BRYAN, GARNIER & CO

INDEPENDENT RESEARCH

GeNeuro

The GeNesis of a disruptive treatment for MS

3rd June 2016

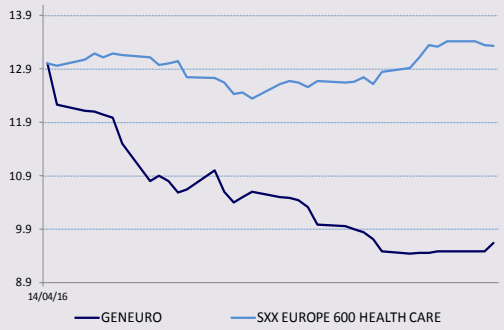
Healthcare

Fair Value EUR18.2 (price EUR9.64) **BUY**

Coverage initiated

Bloomberg	GNRO FP
Reuters	GNRO.PA
12-month High / Low (EUR)	13.0 / 9.4
Market capitalisation (EURm)	141
Enterprise Value (BG estimates EURm)	141
Avg. 6m daily volume ('000 shares)	4.20
Free Float	14.2%
3y EPS CAGR	NM
Gearing (12/15)	NM
Dividend yield (12/16e)	NM

YE December	12/15	12/16e	12/17e	12/18e
Revenue (EURm)	2.54	6.23	4.52	32.01
EBIT (EURm)	-4.32	-10.23	-12.92	6.22
Basic EPS (EUR)	NM	NM	NM	NM
Diluted EPS (EUR)	NM	NM	NM	NM
EV/Sales	NM	NM	NM	NM
EV/EBIT	NM	NM	NM	NM
P/E	NM	NM	NM	NM
ROCE	NM	NM	NM	NM

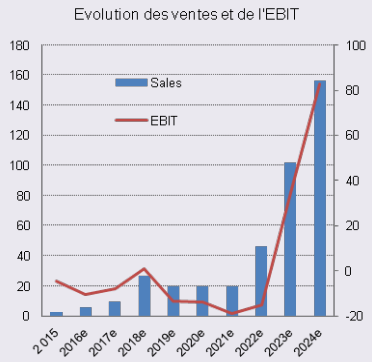


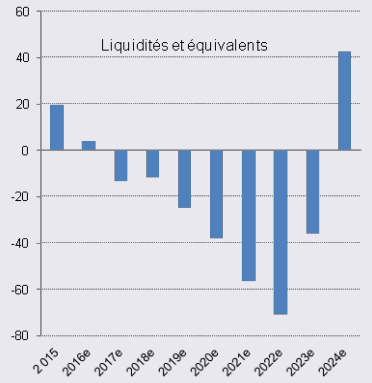
GeNeuro has taken a completely innovative and disruptive approach to treating a number of autoimmune diseases including multiple sclerosis, based on a technology that allows acting on the underlying process and potentially on one of the causes of the disease. If it came through, this approach would constitute a breakthrough and the product would probably become the new standard treatment for MS.

- Considering that the MSRV-Env envelope protein is highly expressed in the white matter of patients with MS lesions and after having characterised the pro-inflammatory and neurodegenerative modes of action of this protein, a causal relationship seems to be, if not demonstrated, at least likely. As a result, GeNeuro has developed an antibody that specifically targets this protein and that is intended to have an anti-inflammatory and remyelinating effect.
- The antibody is currently entering Phase IIb (260 patients) for RRMS with the financial support of a partner, Servier, which will bear the resulting costs. At the end of that phase, Servier will be able to exercise an option to acquire ex-US and ex-Japan selling rights for the drug as a treatment for MS, while GeNeuro will retain its selling rights for the US and Japanese markets and for all other indications.
- In view of the trends and geographic distribution of the MS market, there is very significant sales potential for GeNeuro. Servier could make milestone payments for a total of up to EUR325m, and it is likely to pay royalties of between 8 and 15% on its sales. In the US, GeNeuro will be free to choose what it considers to be the best strategy for maximising the value of its asset: either operating on its own or through a partnership.
- Based on the information currently available, we deemed it appropriate to base our valuation of GeNeuro exclusively on the MS indication. With a probability of success estimated at between 25% and 30%, a peak penetration rate of 10% in RRMS and a price in line with today's most effective treatments, our **median FV stands at EUR18.2.**

Analyst:
Eric Le Berrigaud
33(0) 1 56 68 75 33
eleberrigaud@bryangarnier.com

Sector Analyst Team:
Mickael Chane Du
Hugo Solvet





Company description

GeNeuro is a spin off from bioMerieux that was done back in 2006. The company has evidenced a causal link between the presence of endogenous viruses called HERV and development of auto-immune diseases. The more mature data available are in multiple sclerosis (MS) and a drug candidate is currently in phase IIb in this indication. . GeNeuro keeps significant rights although an agreement with Servier has been signed in. GeNeuro successfully achieved its IPO in April 2016 when it raised EUR33m.

Simplified Profit & Loss Account (EURm)	**2015**	**2016e**	**2017e**	**2018e**	**2019e**	**2020e**	**2021e**	**2022e**	**2023e**	**2024e**
Revenues	2.5	6.2	4.5	32.0	20.0	20.0	20.0	46.2	99.6	156
Change (%)	*-65.2%*	*145%*	*-27.4%*	*608%*	*-37.5%*	*0.0%*	*0.0%*	*131%*	*116%*	*57.0%*
R&D expenses	(5.0)	(10.7)	(13.2)	(18.7)	(29.1)	(29.1)	(24.1)	(14.1)	(9.1)	(9.1)
Change (%)	*36.3%*	*116%*	*23.3%*	*41.6%*	*55.5%*	*0.0%*	*-17.2%*	*-41.5%*	*-35.5%*	*0.0%*
EBIT	(4.3)	(10.2)	(12.9)	6.2	(13.5)	(13.6)	(18.7)	(14.8)	32.8	83.0
Change (%)	*-296%*	*-137%*	*-26.3%*	*-%*	*-317%*	*-0.8%*	*-37.3%*	*-20.6%*	*-%*	*153%*
Financial results	(0.14)	0.0	(0.11)	(0.26)	(0.38)	(0.49)	(0.57)	(0.66)	(0.37)	0.30
Pre-Tax profits	(4.5)	(10.2)	(13.0)	6.0	(13.9)	(14.1)	(19.2)	(15.5)	32.4	83.3
Tax	(0.02)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	(4.6)
Net profit	(4.5)	(10.2)	(13.0)	6.0	(13.9)	(14.1)	(19.2)	(15.5)	32.4	78.6
Restated net profit	(4.5)	(10.2)	(13.0)	6.0	(13.9)	(14.1)	(19.2)	(15.5)	32.4	78.6
Change (%)	*-353%*	*-128%*	*-27.4%*	*-%*	*-333%*	*-1.6%*	*-36.5%*	*-19.5%*	*-%*	*143%*
Cash Flow Statement (EURm)										
Operating cash flows	11.8	(16.0)	(17.1)	1.5	(13.1)	(13.2)	(18.2)	(14.4)	33.3	78.8
Change in working capital	(15.9)	5.8	4.3	4.8	(0.29)	(0.32)	(0.35)	(0.35)	(0.36)	(0.36)
Capex, net	0.07	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Dividends	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Free Cash flow	NM	(16.8)	(17.6)	0.91	(13.8)	(13.9)	(19.0)	(15.2)	32.4	78.0
Balance Sheet (EURm)										
Tangible fixed assets	0.07	0.07	0.08	0.08	0.08	0.09	0.09	0.10	0.10	0.10
Intangibles assets	0.15	0.13	0.11	0.09	0.07	0.05	0.03	0.01	(0.01)	(0.03)
Cash & equivalents	19.6	33.9	16.7	17.9	4.4	(9.3)	(28.1)	(43.1)	(10.3)	68.9
current assets	20.5	34.9	17.7	18.9	5.4	(8.3)	(27.1)	(42.1)	(9.2)	70.0
Total assets	20.8	35.1	17.9	19.1	5.6	(8.2)	(27.0)	(42.0)	(9.1)	70.1
L & ST Debt	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Shareholders' funds	1.7	21.8	8.8	14.7	0.87	(13.2)	(32.5)	(48.0)	(15.5)	63.1
Total Liabilities	19.1	13.3	9.1	4.3	4.7	5.1	5.5	5.9	6.4	7.0
Capital employed	17.1	11.3	7.0	2.2	2.5	2.8	3.1	3.5	3.8	4.2
Ratios										
Operating margin	NM	NM	NM	NM	NM	NM	NM	NM	32.92	53.06
Tax rate	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Net margin	NM	NM	NM	NM	NM	NM	NM	NM	32.55	50.29
ROE (after tax)	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
ROCE (after tax)	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Gearing	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Pay out ratio	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Number of shares, diluted	12,120	14,658	14,658	14,658	14,658	14,658	14,658	14,658	14,658	14,658
Data per Share (EUR)										
EPS	NM	NM	NM	NM	NM	NM	NM	NM	2.21	5.36
Restated EPS	NM	NM	NM	NM	NM	NM	NM	NM	2.21	5.36
% change	-	-	-	-	-	-	-	-	-	*143%*
BVPS	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
Operating cash flows	NM	NM	NM	NM	NM	NM	NM	NM	2.27	5.38
FCF	NM	NM	NM	NM	NM	NM	NM	NM	2.21	5.32
Net dividend	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM

Source: Company Data; Bryan, Garnier & Co ests.

