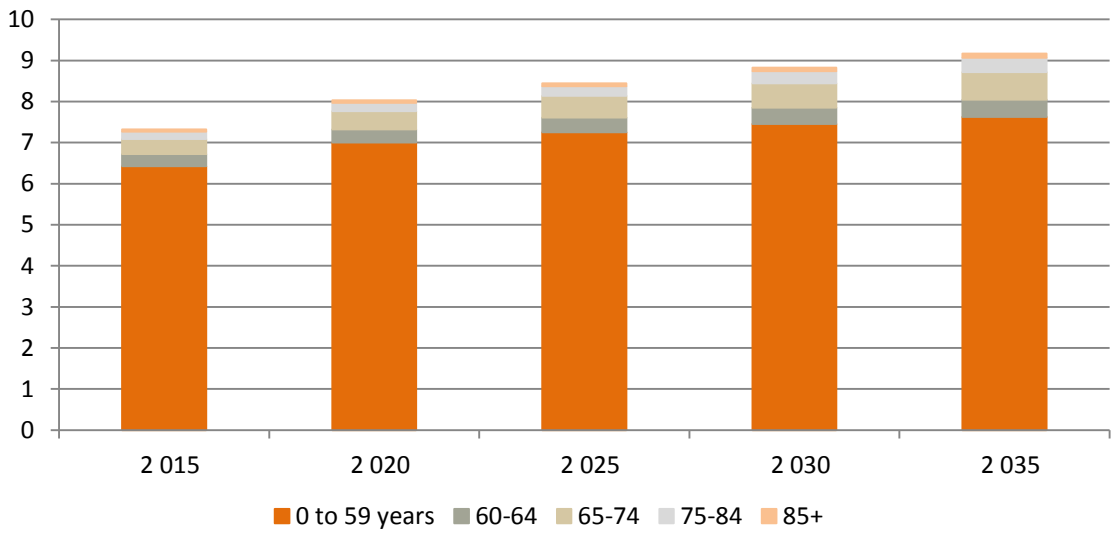
Population aging is expected to gather pace over the next 20 years

1.1 A 70% increase in the population over 60 years old by 2035

The worldwide population of persons over 60 years old already represents 895 million persons in 2015. This population should rise to 1.542 billion persons by 2035, an increase of 72% (compound average growth rate (CAGR) = 2.8%/year on average vs. 0.9% for the overall world population) over the period. Note that the growth in these age groups between 1950 and 2010 equalled 2%/year. Population aging can therefore be expected to accelerate over the next 20 years. The longer-term forecasts are even more striking. The number of person over 60 years old should equal two billion in 2050, corresponding to 21% of the total 9.5 billion world population vs. 12% in 2015.

1 – Focus on age-related disorders

Estimated world population trends from 2015 to 2035 by age groups (billions)



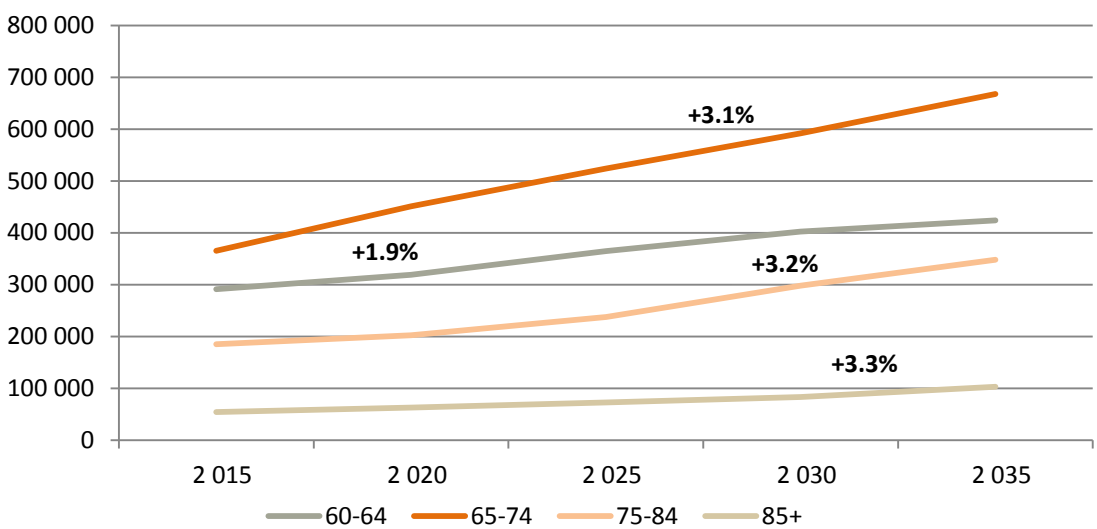
Source: United Nations, Department of Economic and Social Affairs, Population Division (2013)

Population growth will be greatest in the oldest age groups

It should be noted that this growth is more significant in the oldest age groups. The population of persons between 60 and 64 years old should grow by +1.9%/year over the next 20 years. Age groups over 65 years old should show much higher growth rates ranging from +3.1% to +3.3%/year over the same period. In particularly, there will be over 100 million persons worldwide over 85 years old in 2035. The number of persons 100 years old and older worldwide should at least triple over the same period from 500,000 to 1.6 million (+5.9% per year).

This aging can be explained by several factors: demography in the developed nations, better care for senior citizens, medical progress, the increase weighting of highly populated countries (China, India etc.) that should in turn see their population pyramid swell on the upper end etc.

Estimated worldwide senior citizen population trends from 2015 to 2035 by age group (thousands)
Compound average growth rate (CAGR) in %



Source : United Nations, Department of Economic and Social Affairs, Population Division (2013)

1 – Focus on age-related disorders

1.2 Mechanisms of aging

Aging is a complex and multi-factorial phenomenon that notably involves (according to *Corpus de Gériatrie, CHUPS Jussieu*):

- **Genetic factors**: Certain genotypes are found more frequently on average in persons 100 years old or older than in younger persons, thereby indicating that particular genetic predispositions are associated with greater lifespans. In **cells with very lower renewal capacity** that have the age of the person (neurons, muscle cells etc.), aging is notably characterised by the accumulation of pigments called **lipofuscins**, the result of the incomplete digestion of intercellular organelles. In the case of **renewable cells**, which do not have unlimited renewal capacity, the end of chromosomes (telomere) loses a fragment of DNA with each cell division cycle. After several divisions, the function of the telomeres, which contribute to maintaining the stability of the DNA of chromosomes, is altered. This could be the basis of the "biological clock". The modification of the DNA has numerous consequences by modifying the expression of certain genes and the synthesis of the proteins that they direct or by perturbing the cell cycle. Programmed cell death or **apoptosis** is determined by the expression of specific genes,

The end of chromosomes (telomere) loses a fragment of DNA with each cell division cycle

- **Protection against free radicals and oxidative stress:** Free radicals are highly reactive atoms or groups of atoms produced in connection with the metabolism of oxygen that cause significant oxidative stress capable of altering DNA and the fatty acids of the cell membrane. The organism protects itself against these radicals in several manners, such as antioxidant enzymes (superoxide dismutase, peroxidase etc.) or vitamin A, E and C. In the aging process, this equilibrium is altered with both increased production of free radicals within mitochondrions and less effective systems of protection. Another system of protection of the organism, heat shock proteins (HSP), is altered in the process of aging. The HSP represent a family of proteins produced in response to aggression, heat shock, traumatism and glucocorticoids (stress proteins). In the aging process, the secretion of these proteins is reduced and their secondary effects are diminished due to a defect in the transduction of the intra-cellular signal.

In the aging process, the secretion of proteins is reduced and their secondary effects are diminished

- **The non-enzymatic glycation of proteins**: The importance of the glycation of proteins has been highlighted by the effect of drugs that inhibit glycation, leading to a slowdown in the aging of certain functions. Diabetes mellitus is accompanied by exaggerated glycation of proteins linked to increased blood sugar levels. As such, diabetes is viewed in certain ways as a model of accelerated aging and there are numerous analogies between the effects of diabetes and the effects of aging.

1.3 Principal diseases associated with aging

Aging corresponds to the ensemble of physiological and psychological processes that modify the structure and functions of the organism over its lifespan. Starting with maturity, the term used is senescence. Aging results from the intrinsic effects of genetic factors (intrinsic aging) and environmental factors to which the organism is exposed throughout its lifespan. Aging is a slow and gradual process that should be viewed differently than the symptoms of diseases.

1 – Focus on age-related disorders

The so-called degenerative diseases are diseases in which one or several organs are gradually altered. The causes can be the accumulation of biological products or toxins or the prolonged absence of a biological substance necessary for the proper functioning of cells, thereby leading to gradual loss of functions of the organs in question.

Aging consequently leads to a reduction in the functional capacities of the organism and an insensible diminution of the functional reserve of all the organs and regulatory functions. This diminution in functional reserves leads to a reduction in the organism's ability to react to situations of aggression, initially seen in situations of stress (effort, acute illness, grief etc.). Similarly, several systems of regulation of physiological parameters are less effective in older persons. This functional reduction linked to aging varies substantially from one organ to another (inter-organ differential aging). Additionally, for the same age, the alteration of a given function varies substantially between one older person and another (inter-individual differential aging). Consequently, the chronological age (that listed on identity cards) can not be used as an index to compare different older subjects.

Several systems of regulation of physiological parameters are less effective in older persons

Aging is accompanied by numerous modifications in the organism. Three of the best known are:

- **Metabolic aging**

The composition of the body changes with age. At constant weight, there is a reduction in the lean body mass through the diminution of the muscle mass (particularly in sedentary subjects) and a proportional increase in body fat (particularly visceral). The food requirements (qualitative and quantitative) of older persons are essentially identical to those of younger adults with the same level of physical activity. The carbohydrate metabolism is modified as persons age. The tolerance to a glucose load is reduced in older persons not suffering from diabetes mellitus or obesity, indicating a certain degree of resistance to insulin.

- **Nervous system aging**

Numerous neuropathological and neurobiological modifications of the central nervous system have been identified in the aging process. These modifications principally include the diminution in the number of cortical neurons, the rarefaction of the white matter and the diminution of certain intracerebral neurotransmitters. The central motor and sensory functions remain essentially unchanged in the aging process. In contrast, the aging of the central nervous system leads to an increase in reaction times and a moderate reduction in memory performances, notably concerning the acquisition of new information. Aging is accompanied by a reduction and destructuring of sleep. The diminution of the secretion of melatonin by the epiphysis partially reflects a disorganisation of circadian rhythms in older persons. The reduction in the sensitivity of thirst receptors (osmoreceptors) and the modifications in the metabolism of arginine vasopressin (AVP) at least partially reflects the reduction in the sensation of thirst in older persons. All of these modifications act to increase the cerebral vulnerability of older persons to aggressions (notably the confusional syndrome risk).

- **Sensory organs aging**

The retina changes with age, potentially leading to AMD (age related macular degeneration)

Over time, the reduction in the visual accommodation (presbyopia) interferes with near vision. In fact, this process begins in childhood. However, the functional consequences only appear around 50 years old. Gradual clouding of the eye's lens can also take place starting at a later age and affect vision (cataracts). Similar, the retina changes with age, potentially leading to AMD (age related macular degeneration).

1 – Focus on age-related disorders

The aging of the cochleovestibular system is characterised by gradual loss of hearing (principally involving high pitched sounds), leading to a presbyacusis. The data concerning modifications in taste and/or smell in the aging process is more controversial.

- Other consequences of aging

Numerous other consequences involved the cardiovascular system, the respiratory, digestive, musculoskeletal and urinary systems, the sexual organs, the skin, the immune system etc. should be noted.

The most common diseases associated with aging are :

- Alzheimer's and Parkinson's disease
- Osteoporosis
- The diminution in muscle mass and function (sarcopenia)
- Arthritis
- Cataracts, glaucoma, age-related macular degeneration (AMD)
- Coronary disease and heart failure
- Kidney failure etc.

1.4 A gap between preventive solutions and heavy treatments

There are numerous approaches to aging, ranging from prevention to nutritional supplements to heavy and expensive treatments

There are numerous approaches to aging, ranging from prevention (quality of life, nutrition, physical exercise etc.) to nutritional supplements to heavy and expensive treatments (injections of hormones, monoclonal antibodies etc.) that uniquely target the late stages of diseases, sometimes corresponding to only 10-20% of the populations affected (as for example in the case of AMD). The difficulty lies in taking a position at an intermediate stage between:

- the diagnosis of a disease, after which it is no longer a question of prevention, with the disease have evolved for a long time before the first symptoms appear
- the late stage of the disease (most often irreversible), which requires a heavy and multidisciplinary approach

Numerous theories attempt to explain the results obtained in the different models of aging, particularly the **caloric restriction theory**, which has established that caloric restriction lengthens the lifespan and that certain natural substances such as resveratrol extracted from grapes allow this process to be mimicked (Fontana, 2010).

This theory has shown that severe caloric restriction in rats and monkeys reduces the incidence of age-related diseases (cancers, neurodegenerative diseases, muscle wasting linked to age). However, there is no proof that the same effect would be seen in humans. Weight loss caused by the undernutrition of an older person is a worrying factor, as is can rapidly lead to death (for example in Alzheimer's, Parkinson's disease and Charcot's disease). Caloric restriction can prove to be dangerous in older persons.

A CNRS (Centre National de la Recherche Scientifique, France) team has identified a hormone in the *C. elegans* worm produced in response to caloric restriction. This steroid hormone (dafrachronic acid) is required to the prolongation of the lifespan but is also implicated in the decline in fertility linked to the diet. This discovery therefore established a direct link between the increase in the lifespan and the reduction in reproductive capacities when the diet is poor in calories. This team also discovered the receptor through which the dafrachronic acid acts in the cell nucleus.

1 – Focus on age-related disorders

A large number of genes are activated in the presence of this hormone, with a portion leading to a decline in fertility and another portion leading to a slowing in aging. By disassociating these two types of responses, the goal is to artificially trigger the protective effect in terms of age-related diseases without suffering from the associated negative effects. Therapeutic applications could be found over the longer term, as the identified hormone and its receptor have close relatives in mammals and humans. Humans have seen the development of a particular organ (the brain) that consumes 20% of the total daily energy. It is therefore necessary to provide it with sufficient energy over the day to enable it to function. The fact that there are closely related molecules and receptors in C. elegans and humans does not mean that identical effects to those seen in worms would be obtained by directing products at this system in humans, as nature reuses molecular motifs over the course of evolution in order to develop solutions with completely different manifestations despite the fact that the molecular motifs appears to resemble each other.

The **free radicals theory** highlights the role of oxidative stress (particularly photo-oxidative stress) in the cell death process (apoptosis) involving exposed cells (such as certain retina cells) and suggests the use of antioxidants such as Vitamin C and E to treat AMD with a certain degree of effectiveness (AREDS report, 2007).

1.5 Focus on motor and visual functions in diseases without treatments

Two areas are being targeted in particular: mobility disorders and vision disorders

The poly-pathologies seen with aging imply the taking of a substantial number of drugs (6.4 per day on average) by older persons. They are also responsible for their loss of autonomy, which involves cognitive functions (intelligence, behaviour, language), motor functions (notably the lower limbs) et and sensory functions (vision and hearing).

Biophytis has chosen to focus on pathologies specifically related to aging for which there are no treatments at present. Two areas are being targeted in particular:

- mobility disorders
- vision disorders

Central nervous system (CNS) disorders are not being targeted for the moment. Cancer, which is often associated with aging, is also not being targeted by Biophytis.

2 – An original two-stage business model

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2 – An original two-stage business model

Biophytis' objective is to meet the needs of patients already diagnosed in so-called intermediate phases for which there are no treatments. Biophytis' business model involves two phases:

a. bring its programmes through clinical proof of concept (Phase IIb) of the drug family, completed by the description of the mechanism of action, the demonstration of good safety of the drug candidates and their characterisation in secondary indications

b. followed by the signing of partnerships at the end of phase II clinical trials with pharmaceutical companies to accompany regulatory development through commercial launch. Biophytis is targeting an initial licensing agreement in 2017.

