A causal approach to changing the course of neurodegenerative diseases

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GeNeuro’s mission

To change the course of neurodegenerative and autoimmune diseases

- Leveraging the biology of human endogenous retroviruses (HERVs) to neutralize causal factors associated with these disorders

- Approach validated through 2-year Phase II results on key markers of disease progression in Multiple Sclerosis

- Clear path to deliver full value of its approach to all stakeholders
  - Trial with Karolinska Institutet on patients with disability progression without relapses
  - Preclinical program against Amyotrophic Lateral Sclerosis in partnership with the NIH
Targeting key causal factors in multiple sclerosis through HERV Biology
1. Retroviral infection of primate germline

2. All offspring’s cells contain endogenized retrovirus (ERV).

3. New infections and endogenization.

4. Endogenization of multiple ERV families.
The integration of ERVs is a continued process. Human ERVs represent today 8% of the total DNA. New infections and endogenization lead to the incorporation of viral Pol, Gag, and Env proteins into the human genome. This process results in 8% of total human DNA being comprised of Human ERV (HERV) DNA.
Non-Ubiquitous / Unfixed HERV-K copies
Wildschutte, J.H. et al. PNAS 2016

Non-Ubiquitous / Unfixed HERV-W copies
J. Thomas, H. Perron, C. Feschotte; Mobile DNA, 2018

The Human Genome
Potentially underlies disease genetic susceptibility or risk

Potential genetic variations across different populations:
- West Eurasia (75)
- Central Asia, Siberia (27)
- East Asia (47)
- America (22)
- Africa (44)
- South Asia (39)
- Oceania (25)
Environmental infectious factors can activate HERV elements

HERVs may be the missing link between viral infections and poorly understood autoimmune / neurodegenerative diseases

Pathogenic HERV proteins found at high levels in affected organs (e.g., Brain in MS)

pHERV Env toxicities demonstrated on:
- Microglia
- OPCs
- Pancreatic beta islet cells
- Motor Neurons
- Schwan cells
- Others…
Consistent presence of pathogenic HERV-W Envelope protein (pHERV-W Env) in the brains of MS patients

Highly expressed in active MS lesions

- Consistently found in MS brains
- Expression levels correlate with lesion activity
- Present from earliest to latest stages of disease
- Env is predominantly present in microglial/monocytic cells in the MS brain belonging to the innate immune system

From the outset of disease, Multiple Sclerosis is marked by neuroinflammation and axonal loss/brain atrophy.

RRMS

- Frequent inflammation, demyelination, axonal transection plasticity and remyelination

SPMS

- Continuing inflammation, persistent demyelination
- Infrequent inflammation, chronic axonal degeneration gliosis

Time since onset of disease

- **Inflammation**: Inflammation mediated by adaptive immunity (B and T lymphocytes)
- **Axonal loss**: Neuronal damage mediated by innate immunity (activated microglia) and accelerated by hampered remyelination (oligodendrocyte precursor cells)

Adapted from Compston et al., The Lancet 2002 - RRMS: Relapsing-Remitting MS; SPMS: Secondary Progressive MS
Present understanding on disability build-up in MS

Three clinical descriptors may explain the disease course of all MS patients:

- Relapse with complete recovery
- Relapse-associated worsening (RAW)
- Disability progression independent of relapse activity (PIRA)

Confirmed disability progression (CDP)

Source, X. Montalban, presentation at Charcot Meeting; Adapted from FD Lublin, et al., Neurology 2014; L. Kappos, et al., Poster ECTRIMS 2018; L. Kappos et al., Multiple Sclerosis 2018
Despite progresses made, the need to address disease progression remains a huge opportunity.

**ORATORIO trial - Ocrevus in PPMS patients**

Primary Endpoint: Time to Confirmed Disability Progression for ≥12 Weeks

Source: X. Montalban et al., New England Journal of Medicine, Jan 2019; Adapted from X. Montalban et al., Presentation at Charcot 2019
Known drivers of multiple sclerosis and existing therapeutic agents

Relapses and Associated worsening
T- and B-cells are selectively recruited to the CNS

Progression independent of relapse activity
CNS resident Microglia and Macrophages

Impaired repair mechanism, relevant to all worsening
Dysfunctional Oligodendrocyte Precursor Cells (OPCs)

Target of most DMTs
• $\alpha$-CD20s mAbs
• $S_1P_{1/n}$ agonists
• $\alpha$-integrin mAb
• etc.