Table of contents

1. Investment Case

Why the interest now?

The reason for writing now

Market and innovations in the treatment of MS are attracting much attention and GeNeuro's solution could result in the emergence of a disruptive therapy. Furthermore, the partnership with Servier has recently been taken to a new level. In inflammatory diseases, drugs usually reveal their true potential during Phase IIb studies and GeNeuro's for GNbAC1 has just started with first patient recruited.

Cheap or Expensive?

Valuation

Our valuation of GeNeuro is currently exclusively based on GNbAC1 as a treatment for MS, for which sufficiently mature data are currently available to anticipate a market launch around the beginning of the next decade and to apply probabilities of success. However, other developments that are underway on the same HERV group of potential targets might also be positive factors for the valuation but we keep them as pure upside. With GNbAC1 in MS alone, we derive a FV of EUR18.2 that represents almost double the current stock price.

When will I start making money?

Catalysts

GNbAC1 has just entered Phase IIb and GeNeuro is expected to keep the financial community up to date with patient enrolment, and also about whether the company comes to an agreement with US authorities to include a cohort of US patients (IND), which should take place in the Autumn. Furthermore, although the attention is largely focused on MS, 2016 will also be a year for confirming the utility of GeNeuro's research in the treatment of other conditions such as diabetes mellitus type 1 or demyelinating polyneuropathy.

What's the value added?

Difference from consensus

We are not sure there is any relevant consensus on GeNeuro but we think we have a good understanding of the main drivers of the MS market because we also cover most of the other companies involved in this field.

Could I lose money?

Risks to our investment case

The main risk associated with this investment case has to do with the development of its main product, GNbAC1, in the treatment of multiple sclerosis, which is the indication whose development is most advanced. This is why, at this stage, we have decided to base our valuation of GeNeuro exclusively on this indication. Any unforeseen event occurring during Phase IIb would have a significant impact on the valuation.

Please see the section headed "Important information" on the back page of this report.

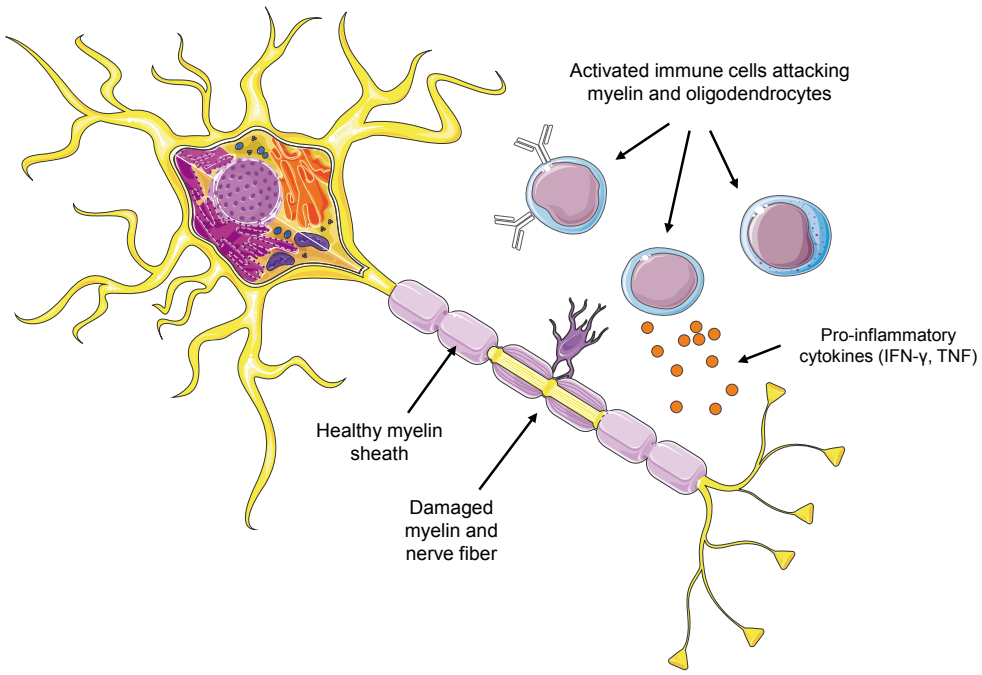
2. Multiple sclerosis and the MS drug market

2.1. What is multiple sclerosis?

The disease attacks myelin

Multiple sclerosis is a chronic autoimmune, inflammatory disease that damages the central nervous system. It attacks myelin (the biological sheath surrounding axons), which insulates and protects nerve fibres responsible for the communication between a neuron and its target cell. When it is attacked, the propagation speed of nerve impulse often decreases at first, and then it often leads to motor, sensory and cognitive impairments, and eventually to an irreversible disability.

Fig. 1: Multiple sclerosis – pathogenesis



In MS, immune cells attack 1/ myelin sheath (the protective coating of nerve fibers); 2/ oligodendrocytes (which are responsible for producing myelin), thereby preventing re-myelination.

Source: Bryan, Garnier & Co ests.

The cause of MS is unknown although a few facts should be noted:

- It is twice as common in women as in men;
- The first symptoms usually appear in adults in their thirties or forties;
- It is far more common in people who live closer to the North and South poles, which means sunlight exposure could have an influence although it has not been clearly determined;
- Genetic susceptibility to MS has been studied since several genetic variants related to the disease have been found;
- A possible infectious origin has also been mentioned, and we will obviously come back to this theory in this report since the founding teams of GeNeuro based their research on this hypothesis.

Despite a lack of certainty regarding aetiology, it is quite easy to diagnose multiple sclerosis (MS) even if the course of the disease is unpredictable and varies a lot from one patient to another, and the appearance of the first symptoms is heterogeneous. One of the difficulties is to establish a diagnosis after the first episode because, since MS is a chronic condition, at least two events are necessary to confirm the diagnosis, generally via MRI. It is estimated that 40% of episodes leave a slight sequela, which means most of them are not symptomatic and are thus difficult to interpret.

Beside the disease itself, it is also important to determine its exact form since it will have an impact on the therapeutic strategy to be adopted. There are two main forms of MS:

- **The most frequent form is called relapsing-remitting (RRMS) and it represents around 85% of cases at the time of first diagnosis.** It is more common in younger subjects and it is characterised by a succession of attacks called relapses or exacerbations which happen on average every 3 years although this is extremely variable between subjects (sometimes 10 years can pass between the first and the second exacerbation). It should however be noted that, after 20 years, half of RRMS cases develop into **a form called secondary progressive (SPMS)** where the disease is no longer characterised by exacerbations and instead is constantly and progressively evolving, with or without additional exacerbations.
- **The primary progressive subtype (PPMS) is less common (10 to 15% of cases)** and happens later in life but presents a poorer prognosis since it may very quickly develop into a disability for the patient.

The number and nature of the exacerbations are not correlated with the level of disability. Thus, although the concept of relapse has become important for drug development because it is an indicator of efficacy, the main issue for specialised neurologists is to keep the disease from becoming a disability, especially by preventing axonal degeneration.

2.2. What are the current standard treatments?

Let us review the biology behind MS. Although the exact cause is unknown, lymphocytes are activated, they cross the blood-brain barrier and differentiate into Th1 cells (aggressive) and Th2 cells (regulatory). There are fewer Th2 cells and they are less functional than Th1 cells but they are completed by other regulatory T cells (T-reg) produced by other cytokines. These Th1 cells are the ones that attack myelin in the brain white matter, once they have crossed the blood-brain barrier.