Signing of partnerships at the end of phase II clinical trials

2.1 A first generation of drugs based on natural active ingredients

Biophytis has developed a research and development platform of drug candidates based on natural substances derived from medicinal plants and/or foods in order to treat age-related diseases. Secondary plant metabolites are substances whose diversity largely exceeds that generated by synthesis of the most extensive small molecule chemical libraries. Biophytis has assembled a unique collection of natural substances derived from medicinal plants and/or foods (called in this case phytonutrients), issued in particular from the tropical vegetable biodiversity obtained from its subsidiary based in Brazil. Biophytis then developed cell and animal models of age-related diseases, targeting in particular the degenerative processes in muscles or the retina. Biophytis has in this manner identified natural substances that block or slow these processes and has studied the molecular mechanisms involved in the aging of these organs, particularly the molecular targets of these substances.

Biophytis has identified natural substances that block or slow aging processes

The current list of nutrients contains numerous elements:

- Essential fatty acids: linoleic acid (omega-6 fatty acid with the shortest carbon atoms chain), α-linoleic acid (omega-3 fatty acid with the shortest carbon atoms chain)
- Essential amino acids (included in proteins): isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine etc.
- Vitamins: A, B1, B2, C, D, E, K etc.
- Dietary minerals: sodium (Na), potassium (K), magnesium (Mg), calcium (Ca), chrome (Cr), molybdenum (Mo), manganese (Mn), iron (Fe), cobalt (Co), copper (Cu), zinc (Zn), phosphorus (P), sulphur (S), selenium (Se) etc.
- Oligo-elements: vanadium (V), nickel (Ni), boron (B), silicon (Si).

Several essential and indispensable nutrients such as vitamin C are sometimes classified as phytonutrients, as they are present in plants. The biological function of the majority of phytonutrients in humans remains unknown. **It is by understanding the relationship between these phytonutrients and the mechanisms of degeneration that Biophytis identifies families of substances present in very low doses in our food environment** that are able to act directly on the disease mechanism and potential enable it to be slowed effectively and durably. Additionally, given the stage of these diseases when they are diagnosed and based on current knowledge, it is relatively unlikely that they can be cured. This implies that patients will have to undergo continuous treatment over several years in order to block or slow the progress of the disease.

2 – An original two-stage business model

This raises the problem of the acceptability of the treatment in terms of its manner of administration and potential side effects on the organism. This is the objective of the phase I (tolerance) and phases II and III (effectiveness) clinical trials. Biophytis is conducting these trials on its own for the "01" drug through the phase II clinical trial.

By focusing on **candidate families issued from substances to which the organism is already naturally exposed through foods (phytonutrients), Biophytis has identified drugs that in principle offer a favourable pharmacological profile.**

2.2 Chemical synthesis generating a second generation of patented drugs

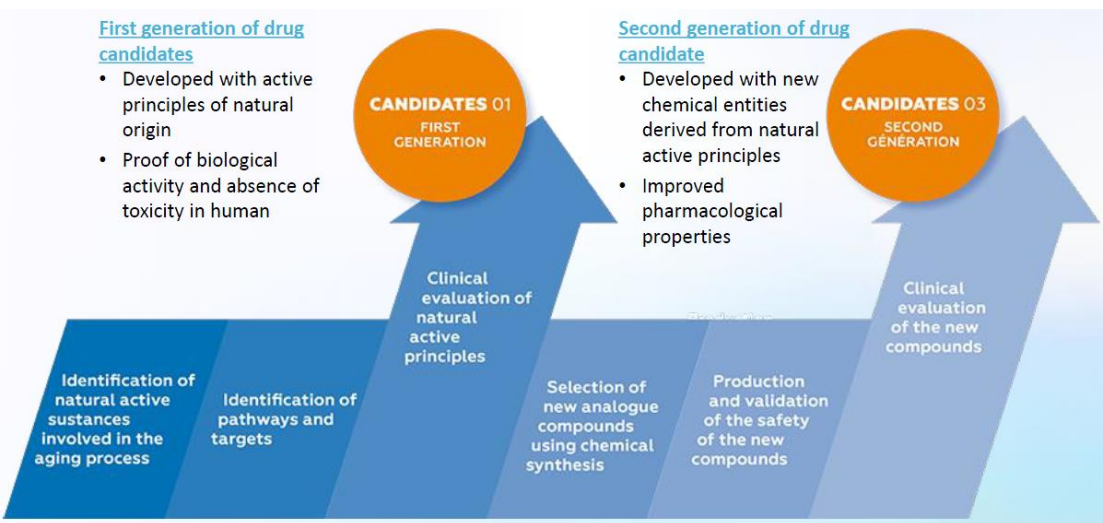
Biophytis selects 1st generation drug candidates and then 2nd generation drugs …

Starting with the selected phytonutrients, Biophytis is developing two categories of drug candidates for each disease :

1. **First generation candidates (Series BIO 01)** based on the development of the natural substance extracted from the food or medicinal plant serving as the pharmaceutical **active ingredient**. The first generation of drug candidates is issued from a phenotypic screening process in connection with the cell and animal models of the disease, without a priori knowledge of the molecular targets. Their nutritional origin enables **the acceleration of the clinical development of the drug candidates due to humans' exposure to these substances through foods and their very low toxicity. The identification of these substances' effects on the aging process will allow the patenting of their use** in the treatment of the targeted diseases.

…based on the development of a proprietary analogue

2. **Second generation candidates (Series BIO 03)** based on the development of a proprietary drug analogous to the substance. The second generation of drug candidates is being developed on the basis of a precise understanding of the **mechanisms of action** of the first generation products, particularly the molecular targets of the drug candidates. **Drugs analogous to the natural substances are synthesised through medicinal chemistry** and selected in the pre-calibrated cell models. The synthesis of original drugs allows improvements in certain pharmacological properties (particularly the **bioavailability** of drugs) and the **patenting of chemical formulas** of the drug candidates under development. Their clinical development will require prior validation in regulatory pre-clinical and clinical (phase 1) studies to evaluate their possible toxicity in humans.



Source: Biophytis

2 – An original two-stage business model

Clinical proof of concept for the first generation drug candidates

This strategy has several advantages:

- It enables earlier **clinical proof of concept for the first generation drug candidates**
- It enables the **de-risking of the profile of each drug candidate**:
    a. the tolerance is established, with the active ingredient coming from **nutrients known by the organism**
    b. the final drug (second generation) has an identical or nearly identical (analogue) structure as the initial drug
- It enables the company **to seek out a partner without waiting for the final results for the second generation drug**, potentially enabling it to gain two years.

A relatively de-risked approach

Biophytis has as such developed BIO103, a drug candidate in pre-clinical development for the treatment of sarcopenic obesity, and has started the optimisation phase for BIO203, a drug candidate for the treatment of AMD.

2.3 Package sale at the end of phase II

When the effectiveness results for the BIO 01 drugs (phase II-b) are obtained, Biophytis will be able to deliver a phase III package to a potential partner containing:

- The initial drug with clinical proof of effectiveness
- A description of the mechanism of action
- An already formulated chemical synthesis
- A second generation product with improved pharmacological properties compared to the first generation

2.4 Two drugs in clinical trials in sarcopenic obesity and AMD

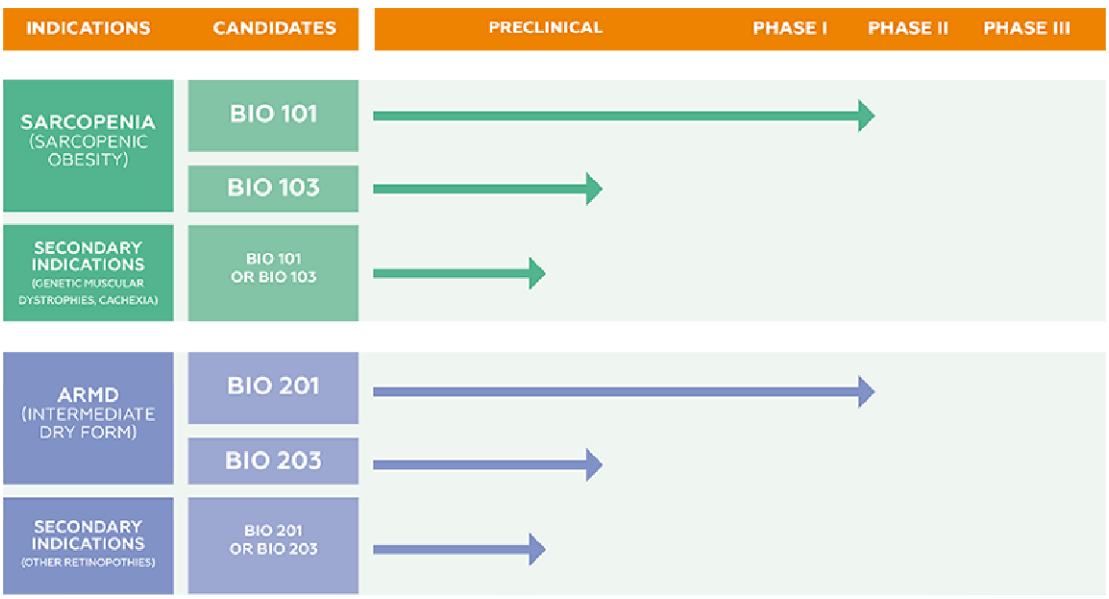
Two drugs have been selected and will enter into phase IIb clinical trials in 2015

Two drugs have been selected and have entered into clinical trials:

1. BIO101, a drug candidate in phase II clinical development for the treatment of sarcopenic obesity, to be followed by BIO 103 by 2017e
2. BIO201, a drug candidate in clinical development for the treatment of so-called “dry” AMD (age related macular degeneration). This drug entered into phase II trials in 2015 and will be followed by BIO 203 two years later.

2 – An original two-stage business model

Biophytis Pipeline



Source: Biophytis

The first generation drug candidates BIO101 and BIO201 are slated to enter into phase IIb clinical development in 2015

The first generation drug candidates BIO101 and BIO201 are slated to enter into phase II clinical development in 2015. The clinical protocols are in the process of being drawn up, Biophytis is negotiating contracts with the clinical centres and the production of clinical batches is ready to be launched. The second generation drug candidate BIO103 will be ready to enter into the regulatory pre-clinical phase end 2015/early 2016. BIO203, which is in the optimisation and galenical development phase, could enter into the regulatory pre-clinical phase a few months later.

Note that each of these drugs could be associated with secondary indications that we have not taken into account in this report and in our valuation:

- Muscular dystrophy, cachexia for BIO 101
- Diabetic retinopathy and other retinopathies for BIO 201

3 – The BIO101/BIO103 pair: sarcopenic obesity

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3 – The BIO101/BIO103 pair: sarcopenic obesity

3.1 An increasingly widespread pathology

Muscular degeneration or sarcopenia is a process that accelerates with age, It is defined in Europe as the **diminution of the muscular mass and function associated with a decline in physical performances:**

- the muscle mass declines by approximately 1-2% per year after the age of 50
- the function declines by 1.5% per year between 50 and 60 years old and then by 3% per year after 60

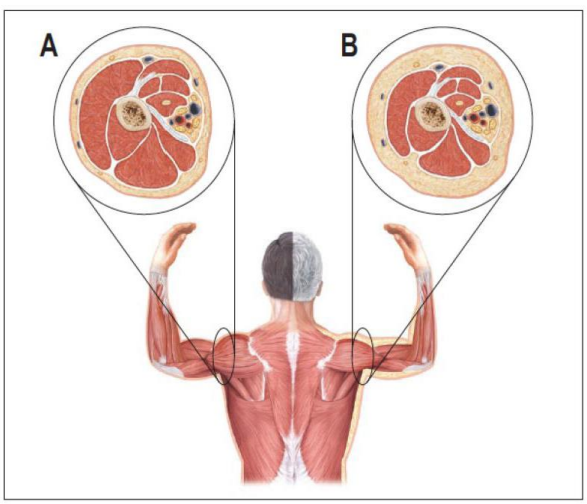
Aging is accompanied by a modification in the body's composition …

Aging is accompanied by a modification in the body's composition, with an increase in the fat mass and a reduction in the lean mass (bone mass, organs, and muscular tissue). This takes the farm of a loss of muscle mass and function that underlies a general deterioration in the physical condition. The atrophy of muscle fibres, i.e. the diminution of their diameter, and the reduction in their number are responsible for this diminution in muscle mass.

… with an increase in the fat mass and a reduction in the lean mass

As shown in the following image, the changes in the composition of the body in case of sarcopenia (B) compared to a young adult (A) correspond to a **loss of muscle mass and an increase in fatty tissue** around and between the muscles, the consequence (among others) of physical inactivity and an inadequate diet. These changes are further amplified in obese persons (Benton et al., 2011),

The increased prevalence of obesity in older persons has led to the definition of the concept of sarcopenic obesity



Source : American Journal of Nursing, December 2011

3 – The BIO101/BIO103 pair: sarcopenic obesity

The increased prevalence of obesity in older persons has led to the definition of the concept of sarcopenic obesity focusing on the risk of accumulating metabolic muscular changes associated with aging and obesity. The lack of a consensual definition of sarcopenic obesity has led to a broad variation in the prevalence of this pathology. The study of metabolic anomalies associated with sarcopenic obesity appears important, as these subjects show an increase risk of developing a functional handicap. In effect, obesity aggravates sarcopenia and the degradation of functional capacities.

Sarcopenic obesity is defined using several measurable parameters

Body mass index classifications

Classification	BMI (kg/m²)	Obesity Class
Underweight	<18.5	
Normal	18.5-24.9	
Overweight	25-29.9	I
Obesity	30-39.9	II
Extrem Obesity	>40	III

BMI= Body Mass Index

Source : National Heart, Lung, and Blood Institute

The obesity / sarcopenia association varies depending on the definitions, the following table defines sarcopenic obesity based on several measurable parameters such as weight, fatty mass, the skeletal muscle mass index, the body mass index and the waist circumference :

Body Composition phenotype characteristics

	Sarcopenic	Obese	Sarcopenic Obese
Weight	Low	High	Normal
Fat Mass	Low/normal	High	High
SMM	Low	Normal/high	Low
BMI (kg/m²)	Low	High	Normal
Waist Circumference	Low/normal	High	Normal/high

BMI, body mass index - SMM, skeletal muscle mass

Source : Waters et Baumgartner, Clin Geriatr Med 27 (2011) 401–421

In 2000, 31% of American adults were considered to be obese versus 23% in 1990

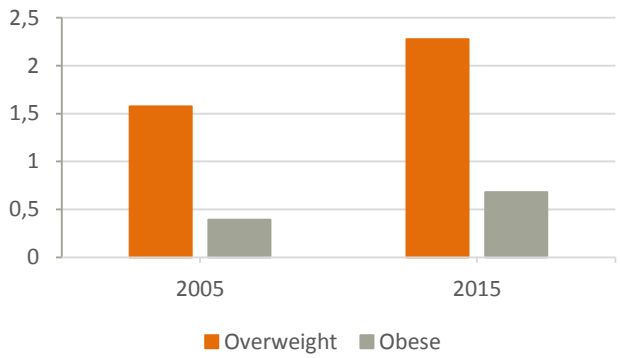
In 2000, 31% of American adults were considered to be obese (BMI body mass index > 30) versus 23% in 1990. This percentage reached 34% in the United States in 2012 and 15% in France.

3 – The BIO101/BIO103 pair: sarcopenic obesity

According to the WHO (see chart below), the worldwide population of overweight persons should rise from 1.6 to 2.3 billion persons between 2005 and 2015 (+4% per year). The population of obese persons should grow even faster (400 million persons in 2005, 700 million in 2015, corresponding to +6% per year) :

The population of overweight persons should rise from 1.6 to 2.3 billion persons

Worldwide obesity trends, 2005/2015



Source: World Health Organization (WHO)

3.2 A market totalling several tens of billions of euros in the developed nations

According to sources, sarcopenic obese (SO) persons represent between 5% to 15% of older persons, corresponding to around 70 million persons in 2015. Taking only the population of the most developed nations, we estimate that 42 million persons suffer from this pathology in 2015, corresponding to a market totalling several billion euros.

