GeNeuro S.A. (GNRO.PA)

Initiation Report

LifeSci Investment Abstract

GeNeuro (EPA: GNRO.PA) is a Swiss pharmaceutical company focused on the treatment of autoimmune diseases potentially mediated by the pathogenic expression of human endogenous retroviral (HERV) genetic elements. The retroviral protein MSRV-Env is ubiquitously expressed in multiple sclerosis (MS) lesions and has been proposed to be a causal trigger underlying MS pathology. GeNeuro is currently evaluating GNbAC1, a neutralizing antibody against MSRV-Env, in a Phase IIb study in collaboration with their partner Servier and expects to report preliminary results in the fourth quarter of 2017. In addition, GeNeuro has a broad portfolio of antibodies to address HERVs that have been linked to other autoimmune diseases.

Key Points of Discussion

■ **Targeting Potential Causal Factor for Multiple Sclerosis.** GeNeuro’s lead candidate is GNbAC1, a monoclonal antibody against the envelope protein of the multiple sclerosis associated retrovirus (MSRV-Env). This is a human endogenous retroviral (HERV) genetic element that is silent in healthy people but ubiquitously expressed in multiple sclerosis (MS) lesions. MSRV-Env has been shown to activate the toll-like receptor 4 (TLR4) pathway, a component of the innate immune system, and has been proposed as a causal trigger to the neuroinflammation and neurodegeneration seen in MS. GNbAC1 may prevent the immune activation thought to set the disease process in motion, reflecting a novel treatment strategy that could be highly disruptive to the MS treatment landscape.

■ **Partnership with Servier Provides Strong Validation of MS Program.** GeNeuro has a partnership agreement with Servier, a privately-held French company with an industry leading CNS product portfolio and a footprint in 148 countries. The partnership covers the use of GNbAC1 to treat MS. Servier is providing €37.5 million ($42.4 million) to finance the Phase IIb trial and has an option to license GNbAC1 after trial completion. Following the exercise of this option agreement, Servier would cover the cost of Phase III development. Importantly, GeNeuro has retained full rights in the US, which represents about two-thirds of the MS market, as well as Japan. The Company also has full rights to develop GNbAC1 in other indications, and Servier has the right of first negotiation within its territories. GeNeuro is eligible to receive up to €325 million ($366 million) in development and sales milestone payments as well as tiered royalties. The favorable terms of this deal put GeNeuro in an excellent position to develop GNbAC1 as well as other therapies for HERV-mediated diseases.

Expected Upcoming Milestones

■ H2 2016 – Launch Phase IIa proof-of-concept study for GNbAC1 in type 1 diabetes.
■ 2017 – Completion of enrollment for Phase IIb study in MS.
■ Q4 2017 – Preliminary results from CHANGE MS Phase IIb study in RRMS.
Phase IIa Data Show Early Signs of Efficacy and Favorable Safety Profile. GeNeuro has reported positive data from a Phase IIa study that tested the safety, tolerability, and pharmacokinetics of GNbAC1 in 10 MS patients. GNbAC1 was found to be safe and well-tolerated and showed no signs of immunogenicity or broad immunosuppression. In addition, although the sample size in this study was small, the trial did show a slowing of disability progression, providing an early indication of GNbAC1’s potential efficacy. The trial also demonstrated a pharmacokinetic profile suitable for once-monthly dosing and significant reductions in MSRV mRNA transcripts, which are also early indicators of the drug's activity. Since MSRV-Env lacks an endogenous physiological function, blocking this protein is not expected to have substantial off-target effects and the Phase IIa data provide an initial confirmation of this hypothesis.

Large Market Opportunity for Disease-Modifying MS Therapies. GNbAC1 has the potential to be highly disruptive to the MS market. If found to be effective, GNbAC1 would likely be used in a large proportion of relapse remitting MS (RRMS) patients. Due to its differentiated mechanism of action, it is likely that GNbAC1 could be used in combination with other MS therapies. Based on the market share of approved RRMS drugs, the total market opportunity for GNbAC1 is in the range $1.9 billion to $3.9 billion. However, if GNbAC1 is shown to substantially alter the disease course relative to what is achieved with existing treatments, then GeNeuro may be able to capture a larger portion of the market. There is also substantial upside potential if GNbAC1 is shown to be effective in progressive stages of the disease.

Complications from Broad Suppression of the Immune System with Existing MS Therapies. Many of the newer MS therapies modulate the immune system through broad effects on lymphocytes. Although these newer drugs have generated a lot of optimism in the potential for improved patient outcomes in MS, the safety concerns associated with these immunomodulatory drugs makes the prescription and monitoring of their use cumbersome. The induced alterations to the immune system may predispose MS patients to opportunistic and community-acquired infections, altered vaccine responses, malignancies, and autoimmune diseases. In rare cases, the use of Biogen’s (NasdaqGS: BIIB) Tysabri (natalizumab), Novartis’ (NYSE: NVS) Gilenya (fingolimod), or Biogen’s Tecfidera has been associated with the development of progressive multifocal leukoencephalopathy (PML), a rare demyelinating CNS disorder. GeNeuro’s strategy of blocking the activation of the immune system by MSRV-Env, a protein with no physiological function, is a more targeted approach than existing immunomodulators that may reduce the potential for complications associated with broad immune suppression.

Broad Potential to Treat Other Autoimmune Diseases with GNbAC1 and Other Anti-HERV Antibodies. The existing scientific literature suggests that a drug with anti-HERV activity may be effective in many autoimmune conditions in addition to MS, such as chronic inflammatory demyelinating polyneuropathy (CIDP) and type 1 diabetes (T1D). MSRV-Env expression has been implicated in both of these conditions as a potential causative agent underlying autoimmune activity. GeNeuro’s anti-HERV platform and expertise in HERV-mediated disease could allow for GeNeuro to develop disruptive therapies for these indications. The Company also has a preclinical candidate against HERV-K that is in development for amyotrophic lateral sclerosis (ALS). The extent to which other human diseases are linked to the expression of retroviral elements is not fully known. In the future, other HERV families may be

identified as targets for disease-modifying therapy. GeNeuro has founded an annual medical meeting to focus on HERV-mediated disease, which should foster collaboration and further development in the emerging field of HERV biology.

Financial Discussion

Second Quarter 2016 Financial Results. On July 18th, GeNeuro reported financial results for the second quarter of 2016. For the quarter, GeNeuro spent €2.6 million ($2.9 million) of cash in operating and investment activities. The Company also recognized a €2.5 million ($2.8 million) in revenue as a result of a milestone payment from Servier. As of June 30, 2016, GeNeuro had cash and cash equivalents of €42.4 million ($47.9 million), which should be sufficient to fund operations through 2018. The Company expects to report full financial results for the first half of 2016 on September 29, 2016.

Initial Public Offering. On April 14th, GeNeuro announced the completion of an initial public offering (IPO) on the Euronext Paris exchange. The 2,538,50 new shares were priced at €13.00 ($14.65) per share, and the deal raised a total of €29.4 million ($33.1 million) in net proceeds. Immediately following the IPO, GeNeuro had a market capitalization of roughly €190 million ($214 million).
Table of Contents

Company Description.......................................................................................................................... 5
GNbAC1: Monoclonal Antibody against MSRV-Env to Treat Multiple Sclerosis .................................................. 6
  Mechanism of Action.......................................................................................................................... 6
  MSRV-Env Induces Pro-Inflammatory Effects through TLR4 Pathway .................................................. 7
  Using MSRV-Env to Create Mouse Model of MS.................................................................................. 8
  Blockade with GNbAC1 Dampens Effects of MSRV-Env .................................................................. 10
  Safety Profile....................................................................................................................................... 12
Multiple Sclerosis .................................................................................................................................... 12
  Causes and Pathogenesis .................................................................................................................... 14
  HERV-W in Multiple Sclerosis............................................................................................................ 14
  Activated Microglia in MS.................................................................................................................... 16
  Microglia as Antigen-Presenting Cells (APCs)...................................................................................... 16
  MSRV and TLR4 Expression on Endothelial Cells................................................................................ 16
  MSRV and the Inhibition of Remyelination.......................................................................................... 16
  Diagnosis and Symptoms ................................................................................................................... 17
  Treatment............................................................................................................................................ 18
Disease Market Information .................................................................................................................... 21
  Epidemiology....................................................................................................................................... 21
  Market Size.......................................................................................................................................... 21
  Pricing and Market Share Analysis....................................................................................................... 22
Clinical Data Discussion .......................................................................................................................... 24
  CHANGE MS Phase IIb Trial with GNbCA1 in Multiple Sclerosis ......................................................... 28
Competitive Landscape........................................................................................................................... 29
GNbAC1 to Treat Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) ........................................... 30
GNbAC1 to Prevent Autoimmune Destruction of Beta Cells in Type 1 Diabetes.......................................... 32
GNbAC1 to Treat Other HERV-Mediated Diseases................................................................................ 32
Intellectual Property & Licensing............................................................................................................. 33
Management Team............................................................................................................................... 33
Risk to an Investment............................................................................................................................... 35
Analyst Certification............................................................................................................................... 36
Disclosures............................................................................................................................................. 36
Company Description

GeNeuro is a clinical-stage company focused on the development of therapies targeting pathogenic expression of human endogenous retroviral (HERV) genetic elements, which are thought to underlie a wide range of autoimmune conditions. The Company was spun out from bioMérieux in 2006 and completed an initial public offering in April 2016 on the Euronext Paris exchange. GeNeuro’s lead product candidate, GNbAC1, is a neutralizing antibody against the envelope protein of the multiple sclerosis associated retrovirus (MSRV-Env). MSRV-ENV is a protein encoded by a gene of endogenous retroviral origin, that is normally silent but is ubiquitously expressed in active lesions found in patients with multiple sclerosis (MS).