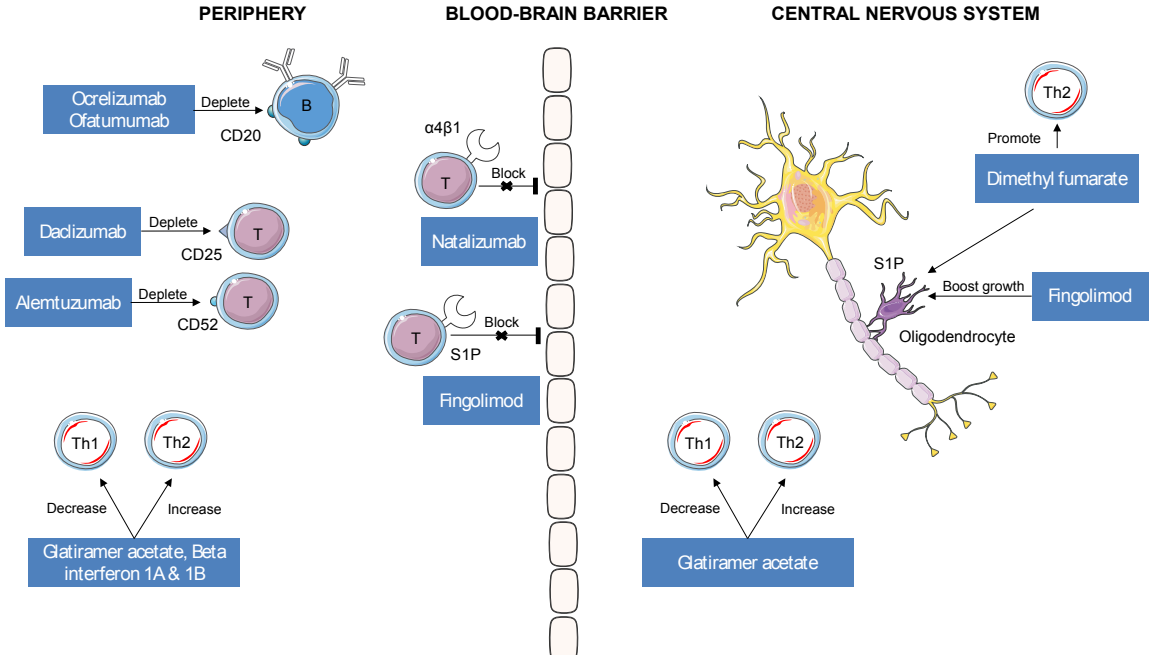
There is no treatment targeting the causes of the disease

Absolutely all existing treatments for MS are aimed at slowing down the progression of the disease, at reducing the number of inflammatory crisis and at improving quality of life for patients. The objective of historical treatments (interferons) was to increase the number of T-reg and offset the effects of Th1 cells on demyelination. As for glatiramer acetate, its objective was to create a decoy meant to be attacked by these Th1 instead of myelin, but the effect is only partial.

Besides being available in oral dosage forms, the most recent treatments also proved to have a greater efficacy in decreasing the number of exacerbations and the progression of the disease. However, they had a stronger impact on the immune system by suppressing lymphocytes production in T cells or by confining them at lymph node level, thereby increasing the risk of infection. Some of these treatments, although highly effective, generate a rebound effect following discontinuation, which is something that must be taken into account when starting treatment for a chronic progressive disease.

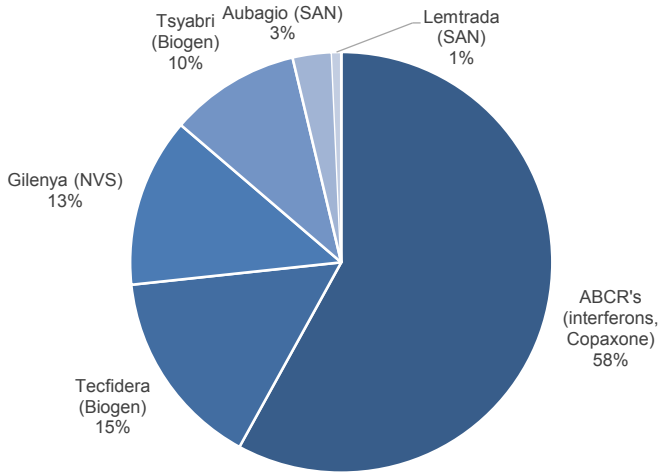
This is why, despite relatively undeniable improvements, the most recent drugs have not eliminated the use of interferons or Copaxone (see Fig.3), even in newly diagnosed patients because the offer a very good tolerability profile and efficacy that can be very satisfactory for several years. In RRMS cases, tolerability is key when the physician and the patient select a therapy.

Fig. 2: Multiple sclerosis – Mechanism of action of existing treatments



Source: Bryan, Garnier & Co ests.

Fig. 3: MS – Market share of the different treatments (2014)



Source: Evaluate Pharma

MS: a USD20bn market

However, despite these imperfections, the MS drug market has become a relatively significant market and is worth over USD20bn. It grew strongly in the past few years due to the emergence of new treatments supposedly positioned on more advanced lines of treatment and which strongly increased the average cost of MS treatment due to their higher cost but also because of the inflation they generated on the entire therapeutic arsenal against MS, especially in the US where price increases are allowed during the entire life cycle of a drug.

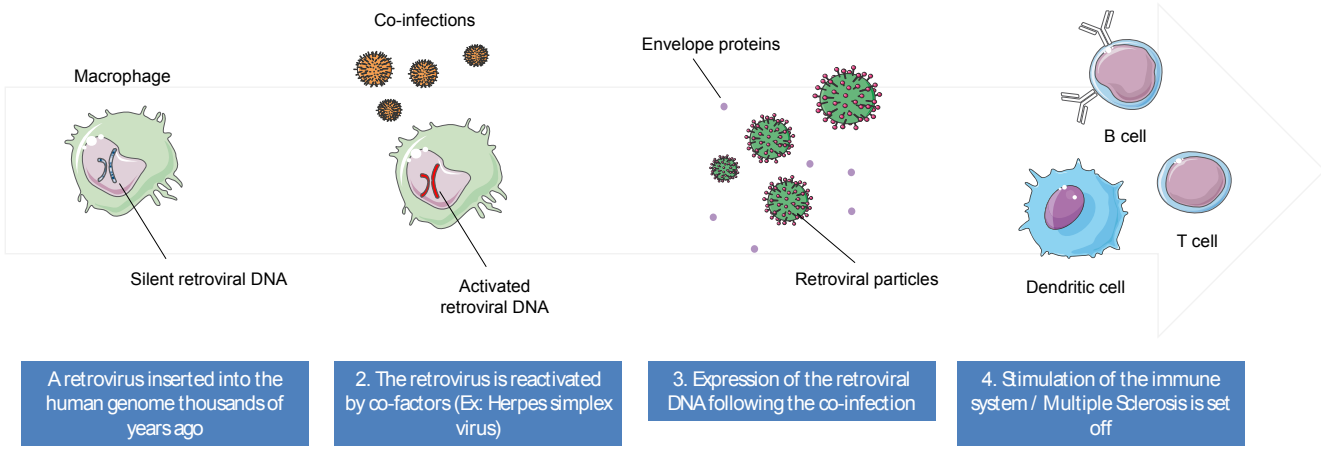
3. GNbAC1: a potential game changer

3.1. MS might have an endogenous retroviral origin

An intriguing lead seems to be taking an increasing importance in the scientific community: what if multiple sclerosis had an endogenous retroviral aetiology? More precisely, **it is possible that the causes of this disease lie in retroviral DNA sequences** remaining from infections that may have occurred several thousand years ago.

Usually, this part of our genome is completely silent and does not result in protein synthesis… But it is believed that this dormant DNA can be activated and result in an immunopathological phenomenon whenever an environmental cofactor is present (e.g. infection by herpes simplex virus). Several proteins would then be produced from these sequences and could be the source of the autoimmune response that characterises the disease.

Fig. 4: Potential role of endogenous retroviruses in pathogenesis



Source: Bryan, Garnier & Co adapted from company presentation

Among the endogenous viruses of interest, MSRV/HERV-W (multiple sclerosis-associated retrovirus/human endogenous retrovirus type W) particularly stands out in screenings for the following reasons:

- Post-mortem analyses show that **the resulting protein (Env) is very strongly expressed in the white matter** (composed of axons and myelin sheaths surrounding them) on the plaques in patients suffering from multiple sclerosis. This is the case regardless of the severity of the disease from the stage with new lesions defined as "pre-plaques" up to advanced forms where the protein is present in large amounts in microglial cells. This protein is also detectable in the bloodstream of patients whereas it is not in healthy subjects or patients suffering from other neurological pathologies (see Fig. 3), which means that it is a very specific marker of MS.