The following chart illustrates in an approximate manner the complex crossing of these two populations:

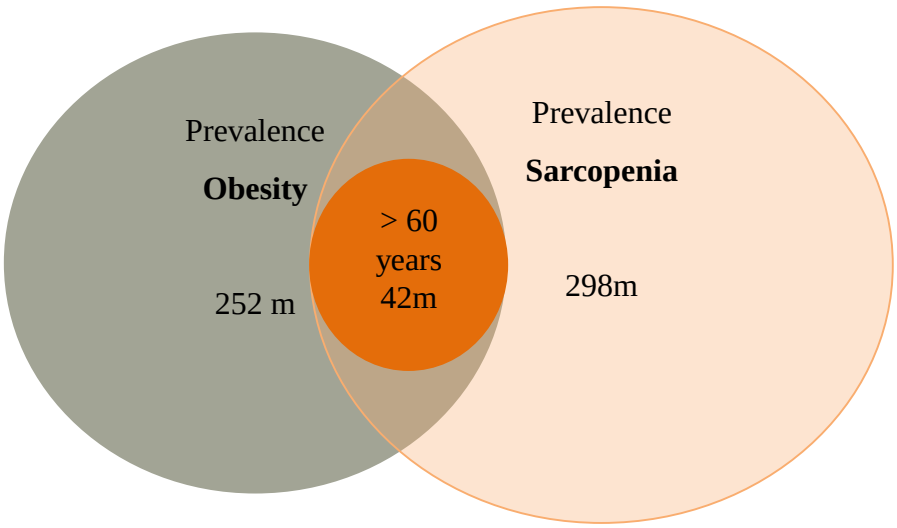
- On the left hand side of the chart, obesity affects on average 20% of the total population (all ages) of the most developed nations, corresponding to an estimate of around 252 million persons in 2015,
- On the right hand side, the population of persons over 60 years old in the most developed nations equals an estimated 298 million persons in 2015. Sarcopenic obesity is affecting a growing percentage of these populations of older persons aged over 60, with prevalence ranging from 5% for those 60-65 years old to 40% for 80 years on over, corresponding to a total of 42 million persons. That said and as seen above, the percentage of older persons is increasing there growth rates are rising more rapidly (+3.3%/year forecast through 2035 for persons >80 year old) than for persons 60-65 years old (+1.9%/year).

Sarcopenic obese (SO) persons represent between 5% and 15% of older persons

3 – The BIO101/BIO103 pair: sarcopenic obesity

Worldwide (see chart below), the WHO estimates that the population of overweight persons should rise from 1.6 to 2.3 billion between 2005 and 2015 (+4% per year), The population of obese person should grow more rapidly (400 million persons in 2005, 700 million in 2015, corresponding to +6% per year).

Association of the population of obese persons and older persons with sarcopenia (m = million persons, developed nations)



Source: Invest Securities estimates

Sarcopenic obesity is a pathology affecting a growing number of overweight or obese persons (10% of those over 60 years old). These persons present **increased wasting of skeletal muscles masked by the accumulation of fatty masses in these muscles.**

The loss of muscle mass and/or function leads to a gradual loss of mobility and autonomy

The skeletal muscles contain several types of fibres. Type II fibres are powerful but tire rapidly, while type 1 fibres are less powerful but allow prolonged efforts. **The atrophy of muscle fibres, i.e. the diminution in their diameters, is responsible for the diminution in muscle masse** with age. This atrophy does not affect all types of muscle fibres in similar manners. Type II fibres are more affected with age. This atrophy is linked at the same time with a change in the capacity of muscle tissue to synthesise muscle proteins and was as to aggravated degeneration processes.

The loss of muscle mass and/or function increases the risk of falls and fractures and leads to a **gradual loss of mobility and autonomy**. The loss of the metabolic quality of the skeletal muscles, particularly their capacity to oxidise carbohydrates and lipids and to synthesise proteins, **considerable increases the risk of diabetes and cardiovascular diseases in patients who are often treated** for one or the other of the following pathologies: arterial hypertension, diabetes, heart failure.

3 – The BIO101/BIO103 pair: sarcopenic obesity

The most exhaustive prevalence study (n=4,652 patients 60 years old and older, median age of 71 years) based on the National Health and Nutrition Survey III (1988-1994) data estimated that the proportion of **sarcopenic obese subjects equalled 29% of the total population aged over 60 years old**. Extrapolating this figure, we can estimate that the number of persons concerned in the United States alone equals 19 million,

Estimated prevalence of sarcopenia, obesity and sarcopenic obesity in the United States (NHNS III)

Population > 60 years (n = 4652, including 57% women)	Women	Men	TOTAL
Sarcopenic prevalence (%)	35.4%	75.5%	53.0%
Obese prevalence (%)	60.8%	54.4%	58.0%
Sarcopenic obesity prevalence (%) people over 60	18.1%	42.9%	29.0%

Source: Invest Securities based on European Journal of Clinical Nutrition 68, 1001-1007, September 2014

A cost of $18.5bn for the US health system, corresponding to nearly $1,000 per patient per year

Given the magnitude of obesity in the United, these figures currently can not be extrapolated to all the most developed nations and even less to the overall world population.

The only available economic impact study indicates a cost of $18.5bn for the US health system, corresponding to nearly $1,000 per person per year.

3.3 No effective treatment available

Sarcopenia can be combatted by:

- **Physical activity** through a daily programme of 30 minutes of physical exercise, preferentially resistance exercises that reinforce the muscle function and mobility. Physical exercise over a period of eight weeks can by itself lead to a 180% improvement in muscle function and an 11% improvement in muscle mass (Fiatarone et al., 1994).
- An **appropriate diet** is necessary to supply adequate amounts of protein synthesis substrates. In effect, the digestive tract in older persons tends to sequester the amino acids for its own account. The quantity of ingested proteins should therefore be increased to insure that the post-meal concentration of amino acids becomes sufficient to stimulate muscular protein synthesis (Symons et al., 2007). Nevertheless, no vegetable nutrition products (proteins, amino acids, vitamin D etc.) have had their health claims validated by the EFSA (European Food Safety Agency) ;

A medical approach is necessary

- **The medical approach** includes numerous products belonging to different drug classes that have been tested in clinical studies target sarcopenic subjects. These products include:
    - Protein synthesis substrate drugs: amino acids or their metabolites
    - Anabolic hormones or their variants, the SARM (Selective Androgen Receptor Modulators), with studies conduction by major pharmaceutical companies such as MSD, Pfizer, AstraZeneca and Takeda. The majority of these studies were halted due to side effects and cancer risks.

3 – The BIO101/BIO103 pair: sarcopenic obesity

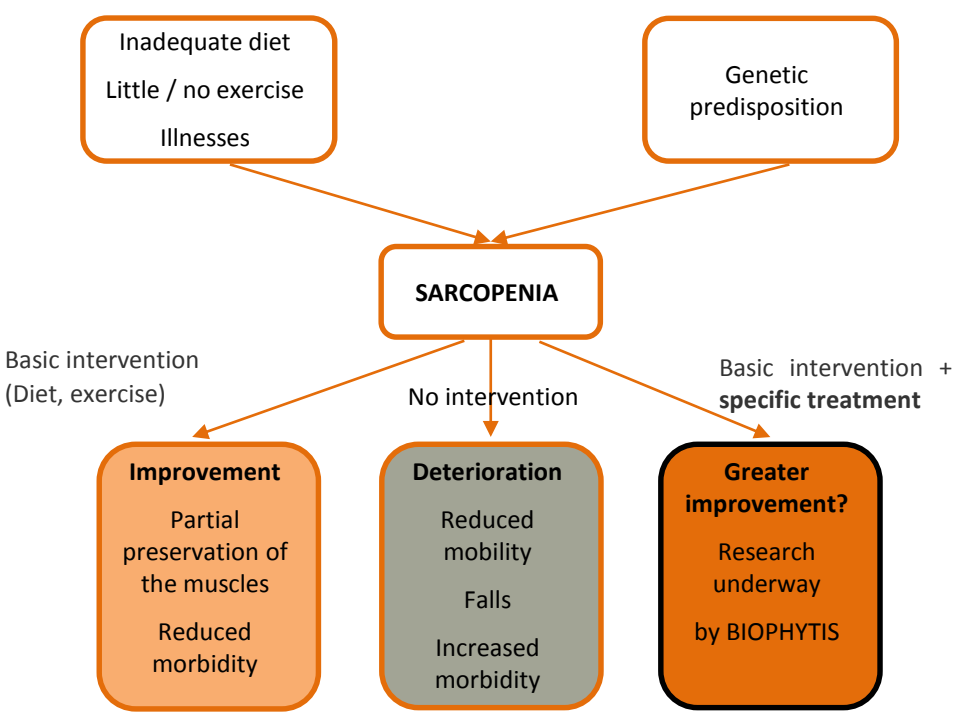
Antibodies that aim to increase the size and function of muscle fibres by blocking the pathway of myostatin

- Myostatin inhibitors (antibodies, soluble receptors): Pfizer, GSK, Sanofi, Novartis, Eli Lilly etc. have development projects for drug candidates in phase I or II based on the use of therapeutic antibodies that inhibit myostatin for the treatment of severe forms of sarcopenia. These groups are additionally conducting related studies in genetic muscular dystrophies such as Duchenne muscular dystrophy and cachexia. One of the most advanced drugs is BYM338 (bimagrumab, Novartis), which was awarded breakthrough therapy status by the FDA in 2013 in sporadic inclusion body myositis (sIBM) and is also in phase II trials in other indications, including sarcopenia. BYM338 is an antibody that aims to increase the size and function of muscle fibres by blocking the pathway of myostatin, a natural inhibitor of muscle growth.

- Drugs targeting the renin angiotensin system such as ACE inhibitors (with as primary indication arterial hypertension and heart failure) and the angiotensin II and angiotensin 1-7 antagonists (or its agonists)

- Beta blockers (adrenergic receptor inhibitors)

In cases of average severity (the target of Biophytis), a combination of physical exercise, appropriate diet and medication is probably the best approach. The difficulty consists of demonstrating clinical proof of concept by determining the portion of the improvement attributable to the drug compared to that of physical exercise and/or diet. **This is what Biophytis plans to show in its current clinical development phase (phase II, to be discussed below).**



Source: Biophytis

3 – The BIO101/BIO103 pair: sarcopenic obesity

3.4 Bio 101/103 activates the renin-angiotensin system Mas receptor

The observation in interventional studies of the physical capacity of older patients treated with certain ACE (angiotensin conversion enzyme, an element in the renin-angiotensin system (RAS) cascade regulating arterial pressure) inhibitors has shown that this treatment can improve the mobility of older patients.

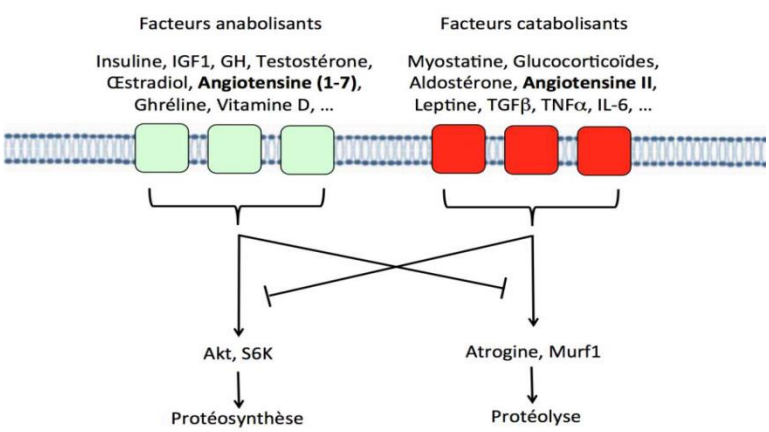
Biophytis has focused its efforts on **the activation of one of this system's receptors, the Mas receptor**. The regeneration of the muscle depends on its ability synthesis the proteins (actin and myosin) that make up the fibres and to produce new muscle cells (myoblasts) that combine with the existing myotubes. The ability of satellite cells to assure the renewal of muscle fibres declines in older persons. The variations in the size of muscles therefore depends on the variations in the size and number of myotubes. The muscle mass is subject to precise multifactorial control with:

- **stimulating** factors, such as testosterone, IGF-1 and Vitamin D, and
- **inhibitor** factors, such as myostatin, produced by the muscles themselves

With age, several hormonal changes take place that disrupt this equilibrium and lead to an imbalance between the two types of factors in favour of those that promote muscular degeneration.

Muscle loss results from a decline in protein synthesis and an increase in proteolysis

In sarcopenia, muscle loss results from a decline in protein synthesis linked a reduction in anabolic factors and an increase in proteolysis, the consequence of an increase in catabolic factors (principally myostatin) or even cell death (apoptosis).



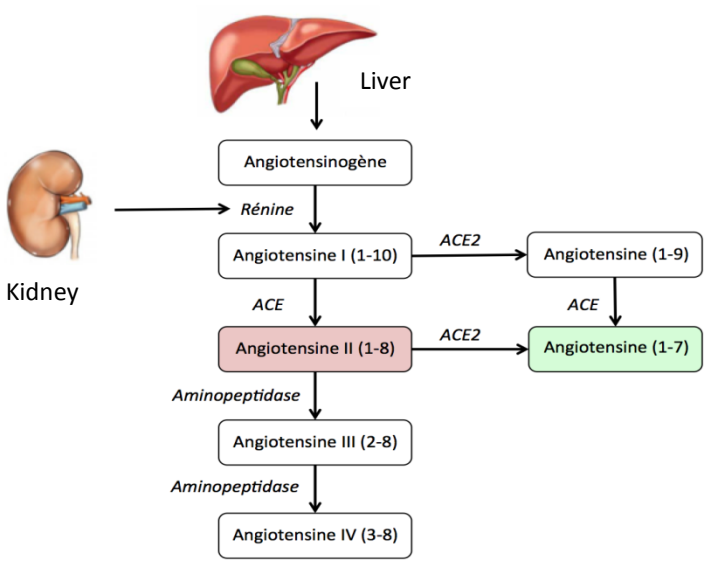
Source: Biophytis

There is also a neuro-degenerative aspect of sarcopenia linked to the reduction in the number of motor neurons and muscle motor plates, which are essential for muscular activity (Lynch and Ryall, 2008). Aggravating factors such as malnutrition, kidney failure and diabetes can influence the severity and early onset of sarcopenia.