No approved drugs
pHERV-W Env acts on key cells associated with MS disease progression: Microglia and OPCs

**pHERV-W Env**
- induces an aggressive phenotype (M1) in TLR4+ microglial cells
- activates microglia to associate themselves with myelinated axons
- decreases microglial expression of regenerative factors

** fuels microglial-dependent neurodegeneration in MS **

**TLR4+ (●) Microglia**

**pHERV-W Env**
- induces release of cytokines & activates NO synthase
- reduces myelin protein expression
- significantly reduces OPC differentiation capacity

** drives OPC mediated remyelination failure **

**TLR4+ (●) Oligodendrocyte Precursor Cell (OPCs)**

Sources: Kremer et al., Ann Neurol 2013; Antony et al., Nat NeuroSci 2004; Madeira et al, JNeuroimmunol 2016; Rolland et al., J Immunol 2006; Kremer, Gruchot et al. PNAS May 2019
Microglia activation yields aggressive phenotype

pHERV-W Env activates microglia in neuron / oligodendrocyte co-cultures, leading to axonal injury due to increased TNFα.

• Release of axonal neurofilament light chain (NFL)
• Release of synaptophysin (SYP)

Microglia are directed towards myelinated axons

In neuron / oligodendrocyte / microglia co-cultures pHERV-W Env induces microglia to associate themselves with axonal structures.

Regenerative factors in microglia decreased

Stimulation of microglia with pHERV-W ENV leads to significant decrease of regenerative genes transcription (IGF-1, CSF-1, FGF-2) in microglia.

Source: Kremer, Gruchot et al., PNAS, May 2019
pHERV-W Env drives OPC mediated remyelination failure

**OPCs express increased levels of cytokines & iNOS**
pHERV-W Env stimulation of rOPCs *in vitro* leads to a strong induction of iNOS expression. Proinflammatory cytokines such as TNFα, interleukin (IL)-1β, and IL-6 are highly upregulated upon stimulation with pHERV-W Env.

**OPC differentiation capacity is significantly reduced**
pHERV-W Env markedly decreases number of OPCs expressing early (E) and late (L) markers of myelin:
- 2’,3’-cyclic nucleotide 3’-phosphodiesterase, CNPase, (E)
- Myelin basic protein, MBP, (L)

Source: Kremer et al., Ann Neurol 2013
Temelimab neutralizes pHERV-W Env mediated damage through microglia and OPCs

- Recombinant, humanized IgG4-κ mAb
- PK approx. dose linear, Half-life ≈ 1 month
- Binds with high affinity to pHERV-W Env ($K_d = 2.2$ nM)
- Blocks pHERV-W Env activation of TLR4
- Rescues MBP* expression in OPCs

*MBP: Myelin Basic Protein; marker of OPC maturation


In vitro myelinating co-cultures displaying the temelimab mediated rescue of myelinated segments (MBP in red)
Clinical data show positive effects of temelimab (*GNbAC1*).

1. **Evolution of Cortical Atrophy over 96 weeks**

   - Percentage change in brain volume from baseline *CHANGE-MS to ANGEL-MS* in cerebral cortical volume over 96 weeks.
   - Median % change from baseline:
     - Control: (1.29) 42%
     - 6mg/kg: (1.27) 41%
     - 18mg/kg: (0.75) 49%

   - Median reduction at week 48 in ANGEL-MS:
     - Control: (0.29)
     - 6mg/kg: (0.27)
     - 18mg/kg: (0.75)

   - Relative reduction of atrophy:
     - Control: 42%
     - 6mg/kg: 41%
     - 18mg/kg: 49%

   - *Dose effect p=0.058*.