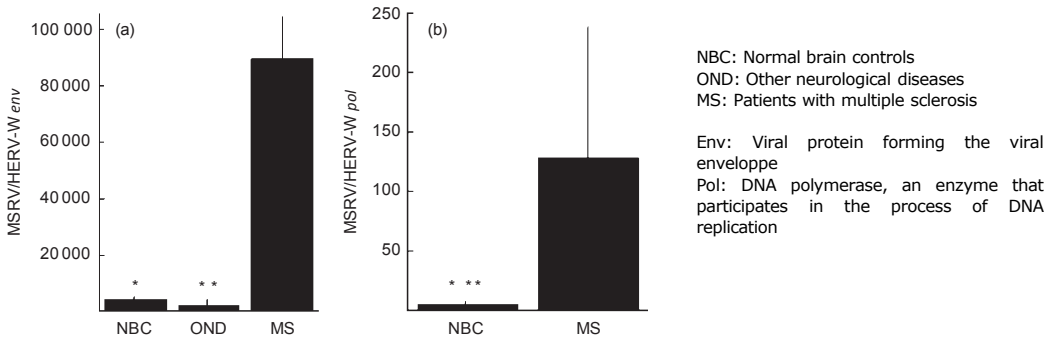
The MSRV-Env protein might play a significant role in the genesis and development of MS

- The MSRV-Env protein might play a significant role in the genesis and development of the disease as a TLR4 agonist, TLR4 being one of the receptors present at the surface of innate immune cells (macrophages in particular) but also of oligodendrocyte precursor cells (which are responsible for myelin production).

This protein of viral origin could be at the root of: 1/ the inflammatory process which characterises MS (activation of TLR4 leading to the production of chemical messengers such as IFN-gamma, IL-6 et IL-1β); but also of 2/ the axonal degeneration process due to its ability to inhibit the differentiation of oligodendrocyte precursor cells (Kremer *et al*, 2013).

- The level of expression of the MSRV-Env protein is believed to be correlated with the severity of the disease, as measured by the EDSS score (Sotgiu *et al*. 2002).

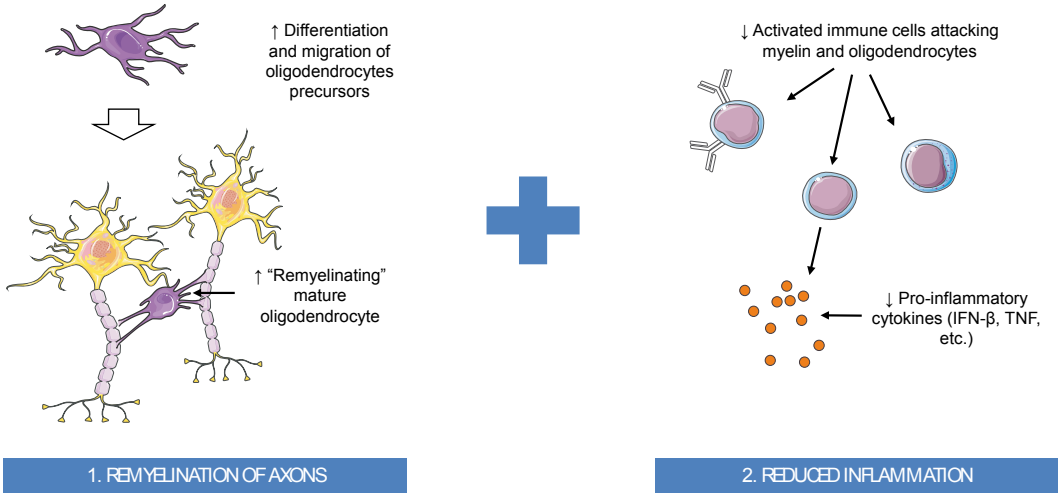
Fig. 5: Expression of the MSRV-Env protein in the brain of healthy subjects and patients with MS



Source: Adapted from Mameli et al, J Gen Virology 2007

3.2. GNbAC1: an approach that might allow for the interruption of the disease

Fig. 6: Mechanism of action of GNbAC1



Source: Bryan, Garnier & Co.adapted from company presentation

GNbAC1 is a humanised monoclonal antibody targeting/ neutralising the MSRV-Env protein

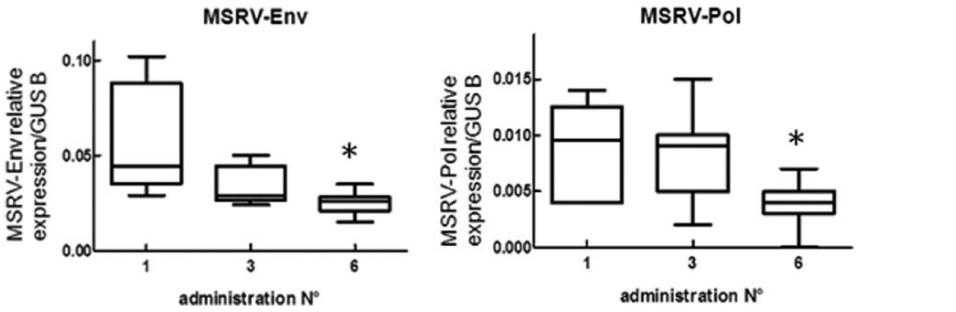
GNbAC1 is a humanised monoclonal antibody targeting/neutralising the MSRV-Env protein. By preventing the interaction between this protein and the TLR4 receptor, GNbAC1 could have a double beneficial effect: 1/ by reducing the number of pro-inflammatory cytokines, and consequently, the lymphocyte populations, which are at the core of the autoimmune response; and 2/ by stimulating the increase in oligodendrocytes.

The mechanism of action is very original in itself, but we would like to highlight the following:

- **Unlocking the maturation and migration of oligodendrocytes is a key differentiator for the GNbAC1 approach** compared to currently available therapeutic approaches. Oligodendrocytes are essential to myelin production and thus to the remyelination process (Keirstead *et al.* 1999; Podbielska *et al.* 2013), and as such it is not impossible that GeNeuro's approach might be able to interrupt the neurodegenerative process. Since oligodendrocytes are not targeted by the disease, they remain able to restore destroyed myelin. However, this process is very slow (it has been said that it takes two years for a few axons and near a decade for a brain) and the disease is rarely completely stopped to a point where this restoring process would be able to start, which is when we could truly speak of reversibility.
  Other projects currently under development also focus on activating remyelination, via different pathways. However, as discussed later on, this single-pathway mechanism of action could limit the addressable market of these other approaches.

- **The last element to be highlighted is far from minor.** It seems that the administration of GNbAC1 also results in a transcriptional repression of the MSRV-Env gene (see Fig. 12). There is still no explanation behind this phenomenon, but it is certain that it is a strong argument in favour of the product's long-term efficacy...

Fig. 7: MSRV-Env transcript levels following the administration of GNbAC1



Source: Derfuss et al 2015

3.3. Other approaches focusing on remyelination: promising but incomplete

We have identified several drug candidates with a potential remyelinating effect: GSK239512, BIIB061, etc. but we will focus on Biogen's anti-LINGO-1 antibody (BIIB033) since 1/ it is the "first-mover" in this category, and 2/ Phase II results should have been published early in the year and despite a delay are still expected around mid-year. If the trial is a success, it is very likely that the interest in this type of approach will increase (especially since the number of potential targets is relatively high).

Fig. 8: Potential targets in approaches aimed at activating remyelination

Targets	Mechanism of action
LINGO-1	Inhibition of oligodendrocyte precursor cell (OPC) differentiation
Noth Signalling	Involved in both promotion and inhibition OPC differentiation
Wnt Signalling	Controls timing of maturation of oligodendrocytes via inhibition of immature progenitors
RXR Signalling	Promotes OPC differentiation
Hyaluronan	Inhibition of OPC maturation, production by astrocytes
Sema3A	Inhibition of OPC recruitment
Sema3F	Promotion of OPC recruitment and division

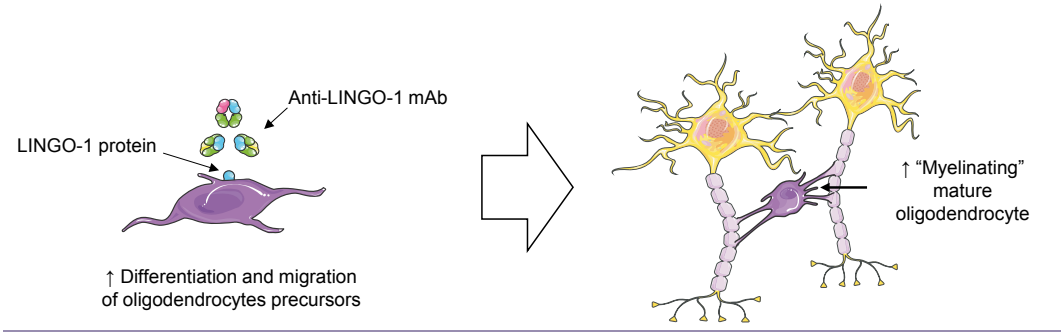
Source: Bryan, Garnier & Co.