3 – The BIO101/BIO103 pair: sarcopenic obesity

Angiotensin II is a peptide with very powerful vasoconstrictive properties

The renin-angiotensin-aldosterone system acts to maintain an equilibrium between the Na+ (sodium) ions and water, referred to as sodium / fluid homeostasis. To achieve this, the renin, an enzyme secreted by the kidney, cleaves the angiotensinogen produced by the liver in order to form angiotensin I. This is then sera cleaved by a conversion enzyme (ACE) into angiotensin II, a peptide with very powerful vasoconstrictive properties. Excess angiotensin II is therefore an important cause of hypertension and ACE inhibitors are traditionally used to treat arterial hypertension. This system can generate a large number of biologically active peptides,



Source : Biophytis

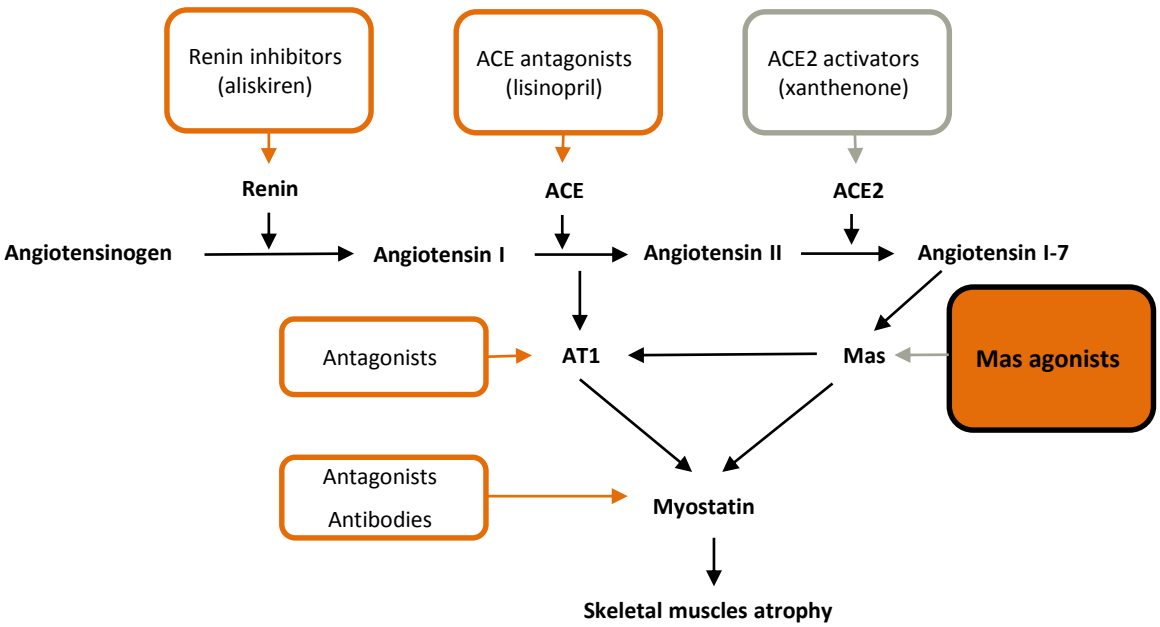
The skeletal muscle cells are targeted by angiotensin II through the AT1R receptor. As such, it appears that **angiotensin II is in principle a major factor in the appearance of sarcopenia** (Yoshida et al. 2013):

Angiotensin II is in principle a major factor in the appearance of sarcopenia

- directly through its AT1 receptor, which provokes resistance to insulin and IGF-1, and
- Indirectly through the increased production of myostatin, glucocorticoids, TNF-alpha and IL-6 (Yoshida et al., 2013). These effects can also include a reduction in the autocrine production of IGF-1.

Other elements of the RAS system appear to be able to act on the muscle function. Angiotensin 1-7, formed by an enzyme called ACE2, and its receptor (Mas) have been discovered recently. Angiotensin 1-7, the endogenous ligand of the Mas receptor, blocks numerous actions of angiotensin II and is implicated in cardiovascular, renal and metabolic regulation. **Developing agonists of the Mas receptor in order to treat sarcopenic obesity is an original idea.** No product of this type is mentioned in the scientific literature in terms of treatment for this indication.

3 – The BIO101/BIO103 pair: sarcopenic obesity



Source : Biophytis

The stimulation of Mas could be more effective in promoting muscular anabolism than the inhibition of the ACE and would in particular have more important metabolic effects on fatty tissue than the inhibition of the ACE.

Biophytis has chosen a family of plant-based molecules from which is has developed the two drug candidates, BIO 101 and BIO 103

Biophytis has chosen a family of plant-based molecules (400), analogues of insect hormones, that in particular posses anabolic and anti-diabetic properties. However, it has still not been established that these molecules constitute the active ingredients of the extracts used. These molecules different substantially from hormones in mammals and human and as such do not interfere with their hormonal systems. They additionally show very low toxicity (oral LD50 > 9 g/kg).

The two drug candidates BIO 101 and BIO 103 were developed from this molecule. BIO 101 is derived from the natural molecule while BIO 103 is derived from the hemisynthesis associated with a screening of over a 100 derivative molecules, with the objective of selecting a molecule with improved activity and bioavailability.

BIO 101 was chosen for the following properties:

- it stimulates protein synthesis (hepatocytes, myocytes)
- it has hypoglycemic effects
- it has cholesterol lowering effects

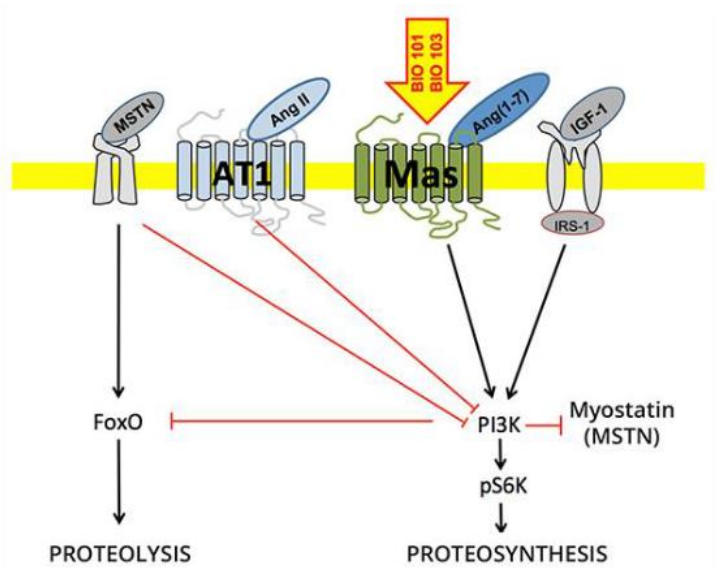
Mechanism of action: the involvement of Mas

Biophytis has identified the principal mechanism of action of BIO 101 that is responsible for the muscular anabolic effect and involves the Mas receptor.

3 – The BIO101/BIO103 pair: sarcopenic obesity

With different pharmacological factors arguing in favour of a membrane effect via a G protein (Gorelick-Feldman et al., 2010), Biophytis initially prepared conjugates between BIO 101 and serum albumin and observed that the compound attached by the 22-OH remained active at the same time is was unable to enter the cells, This confirmed **a membrane action**.

The mechanism of action by which BIO101 and BIO103 stimulate anabolism in the muscle is schematised below:



Source: Biophytis

3.5 Results of cell tests and pre-clinical trials

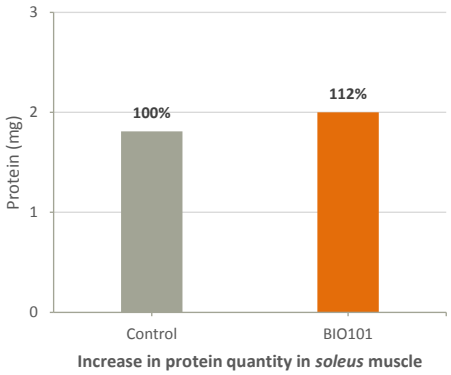
The muscles were heavier and contained more proteins

The tested drugs limited the appearance of obesity

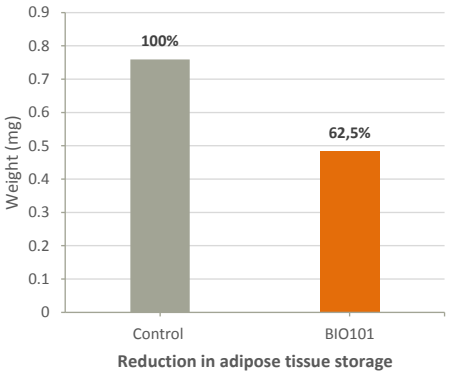
Biophytis has conducted several studies:

1. cell tests that have verified that BIO101 inhibited the expression of myostatin in a dose-dependent manner
2. tests on sarcopenic obesity animal models that demonstrated, following five studies conducted from 2007 to 2013 on 46 mice and rats fed with a high cholesterol diet and administered BIO101 orally, that:
    a. the muscles were heavier and contained more proteins
    b. the tested drugs limited the appearance of obesity
    c. the expression of myostatin was reduction while the expression of myogenesis markers was increased

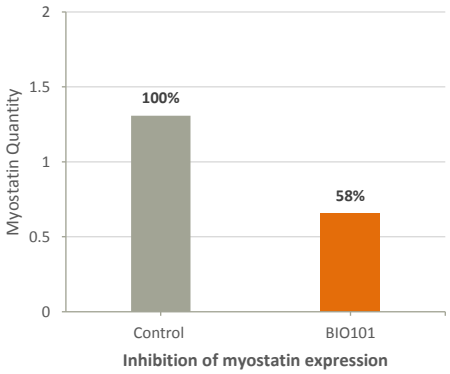
3 – The BIO101/BIO103 pair: sarcopenic obesity



Increase in protein quantity in *soleus* muscle



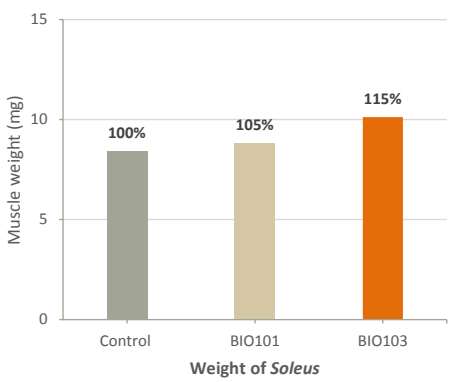
Reduction in adipose tissue storage



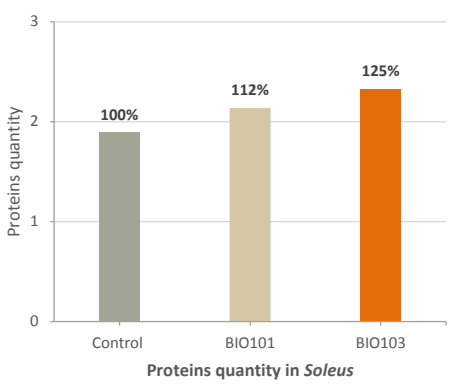
Inhibition of myostatin expression

Source : Biophytis

These trials were the subject of five publication from 2012 to 2015. Note (see chart below) a comparative analysis of BIO103's effect on the soleus versus placebo:



Weight of *Soleus*



Proteins quantity in *Soleus*

Source : Biophytis

Even when BIO 101 offers only a modest improvement, BIO 103 shows significantly greater additional effectiveness

The above chart demonstrates both:

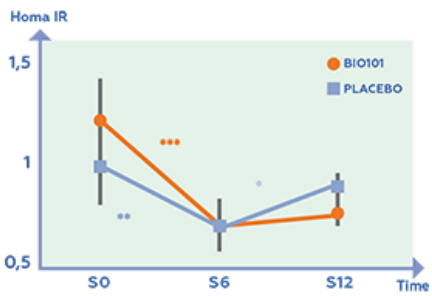
- the effectiveness of BIO 101, observed at this stage on two levels:
  - in terms of the muscle weight
  - in terms of the quantity of proteins in the soleus (calf muscle), a measure of the muscle function, a major factor in the clinical improvement
- the strategy of Biophytis given that even when BIO 101 offers only a modest improvement vs, the control group (+12% in terms of the quantity of proteins, +5% in the soleus), BIO 103 shows significantly greater additional effectiveness (+25% and +15% respectively).

3 – The BIO101/BIO103 pair: sarcopenic obesity

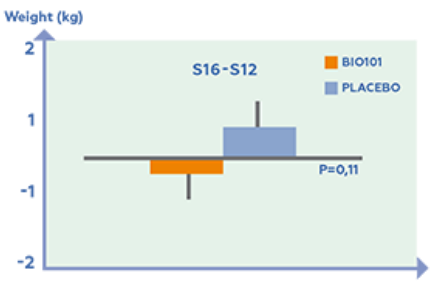
3.6 Phase I clinical results for BIO101

Biophytis has since conducted phase I/II clinical trials on 60 non-obese volunteers since 2013. The effects of BIO101 were evaluated in a clinical study conducted at the Pitié Salpêtrière Hospital (Prof. Karine Clément) involving these non-obese volunteers after chronic oral administration during three months (six weeks of a low-calorie diet followed by six weeks of a normal calorie diet). The results confirmed :

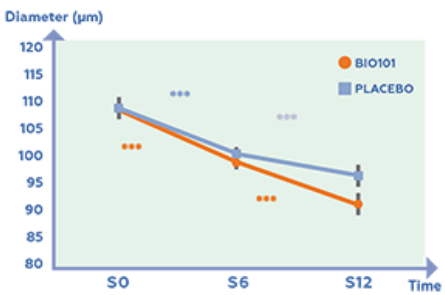
- **the absence of toxicity** (no serious undesirable effects seen) as the studied dos (40 mg/day)
- an **increase in the sensitivity to insulin** (see chart below)
- a **significant reduction in the abdominal fat mass** (see chart below).



Improvement of sensitivity to insulin



Limitation of fat mass increase



Reduction in adipocytes size

One star signifies p<0.05 ; two stars** p<0.01 ; three stars*** p<0.001*

Source: Biophytis

If these figures are confirmed in phase IIb, this should allow an improvement in the physical mobility of patients and reduce the cardiometabolic risk.

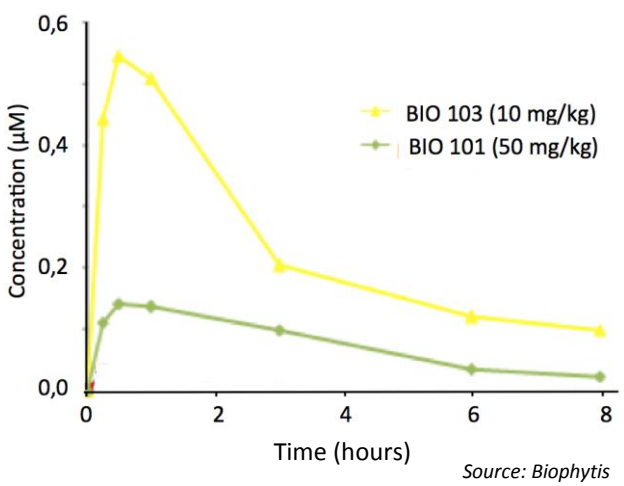
The development of BIO103 consisted of synthesising over 150 new chemical molecules derived by hemisynthesis of BIO101 in over five chemical series

The development of BIO103 consisted of synthesising over 150 new chemical molecules derived by hemisynthesis of BIO101 in over five chemical series. These molecules were evaluated in several in vitro (particularly in the C2C12 muscle cells) and in vivo (particularly in the obese mice model) tests.

BIO103 was selected at the completion of this process and demonstrated an **improved pharmacological profile compared to BIO101**, **with bioavailability 20x greater than BIO101** and improved in vivo activity in the animal model at a lower dose.

Improved bioavailability of BIO103 vs. BIO101

Increase in the bioavailability of BIO103 vs. BIO101 (oral administration)



Source: Biophytis

3 – The BIO101/BIO103 pair: sarcopenic obesity

3.7 Planned phase II development of BIO101 in 2015 and BIO103 in 2017

The next development stage will consist of:

- Determining the effective therapeutic dose of BIO101 in a phase IIb clinical study:
  - involving **180 obese patients with intermediate sarcopenia**
  - multicentre double blind trial versus placebo
  - 100 mg vs. 350 mg vs. placebo
  - duration of six months
  - endpoints:
    - **Primary: six minute walk**
    - Secondary: wrist strength, walking speed, lean body mass and fat body mass
- Evaluating the safety of BIO103 in animals by establishing a regulatory pre-clinical file and in humans through a phase I study.

The primary endpoint in phase IIb will be the six minute walk test

The objective of the clinical study is to evaluate the effect of the BIO101 product on the muscle function in persons who are over 70 years old, obese (BMI = 30-34) and sarcopenic (muscle mass index between 8.51-10.75 kg/m² for men and 5.7-6.75 kg/m² for woman). Two doses of BIO101 (100 and 350 mg) will be compared to placebo.