MSRV-Env has been shown to activate the toll-like receptor 4 (TLR4) pathway, a component of the innate immune system, and is suspected to be a causal factor triggering the neuroinflammatory and neurodegenerative cascade in MS patients. In contrast, existing therapies for MS focus on dampening the severity of the immune-mediated attack rather than preventing the primary cause of autoimmune activation. GeNeuro is currently testing GNbAC1 in a Phase IIb study in 260 patients with relapsing-remitting MS (RRMS) and expects to report preliminary results in the fourth quarter of 2017. Positive results in this trial could provide important validation of the Company’s novel treatment strategy for MS and encourage further exploration of anti-HERV therapeutics as treatments for a range of autoimmune diseases.

The Company has a partnership with Servier (private) covering the treatment of MS with GNbAC1. GeNeuro is responsible for the development of GNbAC1 through the completion of the Phase IIb study, after which Servier can exercise the option to license the product for all markets excluding the US and Japan. Servier is providing €37.5 million ($42.4 million) to finance the Phase IIb trial. Following the exercise of this option agreement, Servier would cover the cost of Phase III development and pay GeNeuro up to €325 million ($366 million) in milestone payments as well as tier royalties on net sales. GeNeuro has retained full rights to GNbAC1 for the treatment of MS in the US market, which is where two-thirds of MS drug revenue is derived, as well as Japan. GeNeuro has also retained full rights to develop GNbAC1 for other HERV-mediated diseases. The Company plans to launch Phase II proof-of-concept studies for GNbAC1 in chronic inflammatory demyelinating polyneuropathy (CIDP) and type 1 diabetes (T1D), two autoimmune disorders in which the underlying disease pathology has been linked to the pathogenic expression of MSRV-Env. Figure 1 shows GeNeuro’s full development pipeline for HERV-mediated diseases.

Figure 1. GeNeuro’s Development Pipeline

Source: LifeSci Capital
GNbAC1: Monoclonal Antibody against MSRV-Env to Treat Multiple Sclerosis

GNbAC1 is a recombinant, humanized monoclonal antibody against the envelope protein of the multiple sclerosis-associated retrovirus (MSRV-Env). MSRV was first discovered in the late 1980s in the cerebrospinal fluid (CSF) of an MS patient and later identified as a member of the human endogenous retrovirus type W (HERV-W) family. HERVs comprise roughly 8% of the human genome, reflecting retroviral integrations into our genome over the course of human evolution. The human genome possesses roughly 30 env HERV-W related regions, and this number can vary substantially across individuals. While normally not expressed, or silent, MSRV-Env retroviral elements can be transactivated by exposure to certain herpes viruses. MSRV-Env activation in perivascular macrophages is thought to lead to activation of the toll-like receptor 4 (TLR4) pathway, a component of the innate immune system, resulting in a cascade of pro-inflammatory effects responsible for MS pathology. As a neutralizing antibody against MSRV-Env, GNbAC1 may halt activation of the innate immune response that is believed to underlie the disease process.

GeNeuro is currently conducting the CHANGE MS Phase IIb study in 260 RRMS patients to evaluate the safety and efficacy of GNbAC1 and expects to report preliminary results from the trial in the fourth quarter of 2017. A prior Phase Iia study showed the treatment to be safe and well-tolerated and provided initial indications of slowing the disease progression. Results from the Phase IIb study could provide important validation of this novel treatment strategy and its underlying retroviral hypothesis for MS.

Mechanism of Action. GNbAC1 is a humanized immunoglobulin 4 (IgG4) monoclonal antibody against the HERV-W envelope protein MSRV-Env, a HERV element found in our genome. While normally silent, the activation of MSRV-Env expression in the brain is thought to be a potential trigger of MS pathology. By binding to MSRV-Env, GNbAC1 prevents activation of the TLR4 pathway, a component of the innate immune system. The activation of the TLR4 pathway results in many of the classic features of MS pathology, including the opening of the blood-brain barrier, the release of pro-inflammatory cytokines, and inhibition of the remyelination process. Blocking TLR4 activation with GNbAC1 may halt a key signal that pushes the immune system into a pro-inflammatory state and could potentially dampen the disease severity or arrest the disease process entirely.

In addition, TLR4s are expressed on oligodendrocyte precursor cells (OPCs) and its activation has been shown to inhibit the process of remyelination. TLR4 activation on OPCs disrupts the differentiation of these cells, which is a key step in the process of remyelination. The incomplete or absent attempt at remyelination compromises axonal conduction in neurons and leads to neurodegeneration in progressive stages of the disease. Thus, GNbAC1 may eliminate the pro-inflammatory state that is inhibitory to the maturation of OPCs and promote remyelination in MS lesions. In an in vitro study, collaborating investigators demonstrated that GNbAC1 could reduce HERV-W mediated blockade of OPC maturation. This could permit myelin repair, which has not yet been achieved with existing therapies.

MSRV-Env Induces Pro-Inflammatory Effects through TLR4 Pathway. Preclinical studies have demonstrated that MSRV viral particles or the MSRV envelope protein (MSRV-Env) are capable of eliciting pro-inflammatory responses. Figure 2 shows the release of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), from purified human monocytes in response to 24 hours of stimulation with MSRV particles (black) or mock control (gray).

**Figure 2. Pro-Inflammatory Cytokine Release Following MSRV Exposure**

Even just the surface subunit of MSRV-Env protein (Env-SU) exerts pro-inflammatory effects. Investigators tested whether the Env-SU fragment was sufficient to elicit phenotypic changes tied to dendritic cell (DC) maturation. While immature and mature DCs express CD11c, the upregulation of MHC class II expression is specific to mature DCs. Following 24 hours of incubation, there was a large increase in the percentage of cells double-labeled for CD11c and MHC class II, indicative of DCs differentiating into a mature state. The results obtained by stimulating DCs with Env-SU was comparable to DC stimulation with lipopolysaccharide (LPS), a bacterial endotoxin capable of stimulating the release of pro-inflammatory signals.

**Figure 3** shows the release of cytokines following the stimulation of DCs with Env-SU or LPS, used as a reference. Stimulation with Env-SU induced the release of pro-inflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα), in a dose-dependent manner. The amount of cytokine release resulting from 2 µg of Env-SU was comparable to the release induced by LPS stimulation. The investigators also confirmed that this cytokine release directly resulted from stimulation with Env-SU by successfully blocking the effect with an anti-Env monoclonal antibody.

---


Repeating this experiment in transgenic mice containing a knockout of the toll-like receptor 4 (TLR4) gene diminished cytokine production in response to MSRV-Env stimulation. This demonstrated that MSRV-Env stimulates immune cells through the TLR4 pathway, which is a component of the innate immune system. The same effect was observed in knockout mice of the CD14 protein, which is a co-receptor with TLR4. Through activation of TLR4 receptors, the envelope protein of MSRV is thus capable of triggering neuroinflammatory responses.

Using MSRV-Env to Create Mouse Model of MS. Traditionally, MS has been studied in mouse models through the induction of experimental autoimmune encephalomyelitis (EAE), an autoimmune condition that mimics much of the MS pathology. EAE is commonly induced by introducing a myelin protein fragment, such as myelin basic protein (MBP) or myelin oligodendrocyte glycoprotein (MOG), concurrently with *Mycobacterium tuberculosis* and pertussis toxin.\(^\text{11}\) Instead, investigators studying MSRV-Env created a mouse model of EAE induced by the administration of MOG concurrently with the surface subunit of MSRV-Env protein (Env-SU).\(^\text{12}\) Figure 4 shows 4 groups of mice with EAE induced through one of the following methods:

- MOG35-55 in complete Freund’s adjuvant (CFA) containing *Mycobacterium tuberculosis* (orange).
- 10 µg of MSRV-Env-SU + MOG35-55 + incomplete Freund’s adjuvant (IFA) (dark blue).
- 50 µg of MSRV-Env-SU + MOG35-55 + incomplete Freund’s adjuvant (IFA) (light blue).
- MOG35-55 in incomplete Freund’s adjuvant (IFA) (green).

This experiment clearly shows that mice immunized with MSRV-Env in the presence of the MOG peptide fragment develop EAE 4-8 days after immunization. Upon histological analysis, these mice had evidence of demyelinating neuroinflammation. In addition, the 50 µg cohort (light blue) reached a clinical score of 2.5, while the 10 µg cohort (dark blue) reached a clinical score of roughly 1.0, indicating that the response may be dose-dependent. The clinical score elicited with 50 µg of MSRV-Env-SU even exceeded the clinical score induced in the classical EAE mouse model (orange). Clinical scores were defined in the following manner:

\(^\text{11}\) Miller, SD, et al., 2010. Experimental Autoimmune Encephalomyelitis in the Mouse.

0 – No signs.
1 – Loss of tail tonicity, hyper-reflexia of hindlimb(s), or unilateral hindlimb weakness.
2 – Bilateral hindlimb or forelimb weakness.
3 – plus unilateral paralysis or major deficit.
4 – Complete hindlimb or forelimb paralysis.
5 – plus partial paralysis or major deficit of opposite limbs.
6 – Death.

These results indicate that MSRV-Env can be used instead of Mycobacterium tuberculosis to induce EAE. The Env-based EAE model may be preferable, since this protein is ubiquitously found in MS lesions and Mycobacterium tuberculosis are not. This experiment provides supportive evidence linking MSRV-Env to the pathogenesis of MS.