- **Focus on Biogen's anti-LINGO-1 antibody**

The LINGO-1 protein is usually expressed at the surface of neurons or oligodendrocytes (whether they are mature or not) in the central nervous system. It is believed that its expression 1/ is stronger in patients with MS, and 2/ results in a blockade of the maturation of oligodendrocyte precursors (thus slowing down the (re)formation of myelin). It is thus assumed that its inhibition helps normalise the life cycle of these players, which are essential to the white matter. But all this remains very theoretical.

Phase I primary clinical data have mostly established the safety of use of this antibody, and the fact that it could cross the brain-blood barrier (it should be noted that no dose-effect relationship has been observed). However, no response was detected, although this lack of signs of activity was probably due to study design (short treatment duration).

Fig. 9: Mechanism of action of the anti-LINGO-1 antibody



Source: Bryan, Garnier & Co

■ **What is the market access for this approach?**

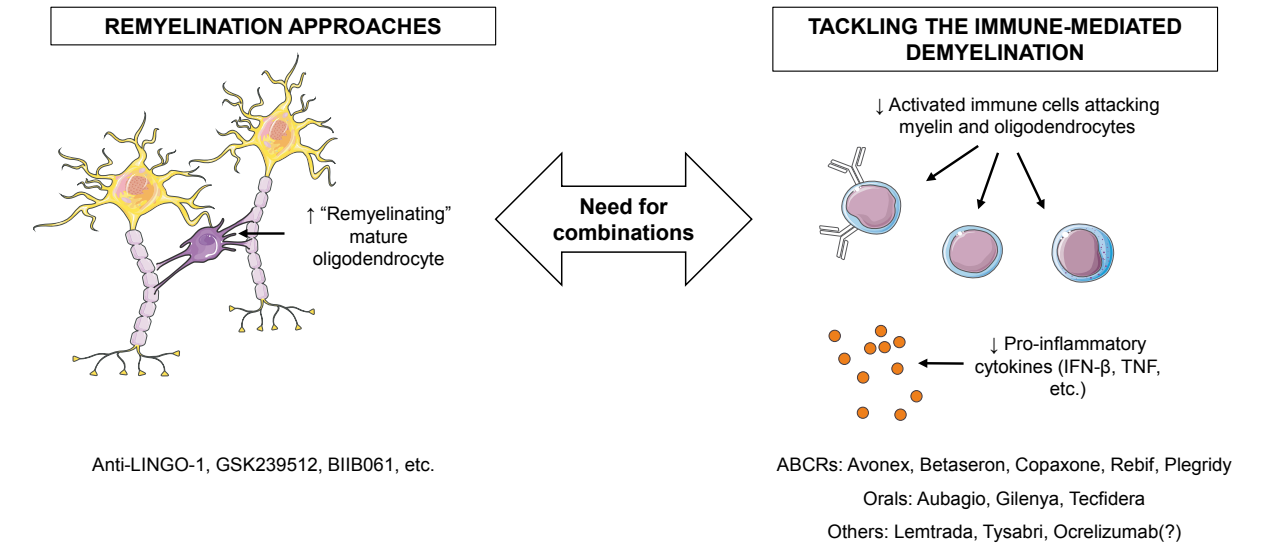
A potential issue of price and tolerability

Since these candidate drugs only focus on the remyelination process, we identified at least two important challenges:

- It is more than likely that these approaches will be combined with immunosuppressive drugs in order to decrease the risk of disease progression as much as possible (for instance, Phase II BIIB061 trial included the addition of Avonex, an interferon beta 1a). This poses **the question of the price competitiveness of the combination as well as what efficacy objective should be pursued** (especially if Biogen wishes to place it as a first-line treatment).
  From a strategic point of view, Biogen should build a clinical package including other products from its portfolio (Avonex, but also Tecfidera, or even Tysabri), and use the anti-LINGO-1 antibody as leverage for its market shares. In this perspective, we would not be surprised if companies without any project in the field of remyelination tried to catch up by concluding partnerships with those which have them (GSK? Vertex?).

- **There is also an issue with the security profile of the combination since it will affect its positioning within the different lines of treatment.** Primary clinical data have not showed any major side effects; but two elements call for caution: 1/ dose levels tested so far will probably be lower than those selected afterwards, which means we do not know exactly the toxicity profile of this compound at "commercial" dosages; 2/ will the fact that the antibody is humanised be a problem in a chronic disease such as MS?

Fig. 10: Why is it necessary to combine these approaches with immunosuppressants?



Source: Bryan, Garnier & Co

Although this approach should not be underestimated, in particular in view of its current stage of clinical development and of the support provided by large MS players, we believe that, at this stage, they do not pose a threat to GeNeuro and its GNbAC1 project. The latter seems to be have the advantage of an action which is both anti-inflammatory and remyelinating; thus it is more complete and more likely to receive approval as monotherapy.

4. A transformative deal with Servier

4.1. A need for financial support

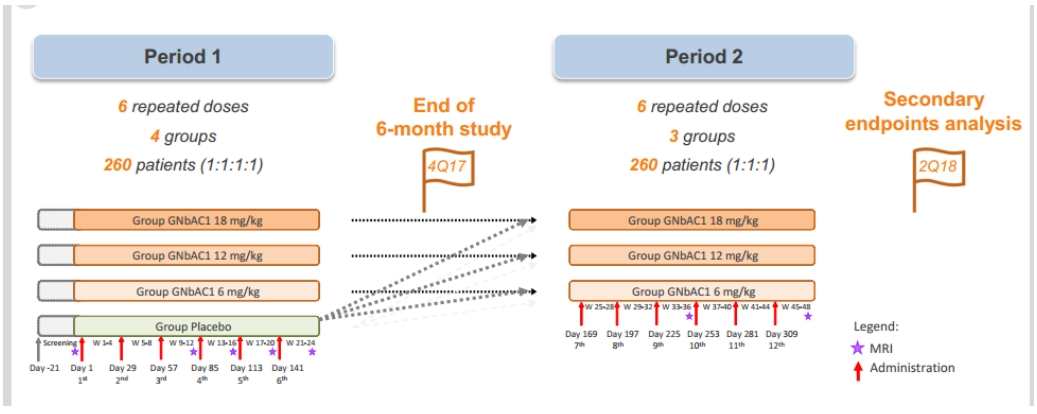
At the development stage that GNbAC1 has reached in multiple sclerosis, GeNeuro obviously needed financial support both from financial markets –hence the IPO project– and from a pharmaceutical company that would assist in going through the last clinical and regulatory steps of the development of the candidate drug.

A partnership was needed for the Phase IIb study

GeNeuro has just initiated the CHANGE-MS Phase IIb study, which will include 260 patients suffering from relapsing-remitting MS to be recruited in the European Union and Eastern Europe. The study has been designed in two parts:

- During the first period, patients will be assigned to 4 different arms: 3 active arms, each receiving a different dose level of GNbAC1 (6 to 18 mg/kg), versus a placebo arm. All groups will be administered 6 doses over a 6-month period and efficacy will be evaluated based on the number of visible brain lesions on monthly MRIs from the second month and at the end of the study period (which is actually too short to record trends in terms of MS exacerbations). Higher doses will be tested in order to evaluate whether they produce a different magnitude of response or a different time to onset of action, which might not be the strong point of this therapeutic approach compared to other approaches. The results are due by Q4 2017/Q1 2018;
- During the second period, placebo patients will cross over to one of the three treatment arms and there will only be three treatment arms left, still with monthly injections of GNbAC1 and quarterly MRIs. This second period will also last 6 months and all data from the primary and secondary endpoints should be available around mid-2018.

Fig. 11: Design of the Phase IIb study of GNbAC1 in MS



Source: Company Data

Extension in the US is under discussion

Patient recruitment will start in Q2 2016, leaving GeNeuro time to continue and finalise discussions with US authorities in order to be allowed by the FDA to conduct clinical trials in humans on GNbAC1 (IND approval), in which case the protocol of the Phase IIb study will need to be amended to include patients from some US centres. However, these US patients can be considered as "good to have" but not as a prerequisite or even a risk to the timely completion of the study. At this stage, we believe the total cost of the study can be estimated at EUR20m.

According the terms of the licence agreement with Servier, GeNeuro will receive EUR37.5m from its partner in order to conduct the Phase IIb study. EUR25.5m were already paid in 2014-15 and the remaining EUR12m will be paid by the end of the study. If Servier were to terminate the agreement with GeNeuro before the last visit of the last patient during the Phase IIb study, Servier would have to pay for the costs incurred by the latter up to a maximum amount of EUR12m.