Evaluate the effect of the BIO101 on the muscle function in persons who are over 70 years old, obese and sarcopenic

The pharmaceutical active ingredient will, as in the phase I study, be extracted from *Stemmacantha carthamoides*, a plant with food and medicinal uses cultivated in China and purified to reach pharmaceutical quality. The production of clinical batches could begin over the coming weeks. The company announced on 21 September the signing of a partnership agreement with the US company Patheon for the production of clinical batches, the first step for the phase 2b clinical study of the BIO101 candidate drug in sarcopenic obesity. In the framework of this partnership, Patheon will be responsible for the production of the clinical batches of BIO101. These batches will be used by BIOPHYTIS in the phase 2b study to be launched in Europe after obtaining authorisation from the regulatory authorities.

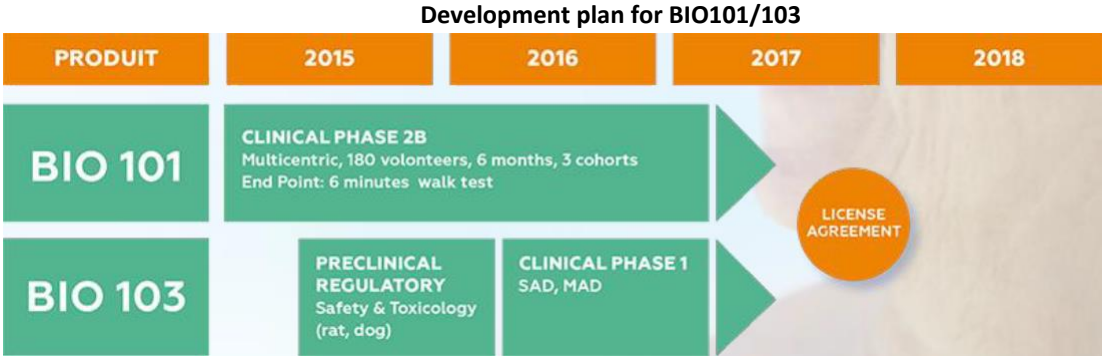
180 sarcopenic obese patients will be recruited in several clinical investigation centres in France, with the Pitié-Salpêtrière Hospital serving as the coordinating centre. The study will be conducted by a CRO (Contract Research Organisation). **The primary endpoint will be the six minute walk test**, which reflects to ability to perform normal daily activities. Several secondary endpoints (including muscle function, body mass makeup and plasma parameters) will also be evaluated in this study. The investigation phase will run six months.

The results for BIO101 should be published by mid-2017. For its part, BIO103 will enter into the regulatory pre-clinical phase, followed by phase I, in 2016. **We anticipate a sale of the BIO101 /BIO103 pair following the phase IIb results for BIO101 in 2017.**

Development plan for BIO101/103

180 sarcopenic obese patients in phase IIb

Results expected in 2017



Source: Biophytis

3 – The BIO101/BIO103 pair: sarcopenic obesity

3.8 We are assuming €600m in revenues for BIO101/BIO103

Sale of the BIO101 / BIO103 pair after the phase IIb results for BIO101 in 2017

Our assumptions concerning the market and revenues for Biophytis are based on:

- the projected world population looking out to 2030/2035, after the expiration of Biophytis' patents
- projections for the age groups over 60 years old

World population (thousands), 2015-2035 trends

Years	0 to 59 years	60-64	65-74	75-84	85+	% >60 years
2 015	6 429 454	291 342	365 389	184 740	53 857	**12%**
2 020	7 000 692	318 764	450 959	202 499	62 599	**13%**
2 025	7 249 008	364 891	523 846	237 706	72 853	**14%**
2 030	7 451 844	402 028	591 870	298 092	83 132	**16%**
2 035	7 624 981	423 726	667 807	348 073	102 586	**17%**

Source : United Nations, Department of Economic and Social Affairs, Population Division (2013)

€600m in revenues over the long term

As we have seen, the percentage of persons 60 years old and older in the world population should rise from 12% to 17% over the next 20 years, with even stronger growth in the oldest age groups.

- projections for the most developed regions, the only regions able to support the financial of this type of care
- the prevalence of obesity by age groups
- our assumptions regarding the association of sarcopenia / obesity ("SO")

3 – The BIO101/BIO103 pair: sarcopenic obesity

Population affected by sarcopenic obesity (SO) – 2015-2035e trend (thousands), developed nations

North America	60-65 years	65-74	75-84	85+	cumul (000)
SO prevalence	16%	25%	35%	40%	
2015	3 434	7 690	5 506	2 780	**19 411**
2020	3 801	9 213	6 467	2 963	**22 444**
2025	3 837	10 360	8 229	3 272	**25 698**
2030	3 567	10 983	9 967	3 955	**28 472**
2035	3 469	10 693	11 354	5 149	**30 665**
yoyc 2015-2035	0.1%	1.7%	3.7%	3.1%	2.3%
Others developed					
SO prevalence	10%	10%	10%	10%	
2015	5 656	8 691	5 788	2 177	**22 312**
2020	5 741	9 737	5 915	2 465	**23 857**
2025	5 935	10 182	6 465	2 826	**25 407**
2030	5 804	10 513	7 271	3 053	**26 642**
2035	5 854	10 662	7 641	3 591	**27 747**
yoyc 2015-2035	0.2%	1.0%	1.4%	2.5%	1.1%
TOTAL developed countries					
2015	9 090	16 381	11 294	4 957	**41 723**
2020	9 542	18 950	12 382	5 428	**46 302**
2025	9 772	20 542	14 693	6 098	**51 105**
2030	9 371	21 496	17 238	7 009	**55 114**
2035	9 324	21 354	18 995	8 739	**58 413**
yoyc 2015-2035	0.1%	1.3%	2.6%	2.9%	1.7%

** Yoyc = year on year change*

Source: Invest Securities

The population suffering from sarcopenic obesity in the most developed nations should rise from 42 million persons in 2015e to 58 million in 2035e

We estimate that the population suffering from sarcopenic obesity in the most developed nations should rise from 42 million persons in 2015e to 58 million in 2035e, corresponding to average annual growth of 1.7%. The average prevalence should rise to the strong growth in the older age groups. Our assumptions do not take into account an increase in the prevalence by age groups over the next 20 years, even if we could fear an "alignment" with the North American epidemiology in numerous countries. In contrast, we could hope for collective awareness in North America that would result in a reduction in the weighting of the obese population in this zone.

Substantial cost savings for the society if an effective treatment delays the entry into dependency

- the anticipated price for the BIO101/103 treatment. We assume a price of €50 per month (€600 per year) midway between the price of chronic treatments for hypertension, diabetes and obesity (partially covered by health insurance) and the much high prices (10-20x) of treatments for more severe diseases requiring more expensive drugs such as Lantus, Lovenox etc. Additionally:
  - this is a medicinal approach based on clinical results showing that BIO101/103 should show significant higher effectiveness than a food supplement
  - the population under consideration is found in the developed nations, in principle able to pay and in the majority of cases benefiting from health insurance
  - the estimate cost of obesity equals, as was seen in an American study, $18bn, corresponding to nearly $1,000 per patient based on the prevalence figures for North America in the above table
  - if an effective treatment delays the entry into dependency, the cost savings for the society is substantial given the cost of stays in retirement homes (€3,000 per months in France for example)

3 – The BIO101/BIO103 pair: sarcopenic obesity

A market share of 20% is possible, ultimately corresponding to nearly one million patients and €600m in peak sales

- The initial target population of 42 million persons starting in 2015 is reduced by several factors:
  - access to healthcare in the developed nations is estimated at 80%
  - the prescription rate is estimated at 27%
  - we have assumed a 50% compliance rate

As such, **the addressable target population equals 4.4 million persons**. As Biophytis is one of the only players on this market and given that we anticipate an agreement with a major worldwide group, we believe that **a market share of 20% would be reasonable, ultimately corresponding to nearly one million patients and €600m in peak sales at a treatment price of €600/year.**

4 – The BIO201/BIO203 pair: dry AMD, a virgin market

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4 – The BIO201/BIO203 pair: dry AMD, a virgin market

4.1 AMD, a slowly progressing disease that can lead to blindness

The most common cause of vision loss is the development of macular degeneration with age

The most common cause of vision loss is the development of macular degeneration with age. The macula is the ensemble of photosensitive cells in the central portion of the retina. The malfunctioning of these cells causes the central vision to be fuzzy, grey, distorted or even non-existent. The peripheral vision is not affected. AMD is a multi-factor disease associated with aging with several associated risk factors such as genetics, sex, diet, hypertension, smoking and the exposure to the sun. Late stage AMD is found more frequently with person with fair skin than in other groups. Women are more affected than men *(Hyman and Neborsky 2002*). Nevertheless, **the strongest and most consistent risk factors are smoking (including passive smoking) and age**. Smokers develop AMD 3-4x more often and ten years earlier than non-smokers.

The prevalence of AMD is high, above all starting at 70 years old, Around ten million persons suffer from AMD in the United States. 28% of persons over 74 years old in the United States suffer from this disease.

Prevalence of AMD by age group in the United States

Age group	40-49	50-59	60-69	70-79	> 80 years	Average
Prevalence in 100 persons	0.1%	0.4%	0.7%	2.4%	11.8%	**1.7%**

Source : MedTRACK

The worldwide prevalence of AMD equals 13% for persons over 85 years old

More generally, the worldwide prevalence is estimated at 1.6% between 65 and 74 years old, 5% between 75 and 84 years old and 13% over 85 year old, levels rather similar to those seen in the United States. The worldwide prevalence is tending to increase given that, as we have seen, world population growth is higher in the oldest age groups, with the population of persons between 60 and 64 years old slated to grow by +1.9%/year over the next 20 years and the population of persons over 65 years old slated to grow at a much faster rate of between +3.1% to +3.3%/year over the same period. In particular, there should be over 100 million persons over 85 years old worldwide in 2035, with a prevalence of 13%.

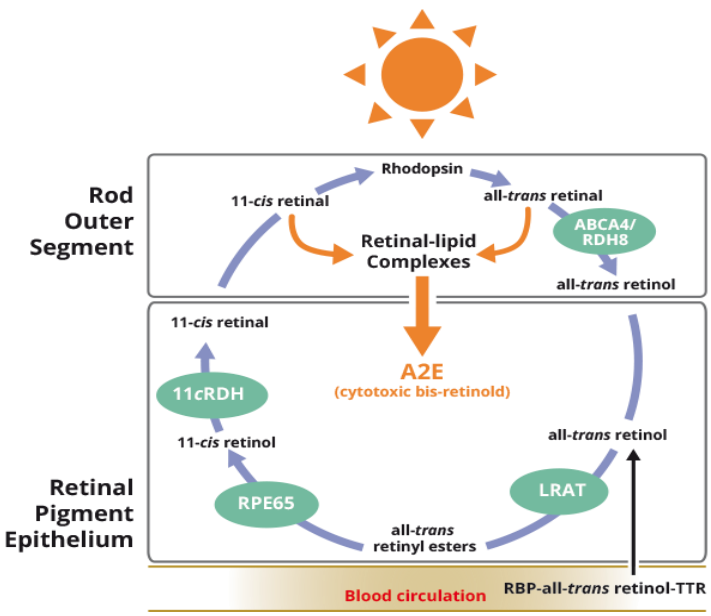
Oxidative stress and inflammation are important factors contributing to the pathogenesis. Theories concerning the aetiology of AMD include hydrodynamic modifications in the Bruch membrane caused by a gradual accumulation of extra-cellular material containing lipids and the senescence of the retinal pigment epithelium (RPE). The development of AMD originates in the impairment of the functioning of the RPE cells.

In the retina, the photoreceptor cells (cones and rods) are associated with the RPE, which assures trophic and metabolic functions. The RPE cells play a major role in phagocytosis, assuring the renewal of the distal ends of photoreceptor cells and thereby contribute to the renewal of photoreceptor structures (cones and rods). Sensitivity to light is assured by rhodopsin, which groups cis-retinal and a protein, opsin.

4 – The BIO201/BIO203 pair: dry AMD, a virgin market

A2E, a derivative of two visual pigment molecules, accumulates in large quantities in the RPE cells. In the presence of (blue) light and oxygen, this molecule oxidises.

Role of RPE in the retina



Source : Biophytis

Under the effect of light, the retinal is isomerised and detaches from the opsin. The return to its original form, which is essential to its activity, brings into play a sequence of reactions for which photoreceptors and the retinal pigment epithelium (RPE) are jointly responsible.

Following a malfunction of the visual pigment cycle (associated with age or genetic defects), A2E, a derivative of two visual pigment molecules, accumulates in large quantities in the RPE cells. In the presence of (blue) light and oxygen, A2E oxidises some or all of its double bonds and the molecules formed in this manner react with various cellular constituents, disrupting the activity of the RPE (Sparrow et al, 2000). As a result, the RPE cells accumulate waste products called Drüsen (glands in German) that can accumulate between the RPE cells and their basal membrane (Bruch's membrane). The Drüsen cause deformations of the retina and therefore in the perceived images.

The Drüsen cause a deformation of the retinal image, the prelude to AMD

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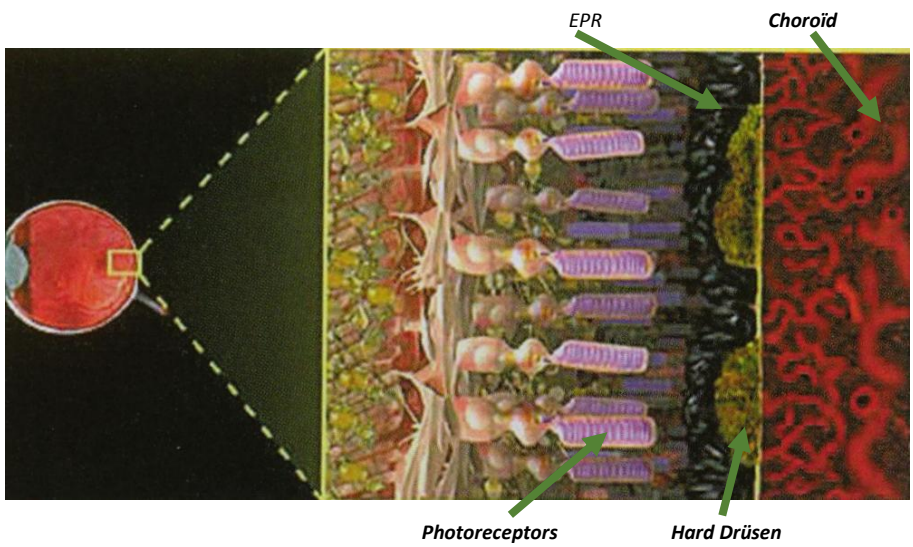


Source: Invest Securities based on the Lycée Marie Curie Vire

4 – The BIO201/BIO203 pair: dry AMD, a virgin market

With age, the RPE stores greater quantities of lipofuscin. The Drüsen deposits are the site of inflammatory reactions that contribute to further disrupting the RPE cells. Their death (apoptosis) is followed by the death of the photoreceptors to which they had been associated and the central vision is gradually impaired.