2. **Evolution of Cortical MTR(2) signal over 96 weeks**

   - Change in mean MTR signals (% units) from baseline *CHANGE-MS* to *ANGEL-MS* Week 48.
   - CC Band 2 (Dose effect *p=0.035*): 0.768 vs 0.000.
   - *CHANGE-MS Baseline*: 1.000 vs 0.000.
   - *ANGEL-MS Week 48*: 1.000 vs 0.768.

3. **Reduction of Black Holes at week 48**

   - Median reduction between 18mg/kg group and control group in new larger T1 Black Holes:
     - 18mg: 63%
     - 12mg: 63%
     - 6mg: 63%

   - *Mean Number of Lesions* (95% CI):
     - 0.0 0.5 1.0 1.5 2.0

4. **Very well tolerated drug**

   - Adverse Events (AEs):
     - 18 mg/kg (N=77): 34 (44.2%)
     - 12 mg/kg (N=68): 32 (47.1%)
     - 6 mg/kg (N=74): 33 (44.6%)

   - Serious Adverse Events (SAEs):
     - 18 mg/kg (N=77): 5 (6.5%)
     - 12 mg/kg (N=68): 1 (1.5%)
     - 6 mg/kg (N=74): 6 (8.1%)

   - Serious Related AEs:
     - 18 mg/kg (N=77): 3 (3.9%)
     - 12 mg/kg (N=68): 0
     - 6 mg/kg (N=74): 0

   - AEs Leading to Study Discontinuation:
     - 18 mg/kg (N=77): 2 (2.6%)
     - 12 mg/kg (N=68): 1 (1.5%)
     - 6 mg/kg (N=74): 1 (1.4%)

   - Fatality:
     - 18 mg/kg (N=77): 1 (1.3%)
     - 12 mg/kg (N=68): 0
     - 6 mg/kg (N=74): 0

---

(1) Dose effect analyzed by linear regression, SAS analysis proc GLM; (2) MTR = Magnetization transfer ratio; (3) T1 hypointense lesion ≥ 14mm3 volume; (4) Patient had previously voluntarily exited the study; the Investigator considered the event as unrelated.
Recent two-year clinical data validates GeNeuro’s approach against disease progression in MS

Supporting pre-clinical data

- **Neurodegeneration reduced by**
  - directly *acting on* proinflammatory *microglia*, the key immune cells in PMS, responsible for lesion growth and exacerbation

- **Neuroregeneration enabled by**
  - rescuing the negative impact of pHERV-W Env on *OPC* maturation - the key cells in the remyelination process.

- **No direct effect on T/B lymphocytes** and thereby not compromising adaptive immunity

- **Excellent preclinical safety package** based on a stabilized IgG4 backbone, low immunogenicity and a linear PK at all doses

Clinical observations

- Reduction of Brain Atrophy
- Reduction in new T1 Black Holes
- Benefit on Magnetization Transfer Ratio
- Effects on markers associated with disease progression not due to immune modulation
- Excellent tolerability in clinical trials

➢ Clear positioning against *disability progression*, the key unmet medical need in MS

Temelimab positioning and further development against disability progression in MS
FDA has outlined “non-active SPMS” as a distinct population for future trials

FDA Press release for siponimod’s approval, March 26, 2019

• “In some patients, disability may progress independent of relapses, a process termed secondary progressive multiple sclerosis (SPMS). In the first few years of this process, many patients continue to experience relapses, a phase of the disease described as active SPMS.

• Active SPMS is one of the relapsing forms of MS, and drugs approved for the treatment of relapsing forms of MS can be used to treat active SPMS.