Figure 4. MSRV-Env Can Induce Experimental Autoimmune Encephalopathy

In mice with EAE induced by Env-SU, cultured T lymphocytes from the spleen secreted interferon gamma (IFNγ) in a dose-dependent manner in response to MOG, a structural protein found in the myelin sheath. Figure 5 quantifies the amount of IFNγ released in response to MOG35-55 protein fragment following immunization with either MOG35-55/Env-SU (black) or MOG35-55/IFA (white) as a control. The anti-MOG effect was significantly greater at 24, 48, and 72 hours in Env-SU immunized mice compared to control mice, pointing to a specific autoimmune response against this antigen following exposure to Env-SU.
Blockade with G NbAC1 Dampens Effects of MSRV-Env. The pro-inflammatory effects of MSRV can be reversed by blocking activation of TLR4. In a preclinical experiment, pre-incubation of purified monocytes in a solution containing a neutralizing antibody against TLR4 (αTLR4) dampened TNF-α release in response to 24 hours of stimulation with MSRV particles. Treatment with a neutralizing antibody against TLR2 did not produce this effect, confirming the specificity of MSRV to activate TLR4. These results are shown in Figure 6.

Figure 6. Anti-TLR4 Antibody Dampens Cytokine Release Following Stimulation with MSRV

Source: Rolland et al., 2006

Figure 5. IFNγ Release Following Immunization with MOG35-55 and MSRV-Env

Source: Perron et al, 2013
GeNeuro tested the efficacy of GNbAC1 in a mouse model of EAE induced with MSRV-Env. This preclinical study evaluated three variants of anti-MSRV-Env antibodies, including murine (mu-GNbAC1), chimeric IgG1 (ch-GNbAC1-IgG1), and chimeric IgG4 (ch-GNbAC1-IgG4) variants. **Figure 7** highlights the results of this experiment. After 28 days, all of the untreated animals (dark magenta) died or required euthanasia due to complete paralysis. However, all of the mice treated with either chimeric GNbAC1 variant survived, while two mice treated with the mu-GNbAC1 variant did not survive. The results show comparable effects with either the IgG1 and IgG4 variants, indicating that the IgG4 antibody, which have a lower likelihood of inducing antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) than IgG1s, can be used to block MSRV-Env activity. The use of an IgG4 variant of the antibody could reduce the risk of toxicities and off-target effects.

**Figure 7. Clinical Score Reductions Following Treatment with GNbAC1**

![Graph showing clinical score reductions](image)

Source: Curtin et al., 2014

**Figure 8** shows that blocking MSRV-Env with GNbAC1 can rescue the process of remyelination by reducing stress on oligodendrocyte precursor cells (OPCs). MSRV-Env disrupts OPC maturation through TLR4 activation on OPCs, nearly cutting the percentage of MBP-positive OPCs in half (white striped box). However, application of GNbAC1 (gray striped box) restored the rate of myelination, as measured by the presence of MBP, to roughly 87% of baseline (p<0.01), suggesting that GNbAC1 could have a positive impact on remyelination in MS patients.

---


Safety Profile

GeNeuro has demonstrated in multiple clinical trials that GNbAC1 has a favorable safety and tolerability profile. GeNeuro conducted two Phase I studies in healthy volunteers to establish the safety and pharmacokinetic profile of GNbAC1. In the Company’s Phase IIa study, GNbAC1 was found to be safe after a full year of repeated administrations. There have been no infusion reactions, hypersensitivities, or indications of immunogenicity. No maximum tolerated dose was identified in these studies, where the Company was testing 2 mg/kg and 6 mg/kg doses of GNbAC1, allowing them to test several higher doses in the Phase IIb study.

MSRV-Env is not typically expressed in humans and does not have a known function, so sequestering this protein is expected to have minimal physiological impact. In addition, this targeted approach leaves host immunity intact, which may reduce the risk of infections or other health complications as a result of treatment. Due to its different mechanism of action, GNbAC1 may be free of many of the safety concerns associated with existing MS therapies. In GeNeuro’s Phase IIa trial, there were no indications that GNbAC1 has immunosuppressive activity and there was no observed impact on lymphocyte reaction to antigens when GNbAC1 was present.15

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS), which affects the brain, spinal cord, and optic nerves. While the etiology of this disease is currently unknown, researchers postulate that it is triggered by one or more environmental factors in genetically susceptible individuals. In MS, the immune system selectively

targets the myelin sheaths surrounding nerve fibers causing scarring, also known as sclerosis, and damage to the fibers themselves. This can be seen through the development of lesions within the white matter of the brain.

**Figure 9** illustrates a normal myelin sheath surrounding the nerve fiber axon in the top panel, versus exposure of the fiber when the myelin is damaged. Damage to large collections of axons in the brain creates the distinctive MS lesions. Damage to these sheaths causes improper and altered impulse propagation resulting in a range of symptoms, including blurred or loss of vision, numbness in the limbs, lack of coordination and balance, weakness, and cognitive issues. MRI imaging with gadolinium staining can help visualize the lesions and is an important part of the diagnostic process. In addition, T-lymphocytes appear to be involved in directly attacking myelin, and through inflammatory responses can also act to hasten the breakdown process by recruitment of other immune cells and factors.

**Figure 9. Myelin Sheaths – Normal Versus Damaged**

![Myelin Sheaths](image)

*Source: Mayo Clinic*

**Types of MS.** In 1996 the National Multiple Sclerosis Society published the results of an international survey of clinicians who treat patients with MS. The data from the survey showed that a diagnostic consensus existed in the MS field, which led to the description of the four types of MS. These are progressive-relapsing, secondary-progressive, primary-progressive, and relapsing-remitting MS. **Figure 10** provides an explanation of each type of MS and the percentage of patients who are diagnosed with the types. Relapsing-remitting (RRMS) is the most common form of MS.

---

Figure 10. Types of Multiple Sclerosis

<table>
<thead>
<tr>
<th>MS Type</th>
<th>% of Patients at Diagnosis</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive-Relapsing</td>
<td>5%</td>
<td>Steady worsening of disease from start with occasional relapses.</td>
</tr>
<tr>
<td>Primary-Progressive</td>
<td>10%</td>
<td>Steady worsening without any signs of relapses.</td>
</tr>
<tr>
<td>Relapsing-Remitting</td>
<td>85%*</td>
<td>Relapses followed by partial or complete recovery periods.</td>
</tr>
<tr>
<td>Secondary-Progressive</td>
<td>55% of RRMS patients**</td>
<td>Follows relapsing-remitting stage. Disease worsens more steadily with or without relapses.</td>
</tr>
</tbody>
</table>

*Approximately 85% of all MS patients are initially diagnosed with Relapsing-Remitting MS (RRMS)

**Approximately 55% of patients diagnosed with RRMS develop secondary progressive (SPMS) within 10 years

Source: LifeSci Capital

Causes and Pathogenesis. MS is a chronic autoimmune disease of the CNS that results in episodes of immune-mediated attack on myelin throughout the CNS. The cause of MS is not well understood and the disease progression is highly variable among affected individuals. For most patients, MS is characterized by alternating periods of clinical worsening followed by the abatement of symptoms. This disease state is known as relapsing-remitting MS (RRMS). The pathogenesis of MS is thought to involve a range of genetic, environmental, lifestyle, and dietary factors.

All stages of MS are characterized by inflammatory demyelinating lesions in the CNS consisting of lymphocytic infiltrates crossing the blood-brain barrier. In both relapsing-remitting and progressive forms of MS, active tissue damage is linked to activation of microglia in the CNS.17 The loss of myelin and oligodendrocytes can compromise important neuronal support functions in the brain and eventually lead to neurodegeneration. Over the long term, the formation of glial scars and a failure of remyelination to keep pace with demyelination results in permanent tissue injury and contributes to the acceleration of the disease process in progressive forms of MS.18

HERV-W in Multiple Sclerosis. The initial trigger for immune activation in MS is not known, but is thought to involve environmental and/or genetic factors.19 The normally silent env gene encoding the envelope protein of HERV-W is upregulated in all MS lesions and is hypothesized to be a causal trigger for the disease process.20 Expression of MSRV-Env is thought to arise through the process of transactivation, whereby infection with one type of virus is capable of activating protein expression from a different viral family.21 In the case of HERV-W, the herpes simplex virus 1 (HSV-1) and related viruses have been shown to interact with the regulatory regions of HERV-W elements

and transactivate protein expression.\textsuperscript{22} The scientific literature has previously implicated the herpes virus family, including human herpes virus-6 (HHV-6), Epstein-Barr virus (EBV), also known as human herpes virus-4 (HHV-4), and cytomegalovirus (CMV), also known as human herpes virus-5 (HHV-5), in MS pathogenesis.\textsuperscript{23,24,25} Transactivation of HERV-W retroviral elements may explain how these viruses contribute to MS pathogenesis.

Figure 11 shows disability progression in MS patients broken down by the presence (triangles) or absence (squares) of MSRV particles in the cerebrospinal fluid (CSF) at the time of diagnosis.\textsuperscript{26,27} At the start of this observational study, 10 patients were positive for MSRV in the CSF and 8 were negative. MSRV-positive patients showed a greater accumulation of disability progression and clinical re-exacerbations. This included Extended Disability Status Scale (EDSS) score (3-year: \( p=0.008 \); 6-year: \( p=0.004 \)), annual relapse rate (6-year: \( p=0.01 \)), and proportion of patients under treatment (3-year: \( p=0.003 \); 6-year: \( p=0.009 \)). Since EDSS is a 10-point scale, the increase in scores is clinically meaningful, reflecting a jump from minimal to significant disability.\textsuperscript{28}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{image.png}
\caption{Disability Accumulation in MS Patients Based on MSRV Positivity}
\end{figure}

\textit{Source: Sotgiu et al, 2006}


\textsuperscript{25} Lünemann, JD, et al., 2007. Epstein-Barr Virus: Environmental Trigger of Multiple Sclerosis? \textit{Journal of Virology},


Aberrant expression of the HERV-W env gene is thought to induce oligodendrocyte injury through activation of toll-like receptor 4 (TLR4), a part of the innate immune system. Activation of this receptor triggers the release of a variety of pro-inflammatory cytokines that can induce the death of oligodendrocytes, hampering the brain’s ability to regenerate lost myelin. Studies using lipopolysaccharide (LPS), another TLR4 agonist, have confirmed that macrophages and microglia mediate this effect on OPCs.