4.2. But the wish not to be acquired

GeNeuro was looking for a partner like Servier which, unlike others, is a medium-size partner (i.e. with significant financial resources and strong international presence), and which would provide support rather that see in GeNeuro an external growth opportunity. The stake of around 8.6% that Servier took in GeNeuro's capital for EUR15m on December 11, 2016 (implying a total EV of about EUR175m) is significant but not too high and it illustrates the spirit of this partnership. This transaction involved the sale of shares by the ECLOSION 2 fund, a life sciences accelerator from the Geneva region that was present since the spin-off of GeNeuro from bioMérieux in 2006.

Servier has an option to acquire selling rights at the end of Phase IIb but GeNeuro keeps those for the US market

It is also extremely important to highlight another aspect of the agreement with Servier. Once Phase IIb data is released, Servier will have an option valid for 45 days for a licensing agreement, which will be a sort of confirmation of the agreement signed by the two parties. If the option is exercised, Servier will be granted the GNbAC1 license for the MS indication outside the US and Japan, in which case it will finance the whole Phase III development programme and pay GeNeuro up to EUR325m in development (up to EUR60m) and sales-related milestones (up to EUR250m), with an initial payment of EUR15m. In addition, GeNeuro will receive royalties equivalent to a high-single digit/mid-teens percentage of the sales generated by Servier our estimated range will be 8%-to 15%.

However, GeNeuro will retain not only the selling rights for any potential non-MS indications of GNbAC1, but also for the MS indication in the US and Japanese markets. This is especially important for GeNeuro's strategy of value creation, considering that while Japan is a rather small market for MS (low incidence), the US accounts for almost two thirds of total market size in value terms. This situation is the combination of higher prices but also of a treatment strategy where innovative, more aggressive therapies are used more often.

Therefore, GeNeuro will in any case retain control over its product in the lucrative US market and will, in due course, determine what strategy is most appropriate while remaining open to all opportunities. At this stage, it is our understanding that GeNeuro would favour a standalone strategy, considering in particular that the relatively reasonable HR and financial efforts that this would involve are compatible with the resources of a company of its size. Objectively, the decision will ultimately come down to two factors: (i) Phase IIb clinical data: the better they are, the stronger the impact they will have on the commercial success of the product, regardless of the sponsor's reputation and of the resources it devotes to this success; (ii) the competitive environment at the time the product is launched, especially as today's highly-competitive situation might become even more complicated due to the emergence of a number of new treatments including not only Roche's ocrelizumab, which has already been announced, but also S1P agonists (Celgene, Actelion), other anti-CD20 drugs (Novartis) and new drug classes (Biogen's anti-LINGO antibody, Novartis's anti-IL17 antibody, etc.).

The ability of incumbent players to counter the success of a smaller new entrant with less experience in the US market should not be underestimated. This might simply result in a co-promotion or co-marketing agreement, or even an acquisition.

All scenarios are possible in the US

Such a licensing agreement for the markets GeNeuro would retain (especially the US) would force the company to reimburse Servier for part of the development expenses incurred.

However, in our opinion, the only scenario in which GeNeuro would need to open negotiations with other pharmaceutical companies present in the MS market would be that of GNbAC1 showing mixed results in terms of potency or selectivity, which would lead to consider its use as part of combination therapies. At least, the existence of such a backup plan has the advantage of not putting investors in a mere 'all-or-nothing' situation.

5. Financial aspects and valuation

5.1. A buoyant MS market

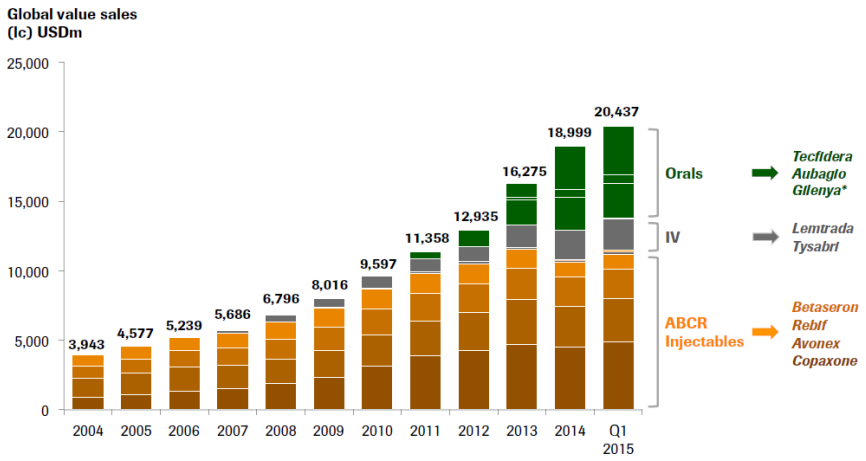
We chose to base our valuation of GeNeuro exclusively on GNbAC1 for the MS indication. This indication is the one whose clinical development is most advanced and whose body of evidence is largest, suggesting a high probability that the drug will have a favourable benefit/risk profile.

This is why we will focus again on the MS market, but this time with the objective of studying its trends and, in particular, the major transformation it is experiencing in terms of medical care and its likely expansion in view of recent and ongoing developments.

An innovation-friendly market

In terms of total sales for all existing treatments, the MS market is now worth over USD20bn. As shown in the graph below, which was presented by Roche during a conference call from the ECTRIMS congress last October, "historical products" (known as ABCR, see also Fig.4) still account for 55-60% of total sales. However, it also appears clearly that growth is exclusively driven by new products, especially oral dosage forms. Among these newer treatments, Tysabri is approaching the maturity stage of its life cycle, Lemtrada is in the early stage and the arrival of Roche's ocrelizumab next year will significantly stimulate the segment referred to here as "IV".

Fig. 12: Growth trend in the MS market



Source: Roche, IMS data Q1 2015

CAGR of global MS market sales over the past three years was between 16 and 17%. And the USD7-8bn increase can be largely attributed to Tecfidera and Gilenya, to a lesser extent to Aubagio.

Historical products remain strong (largely thanks to price increases offsetting lower volumes, especially in the US), which suggests some conservatism among neurologists and also that these drugs are still attractive therapeutic options, especially thanks to satisfactory post-marketing experience and tolerability profiles. However, the observable trend shows that innovation can be rewarded in the MS market. Both Gilenya and Tecfidera became blockbuster drugs only two years after they were launched.

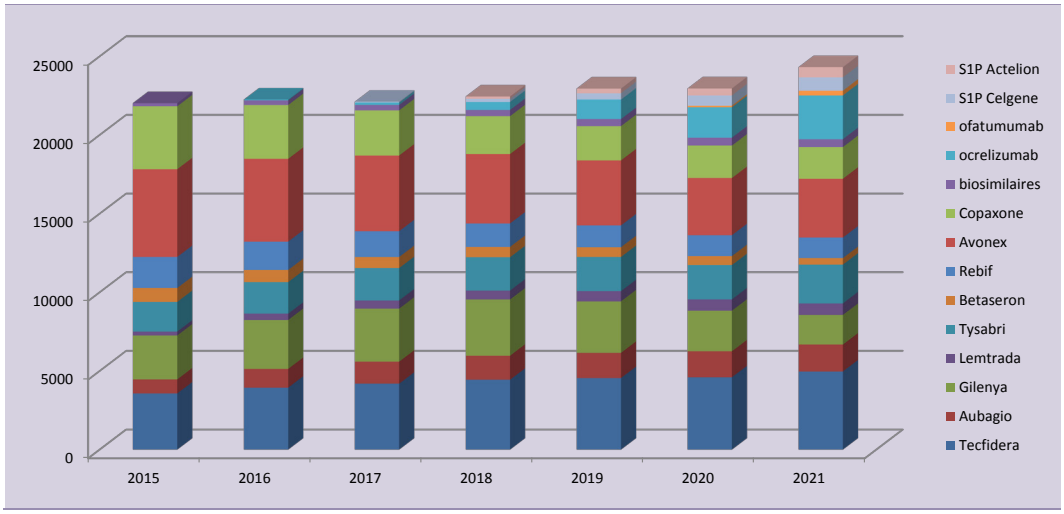
This market environment is obviously very favourable to GeNeuro, whose approach might be even more disruptive than previous innovations.

A market worth near USD25bn in 2022?

Until the potential launch of GNbAC1, which could reasonably be expected for 2022 (2022-2024 according to the company's conservative assumption), other products might be launched and increase the size of the market to around USD25bn according to our estimates, despite the expiry of at least some patents for Copaxone, Aubagio and Gilenya. The main cause of this will be the emergence of an "official" market for PPMS treatments, which will allow recording sales that are not currently monitored due to the fact that many of the products used are haematology-oncology drugs prescribed on an off-label basis (cyclophosphamide, rituximab, etc.). Off-label drug use is estimated at approximately a third of PPMS patients, although with wide geographic disparities.