4.2 Dry AMD (80% of the market) remains untreated

Dry AMD is caused by gradual degeneration of the macula cells. It represents over 80% of case and shows slow progression. …

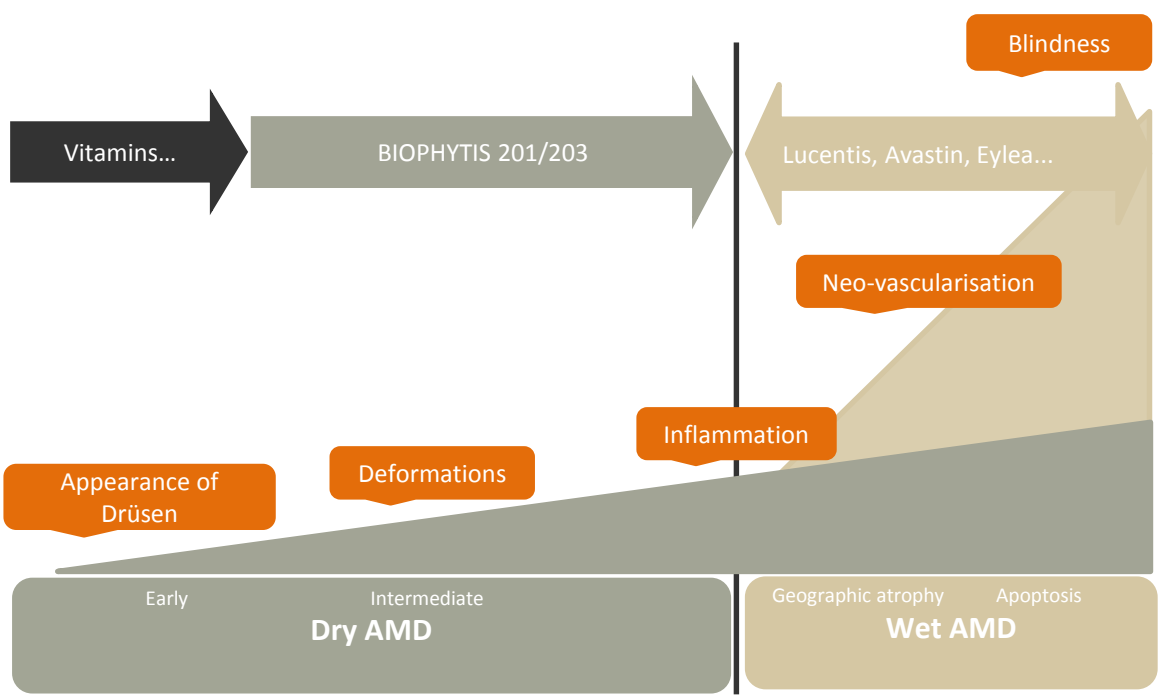
There are **two forms of AMD:**

- **Dry:** Dry AMD is caused by gradual degeneration of the macula cells. It represents over 80% of case and shows slow progression. It can turn into wet AMD (see diagram below).
- **Wet (exudative):** Wet AMD is an excessive vascularisation disease featuring leaks into the choroid of the eye. Wet AMD often shows rapid onset and can quickly lead to severe loss of vision. An estimated 1.5 million persons suffer from wet AMD in the United States, with 200,000 new diagnoses per year. New diagnoses in the developed nations total 500,000 per year. Even if only a minority of patients suffer from the wet form of AMD, the disease is severe in two-thirds of the cases and represents the leading cause of blindness in the developed nations. Additionally, it is the only form that can be treated, with very expensive drugs. Consequently, even if wet AMD represents less than 20% of patients, its market makes up the bulk of the global AMD market in value terms (several billion dollars) as there is no treatment for dry AMD.

…and can evolve into wet AMD

Note that the risk of progression to the second eye is 10% after one year and 42% at five years.

Progression of AMD over time – dry (grey) and wet (beige) forms



Source: Invest Securities

4 – The BIO201/BIO203 pair: dry AMD, a virgin market

The treatment of dry AMD can take several forms depending on the stage of the disease (early, intermediate, atrophy):

The use of antioxidants has been proposed for the treatment of AMD

- **Oxidative stress** is considered to be the principal initial determinant for the different modifications in the retina associated with age. The use of **antioxidants** such as vitamin C and E supplements has therefore naturally been proposed to treat AMD. The AREDS (Age-Related Eye Disease Study) conducted in the United Sates for over ten years by a consortium financed by the NIH (National Institutes of Health) has established the interest of zinc and vitamin C and E based supplements and has detailed the importance of certain nutritional deficiencies, particularly involving lutein and zeaxanthin, the visual pigments covering the retina (AREDS, 2001). The **nutritional supplements** formulated on the basis of the AREDS recommendations have since been prescribed and sold throughout the world reflecting their status as the only available treatment in the hope of slowing the progression of dry AMD into more severe forms. Nevertheless, the effectiveness of this treatment is low and the response appears to vary depending on the patient.

The majority of projects have been halted

- **Concerning the more medical approaches**, the majority of drugs were developed for other pathologies, be they neuro-protective drugs developed to treat cerebral neurodegenerative diseases or generic antioxidant drugs. The physio-pathological mechanisms involved are different, leading to the failure of these strategies. The majority of projects have been halted (Sirion, Acucela, Alcon, Neurotech, Pfizer, Allergan etc.).
- The **corticosteroids** could, thanks to their anti-inflammatory action, slow the progression of AMD. We can note **Alimera's product, which is in early phase development in the treatment o dry AMD in the advanced atrophy stage**. Once again, the goal here is to inhibit the oxidative stress through the NADPH enzyme. **Alimera's Iluvien is an implant** that delivers an intravitreous injection of fluocinolone acetonide for 36 months (sustained release). Commercialised at the price of $8,000-9,000 in Europe since 2013 prix and in the United States at the end of 2014 in diabetic macular oedema (DME), the product could also be developed in dry AMD. Sales totalled $8.4m in 2014 (Europe alone). Sales equalled $2.4m starting in Q1 15 in the United States.
- **MacuClear is developing MC-1101, a (repositioned) systemic antihypertensive drug in the form of eye drops, in phase II/III trials with the goal of facilitating blood circulation in the choroid. This product has been awarded Fast Track status by the FDA in the United States.** The phase II/III study, underway since 2014, has recruited 60 participants from 50 to 85 years old suffering from early to intermediate non-exudative (therefore dry) AMD. **This is probably one of the few products that could compete with BIO201/203.** Results are expected in 2016.

Several projects are targeting advanced stages of AMD

- **Among the antibodies, the most advanced project is probably Novartis/MorphoSys' LFG316, which has been in phase II trials since 2012 but addressed geographic atrophy, the advanced form of dry AMD.** The phase II study is expected to have been completed in June 2015.
- Several early stage projects have emerged recently in **cell therapy / regenerative medicine** (28 clinical trials underway in ophthalmology):
    - **Ocata Therapeutics (ex-Advanced Cell Technology)** is targeting degenerative disorders in the retina. The company is focusing on RPE cells derived from embryonic stem cells. A phase I/II study in AMD and Stargardt's disease in collaboration notably with the Wills Eye Hospital in Philadelphia is testing the safter of RPE derived from embryonic cells in patients suffering from dry AMD. Phase II interim results are expected end 2016.
    - **Bioheart** has a tolerance trial underway based on intravitreal injected fat cells in 100 patients suffering from dry AMD. This study was begun at the end of 2013 and results are expected in 2017.

4 – The BIO201/BIO203 pair: dry AMD, a virgin market

- **StemCells, Inc.** Is developing a cell product to protect the retina derived from human central nervous system stem cells (HuCNS-SC). A phase I/II study begun in 2012 is evaluating the tolerance and effectiveness in the treatment of geographic atrophy la (therefore wet AMD, but dry AMD also appears to be under consideration). Results are expected in 2015.

- In genetic therapy, we can not the **Avalanche Biotechnologies product AVA-101, which combines its genetic therapy platform with a VEGF (vascular growth factor) and has shown good results in visual acuity gain in wet AMD in phase I.** In August 2015, the company announced that it was postponing its phase II-b study in order to resume product dosage and delivery trials. The share price has fallen 70% since the beginning of 2015, when the company's stock market capitalisation exceeded $1bn. Even if this product does not target the same segment as Biophytis, the sharp rise and then steep fall in the share price is a good indication of the stakes involved in AMD.

The potential competitors for Biophytis are the drugs candidates of Alimera, MacuClear, ACT and StemCells. However, they tend to target more severe forms of the disease.

- **In conclusion,** we know of no drug specifically targeting the dry form of intermediate AMD currently available on the market or close to approval. The majority of projects target relatively advanced stages of dry AMD, close to the wet form (geographic atrophy). **We estimate that the potential competitors for Biophytis are the drugs candidates of Alimera, MacuClear, ACT and StemCells.**

4.3 The pharmaceutical groups are focusing on wet AMD

Virtually all the AMD treatment involve wet AMD,

- Before 2000, laser photocoagulation was the only therapeutic option.
- In 2000, the FDA approved **photodynamic therapy (PDT),** in which Verteporfin (Visudyne, from Novartis), a drug activated by light, is delivered by an IV infusion in the arm. Once in the retina's neovessels, the drug is activated by a cold laser light and destroys the undesired blood vessels. In order to be effective, this procedure must be repeated several times and, even in case of success, renewed treatment is necessary after 3-5 years in around 50% of patients. Finally, PDT was uniquely indicated as an appropriate therapy in around 25% of cases of wet AMD.

In 2004, the FDA approved the first anti-VEGF in wet AMD

- Neither laser photocoagulation nor photodynamic therapy restores lost vision. In 2004, the FDA approved the **first anti-VEGF** (Vascular Endothelial Growth Factor) drug for ophthalmological use, pegaptanib, (Macugen), an aptamer that selectively binds to the VEGF. In contrast to PDT, pegaptanib can be used in all forms of wet AMD and not only acts to halt the progression of the disease, but can also partially restore the lost vision.

- In 2006, the FDA registered ranibizumab **(Lucentis, from Genentech/Roche/Novartis)**, an antibody fragment that binds to the VEGF and enables the restoration of the lost vision. Lucentis generated sales of $4.2bn in 2014 (including $2.4bn for Novartis and $1.8bn for Roche). Its high cost (€900 per monthly injection in France for example) has led hospital practitioners to prescribe Roche's Avastin anti-cancer drug (€30-50 per injection) off-label. Genentech developed both these drugs – Avastin sold by Roche as treatment for certain cancers (see below) and Lucentis sold by Roche and Novartis.

Lucentis generated sales of $4.2bn in 2014

4 – The BIO201/BIO203 pair: dry AMD, a virgin market

The Italian antitrust authorities fined the two Swiss pharmaceutical groups Roche and Novartis €182.5m in March 2014 for having illegally colluded to favour the use of Lucentis. There is also strong pressure in France to substitute Avastin for Lucentis, which is the drug that costs the French healthcare system the most (€385m in 2012 according to the French senate official journal dated 5 June 2014).

VEGF is effectively a key protein in the formation of new blood vessels (neoangiogenesis) from existing blood vessels. Abnormal angiogenesis is one of the characteristics of solid cancer tumours. Once a tumours reaches a size of 2 mm, it can no longer divert the nutrients and oxygen that it needs to accompany its growth. The tumour then expresses pro-angiogenic protein, with the more important being VEGF, which incites the cells to produce blood vessels to feed the tumour.

Strong pressure to substitute Avastin for Lucentis

The same angiogenic phenomenon is seen in wet AMD. It is for this reason that certain doctors prescribe the anti-cancer drug Avastin (Roche) to treat AMD rather than Lucentis, which is 20x more expensive. Another anti-VEGF, Eylea (aflibercept) from Regeneron/Bayer, has been commercialised more recently.

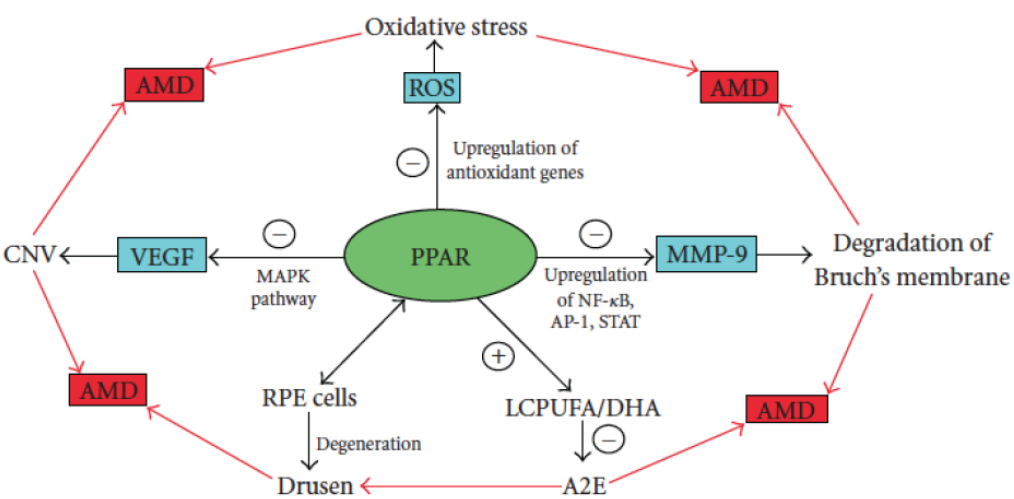
4.4 Preclinical and phase I results for BIO201

Biophytis' research has been focused on drugs to counteract the detrimental effects of A2E, which, as we saw above, accumulates in large quantities in the RPE cells and leads to the appearance of Drüsen, in principle the cause of AMD.

Given that BIO201 is a PPARα agonist, Biophytis has shown that it protects retina cells against the phototoxic effects of A2E

The active pharmaceutical ingredient (API) of BIO201 is extracted from *Bixa orellana*, a bush originating from the tropical region of the Americas. Given that BIO201 is a PPARα agonist, Biophytis has shown that it protects retina cells against A2E in the presence of blue light (oxidative stress), reduces the accumulation of this phototoxic molecule in animal models and finally slows the degenerative process in the retina. Recent date indicates an important role for PPAR (Peroxisome Proliferator-Activated Receptors) nuclear receptors in protection against AMD (Herzlich et al., 2008), notably in connection with inflammation. **Note that this involves PPARα rather than PPARγ, which have a different chemical structure and are known for their cardiovascular toxicity.**

Key role of PPARα nuclear receptors in the protection of the retina



Source: Biophytis

4 – The BIO201/BIO203 pair: dry AMD, a virgin market

The protection provided by BIO201 can be view on several compatible levels. BIO201:

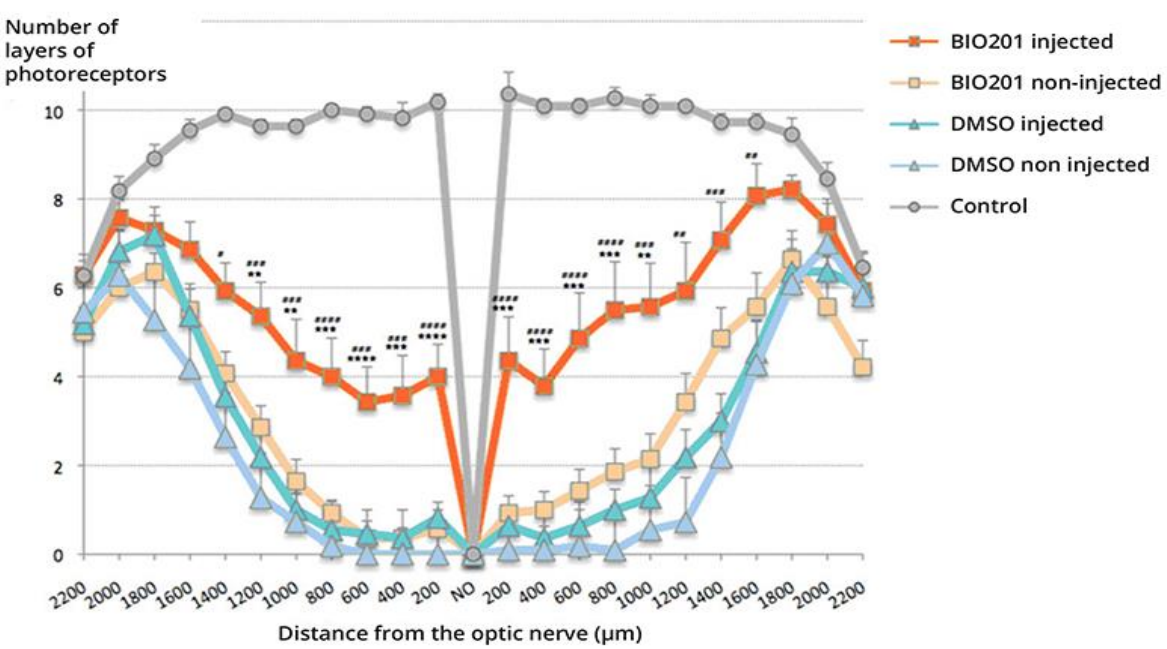
- Plays a role of filter by absorbing the blue light
- reduces the capture of (exogenous) A2E by RPE cells (or stimulates its rejection)
- has an antioxidant effect through the neutralisation of ROS (Tokarz et al., 2013) ;
- has an anti-inflammatory (it is currently not known whether the inflammation is the cause of consequence of AMD) and anti-VEGF action
- protects against apoptosis

Animal models: A study of the dose effect on pig RPE cells with large quantities of A2E and exposed to blue light has allowed the selected of the most active natural substances and to characterise BIO201.