**Activated Microglia in MS.** Microglia are the first cells to respond to injury within the CNS. In multiple sclerosis, activated microglia are found within lesions and release pro-inflammatory signals like interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), nitric oxide (NO), and reactive oxygen species. Oligodendrocytes and their precursor cells are particularly vulnerable to all of these signals.

**Microglia as Antigen-Presenting Cells (APCs).** Activated microglia have been shown to upregulate major histocompatibility complex (MHC) genes, and can act as antigen presenting cells (APCs) to prime infiltrating T cells. Due to the roles of microglia in recycling myelin and phagocytosis of cellular debris in the healthy brain, microglia inherently present myelin antigens through MHC proteins once activated. This has the potential to create a vicious cycle of pro-inflammatory signaling. Presentation of myelin antigens to T cells promotes the differentiation into mature encephalitogenic T cells that attack myelin and oligodendrocytes. This autoimmune response results in cellular debris that further activates microglia and increases antigen presentation to infiltrating T cells, a process known as epitope spreading.

**MSRV and TLR4 Expression on Endothelial Cells.** These signals also induce the upregulation of TLRs on brain endothelial cells, the cells lining all blood vessels and responsible for maintaining the blood brain barrier. Activation of TLR4/CD14 receptors on endothelial cells is thought to contribute to the opening of the blood-brain barrier, a classic feature of MS pathology allowing for lymphocyte infiltration into the CNS. This permits the immune attack on the CNS that leads to MS pathology.

**MSRV and the Inhibition of Remyelination.** The differentiation and maturation of oligodendrocyte precursor cells (OPCs) is a key step in the maintenance of myelin in the CNS. Figure 12 highlights the maturation process for OPCs and the important genes activated during each step. In the final stage, oligodendrocytes make contact with axons and form myelin sheaths. As shown in the figure, mature oligodendrocytes begin to express to myelin basic

---


protein (MBP), myelin-associated glycoprotein (MAG), and myelin oligodendrocyte glycoprotein (MOG), which are critical for the formation of myelin.

**Figure 12. Oligodendrocyte Maturation Process**

Although these OPCs have the capacity to replace lost oligodendrocytes and remyelinate axons following injury, remyelination in MS patients is often incomplete or absent. Researchers have found that OPCs express TLR4 and that its activation by MSRV-Env induces the release of proinflammatory cytokine and nitric oxide synthase (NOS). These stressors reduce the capacity of OPCs to differentiate into mature oligodendrocytes, hindering the process of remyelination. Thus, MSRV-Env expression and its activation of TLR4 on OPCs may account for remyelination failure in MS patients.

**Diagnosis and Symptoms.** Multiple sclerosis is diagnosed using a variety of clinical measures including medical history, neurologic exams, magnetic resonance imaging (MRI) of the brain, an evoked potential test, and analysis of cerebrospinal fluid. The International Panel on MS diagnosis published criteria in 2001 providing guidelines regarding which combination of clinical metrics indicate MS. The clearest measures of MS are relapsing attacks that last for at least 24 hours in the absence of fever or infection, and lesions in the brain. The presence of two or more attacks and two or more lesions is sufficient to make a positive diagnosis. Patients with fewer relapses and fewer lesions require

---


additional tests to confirm MS. **Figure 13** shows an example of brain lesions in a patient with MS. The top panel shows the MRI image of a patient with primary progressive MS, and the arrows point to brain lesions, or areas of inflammation and myelin destruction. The bottom panel is an enlarged image of the two lesions.

**Figure 13. MRI Scans Showing Myelin Damaged Brain Lesion**

![MRI Scans](image)

*Source: van der Kolk, A.G. et al., 2013*

**Treatment.** There are no curative therapies available for MS and existing treatments for RRMS focus on decreasing the frequency of flare-ups, shortening their duration, and alleviating symptoms of the disease in order to improve patient quality of life. There are no drugs approved for primary progressive MS (PPMS) and only one approved for secondary progressive MS (SPMS) called mitoxantrone, although it is rarely used due to its potential for cardiac toxicity and risk of inducing secondary leukemia. **Figure 14** highlights the main disease-modifying treatments approved for RRMS patients. It is worth noting that the exact mechanism of action is not fully understood for many of these agents. However, all these drugs work to dampen immune responses rather than prevent the initial immune activation itself. In addition, there are safety concerns with many of these treatments relating to the broad suppression of host immunity, which can predispose patients to opportunistic infections, autoimmune disorders, and other complications. In rare cases, the use of *Tysabri*, *Gilenya*, or *Tecfidera* has been associated with the development of progressive multifocal leukoencephalopathy (PML), a rare life-threatening demyelinating CNS infection.40

---


Figure 14. FDA-Approved RRMS Drugs

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
<th>Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glatiramer Acetate</td>
<td>Teva’s <em>Copaxone</em>, Novartis/Sandoz’s <em>Glatopa</em></td>
<td>SC QD</td>
</tr>
<tr>
<td>Interferon Beta-1a</td>
<td>Biogen’s <em>Avonex</em>, Pfizer’s <em>Rebif</em></td>
<td>IM QWK, SC TIW</td>
</tr>
<tr>
<td>Interferon Beta-1b</td>
<td>Bayer’s <em>Betaseron</em>, Novartis’ <em>Extavia</em></td>
<td>SC QAD</td>
</tr>
<tr>
<td>Pegylated Interferon Beta</td>
<td>Biogen’s <em>Plegridy</em></td>
<td>SC Q2WK</td>
</tr>
<tr>
<td>Anti-alpha-4 Integrin</td>
<td>Biogen’s <em>Tysabri</em> (natalizumab)</td>
<td>IV Q4WK</td>
</tr>
<tr>
<td>Inhibitor of DNA Synthesis</td>
<td>Sanofi’s <em>Aubagio</em> (teriflunomide)</td>
<td>Oral QD</td>
</tr>
<tr>
<td>S1P1 Antagonist</td>
<td>Novartis’ <em>Gilenya</em> ( fingolimod)</td>
<td>Oral QD</td>
</tr>
<tr>
<td>NFR2 Activator</td>
<td>Biogen’s <em>Tecfidera</em> (dimethyl fumarate)</td>
<td>Oral BID</td>
</tr>
<tr>
<td>Anti-CD25</td>
<td>Biogen’s <em>Zinbryta</em> ( daclizumab)</td>
<td>IV QMT</td>
</tr>
<tr>
<td>Anti-CD52</td>
<td>Sanofi’s <em>Lemtrada</em> (alemtuzumab)</td>
<td>IV Q4WK</td>
</tr>
</tbody>
</table>

*Source: LifeSci Capital*

Existing immunomodulators approved for RRMS dampen immune responses or block access of lymphocytes across the blood brain barrier. However, there are no therapies that attempt to target the trigger underlying the initial activation of the immune system. There is a great deal of uncertainty over the trigger for MS, which has resulted in more drug development focused on damage control as opposed to halting the disease. The current treatment options reflect this reality.

**Glatiramer Acetate (Teva’s (NYSE: TEVA) *Copaxone* and Novartis/Sandoz’s (NYSE: NVS) *Glatopa*).** Glatiramer acetate is a synthetic polypeptide containing random sequences of 4 amino acids from the myelin basic protein (MBP). The mechanism of action is not fully understood, but is thought to act a decoy for the immune system and may induce suppressor T cells that shift the immune system to an anti-inflammatory state. In the 15-year US Glatiramer Acetate Study, greater than 80% of patients treated with glatiramer acetate were still walking without assistance, and these individuals exhibited a reduction in annual relapse rate from 1.12 at baseline to 0.25 per year.41 In addition, MRI studies have shown that glatiramer acetate can reduce inflammatory activity by 33%.

**Beta Interferons (Biogen’s (NasdaqGS: BIIB) *Avonex*, Pfizer’s (NYSE: PFE) *Rebif*, Bayer’s (XETRA: BAYN.DE) *Betaseron*, Novartis’ *Extavia*, and Biogen’s *Plegridy*).** Beta interferons are naturally-occurring cytokines in humans that modulate immune activity and have been shown to reduce relapse rate by one-third. Beta interferons are often used in RRMS patients who cannot tolerate glatiramer acetate. Use of interferon betas leads to

---

flu-like symptoms in 60% of patients receiving interferon betas and can cause liver function abnormalities, leukopenia, and thyroid disease.\textsuperscript{43,44}

**Tysabri (natalizumab) – Biogen.** Tysabri is a monoclonal antibody against the α4 subunit of certain integrin proteins expressed on the surface of leukocytes. These proteins are critical for α4-mediated leukocyte adhesion to endothelial cells, which is critical for the infiltration of inflammatory cells into tissue. There are safety concerns associated with the use of this drug, since it has broad immunosuppressive effects and puts patients at risk of developing progressive multifocal leukoencephalopathy (PML).