• Later, many patients with SPMS stop experiencing new relapses, but disability continues to progress, a phase called non-active SPMS.”
“It is evident that currently available disease modulatory therapies for MS exert very limited effects on the progressive aspect of MS and that this phase starts early in the disease course. A role of pHERV-W Env in progressive disease worsening is supported by accumulating preclinical and clinical evidence. We are excited to explore the therapeutic potential of temelimab in patients progressing without relapses [---] to push the boundaries of current therapeutic possibilities,”

Prof. Fredrik Piehl, Professor of Neurology at the Department of Clinical Neurosciences of the Karolinska Institutet, Press release, November 25, 2019
GeNeuro Offers a Unique, Unencumbered Opportunity in MS…

### Treatment Landscape

<table>
<thead>
<tr>
<th>Targeting Inflammation</th>
<th>Relapsing Remitting MS (RRMS)</th>
<th>Immuno-modulators</th>
<th>ABCRs Approved for RRMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Progressive MS (APMS)</td>
<td>Immuno-suppressors</td>
<td>Orals and Injectables Approved for RRMS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Targeting Neurodegeneration</th>
<th>Non-Active Progressive MS (PIRA)</th>
<th>mAbs</th>
<th>Targeting LINGO-1</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Others</td>
<td>Targeting pHERV–W Env</td>
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<td></td>
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<td>Repurposed</td>
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</table>

### Market Size

- **$22bn market in 2018, attributable almost exclusively to inflammation-targeting treatments**
- **Highly competitive segment:** 2018 was the first year with a decrease in total market for immuno-modulators
- **NO DRUG APPROVED**
- **Acute need for ~30% of MS population**
  - Very high impact on quality of life and healthcare costs for all patients

Sources: EvaluatePharma, Annual reports of companies active in MS
Higher disability leads to increased patient suffering and societal costs

Cross-sectional study conducted in 16 European countries in 2017

Cross-sectional study conducted in 16 European countries on 16,808 participants; costs reported from a societal perspective in 2015€ PPP (adjusted for purchasing power parity).

Sources: Kobelt G., Thompson A. et al., New insights into the burden and costs of multiple sclerosis in Europe, MS Journal Feb. 2017
Few drugs in late development specifically target neurodegeneration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Pharmacology</th>
<th>Proposed Mode of Action</th>
<th>Dev. Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opicinumab</td>
<td>Biogen</td>
<td>Monoclonal antibody IgG1 neutralizing LINGO-1 protein</td>
<td>Favoring oligodendrocyte differentiation and remyelination</td>
<td>Ongoing Phase IIb</td>
</tr>
<tr>
<td>Biotin</td>
<td>MedDay</td>
<td>Vitamin B8/H given at high dose (300mg/day)</td>
<td>Increasing energy supply (ATP, fatty acid) to oligodendrocytes favoring myelin production</td>
<td>Ongoing Phase 3</td>
</tr>
<tr>
<td>Ibudilast</td>
<td>MediciNova</td>
<td>Anti-inflammatory drug, approved in Japan for asthma since 1989</td>
<td>Inhibition of macrophage migration, decrease of TNFα, enhancing survival and maturation of oligodendrocytes</td>
<td>Completed Phase IIb</td>
</tr>
<tr>
<td>Masitinib</td>
<td>AB Science</td>
<td>Selective tyrosine kinase inhibitor developed in neurology, inflammatory diseases and oncology</td>
<td>Inhibiting mast cell degranulation to avoid proteolysis, secretion of vasoamines and release of pro-inflammatory chemoattractants</td>
<td>Phase III ongoing</td>
</tr>
<tr>
<td>Temelimab</td>
<td>GeNeuro</td>
<td>Monoclonal antibody IgG4 neutralizing pHERV-W-Env, associated to MS as a causal factor</td>
<td>Enhancing remyelination and reducing damage by promoting OPC maturation and blocking microglial activation</td>
<td>Completed Phase IIb</td>
</tr>
</tbody>
</table>

Sources: Mellion et al., Neurology 2017; Kremer et al., MSJ 2018 In print; Green et al., Lancet 2017; Company web sites
Temelimab’s strong results pave the way for the continued development against disease progression.