Three studies in mice and rats (n=14 per group) were then conducted by administrating BIO201 orally, through intravitreal injection or by intraperitoneal injection (rats only). The first animal model used mice for which two genes coding the proteins implicated in the visual pigment cycle were deactivated. These mice accumulate substantial quantities of A2E in an early manner, thereby making them very sensitive to blue light. The mice were then exposed to intense blue light, with the extent of the damage suffered by the photoreceptors measures seven days later.

BIO201 showed a very significant protective effect in mice

BIO201 showed (see chart below) a very significant protective effect. The number of layers of photoreceptors remaining on the retina after this manipulations was significantly higher in mice whose eye had received an intravitreal injection of BIO201 (orange curve) compared to both the non-injected eye (BIO201 not injected) as to DSMO (placebo). The control arm did not undergo the A2E + blue light treatment and was therefore not damaged (grey curve).



Source : Biophytis

4 – The BIO201/BIO203 pair: dry AMD, a virgin market

These results are highly significant, as the p ratios are all <0.05 on the chart (above the orange curve), with one star * signifying p<0.05, two stars ** p<0.01, three stars *** p<0.001 and four stars **** p<0.0001.

Phase I/II clinical studies: In a double-blind vs. placebo study involving healthy volunteers (n=47, of which 24 placebo), subjects received BIO201 (purified from *Bixilia*) orally during three months in 2010. The absence of toxicity (no serious undesirable event associated with the product) at the dose studied (35mg/day) and the good bioavailability by oral administration was confirmed. The natural active ingredient can be administered to the general population up to 300 mg/day and its circulation metabolite in humans, the basis of BIO201, can equal up to 42 mg/day.

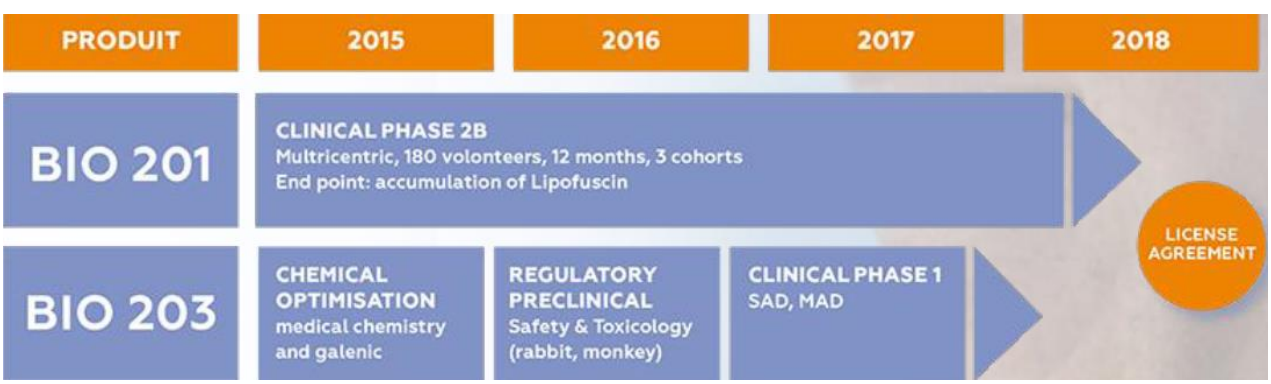
4.5 BIO201 and BIO203 phase I and II development programme

The next development steps involve:

- Determining the effective therapeutic dose of BIO201 through a multi-centre double blind vs. placebo phase IIb clinical study
    - 180 patients suffering from **intermediate AMD**;
    - BIO201 100mg vs. BIO201 350mg vs. placebo
    - Duration: 24 months **(DSMB: intermediate review at 12 months)**
    - Endpoints:
        - **Primary:** accumulation of lipofuscin
        - **Secondary:** visual acuity, ERG, progression to more severe forms. **We believe this final point is important considering that progression to a wet form (geographic atrophy) can very quickly lead to blindness. Slowing this progression would be a major strong point for BIO203.**

The primary endpoint in phase IIb will be the accumulation of lipofuscin

- Complete the optimisation of BIO203 and evaluate its safety in animals and then humans through a phase 1 study. BIO203 is a new molecule selected from the synthesised compounds, analogues of the active natural substances in the animal and cell models of AMD. The dug candidate is in the process of being optimised and appropriate pharmaceutical development should be conducted in order to stabilise the activity of BIO203 for over one month after intravitreal injection. BIO203 could enter into the regulatory preclinical phase in 2016 before entering phase I in 2017 to demonstrate is safety in humans.



Source : Biophytis

4 – The BIO201/BIO203 pair: dry AMD, a virgin market

The route of administration of BIO203 is a potential question. While BIO201 is orally administered, the preferred route of administration of BIO203 appears to be intravitreal injection, even if this has not yet been definitely established. The existing products for the treatment of wet AMD are injected in the eye, representing a constraint for the patient. An oral route of administration or one using eye drops or even the system of Alimera Sciences' Iluvien® for diabetic macular oedema, which requires only a single injection every three years, could in our view make a difference, assuming that the bioavailability is the same, above all if the product must be combined with another injectable.

Injection nevertheless has several advantages:

- bioavailability (use of low doses and no systemic effect) ;
- control of treatment compliance by the ophthalmologist
- better adoption by doctors in the United States, where practitioners bill injections

Only dry AMD is targeted at this point

As with BIO101/103, **Biophytis plans a sale of the B201/203 pair** when:

1. the phase IIb trial of BIO201 is completed in 2018
2. a phase I trial of BIO203 is completed

There exist another factor that could represent additional interest for a possible partner. Only dry AMD is targeted at this point, and the current plan is exclusively focused on clinical proof of concept as to BIO201/203 ability to treat this disease. Biophytis is not targeting wet AMD, where the market is already crowded. Nevertheless, nothing proves that an application in wet AMD is impossible, alone or in combination. Additionally, as we have seen, BIO201/203 could slow the progression to the wet form.

If BIO201/203 slows the progression to the wet form of AMD, the market would be much larger

4.6 Revenues of €800m for BIO201/BIO203

The following table sets out our **assumptions regarding the potential market for BIO201/203** based on UN demographic forecast (assuming average fertility) by age group and on prevelance data for AMD in its dry and wet forms.

AMD target population: world including developed nations, 2015-2035

World total	60-64 years	65-74	75-84	85+	
AMD prevalence	0.7%	1.6%	5.0%	13.0%	Cumul (000)
2015		5 846	9 237	7 001	**22 085**
2020		7 215	10 125	8 138	**25 478**
2025		8 382	11 885	9 471	**29 738**
2030		9 470	14 905	10 807	**35 182**
2035		10 685	17 404	13 336	**41 425**
yoyc 2015-2035		3.1%	3.2%	3.3%	3.2%

Developed countries	60-64 years	65-74	75-84	85+	
AMD prevalence	0.7%	1.6%	5.0%	13.0%	Cumul (000)
2015		1 883	3 681	3 734	**9 297**
2020		2 148	3 881	4 167	**10 196**
2025		2 292	4 408	4 737	**11 437**
2030		2 385	5 059	5 255	**12 699**
2035		2 390	5 442	6 341	**14 174**
yoyc 2015-2035		1.2%	2.0%	2.7%	2.1%

Source : Invest Securities

Revenues of €800m in the developed nations

4 – The BIO201/BIO203 pair: dry AMD, a virgin market

Here again, the high prevalence of AMD in the oldest age groups that should show the strongest growth implies a growth rate for AMD of at least between +2% and +3%/year over the next 20 years. We are not assuming increases in the prevalence by age group. In effect, the principal cause of AMD is smoking, which is falling in the developed nations but rising in the developing nations.

We are only taking into account patients in the developed nations at this point, corresponding to 9.3 million person 65 years old and older (prevalence above 0.7%), adjusted for:

- access to healthcare, corresponding to 78% of this population
- the prescription rate, estimated at 27%
- compliance with treatment, which should be relatively high (66%) as BIO201/203 should involve intravitreal injections, therefore under medical supervision

We estimate a 30% market share for this production, which will be one of the few in this category, corresponding to 388,000 persons

The addressable population in the developed nations alone would therefore equal 1.3 million persons.

- We estimate a 30% market share for this production, which will be one of the few in this category, corresponding to 388,000 persons.
- We estimate that the treatment price could be higher than that of BIO101/103:
    - There is no alternative treatment
    - There is a risk of progression to wet AMD, even if this is not proven
    - We estimate that the price could be between than of Avastin (around €500/year in France for example) and Lucentis (€10,000/year in France, the double in the United States). Negotiations conducted since 2012 with the producer of Lucentis through the French healthcare products economic committee have led to reductions in the price of Lucentis (10% in 2012, 11% in 2013 and 9% in 2014). We estimate that a product without competitors on its market should obtain a higher price than Avastin but significantly lower than Lucentis, which by all evidence should see its price fall. We assume a price of €150/month (€1,800/year) for BIO201/203.

The price could be between than of Avastin and Lucentis

In total, BIO201/203 could generate revenues of nearly €800m based only on the developed nations and probably double this amount if the entire world is taken into account (22 million persons instead of nine million).

5 – Fairly valued while waiting for the two phase II-b studies

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5 – Fairly valued while waiting for the two phase II-b studies

Biophytis' development model corresponds to that of biotechnology company in that it is characterised by:

- preponderant research and development expenses spread over several years prior to commercialisation
- positive cash flow on a distant horizon (2017 at the earliest if an agreement is signed)
- uncertain revenues at the same time expenses looking out 2-3 years are virtually certain

5.1 Valuation using the rNPV method

As Biophytis is entering into phase IIb clinical trials, the risk of failure (attrition rate) is still relatively high and the probability of success (i.e. of products arriving on the market) is still lower than 50%. We have therefore ruled out the DCF methods in favour of the rNPV (risk-adjusted Net Present Value) method that, like the DCF method, involves the calculation of net revenue flows but probabilises these flows based on the advancement of clinical trials. Each of Biophytis' products is value, We then calculate a sum of the parts (the two products here) valuation, to which is added the net cash.

Valuation of BIO101/BIO103 in sarcopenic obesity

The addressable target population equals 4.4 million persons

We have already discussed above our revenues assumptions for BIO101/103:

- The addressable target population equals 4.4 million persons.
- As Biophytis is one of the few players on this market and an agreement with a worldwide pharmaceutical group is expected, we believe that a market share of 20% would be reasonable, ultimately corresponding to nearly one million patients.
- The treatment price is assumed to be €50 per month, corresponding to €600 per year.
- The partner's peak sales would therefore equal €600m four years after commercialisation estimated in 2021.

Based on this scenario, the assumptions underlying the valuation model for BIO101/103 are:

An agreement with a partner is assumed to be signed following the completion of the phase II clinical trial in 2017

1. An agreement with a partner following the completion of the phase II clinical trial in 2017. With an overall value of €125m (22% of sales in year 4 after commercial launch), divided between an upfront payment of €15m on the signing of the agreement and milestone payments totalling €105m (certain occurring in connection with regulatory milestones, others on reaching certain sales levels after commercialisation). We have deducted the 2% fees paid to the Pierre and Marie Curie University.
2. Starting with commercialisation, the partners' revenue flows through the expiration of the patents in 2031 are calculated in the following manner based on the assumptions discussed above:

€m Sarcopenic obesity	*2019e*	*2020e*	*2021e*	*2022e*	*2023e*	*2024e*	*2025e*	*2026e*	*2027e*	*2028e*	*2029e*	*2030e*	*2031e*
Population SO developed countries	***42.00***	***42.71***	***43.44***	***44.18***	***44.93***	***45.69***	***46.47***	***47.26***	***48.06***	***48.88***	***49.71***	***50.56***	***51.42***
Access to health care services	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*	*78%*
Prescription	*27%*	*27%*	*27%*	*27%*	*27%*	*27%*	*27%*	*27%*	*27%*	*27%*	*27%*	*27%*	*27%*
Compliance	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
Eligible patients in developed countries	***4.42***	***4.50***	***4.57***	***4.65***	***4.73***	***4.81***	***4.89***	***4.98***	***5.06***	***5.15***	***5.23***	***5.32***	***5.41***
Market share %			*1%*	*2%*	*5%*	*10%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
Biophytis patients	*-*	*-*	***0.05***	***0.09***	***0.24***	***0.48***	***0.98***	***1.00***	***1.01***	***1.03***	***1.05***	***1.06***	***1.08***
Cost of treatment/year €	*600*	*600*	*600*	*600*	*600*	*600*	*600*	*600*	*600*	*600*	*600*	*600*	*600*
Sales BIO101/103 partner €m	*-*	*-*	***27***	***56***	***142***	***289***	***587***	***597***	***607***	***618***	***628***	***639***	***650***

Source : estimations Invest Securities

5 – Fairly valued while waiting for the two phase II-b studies

Probability of success of 28%

3. These revenues are then probabilised at 28% (chances of arrival on the market of a drug in phase II according to diMasi and Grabowski, Tufts Center for the Study of Drug Development). Note that this probability rises to 60% in phase III.
4. Biophytis' share is estimated at 12% of royalties on sales less the 2% fee paid to the Pierre and Marie Curie University.
5. Product development costs are estimated at €13m between 2015 and 2017.
6. A discount rate of 13.8% was applied to the revenue flows, with a beta (2.24) double that of the Next Biotech index (1.12). This discount rate was 15.3% at the time of the IPO. This essentially explains the difference in our valuation (€59m excluding cash vs. €45m at the time of the IPO).

Risk free rate	0,91%	09/15/2015	OAT
Market premium	5,75%	09/15/2015	Source FactSet
beta	2,24	09/15/2015	Source FactSet
Discount rate	13,8%		

Discount rate of 13.8%

We continue to double the beta despite the success of the IPO and the supplementary fund-raising round, which have lifted the uncertainty regarding the company's financing. We are waiting for the start of the planned phase II-b studies before potentially revising our WACC. The key step will be the authorisation to start the study and the recruitment of the first patient. We anticipate this will more likely occur in H1 2016.

Our rNPV valuation table reflects all the above assumptions and summaries all the revenues flows that we anticipate for Biophytis:

- Upfronts on the signing of licence contracts
- Milestones over time
- Sales by the partner and Biophytis' share after deducting expenses and fees
- All probabilised at 28% and discounted at 13.8%.

rNPV Valuation €m	Phase II OS		Partner	Phase III		AMM	Market										
BIO101/103- Sarcopenia	12/15	12/16	12/17	12/18	12/19	12/20	12/21	12/22	12/23	12/24	12/25	12/26	12/27	12/28	12/29	12/30	12/31
Upfront			15														
Milestones						30	10	20	50								
Sales by partner							27	55	139	283	575	585	595	605	616	626	637
Probabilité de succès 28%							7	15	39	78	159	162	165	168	170	173	176
BIOPHYTIS share 12% (- expenses)	-5	-5	-3				1	2	5	9	19	19	20	20	20	21	21
rNPV BIO101/103	-5,0	- 5,0	2,9	-	-	4,7	1,2	2,1	4,6	2,0	3,7	3,3	2,9	2,6	2,3	2,1	1,9

Source: Invest Securities estimates

Based on these assumptions, the rNPV valuation of BIO101/103 equals €26.1m.