**Gilenya (fingolimod) – Novartis.** Gilenya was the first orally administered drug approved to treat RRMS. The drug is a sphingosine-1-phosphate receptor (S1P1R) modulator that is thought to impact lymphocyte infiltration of the CNS.\textsuperscript{45} In its Phase III program, Gilenya was found to be superior to beta interferons and reduced annualized relapse rate by 48-54%.\textsuperscript{46,47,48}

**Aubagio (teriflunomide) – Sanofi (NYSE: SNY).** Aubagio is an oral agent that inhibits the synthesis of pyrimidine in rapidly proliferating, such as T and B cells. By reducing the proliferation of B and T lymphocytes, Aubagio is able to reduce the extent of lymphocyte infiltration into the CNS and consequently the severity of the inflammatory response.\textsuperscript{49}

**Tecfidera (dimethyl fumarate) – Biogen.** Tecfidera is an oral immunomodulatory agent that leads to activation of nuclear factor (erythroid derived 2)-like 2 (NRF2), which is a key regulator of cellular machinery to prevent oxidative stress.\textsuperscript{50} The drug also has anti-inflammatory effects through the promotion of a Th2 immune response. In the DEFINE Phase III study, Tecfidera was found to be superior to beta interferons with a reduction in annualized relapse rate of 53%.\textsuperscript{51} The drug also has a favorable safety profile relative to other immunomodulators.\textsuperscript{52}

\begin{thebibliography}{99}
\end{thebibliography}
**Lemtrada (alemtuzumab) – Sanofi.** Lemtrada is a monoclonal antibody against the CD52 surface protein, which is expressed on the surface of mature lymphocytes, but not progenitor cells. Binding of the antibody to lymphocytes targets the cells for destruction, reducing the pool of infiltrating lymphocytes at the site of MS lesions. This drug has been approved to treat chronic lymphocytic leukemia (CLL), cutaneous T-cell lymphoma (CTCL), and T-cell lymphoma, and was recently approved for the treatment of RRMS. However, Lemtrada has been associated with opportunistic infections resulting from broad immune suppression and increased rates of autoimmune conditions, which has weighted on physicians and patients considering its use.53

**Zinbryta (daclizumab) – Biogen.** Zinbryta is a once-monthly monoclonal antibody against the CD25 surface protein that was recently approved by the FDA. The drug is infused once per month and is thought to modulate interleukin-2 (IL-2) mediated activation of immune cells.

**Disease Market Information**

**Epidemiology.** The epidemiology of MS is complex. Family history does have an effect on the risk of developing MS, and relatives of MS patients have a 10–50 fold higher rate of developing the disease.54 Women are more likely to have MS than men and most affected individuals are diagnosed during the third or fourth decade of life. Some research suggests that the prevalence increases in individuals that are further from the equator, although this notion has been contested.55 Prevalence varies widely, making it hard to estimate an accurate number of MS patients worldwide. However, a combination of better diagnostic techniques and prolonged survival has led to an increase in prevalence worldwide.55 MS is the most common autoimmune disease affecting the CNS, with roughly 2.5 million diagnosed individuals globally.56 According to the Cleveland Clinic, there are roughly 400,000 MS patients in the US. There are estimated 750,000 MS patients in Europe as well.

**Market Size.** GNbAC1 has the potential to be highly disruptive to the MS market. If demonstrated to be effective, GNbAC1 would likely be used in a large proportion of RRMS patients. GNbAC1 could become a first-line therapy for RRMS patients, in order to prevent conversion to secondary progressive disease. Due to its differentiated mechanism of action, it is likely that GNbAC1 could be used in combination with other MS therapies as well. GeNeuro may also develop GNbAC1 for progressive MS patients, a subset of MS patients for which there are no existing therapies. The Company will decide whether to pursue this indication based on data from the ongoing Phase IIb study. Due to the lack of approved therapies for progressive MS, adoption could be quite high if GNbAC1 is shown to be effective.

**Figure 15** shows the net sales of branded MS drugs from 2011 to 2015. Teva’s (NYSE: TEVA) Copaxone (glatiramer acetate) currently leads the market with 2015 sales of $4.0 billion, although the launch of Novartis/Sandoz’s (NYSE: NVS) generic version, Glatopa, in October 2015 may erode Copaxone sales going forward. Biogen’s (NasdaqGS: BIIB)

---

Tecfidera (dimethyl fumarate) leads among oral branded MS drugs with $3.6 billion in 2015 sales. Last year, there were 6 MS drugs that exceeded $1 billion in sales within a total market worth nearly $20 billion. There is little differentiation among the branded MS drugs, so drugs with novel mechanisms of action could gain wide attention.

Figure 15. Annual Cost and Net Sales in Millions 2011-2015

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Annual Cost</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Injectable</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Copaxone</em> (glatiramer acetate)</td>
<td>Teva</td>
<td>$70,252-85,709</td>
<td>$3,570</td>
<td>$3,996</td>
<td>$4,328</td>
<td>$4,237</td>
<td>$4,023</td>
</tr>
<tr>
<td><em>Aronex</em> (interferon beta-1a)</td>
<td>Biogen</td>
<td>$75,673</td>
<td>$2,686</td>
<td>$2,913</td>
<td>$3,005</td>
<td>$3013</td>
<td>#</td>
</tr>
<tr>
<td><em>Rebif</em> (interferon beta-1a)</td>
<td>EMD Serono</td>
<td>$81,686</td>
<td>$2,355</td>
<td>$2,434</td>
<td>$2,478</td>
<td>$2,446</td>
<td>$1,994</td>
</tr>
<tr>
<td><em>Betaseron</em> (interferon beta-1b)</td>
<td>Bayer</td>
<td>$80,843</td>
<td>$1,556</td>
<td>$1,563</td>
<td>$1,379</td>
<td>$1,094</td>
<td>$914</td>
</tr>
<tr>
<td><em>Extavia</em> (interferon beta-1b)</td>
<td>Novartis</td>
<td>$72,257</td>
<td>$154</td>
<td>$159</td>
<td>$159</td>
<td>$159</td>
<td>*</td>
</tr>
<tr>
<td><em>Tysabri</em> (natalizumab)</td>
<td>Biogen</td>
<td>$75,361</td>
<td>-</td>
<td>-</td>
<td>$1,080</td>
<td>$1,136</td>
<td>$1,527</td>
</tr>
<tr>
<td><em>Lemtrada</em> (alemtuzumab)</td>
<td>Genzyme</td>
<td>$101,219</td>
<td>-</td>
<td>-</td>
<td>$3</td>
<td>$45</td>
<td>$269</td>
</tr>
<tr>
<td><em>Plegridy</em> (pegylated-interferon beta-1a)</td>
<td>Biogen</td>
<td>$75,673</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>$45</td>
<td>#</td>
</tr>
<tr>
<td><em>Oral</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Gilenya</em> (fingolimod)</td>
<td>Novartis</td>
<td>$87,662</td>
<td>$494</td>
<td>$1,195</td>
<td>$1,934</td>
<td>$1,934</td>
<td>$2,776</td>
</tr>
<tr>
<td><em>Aubagio</em> (teriflunomide)</td>
<td>Genzyme</td>
<td>$74,177</td>
<td>-</td>
<td>$9</td>
<td>$221</td>
<td>$576</td>
<td>$966</td>
</tr>
<tr>
<td><em>Tecfidera</em> (dimethyl fumarate)</td>
<td>Biogen</td>
<td>$82,095</td>
<td>-</td>
<td>-</td>
<td>$876</td>
<td>$2,909</td>
<td>$3,638</td>
</tr>
<tr>
<td><strong>Total Branded MS Market</strong></td>
<td></td>
<td></td>
<td>$11,895</td>
<td>$13,405</td>
<td>$15,909</td>
<td>$18,417</td>
<td>$19,435</td>
</tr>
</tbody>
</table>

* Not reported; ^ First treatment course, second treatment course 12 months later is $60,731; # Combined net sales of $2,968 reported for Avonex and Plegridy in 2015

Source: LifeSci Capital

Pricing and Market Share Analysis. Wholesale acquisition costs (WAC) for approved MS drugs ranges from $70,000 to over $100,000 with recent entrants to the market commanding premium pricing. This is shown in Figure 15. Pricing for GNbAC1 if approved will depend on the strength of the data and whether GeNeuro chooses to pursue progressive MS in addition to RRMS. We assume a low price point of $70,000 for a drug with efficacy results in the ballpark of other approved drugs, which is at the low end of many of WAC price for many approved MS drugs. We use a high price point of $120,000 if the GNbAC1 substantially alters the course of the disease.
The current market share breakdown of branded MS drugs may provide some guidance on the potential market penetration for GNbAC1 if approved. Figure 16 shows the market share for branded MS drugs in 2015. The ceiling on market share for existing MS therapies appears to be roughly 20%.

**Figure 16. Market Share of Branded MS Drugs in 2015**

![Market Share of Branded MS Drugs in 2015](source: LifeSci Capital)

If approved, the market share GNbAC1 could fall within 10%, in line with Biogen’s Tysabri, and 20% of the market, on par with Teva’s Copaxone. Both Copaxone and Tysabri are intravenous treatments, which may provide a good reference for the potential uptake of GNbAC1. This would reflect a total market opportunity for GNbAC1 in MS between $1.9 billion and $3.9 billion. The possibility of GNbAC1 being used in combination with other approved MS drugs means that GeNeuro would not necessarily have to take market share from competitors in order to grow sales.

There is substantial upside potential if GNbAC1 is shown to have activity in patients with progressive MS. Since there are no suitable treatment options for progressive MS, broad uptake of GNbAC1 among a majority of these patients could be possible. In this scenario, GNbAC1 sales could grow at a faster rate than other recently launched MS drugs.

GeNeuro is positioning GNbAC1 as a disruptive therapy that could reshape the treatment landscape for MS. If GNbAC1 substantially alters the course of the disease relative to what is achieved with existing treatments, then GeNeuro may be able to capture a larger portion of the MS market. Depending on how completely GNbAC1 is able to affect the underlying disease pathology, peak market share for GNbAC1 could reach 30% or 40% of the market. This scenario would likely involve GNbAC1 entering the market at a substantial premium to existing therapies as well.
Clinical Data Discussion

GeNeuro has successfully completed a Phase IIa study evaluating GNbAC1, which demonstrated a favorable safety and tolerability profile as well as early signs of efficacy. The Company is currently enrolling 260 RRMS patients into a 2-year Phase IIb study and expects to report preliminary data from the trial in the fourth quarter of 2017. The Phase IIb trial is being conducted in collaboration with Servier, who is fully funding this study and plans to fund the global Phase III program for GNbAC1.