To note in our recent interactions with management is that Novartis is very optimistic about the prospects of its recently-acquired anti-CD20 ofatumumab which may have a dual advantage over first-in-class ocrelizumab i.e. convenience and safety. With both Roche and Novartis allocating resources behind the class, we can expect the anti-CD20 family to be a major part of the total market in the next decade.

Fig. 13: Further growth expected until 2021



Source: Bloomberg; Bryan, Garnier & Co ests.

Concerning the geographic breakdown of MS drug sales, considerable differences between products can be observed in all therapeutic classes. The local reputation of the manufacturers seems to have an impact of the sales performance of the products. For instance, US manufacturers are clearly more successful on their domestic market. Although price differences can have a certain impact on revenues, they are not the only factor. This is important in the case of GeNeuro as the company is still the owner of all selling rights for its products in the US. The fact that Biogen products, for instance, generate disproportionately more revenues in the US than in the rest of the world, might be, when the time comes, one of the elements to bear in mind in order to decide whether a partnership is necessary –or appropriate– for marketing GNbAC1 in the US. On the contrary, Gilenya sales are equally distributed between the US and the rest of the world. All in all, the US represents two thirds of the global MS drug market.

5.2. Revenue assumptions

In order to estimate treatment prices, we considered that (1) GNbAC1 will only be launched after going through the clinical and regulatory selection processes and (2) its unique and innovative approach will be recognised and, therefore, priceable based on today's most expensive treatments as a minimum, i.e. EUR20,000-25,000 per year in the eurozone, CHF25,000-30,000 in Switzerland and around USD60,000 in the US.

A price in the range of today's highest prices

The whole sales model for GNbAC1 in the US and Europe, which is based on a series of assumptions, is shown in Appendices 1 and 2 of this report. Assumptions include market share by indication (up to 10% for RRMS and SPMS and up to 20% for PPMS) and prices by market (on average, EUR23,000 in Europe and USD60,000 in the US). Given the current stage of development of the product, we applied standard probabilities of success of 30% for Europe and a probability of 25% for the US in order to take into account that the drug has not received IND approval yet. If IND approval was granted in 2016 and if a significant number of patients were recruited in the US for the Phase IIb study, then a PoS of 30% for the US market could be assumed, which would have an impact of around EUR60m on EV.

GeNeuro's top line will include, on the one hand, the direct sales in the regions kept by GeNeuro (US mainly) that would be generated after a market launch in 2022 (conservative estimate) and, on the other hand, milestones and royalties to be paid by Servier in application of the agreement:

- Clinical milestones (1): these are of several types, i.e. short-term clinical, regulatory and commercial. GeNeuro received EUR17.5m at the end of 2015, which will be recognised in the accounts throughout the period of the study that they are intended to finance (2015-2018), as usual. Until the end of Phase IIb, Servier will have to pay GeNeuro EUR12m but we believe it is more reasonable to expect this payment for the end of the study, i.e. in 2018. Then, there will be the question of whether Servier exercises its option at the end of Phase IIb. If it does, GeNeuro will receive EUR15m.

EUR310m of milestones still to be received from Servier

- Clinical milestones (2): the sum of other potential milestones to be received by GeNeuro might add up to EUR310m, including EUR60m to finance a first Phase III study in RRMS. We believe the Phase III clinical program might be more ambitious and should consist of two studies regarding RRMS and at least one regarding PPMS (as Roche did for ocrelizumab). Then, a milestone extension might potentially be negotiated with Servier. For our calculations, we have distributed equally the EUR60m of Phase III milestones between 2019, 2020 and 2021. The last payment should be made during the approval of GNbAC1 by the EMA.

- Commercial milestones: these are always the most difficult to estimate and to spread over time because the exact terms of the agreement remain confidential. These milestones add up to EUR250m but it is not certain that GeNeuro will receive this total potential amount. In fact, that depends on the triggers. In this case, our understanding is that they are broadly designed as cumulative revenue thresholds (vs. revenue thresholds on a 12-month rolling period). On this basis, and according to the same philosophy as royalties, we assumed that there were 4 trigger thresholds at EUR500m intervals between EUR500m and EUR2bn. In terms of revenues accumulated year after year, we assumed that each of these 4 trigger thresholds will be met between 2023 and 2027 with a 5% rate (see Fig. 19). We have applied a risk-adjustment of 70%.

Fig. 14: Estimated revenue milestones to be paid by Servier

	2023	2025	2026	2027
Trigger threshold	EUR500m	EUR1,000m	EUR1,500m	EUR2,000m
Estimated milestone	EUR25m	EUR50m	EUR75m	EUR100m

Source: Bryan, Garnier & Co ests.

Average effective royalty rate could tend toward 10%

As regards royalties, we assumed progressive rates between 8 and 15%. In such cases, rates increase by levels and we assumed four progressive levels in this case (see Fig.20): at 8, 10, 12 and 15% every EUR500m of cumulative revenues. Based on revenues generated by Servier of about EUR1bn, the average effective royalty rate would stand at 9.0% in 2031. For that year, GeNeuro would be entitled to receive EUR89m of royalties. It should be borne in mind that we apply a probability of success of 30%.

Fig. 15: Estimated royalties to be received from Servier

	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
8% rate [0 - 500]	85.0	170.1	255.5	341.1	426.8	500.0	500.0	500.0	500.0	500.0	500.0
10% rate [500 - 1000]			0.0	0.0	0.0	25.6	124.6	223.9	349.1	487.4	488.6
12% rate [1000 - 1500]					0.0	0.0	0.0	0.0	0.0	0.0	0.0
15% rate [>1500]							0.0	0.0	0.0	0.0	0.0
Average effective rate	8.0%	8.0%	8.0%	8.0%	8.0%	8.1%	8.4%	8.6%	8.8%	9.0%	9.0%

Source: Bryan, Garnier & Co ests.

Regarding the US, and based on penetration rates broadly similar to Europe and on an annual cost of treatment of USD60,000, peak sales would be over EUR2bn before applying probabilities.

5.3. The cost structure is also modified

Of course, GeNeuro's cost structure will also show a strong increase in operating costs as the company is getting stronger in order to accelerate the clinical development of GNbAC1 and, more generally, now that the IPO has been successfully achieved, to accelerate other projects. The company recently reinforced its management team and will have to finance more expensive clinical studies than the current ones (in particular Phase III studies on GNbAC1 in RRMS and PPMS), with a larger cohort of US patients, resulting in a much higher cost per patient than in Phase IIb.

As mentioned above, we have estimated that the Phase IIb study, which is starting now, should cost between EUR15m and EUR20m. The cost of Phase III studies, which should be somewhere between EUR80m and EUR90m, will be spread between H2 2018 and 2021 and we think it might be increased depending on the endpoints and comparators to be selected, the number of target indications and the location of the centres.

Structural costs should also rise as, based on the success of the IPO, the company can now hire new employees in 2016 mainly in R&D. In 2015, the company recruited two new managers (CMO and CFO) and after the IPO, the CEO's compensation will have a different impact on the company. A growing staff also means larger premises and more overhead costs (travelling expenses, communication, etc.).

We finally decided to assume that GeNeuro was capable of financing its own development. In that case, structural costs would increase by more than 50% between 2015 and 2016.

In the medium term, it is obvious that the strategy to be adopted for launching GNbAC1 in the US might have an impact on the structure of operating costs at group level. Both the manufacturing costs of the drug and the sales and marketing infrastructure would need to be taken into consideration.

In the first case, we made the basic assumption of a gross margin of 80%. In the second case, there are several ways to estimate the cost of having an MS infrastructure in the US but Roche does not apparently consider it insignificant for ocrelizumab. We could consider the infrastructure developed by Ipsen for Somatuline for a cost of around EUR30m as a benchmark, but MS requires bigger investments. Another approach could be to use a percentage of sales, say at least 5%, which would mean an annual EUR100m. This figure seems rather reasonable, even if a larger amount is invested for the launch. We finally decided to use this figure but we applied the same probability as for revenues (25%).

Payments to BioMérieux in case of success

The last point to be discussed on the operating section of the income statement is the existence of an agreement between GeNeuro and BioMérieux that provides for clinical and regulatory milestones and royalties to be paid by GeNeuro on direct sales, but also on royalties to be received from Servier. In total, milestone payments might add up to approximately EUR70-80m if all development stages are completed, even though only EUR350k have been paid so far.