5 – Fairly valued while waiting for the two phase II-b studies

rNPV valuation of BIO201/BIO203 in dry AMD

We already discussed our revenue assumptions BIO201/203 above. Our conclusions were:

- The addressable target population equals 1.29 million persons (most developed countries only).
- As Biophytis is one of the few actors on this market and an aggress with a major worldwide group is planned, we believe that a market shares of 30% would be reasonable, ultimately corresponding to 500,000 patients. This market share was estimated based on the description of the competition set out above. Starting with the wet AMD market (the only reference at this point), which totals $6bn (with Lucentis posting $4.4bn in sales in 2014) and represents over 80% of the total AMD market, we can deduce that, assuming the same prices, the total AMD market would total $30bn, including $24bn (80%) for dry AMD. The prices of treatments of dry AMD should be much lower than those for wet AMD, which granted involves the most severe form of the disease (neovascularisation). However, wet AMD treatment prices should come under pressure:

An addressable target population of 1.29 million persons in the developed nations

  - from the competition, with Lucentis no longer being the only treatment
  - from the healthcare systems
  - From substitution in favour of Avastin or other drugs, 20x less expensive

Prices under pressure in wet AMD

- We estimate that a price 10x lower than Lucentis is realistic, corresponding to a market of $2.3bn for dry AMD. If two out of the four possible competitors (even if they target a more advance form of dry AMD than Biophytis, which is targeting the intermediate form) mentioned above arrive on the market, a market share of 30% each would give revenues of $800m, comparable to our sales estimate for BIO201/203 of €800m.

The price could be 10x lower than Lucentis

- The price of the treatment is assumed to equal €150m per month, corresponding to €1,800 per year (see above).
- Peak sales for the partner are estimated €800m following an estimated commercial launch by the partner in 2023.

Based on this scenario, the assumptions underlying the valuation model for BIO201/203 are summarised in the following table:

1. A deal is expected to be signed with a partner following the completion of the phase II clinical trial in 2018. With an overall value of €195m (23% of peak sales), this figures is divided between an upfront of €25m on the signing of the agreement and milestone payments of €170m, with certain triggered by reaching regulatory milestones and others on reaching certain levels of sales following commercialisation. We have deducted 2% fees to be paid to the Pierre and Marie Curie University.
2. Starting with commercialisation, the partners' revenue flows through the expiration of the patents in 2034 are calculated in the following manner based on the assumptions discussed above:

5 – Fairly valued while waiting for the two phase II-b studies

€m dry AMD	2023e	2024e	2025e	2026e	2027e	2028e	2029e	2030e	2031e	2032e	2033e	2034e
Population AMD developed countries	**10.10**	**10.32**	**10.53**	**10.75**	**10.98**	**11.21**	**11.44**	**11.68**	**11.93**	**12.18**	**12.44**	**12.70**
Access to health care systems	78%	78%	78%	78%	78%	78%	78%	78%	78%	78%	78%	78%
Prescription	27%	27%	27%	27%	27%	27%	27%	27%	27%	27%	27%	27%
Compliance	66%	66%	66%	66%	66%	66%	66%	66%	66%	66%	66%	66%
Eligible patients in developed countries	**1.40**	**1.43**	**1.46**	**1.49**	**1.53**	**1.56**	**1.59**	**1.62**	**1.66**	**1.69**	**1.73**	**1.76**
Market share %	1%	2%	5%	10%	20%	30%	30%	30%	30%	30%	30%	30%
Biophytis patients	**0.01**	**0.03**	**0.07**	**0.15**	**0.31**	**0.47**	**0.48**	**0.49**	**0.50**	**0.51**	**0.52**	**0.53**
Cost of treatment/year €	1 800	1 800	1 800	1 800	1 800	1 800	1 800	1 800	1 800	1 800	1 800	1 800
Sales BIO201/203 partner €m	**25**	**52**	**132**	**269**	**549**	**841**	**859**	**877**	**895**	**914**	**933**	**953**

Source: Invest Securities estimates

3. As for BIO101/103, these revenues are then probabilised at 28% (probability of arrival on the market).

Biophytis' share is estimated at 15% royalties

4. Biophytis' share is estimated at 15% royalties on sales reduced by a 2% fee paid to the Pierre and Marie Curie University.
5. The development costs of the product are estimated at €14m spread out over 2015 to 2017.
6. The same discount rate of 13.8% is applied to the revenue flows.

We arrive at the following rNPV valuation table:

rNPV Valuation €m	Phase II AMD			Partner	Phase III			AMM	Market											
BIO201/203-AMD	12/15	12/16	12/17	12/18	12/19	12/20	12/21	12/22	12/23	12/24	12/25	12/26	12/27	12/28	12/29	12/30	12/31	12/32	12/33	12/34
Upfront				25																
Milestones							30	40	5	15	30	50								
Sales by partner									25	51	129	264	538	825	842	860	878	896	915	934
Probability of success 28%									7	14	36	73	149	228	233	238	243	248	253	259
BIOPHYTIS share 15% (- expenses)	-5	-5	-4			0	0	0	1	2	5	11	22	34	35	36	36	37	38	39
rNPV BIO201/203	-5,0	-5,0	-4,0	5,4	-	-	3,0	3,1	0,6	1,4	2,6	4,2	3,3	4,4	4,0	3,6	3,2	2,9	2,6	2,3

Source: Invest Securities estimates

Based on these assumptions, the rNPV valuation of BIO201/203 equals €32.5m pre-money.

Summary rNPV valuations of the two products

In summary, the **valuation of Biophytis based on the sum of the two products equals €72.8m**, broken down as follows:

The rNPV valuation of Biophytis equals €11.9m per share

rNPV	€m	€/share
BIO101/103 Sarcopenic obesity	26,1	4,3
BIO201/203 dry AMD	32,5	5,3
Estimated net cash as of 09/22/2015	14,2	2,3
Total valuation of Biophytis	**72,8**	**11,9**

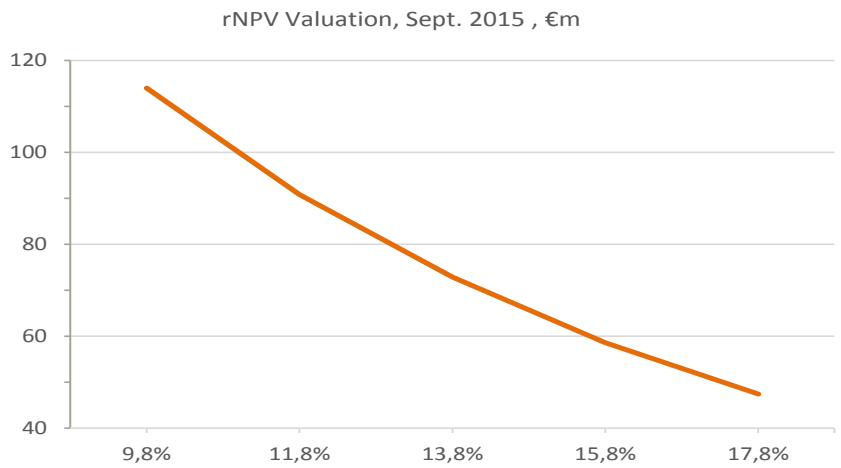
Source: Invest Securities estimates

Our valuation (excluding cash) of €59m is higher than the IPO valuation (€45m) principally due to the discount rate of 13.8% instead of the 15.3% at the time of the IPO, with the betas having fallen over the last three months. We estimated at the time of the IPO that €17m in fund-raising was necessary in order to finance the company's development plan. Thanks to the two consecutive fund-raising rounds in July and August 2015, we estimate that cash currently equals €14m. This should be sufficient for around two years.

These estimates are sensitive to the assumed discount rate, as shown by the following chart, which summarises our estimates for the valuation excluding cash as a function of discount rates ranging from 9.8% to 17.8% :

5 – Fairly valued while waiting for the two phase II-b studies

Sensitivity of the Biophytis valuation to the discount rate



Source: Invest Securities estimates

5.2 Comparisons with listed companies

The peer comparisons method is not pertinent

- As Biophytis does not have revenues or profits, the peer comparison method can not be used, with peer companies most often also not having available data.
- The only valid approach in our view (and for information purposes only) is the comparison listed French companies with pipelines in comparable stages of advancement as Biophytis, i.e. in phase I and/or II clinical trials. None of these companies have products comparable to those of Biophytis.

Company	Date IPO	IPO price €	Raised Cash €m	EV €m at IPO	IPO market cap €m	Market cap 09/18/15	Price 09/18/15
Sensorion	avr-15	4,5	8	15	23	45	8,9
Quantum	janv-15	6,3	13	40	53	64	9,3
TxCell	avr-14	5,6	16	48	64	99	7,7
Hybrigenics	ns	ns	ns	ns	ns	46	1,3
Average	**-**	**-**	**12**	**34**	**47**	**64**	**-**
BIOPHYTIS	juil-15	6,0	10	23	33	75	12,3

Source: FactSet and Invest Securities estimates

- We would also note for information purposes a few listed companies in France and the United States working in areas close to that of Biophytis in the ophthalmology sector. The only companies operating in the same area as Biophytis, i.e. dry AMD, are StemCells Inc. and Alimera, with the latter having already introduced a product on the market. As noted previously, we mention Avalanche only to understand the stakes involved with wet AMD. The French companies Nicox andPixium are not comparable to Biophytis.

Company	Indications	Pipeline				Deals	Market cap 09/18/15
		Phase I	Phase II	Phase III et +	Commercialisés		€m
Nicox FR	Ophtalmology	1	-	5	2	Bausch+Lomb	197
Pixium Vision FR	Retina Implants		*		0	-	74
StemCells US	CNS, dry AMD	2	2	0	0	-	49
Alimera US	DME, dry AMD	1	0	0	1	-	108
Avalanche Biotech US	Wet AMD	0	1	0	0	Regeneron +	254
BIOPHYTIS	**SO+AMD**	**-**	**2**	**-**	**-**	**-**	**75**

Source : Nasdaq and Invest Securities estimates

5 – Fairly valued while waiting for the two phase II-b studies

5.3 Overall project cost and financing

Biophytis plans to spend €27m between 2015 and 2017 more or less equally on the two projects sarcopenic obesity and AMD, with €10m in non-dilutive financing (research tax credit, advances and other subsidies) and €17m form equity fund raising.

Cash burn of €7m per year

€10m was raised through the IPO in July 2015, followed by €6m in August 2015. The company therefore has the means to finance its strategy. The planned spending is more or less identical for each of the two products. We estimate the cash burn at €7m/year in 2015 and 2016 for the two products.

In case of a deal, the valuation of BIO101/103 would exceed €100m in 2017e …

A cash shortfall in 2017 could be largely offset by a €15m upfront from a licence sale for BIO101/103. We estimate the probability of this at 50%, corresponding to the probability of a drug going from phase II to phase III clinical trials. When the upfront of €15m from the BIO101/103 licence sale is received, we estimate that the valuation of the BIO101/103 product alone in 2017^{e} would exceed €100m compared to €26m in 2015.

…and that of BIO201/203 €150m in 2018e

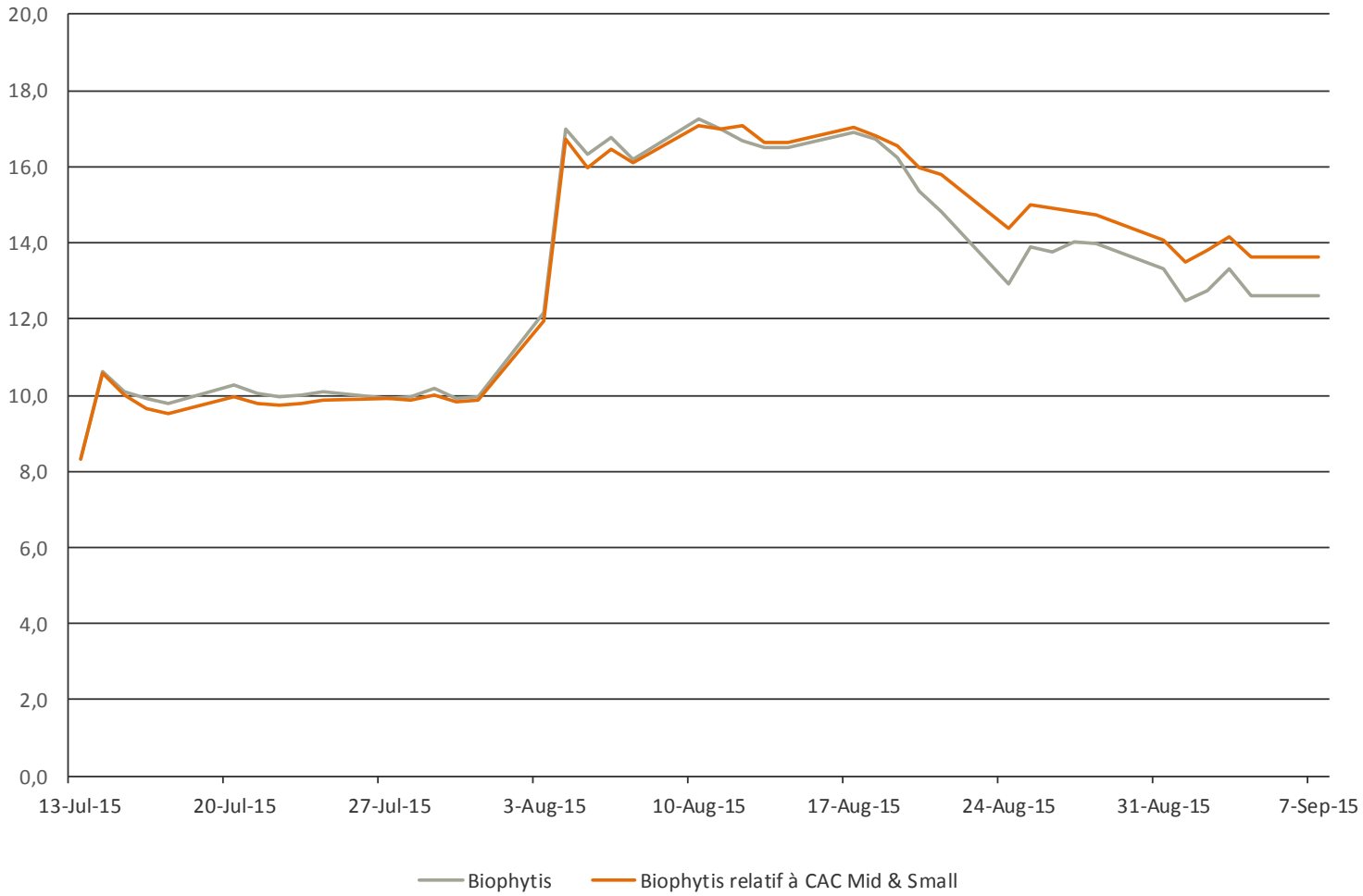
Similarly, if the second product (BIO201/203) is sold in 2018^{e} with an upfront of €25m as we anticipate, the valuation of this product in 2018^{e} would exceed €150m compared to €32m at present.

5.4 Newsflow

- **21 September 2015 :** start of production of clinical batches announced
- **Q4 2015 :** choice of a CRO (Contract Research Organisation) for clinical phase II-b trials
- **H1 2016 :** start of phase II-b studies of BIO101 in sarcopenic obesity and then BIO201 in AMD
- **2016 :** entry into preclinical trials of BIO103 and then BIO203
- **2017 :** phase II-b results for BIO101, followed by a licence agreement
- **2018 :** phase II-b results for BIO201, followed by a licence agreement

Disclaimer

Relative and absolute price change



CONFLICT SCREEN

	Corporate Finance	Treasury stocks holding	Prior communication	Analyst's personal interest	Liquidity contract	Listing Sponsor	Research contract
Biophytis	Yes	Yes	No	No	Yes	Yes	Yes

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