Phase I Trial

This first-in-human study demonstrated that a single administration of intravenous GNbAC1 is safe, well-tolerated, and has a pharmacokinetic profile suitable for once-monthly dosing. The trial did not show any treatment-related or dose-related trends in AEs and there was no evidence of immunogenicity.

**Trial Design.** This randomized, double-blind Phase I study was the first test of the safety and tolerability of GNbAC1 in 33 healthy male volunteers. Subjects were randomized to receive a single intravenous infusion of 0.0025 mg/kg (n=3), 0.025 mg/kg (n=4), 0.15 mg/kg (n=4), 0.6 mg/kg (n=4), 2.0 mg/kg (n=4), or 6.0 mg/kg (n=4) of GNbAC1 or placebo (n=10). The primary endpoint of the study was the safety and tolerability of a single ascending dose of GNbAC1 over 64 days. This was measured by the number of adverse events as well as results of a physical examination, electrocardiogram (ECG), and clinical laboratory tests. Secondary endpoints included the pharmacokinetics of a single dose and immunogenicity of GNbAC1.

**Safety.** Overall, this first-in-human trial demonstrated that GNbAC1 was safe and well-tolerated at all doses tested. All AEs experienced in the trial were mild or moderate in severity and there were no observed treatment-related trends in the prevalence of AEs. There were no serious AEs and none of subjects withdrew from the study due to an AE. The most frequently reported AEs were common infections such as nasopharyngitis, which was observed in 15% of subjects overall. One patient in the 2 mg/kg dose cohort experienced elevated ALT levels, although this was not considered related to the study drug. There were no indications of immunogenicity in the study, suggesting that intravenous infusions of GNbAC1 does not elicit an antibody response in healthy volunteers.

**Pharmacokinetics.** Figure 17 shows the serum concentration of GNbAC1 over the 64 days of the study following a single intravenous infusion. The data show a clear linear dose response and an elimination half-life for the terminal phase of 19-26 days. Estimates based on the active concentrations of MSRV-Env in the periphery and within MS lesions suggest a therapeutic threshold for GNbAC1 of greater than 4,500 ng/mL. The results of this trial demonstrate that patients receiving either the 2 mg/kg or 6 mg/kg dose remained above this level for more than 30 days, which is supportive of a once-monthly dosing schedule.

---

57 https://clinicaltrials.gov/ct2/show/NCT01699555
GeNeuro conducted this Phase Ib study to evaluate higher doses of GNbAC1 than what was originally tested in the Phase I trial. This trial confirmed the favorable safety profile of GNbAC1 at even higher doses and quantified the percentage of antibody that penetrated the blood-brain barrier.

**Trial Design.** This randomized, double-blind, placebo controlled Phase Ib study tested single ascending doses of GNbAC1 in 21 healthy male volunteers.\(^5^9\) Enrolled subjects were randomized into 1 of 3 cohorts to receive intravenous infusions of 6 mg/kg, 18 mg/kg, or 36 mg/kg of GNbAC1. Within each cohort, two subjects received placebo infusions. The primary endpoint was the safety and tolerability of single ascending doses of GNbAC1, including measures of adverse events (AEs), serious adverse events (SAEs), vital signs, electrocardiogram (ECG), and clinical laboratory values. Secondary endpoints included pharmacokinetics, immunogenicity, and the ratio of serum to CSF GNbAC1 concentrations.

**Trial Results.** This trial confirmed the favorable safety profile of GNbAC1 at 18 mg/kg and 36 mg/kg, which is 3 and 6 times higher than the highest dose tested in the Phase I study, respectively. In addition, the trial demonstrated that roughly 0.3-0.4% of the antibody in the serum penetrated the blood-brain barrier and found in the cerebrospinal fluid (CSF).

---

\(^{59}\) https://clinicaltrials.gov/ct2/show/NCT02452996
Phase IIa Trial

GeNeuro conducted this Phase IIa study to test the safety, tolerability, and pharmacokinetics of GNbAC1 in MS patients.\(^{60}\) The trial demonstrated a pharmacokinetic profile suitable for once-monthly dosing and significant reductions in MSRV mRNA transcripts indicative of the GNbAC1’s efficacy. In addition, GNbAC1 was found to be safe and well-tolerated and showed no signs of broad immunosuppression.

**Trial Design.** This randomized, open-label, single-blind, placebo controlled Phase IIa study compared the safety, tolerability, and pharmacokinetics of GNbAC1 to placebo in 10 MS patients.\(^ {61}\) Subjects were randomized into one of two dose cohorts to receive single-dose administration of 2 mg/kg or 6 mg/kg doses of intravenous GNbAC1. One patient in each cohort received a corresponding placebo. Following this treatment, all patients entered into an open-label repeated-dose extension phase for 48 weeks in order to determine the safety of repeated administrations. The primary endpoint was the safety and tolerability of GNbAC1 during the single dose and repeated dose phases. Secondary endpoints included the pharmacokinetics of GNbAC1 following single or repeated doses, measurement of MSRV-ENV markers, magnetic resonance imaging (MRI), and other measures of MS disease activity, and the immunogenicity of GNbAC1.

**Safety.** During the single dose phase, there were a total of 22 adverse events (AEs), all of which were rated as mild or moderate in severity. The most common treatment-emergent adverse events occurring in this phase were fatigue, rhinitis, and headache. During the repeated dose phase, subjects experienced a total of 73 AEs, divided evenly between the two dose groups. There was one serious adverse event (SAE), a case of biliary pancreatitis in a patient with recurrent biliary lithiases, which was deemed not likely related to the GNbAC1. There was no pattern of AEs that could be attributed to GNbAC1 and no AEs leading to discontinuation from the study. In addition, there were no signs of immunogenicity or infusion reactions associated with GNbAC1 throughout the duration of the study and no indication that the drug interferes with the normal functioning of the immune system.\(^ {62}\)

**Pharmacokinetics.** GNbAC1 had a median \(t_{\text{max}}\) of 2 hours and had an elimination half-life (t\(_{1/2}\)) of 27-37 days. This long elimination half-life is supportive of a once-monthly dosing regimen for GNbAC1. Comparing the \(C_{\text{max}}\) and AUC values for the 2 mg/kg and 6 mg/kg doses, GNbAC1 was found to have a linear pharmacokinetic profile within the dose range tested.

**MRI Evaluation.** Enrolled patients underwent magnetic resonance imaging (MRI) at screening, 28 days after the first dose, and 28 days after the 6\(^{th}\) dose. Of the 10 patients treated with GNbAC1, 9 had stable MRIs after 6 months of treatment. Out of the eight patients remaining in the study after 12 months, 8 had stable MRI images compared to baseline. The stability of the brain lesions at 12 months is an encouraging sign of the drug’s efficacy, but must obviously be interpreted cautiously in light of the small trial size.

---


\(^ {61}\) https://clinicaltrials.gov/ct2/show/NCT01639300

**MSRV Expression.** The investigators found that treatment with GNbAC1 led to significant reductions in the expression of MSRV-Env and MSRV-Pol mRNA normalized to the expression of the human β-glucuronidase (GUS B) gene. **Figure 18** highlights the expression of MSRV-Env and MSRV-Pol mRNA transcripts before the first, third, and sixth administration of GNbAC1, as measured by polymerase chain reaction (PCR). Before the sixth dose, the decline in gene expression reached statistical significance relative to baseline for both the MSRV-Env (p=0.029) and MSRV-Pol (p=0.044) transcripts. This result suggests that neutralization of MSRV protein with the GNbAC1 antibody induces the down-regulation of MSRV protein expression, although the mechanism by which this occurs is not presently known. This effect is an initial sign of the drug’s efficacy and is consistent with MSRV-Env transcriptional changes that are observed following treatment with interferon beta and Biogen’s (NasdaqGS: BIIB) Tysabri (natalizumab).

**Figure 18. Transcription of MSRV-Env and MSRV-Pol Before 1st, 3rd, and 6th Dose of GNbAC1**

![Graph showing transcription of MSRV-Env and MSRV-Pol before 1st, 3rd, and 6th dose of GNbAC1](image)

*Source: Derfus et al., 2014*

**Figure 19** highlights the changed in disability progression observed in the study. While these data must be interpreted cautiously in light of the small sample size, the results suggest that treatment with GNbAC1 alters the rate of disability progression. Each patient’s prior progression index (PI) is defined as the average annual change in EDSS score over the history of the patient’s disease. Patients in the 2 mg/kg dose had PI scores ranging from 0.3 to 1.0 and individuals in the high dose cohort had scores ranging from approximately 0.1 to 1.5. Over the course of the study, the EDSS progression index was 0.1 in the low-dose cohort and was -0.1 in the high-dose cohort. These results suggest a substantial reduction in disability progression, although this effect needs to be confirmed in a larger patient population.
CHANGE MS Phase IIb Trial with GNbCA1 in Multiple Sclerosis

GeNeuro is currently conducting a Phase IIb study evaluating GNbAC1 in RRMS patients and expects to report preliminary results from the trial in the fourth quarter of 2017. This trial is being conducted in collaboration with Servier, who is fully funding this Phase IIb trial and plans to fund a global Phase III program for GNbAC1. The trial is designed to confirm the safety and efficacy of GNbAC1.