The corporate tax rate is likely to be of 13% when the company starts paying taxes

There is very little to say about the bottom line of the income statement. We should highlight that we have assumed low interest income on deposits (0.8%). As for corporate tax, the company had a tax loss carryforward of about EUR19m as of the end of 2014. Nevertheless, as losses can only be carried forward for a maximum period of 7 years according to Swiss regulations, we believe that only part of the losses will be utilised. However, since GeNeuro should continue to generate losses until the beginning of the next decade, we believe it will only start paying taxes from 2024. We based our calculations on the overall corporate tax rate of 13% that will soon be adopted by Switzerland (vs. 24.2% including federal, cantonal and communal taxes in Geneva).

5.4. Valuation

For the last time in this report, it is important to recall that our valuation only takes into account the potential of GNbAC1 in the multiple sclerosis (MS) segment.

Having described all the assumptions made in terms of revenues and costs in the above sections, the valuation assumptions themselves now need to be addressed, noting that our valuation is evidently based on a DCF model.

As with other companies that we consider to be at a similar development stage, namely DBV Technologies (slightly ahead in the process) or Innate Pharma, we have opted for a discount rate 15%, which is fairly standard for biotech companies with this type of profile. This implies a beta of 2.1.

Fig. 16: Calculation of discounted FCF

FCF Geneuro (m€)	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031
EBIT	-10 229	-12 920	6 219	-13 501	-13 603	-18 674	-14 833	32 792	82 972	130 862	173 973	214 525	222 954	262 742	317 773	374 504
-Taxes	0	0	0	0	0	0	0	0	-4 638	-17 180	-22 955	-28 437	-29 750	-35 167	-42 632	-50 296
+ D&A	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
- Capex	-4	-4	-4	-4	-4	-4	-4	-4	-4	-4	-4	-4	-4	-4	-4	-4
Change in WCR	-390	-240	-263	-289	-317	-348	-353	-361	-362	-375	-392	-416	-451	-483	-508	-537
Impact of accounting of milestones	-6 206	-4 500	-5 061													
FCF	-16 808	-17 644	911	-13 774	-13 904	-19 006	-15 170	32 447	77 987	113 323	150 642	185 689	192 769	227 108	274 649	323 687
years of discount	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
discount rate	1	0,87	0,76	0,66	0,57	0,50	0,43	0,38	0,33	0,28	0,25	0,21	0,19	0,16	0,14	0,12
discounted FCF	-16 808	-15 342	689	-9 056	-7 950	-9 449	-6 559	12 198	25 494	32 213	37 236	39 913	36 030	36 911	38 816	39 779

Source: Bryan, Garnier & Co ests.

Based on the assumptions presented in this report, the sum of discounted FCF would point to an enterprise value of EUR234m.

More importantly than the discount rate, to which it would be extremely arbitrary to assign a value of around 15%, we believe the main variables are the exact terms of the agreement with Servier (royalty rates, trigger thresholds and milestone levels, etc.), the strategy for launching the product in the US (standalone or partnership?), and the various possible penetration rates. We attempted to select midpoints. A variation of plus or minus 10% from these midpoint provides a valuation range of EUR211-257m.

FV of EUR18.2

After taking into account pension commitments and based on net cash which we estimate at EUR34m at the end of 2016 including the EUR33m raised at the IPO and a EUR4-5m cash burn per quarter as illustrated in Q1 2016, **our FV is EUR18.2 per share.**

Page left blank intentionally

Bryan Garnier stock rating system

For the purposes of this Report, the Bryan Garnier stock rating system is defined as follows:

Stock rating

BUY — Positive opinion for a stock where we expect a favourable performance in absolute terms over a period of 6 months from the publication of a recommendation. This opinion is based not only on the FV (the potential upside based on valuation), but also takes into account a number of elements that could include a SWOT analysis, momentum, technical aspects or the sector backdrop. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.

NEUTRAL — Opinion recommending not to trade in a stock short-term, neither as a BUYER or a SELLER, due to a specific set of factors. This view is intended to be temporary. It may reflect different situations, but in particular those where a fair value shows no significant potential or where an upcoming binary event constitutes a high-risk that is difficult to quantify. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.

SELL — Negative opinion for a stock where we expect an unfavourable performance in absolute terms over a period of 6 months from the publication of a recommendation. This opinion is based not only on the FV (the potential downside based on valuation), but also takes into account a number of elements that could include a SWOT analysis, momentum, technical aspects or the sector backdrop. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.

Distribution of stock ratings

BUY ratings 55.9% NEUTRAL ratings 34.3% SELL ratings 9.8%

Research Disclosure Legend

1	Bryan Garnier shareholding in Issuer	Bryan Garnier & Co Limited or another company in its group (together, the "Bryan Garnier Group") has a shareholding that, individually or combined, exceeds 5% of the paid up and issued share capital of a company that is the subject of this Report (the "Issuer").	No
2	Issuer shareholding in Bryan Garnier	The Issuer has a shareholding that exceeds 5% of the paid up and issued share capital of one or more members of the Bryan Garnier Group.	No
3	Financial interest	A member of the Bryan Garnier Group holds one or more financial interests in relation to the Issuer which are significant in relation to this report	No
4	Market maker or liquidity provider	A member of the Bryan Garnier Group is a market maker or liquidity provider in the securities of the Issuer or in any related derivatives.	No
5	Lead/co-lead manager	In the past twelve months, a member of the Bryan Garnier Group has been lead manager or co-lead manager of one or more publicly disclosed offers of securities of the Issuer or in any related derivatives.	YES
6	Investment banking agreement	A member of the Bryan Garnier Group is or has in the past twelve months been party to an agreement with the Issuer relating to the provision of investment banking services, or has in that period received payment or been promised payment in respect of such services.	YES
7	Research agreement	A member of the Bryan Garnier Group is party to an agreement with the Issuer relating to the production of this Report.	No
8	Analyst receipt or purchase of shares in Issuer	The investment analyst or another person involved in the preparation of this Report has received or purchased shares of the Issuer prior to a public offering of those shares.	No
9	Remuneration of analyst	The remuneration of the investment analyst or other persons involved in the preparation of this Report is tied to investment banking transactions performed by the Bryan Garnier Group.	No
10	Corporate finance client	In the past twelve months a member of the Bryan Garnier Group has been remunerated for providing corporate finance services to the issuer or may expect to receive or intend to seek remuneration for corporate finance services from the Issuer in the next six months.	YES
11	Analyst has short position	The investment analyst or another person involved in the preparation of this Report has a short position in the securities or derivatives of the Issuer.	No
12	Analyst has long position	The investment analyst or another person involved in the preparation of this Report has a long position in the securities or derivatives of the Issuer.	No
13	Bryan Garnier executive is an officer	A partner, director, officer, employee or agent of the Bryan Garnier Group, or a member of such person's household, is a partner, director, officer or an employee of, or adviser to, the Issuer or one of its parents or subsidiaries. The name of such person or persons is disclosed above.	No
14	Analyst disclosure	The analyst hereby certifies that neither the views expressed in the research, nor the timing of the publication of the research has been influenced by any knowledge of clients positions and that the views expressed in the report accurately reflect his/her personal views about the investment and issuer to which the report relates and that no part of his/her remuneration was, is or will be, directly or indirectly, related to the specific recommendations or views expressed in the report.	Yes
15	Other disclosures	Other specific disclosures: Report sent to Issuer to verify factual accuracy (with the recommendation/rating, price target/spread and summary of conclusions removed).	No

Summary of Investment Research Conflict Management Policy is available www.bryangarnier.com

Please see the section headed "Important information" on the back page of this report.

BRYAN, GARNIER & CO

London
Beaufort House
15 St. Botolph Street
London EC3A 7BB
Tel: +44 (0) 207 332 2500
Fax: +44 (0) 207 332 2559
Authorised and regulated by the Financial Conduct Authority (FCA)

Paris
26 Avenue des Champs Elysées
75008 Paris
Tel: +33 (0) 1 56 68 75 00
Fax: +33 (0) 1 56 68 75 01
Regulated by the Financial Conduct Authority (FCA) and the Autorité de Contrôle prudential et de resolution (ACPR)

New York
750 Lexington Avenue
New York, NY 10022
Tel: +1 (0) 212 337 7000
Fax: +1 (0) 212 337 7002
FINRA and SIPC member

Munich
Widenmayerstrasse 29
80538 Munich
Germany
+49 89 2422 62 11

New Delhi
The Imperial Hotel Janpath
New Delhi 110 001
Tel +91 11 4132 6062
+91 98 1111 5119
Fax +91 11 2621 9062

Geneva
rue de Grenus 7
CP 2113
Genève 1, CH 1211
Tel +4122 731 3263
Fax+4122731 3243
Regulated by the FINMA