**Trial Design.** This randomized, double-blind, placebo controlled Phase IIb study is testing the safety, efficacy, and pharmacokinetics of GNbAC1 in treating patients with RRMS. The trial is enrolling 260 RRMS patients who have an Expanded Disability Status Scale (EDSS) score less than 6.0. During the first period of the study, each subject is randomized to receive 6 mg/kg, 12 mg/kg, or 18 mg/kg of intravenous GNbAC1, or placebo every 4 weeks for 6 months. The primary endpoint is the cumulative number of gadolinium (Gd)-enhanced T1 lesions on a brain MRI between 12 and 24 weeks. The Company plans to report preliminary results on this endpoint in the fourth quarter of 2017. Following the end of this randomized period, patients in the placebo group will be re-randomized into one of the three treatment groups and all subjects received GNbAC1 every 4 weeks for an additional 6 months. Final results from this extension phase are expected in the second quarter of 2018.

---

**Figure 19. Rate of EDSS Progression in Treated Subjects**

![Graph showing EDSS progression](https://clinicaltrials.gov/ct2/show/NCT02782858)

*Source: Corporate Presentation*

---

63 https://clinicaltrials.gov/ct2/show/NCT02782858
Competitive Landscape

GeNeuro’s GNbAC1 is a fundamentally novel approach to treating MS and, if demonstrated effective and approved, could substantially reshape the treatment landscape. While there are several drugs in late-stage development for MS, most focus on relapse control and none of them target a potentially causal agent of the disease process. There has been recent excitement over positive Phase III results in progressive MS. Roche (VTX: ROG.VX) has reported positive data with ocrelizumab, their anti-CD20 monoclonal antibody, in primary progressive MS and Novartis (NYSE: NVS) recently announced that siponimod, an S1P1 modulator similar to Gilenya (fingolimod), met the primary endpoint in a trial in secondary progressive MS.

Existing Treatments Focus on Relapse Control. Existing immunomodulators approved for RRMS dampen immune responses or block access of lymphocytes across the blood brain barrier. However, there are no therapies that target the trigger underlying the initial activation of the immune system at the disease onset. There is a great deal of uncertainty over the trigger for MS, which has resulted in more drug development focused on damage control as opposed to halting the disease. The current treatment options reflect this reality. There has been shift towards newer, oral agents, such as Tecfidera, Aubagio, and Gilenya, although this not fundamentally altered the treatment paradigm for MS.

GeNeuro makes a compelling case for the causal factor underlying MS onset being MSRV-Env, an endogenous retroviral element embedded in our genome that is found to be actively expressed in MS lesions and the lymphocytes found within them. Its activation of toll-like receptor 4 (TLR4), a component of the innate immune system, may explain many facets of MS pathogenesis, including the breakdown of the blood-brain barrier, the damage to oligodendrocytes, and the inhibition of remyelination. Targeting this retroviral element represents a truly novel strategy for treating MS. The Company has reported early signs of efficacy in a small sample of patients in their Phase IIa study, and readouts from late-stage trials evaluating GeNeuro’s GNbAC1 will provide important insight into the potential of this strategy.

Lack of Treatments Available for Progressive MS. Despite the approval of 8 classes of drugs for relapsing remitting MS (RRMS), there remains an urgent need for therapies that can address progressive forms of the disease. Without approved therapies, many of these patients forgo treatment. It is likely that the differences in pathophysiology between progressive MS and RRMS accounts for the high rate of discordance when successful RRMS drugs have been tested in progressive MS.64 RRMS is considered to be an immune-mediated inflammatory disorder, while progressive MS is characterized by ongoing and permanent neurodegeneration. Recent positive data from Roche’s ocrelizumab program in primary progressive MS (PPMS) and Novartis’ siponimod program in secondary progressive MS are signs of efficacy in this hard-to-treat patient population. However, it is necessary to interpret these results cautiously in light of previous clinical trial failures in progressive MS with drugs that have the same mechanism of action as ocrelizumab and siponimod.

Complications from Broad Suppression of the Immune System. Many of the newer MS therapies modulate the immune system through broad effects on lymphocytes. Although these newer drugs have generated a lot of optimism in the potential for improved patient outcomes in MS, the safety concerns associated with immunomodulatory drugs

---

for MS makes the prescription and monitoring of their use cumbersome.\textsuperscript{65} The induced alterations to the immune system may predispose MS patients to opportunistic and community-acquired infections, altered vaccine responses, malignancies, and autoimmune diseases.\textsuperscript{66} In rare cases, the use of Tysabri, Gilenya, or Tevifydara has been associated with the development of progressive multifocal leukoencephalopathy (PML), a rare demyelinating CNS disorder.\textsuperscript{67} GeNeuro’s strategy of blocking the activation of the immune system by MSRV-Env may be a more targeted approach than existing immunomodulators that reduces the potential for complications associated with broad suppression of host immunity.

**Ongoing Difficulty Promoting Remyelination.** Following damage to myelin sheaths, attempts are made to remyelinate these stripped axons. Some studies suggest that more remyelination occurs at early stages of the disease, although this is not true in all cases and the remyelination is often insufficient to fully repair the damage.\textsuperscript{68,69} Defects in oligodendrocyte recruitment and maturation are observed in MS and are considered to be substantial impediments to successful remyelination. In addition, the inflammatory environment of MS lesions appears to have inhibitory effects on the process of remyelination.\textsuperscript{70} Biogen’s (NasdaqGS: BIIB) recent failure with opicineumab in the SYNERGY Phase II trial highlights the ongoing difficulty in promoting remyelination. Opicineumab is a monoclonal antibody against the LINGO-1 protein, a signaling molecule that negatively regulates the differentiation of oligodendrocyte precursor cell (OPCs).

GeNeuro has proposed that the process of remyelination is inhibited by the binding of MSRV-Env to TLR4s on oligodendrocyte precursor cells (OPCs) and suggest that GNbAC1 may promote remyelination by disinhibiting OPCs within the lesion sites. If this hypothesis is proven correct, then use of GNbAC1 could promote remyelination in MS patients in addition to preventing immune-mediated damage to the CNS. It is potentially the case that promoting remyelination is not possible through targeting signaling molecules that modulate OPC differentiation without first removing the underlying pathogenic expression of MSRV-Env.

**GNbAC1 to Treat Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)**

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare autoimmune disorder affecting the peripheral nervous system.\textsuperscript{71} The condition is one of a cluster of autoimmune, demyelinating neuropathies and is characterized by progressive, relapsing waves of limb weakness and sensory loss, usually beginning with the legs. Patients often report difficulty walking, climbing stairs, falling, and reduced levels of manual dexterity. Nerve conduction studies, which can detect alterations in the nerve conduction resulting from demyelination, are often performed in order to

definitely diagnose CIDP. The disease pathogenesis is not fully understood and existing treatments focus on reducing symptoms, improving functional status, and if possible, maintaining remission over the long-term. Therapy for CIDP typically involves corticosteroids, plasmapheresis, and/or intravenous immunoglobulin (IVIG). These treatments aim to mitigate damage caused by the disease without affecting the underlying disease pathogenesis. There are roughly 30,000 individuals in the US and 65,000 individuals in Europe with this condition.

**MSRV in CIDP.** The envelope protein of the multiple sclerosis-associated retrovirus (MSRV-Env) has been found in CIDP patients but not healthy individuals or patients with other neurological conditions. In addition, Schwann cells, the cells responsible for myelinating peripheral axons, have been shown to express TLR4, a component of the innate immune system that is activated by MSRV-Env. Figure 20 shows that cytokine release, including interleukin-6 (IL-6; left) and C-X-C motif chemokine 10 (CXCL10; middle), is elevated in human Schwann cells following exposure to MSRV-Env. The right panel of the figure shows the alteration in cytokine release following treatment with either GNbAC1 or LPS-RS, a competitive TLR4 antagonist. GNbAC1 induced statistically significant reductions in cytokine release from Schwann cells. For CXCL10, GNbAC1 reduced release to 25% of control response, which was comparable to blockade of TLR4 with an antagonist. GeNeuro plans to launch a Phase II proof-of-concept study to evaluate GNbAC1 in the treatment of CIDP.

**Figure 20. Cytokine Release in Response to MSRV-Env**

![Cytokine Release](image)

Source: Faucard et al., 2016

---


GNbAC1 to Prevent Autoimmune Destruction of Beta Cells in Type 1 Diabetes

Having found that MSRV-Env is ubiquitously expressed in MS lesions, the investigators screened sera from patients with a wide range of autoimmune conditions to determine whether this retrovirus was found in any other human diseases. This screen found that roughly 40% of patients with type 1 diabetes had positive sera for MSRV-Env. In contrast, patients with other autoimmune diseases, such as either systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), showed no signs of the retrovirus in their sera, suggesting that MSRV-Env could be involved in the autoimmune pathology in type 1 diabetes.

Diabetes is a chronic metabolic disease with an autoimmune origin resulting in unregulated and persistently high blood sugar. Diabetes is separated into two major types. Type 1 diabetes results from an autoimmune disorder rendering the body incapable of making insulin to properly regulate high blood sugar levels. Type 2 diabetes results from improper response of the body to insulin, either by the under-production of insulin or inadequate use of insulin, both of which result in unregulated, high blood sugar levels. Under normal physiological conditions, beta cells in the pancreas produce insulin to regulate blood sugar levels, keeping them from reaching levels that are toxic to the body. In the presence of elevated blood sugar levels, insulin is released, causing the sugar to be taken up and stored by the liver, fat tissue, and muscles in the form of glycogen and triglycerides. High blood sugar can lead to serious complications including heart disease, eye complications, kidney disease, neuropathy, ulceration, gum disease, and infection of the feet and skin, and teeth.

There is no cure for type 1 diabetes and existing treatments involve lifetime insulin replacement therapy to manage the disease. Clinical development for this indication with the potential to shift treatment paradigms is focused on developing an artificial pancreas or replacing beta cells through stem cell transplantation. There are no therapies, approved or in development, that aim to address a causal factor underlying the initial autoimmune attack on beta cells in the pancreas.

Diabetes affects approximately 382 million people worldwide, including 21 million in the US who are diagnosed, and another 8.1 million undiagnosed. According to American Diabetes Association, this includes roughly 1.25 million individuals with type 1 diabetes. In addition, there are roughly 60 million people with diabetes in Europe. Given the large market size and lack of treatments targeting the cause of the disease, there is a large market opportunity for a product like GNbAC1. GeNeuro plans to launch a Phase IIa proof-of-concept study in type 1 diabetes in the second half of 2016.

GNbAC1 to Treat Other HERV-Mediated Diseases

The existing scientific literature suggests that drugs with anti-HERV activity may be effective in a broad range of autoimmune conditions, in addition to MS, CIDP, and type 1 diabetes. GeNeuro’s anti-HERV platform and expertise in HERV-mediated disease could allow for the development of additional disruptive therapies. This may include the development of additional antibodies that target virus particles from other HERV families. The Company has a

---

preclinical program against HERV-K that is in development for amyotrophic lateral sclerosis (ALS). The extent to which other human diseases are linked to the expression of retroviral elements is not fully known, and in the future, other HERV families may be identified as ideal targets for disease-modifying therapy. GeNeuro has founded an annual medical meeting to focus on HERV-mediated disease, which may foster collaboration and further development in this field.

**Intellectual Property & Licensing**

GeNeuro has over 25 years of experience in the field of HERV-mediated disease and has assembled a strong intellectual property portfolio, including 16 patent families covering US, European, and other major markets. These patents cover the antibody therapies targeting MSRV-Env in treating multiple sclerosis (MS), chronic inflammatory demyelinating polyneuropathy (CIDP), type 1 diabetes, and other indications. The broad patent portfolio should preserve the Company’s first mover advantage in the field of HERV-mediated human disease.

The Company has a partnership with Servier (private) covering the treatment of MS with GNbAC1. GeNeuro is responsible for the development of GNbAC1 through the completion of the Phase IIb study, after which Servier can exercise the option to license the product for all markets excluding the US and Japan. Servier is providing €37.5 million ($42.4 million) to finance the Phase IIb trial. Following the exercise of this option agreement, Servier would cover the cost of Phase III development and pay GeNeuro up to €325 million ($366 million) in milestone payments as well as tier royalties on net sales. GeNeuro has retained full rights to GNbAC1 for the treatment of MS in the US market, which is where two-thirds of MS drug revenue is derived, as well as Japan. GeNeuro has also retained full rights to develop GNbAC1 for other HERV-mediated diseases. Servier also has the right of first negotiation on GNbAC1 in other indications within the Servier territories.

**Management Team**

**Jesús Martin-Garcia**  
*Chief Executive Officer*

Jesús began his career in 1983 at the World Economic Foundation, and in 1989 at McKinsey & Co where he led studies in the pharmaceutical and food industries. By 1993, he chose the entrepreneurial path by creating, investing and leading start-ups in Switzerland and the United States. He was for example a co-founder of LeShop in 1996, which became the Swiss leader in e-commerce and was sold to Migros. In 2003, he created Eclosion, a public-private partnership for translating scientific discoveries in the field of life sciences into innovative drugs with disruptive potential. This unique structure was instrumental in the creation of GeNeuro, which was led by Jesús since its creation in 2006. Jesús holds a bachelor's degree in industrial sciences, a master in law from Geneva University and an MBA from Harvard Business School. He serves on the board of several biotech companies and industrial and business associations.

---

Miguel Payró  
*Chief Financial Officer*

Miguel has worked in corporate finance since 1985, first in various Swiss banks and then in industry since 1991, working in strong growth environments, initially with Unilabs SA, a European leader in clinical laboratory testing, for which he was in charge of the Swiss IPO and of numerous M&A transactions and international development. From 2003 to 2015 he was Chief Financial Officer of the Franck Muller luxury watch group in Switzerland, where he led, amongst other things, numerous M&A, tax and shareholder transactions, before joining GeNeuro in 2015 as CFO. Miguel graduated from the University in Geneva with a degree in business administration.

Dr. François Curtin  
*Chief Operating Officer*

François graduated with an MD from Geneva Medical School and obtained a master in medical statistics from the London School of Hygiene and Tropical Medicine. He also has an MBA from Warwick Business School. After several years in academia, he joined Swissmedic, the Swiss medicines agency where he was responsible for the registration and market surveillance of neuropsychiatric drugs. He then joined Serono SA, now Merck Serono, where he worked in clinical and business development. François was the CEO of GeNeuro from 2009 to 2015.

Dr. Hervé Perron  
*Chief Scientific Officer*

Hervé has a PhD in Virology and wrote a doctoral dissertation on neuroimmunology. He is the author of over 120 peer-reviewed publications and patents and is a referee for various scientific journals. He was Research Director of R&D within bioMérieux for the development of in vitro diagnostics for neurological diseases. Hervé was Scientific Director of bioMérieux STELHYS, a spin-off dedicated to the evaluation of developments in upstream research projects. Hervé is a co-founder and Chief Scientific Officer of GeNeuro and the general manager of GeNeuro-Innovation.

Dr. Alois B. Lang  
*Chief Development Officer*

Alois has a PhD degree from the Swiss Federal Institute of Technology of Zurich and he did his postdoctoral training at the University Hospital of Zurich and with the Department of Immunology of Cetus Inc., Palo Alto, USA. He is Professor of Immunology at the Faculty of Medicine of the University of Berne. Alois was Head of Research Immunology and Project Manager at Berna Biotech, Berne, and a co-founder and Chief Scientific Officer of the antibody company Kenta Biotech, Zurich. He is involved in scientific expert working groups and is a regular speaker at major scientific conferences. Since 2007, he has been the Chief Development Officer of GeNeuro.

Robert Glanzman  
*Chief Medical Officer*

Robert received his doctorate in medicine from Wake Forest University School of Medicine in the US. He completed an internship in internal medicine at New York Medical College, a residency in neurology at the University of Michigan,
and a fellowship in diagnostic nuclear medicine at Duke University. Robert spent 7 years as an Associate Clinical Professor, where he had a busy clinical practice, taught residents and acted as principal investigator for clinical studies. Robert has been certified by the American Board of Psychiatry and Neurology since 1994.

Robert joined industry in 1999. He spent eight years at Pfizer, where he had been Senior Medical Director and Team Leader of the medical affairs team for ©Rebif; he then worked for Novartis starting in 2007, with medical responsibility for the successful Phase III development in the US of ©Gilenya and the commercial launch of ©Extavia. In 2009, he was recruited by Roche Group as Group Medical Director and was in charge from 2009 to 2012 of the ocrelizumab development team, leading this project from the end of Phase II through initiation of Phase III. In 2012, he joined Purdue Pharmaceuticals as Director of Clinical Research. In 2013, he was hired by Nektar Therapeutics as Vice President, Clinical Development. Robert has been in charge of the medical affairs of the Company since December 2015.

**Risk to an Investment**

We consider an investment in GeNeuro to be a high-risk investment. GeNeuro has generated limited clinical data to date, and early signs of safety and efficacy may not necessarily translate into late-stage success. There are clinical and commercialization risks associated with their program as well. As with any company, GeNeuro may be unable to obtain sufficient capital to fund planned development programs. There are regulatory risks associated with the development of any drug, and GeNeuro may not receive FDA or EMA approval for its drug candidates despite significant time and financial investments. Regulatory approval to market and sell a drug does not guarantee that the drug will penetrate the market, and sales may not meet expectations.
Analyst Certification

The research analyst denoted by an “AC” on the cover of this report certifies (or, where multiple research analysts are primarily responsible for this report, the research analyst denoted by an “AC” on the cover or within the document individually certifies), with respect to each security or subject company that the research analyst covers in this research, that: (1) all of the views expressed in this report accurately reflect his or her personal views about any and all of the subject securities or subject companies, and (2) no part of any of the research analyst’s compensation was, is, or will be directly or indirectly related to the specific recommendations or views expressed by the research analyst(s) in this report.

DISCLOSURES

This research contains the views, opinions and recommendations of LifeSci Capital, LLC (“LSC”) research analysts. LSC (or an affiliate) has received compensation from the subject company for producing this research report. Additionally, LSC expects to receive or intends to seek compensation for investment banking services from the subject company in the next three months. LSC (or an affiliate) has also provided non-investment banking securities-related services, non-securities services, and other products or services other than investment banking services to the subject company and received compensation for such services within the past 12 months. LSC does not make a market in the securities of the subject company.

Neither the research analyst(s), a member of the research analyst’s household, nor any individual directly involved in the preparation of this report, has a financial interest in the securities of the subject company. Neither LSC nor any of its affiliates beneficially own 1% or more of any class of common equity securities of the subject company.

LSC is a member of FINRA and SIPC. Information has been obtained from sources believed to be reliable but LSC or its affiliates (LifeSci Advisors, LLC) do not warrant its completeness or accuracy except with respect to any disclosures relative to LSC and/or its affiliates and the analyst's involvement with the company that is the subject of the research. Any pricing is as of the close of market for the securities discussed, unless otherwise stated. Opinions and estimates constitute LSC's judgment as of the date of this report and are subject to change without notice. Past performance is not indicative of future results. This material is not intended as an offer or solicitation for the purchase or sale of any financial instrument. The opinions and recommendations herein do not take into account individual client circumstances, objectives, or needs and are not intended as recommendations of particular securities, companies, financial instruments or strategies to particular clients. The recipient of this report must make his/her/its own independent decisions regarding any securities or financial instruments mentioned herein. Periodic updates may be provided on companies/industries based on company specific developments or announcements, market conditions or any other publicly available information. Additional information is available upon request.

No part of this report may be reproduced in any form without the express written permission of LSC. Copyright 2016.