**Strengths of the program**

- Robust and consistent impact on the MRI markers associated with disease progression, confirmed at 96 weeks
  - Reduction of atrophy of brain volumes (Thalamus, Cortex, whole brain),
  - Reduction of Black Holes
  - Maintained MTR values
  - Activity appears to be independent of anti-inflammatory effect
  - Excellent safety for long term treatment, as monotherapy or in combination
  - Corroborated by accumulating scientific evidence of the pertinence of the mode of action

**Further data to be generated**

- Generation of data in progressing MS population
- Define the optimal dose
Selection criteria for non-active progressive patients

Pre-IND response from the FDA, Sept. 2019

• GN’s Clinical question: definition on non-active progressive MS

  FDA’s response: “We recommend that a study intended to support a drug effect on progression of disability in progressive MS that is independent of an effect on relapses should exclude, at a minimum, all patients who experienced a relapse within at least 2 years prior to study entry”

GeNeuro’s options for patient selection

• Patients need to have a clearly documented progression of disability over the last two years, AND

• Patients need to be followed closely to ensure no relapse activity over the last two years, which may be due to:
  • The natural course of the disease, and /or
  • An effective DMT, limiting inflammatory damage without stopping disability progression
The “Karolinska” study – A bridging study to explore doses and effect on the target population

Objective

• Document temelimab’s safety and efficacy at higher doses, with same + latest exploratory biomarkers of neuroprotection, in patients with progressing disability without relapses

• Truly addressing “progression independent of relapse activity” (PIRA), as patients’ inflammatory activity will be controlled through a DMT

At the Karolinska’s Academic Specialist Center:

• Largest MS Center in Sweden with 2’400 MS patients

• Highly regarded research Center, with access to latest equipment and biomarkers

Timelines

• First patient in 1Q2020, 1-year treatment; Top-line results 3Q2021

Output

• Safety and differences in efficacy measures through latest neuroprotection biomarkers at higher doses of temelimab versus placebo
The “Karolinska” study with temelimab

**Phase II study outline:**
- Karolinska’s Academic Specialist Center; PI: Fredrik Piehl MD PhD
- RMS patients with confirmed disability progression in the absence of relapse activity (PIRA)
- Relapse activity is managed thanks to B-cell depletion with rituximab (anti-CD20 mAb)
- Monthly administration of temelimab 18, 36, 54 mg/kg vs placebo
- Initially 40 patients with confirmed progression over the last year, with EDSS of 3.0-5.5
- Bridging CHANGE-MS and ANGEL-MS MRI endpoints, and adding novel biomarkers linked to disease progression, myelin integrity and axonal density
- Planned FPI: Q1 2020; LPO: Q3 2021
The “Karolinska” study - Endpoints bridge to previous studies and explore markers of myelin and axonal integrity

Primary endpoints

• Safety and tolerability of temelimab

Secondary endpoints (bridged to CHANGE and ANGEL-MS studies)

• MRI measurements documenting baseline versus week 48 in:
  ➢ Volume of thalamus, cortex + globus pallidum
  ➢ Number and volume of black holes
  ➢ Change in myelin integrity by magnetization transfer ratio (MTR)

• Markers of neurodegeneration / neuroprotection in biofluids (NfL, neurogranin, MBP, etc.)

Exploratory endpoints (based on novel myelin and lesion imaging)

• MRI measurements documenting baseline versus week 48 in:
  ➢ Markers of myelin integrity, myelin fraction (REMyDI) and axonal density (multi shell diffusion) in lesions and slowly evolving lesions vs normal appearing white matter (NAWM)

• Clinical assessments documenting baseline versus week 48 in:
  ➢ Overall Disability Response Score (ODRS) – multicomponent clinical endpoint
High unmet medical need with multiple options for Phase II/III and/or Phase III development

Development options

• As a monotherapy or on top of existing DMTs
  • Extension and enlargement of the Karolinska trial, seeking clinical endpoints at two years
  • As monotherapy, in non-active progressive MS patients, as clear regulatory entry point; and / or
  • On top of a number of existing DMTs, to enlarge addressable patient population (but also increasing trial’s number of patients due to baseline diversity)

• Combination with a Partner’s existing DMT
  • Temelimab’s safety profile allows a combination with existing anti-inflammatory drug, to slow-down / prevent progression on treated Relapsing MS patients (rendered “non-active” by their anti-inflammatory treatment)
Ultimate objective in MS
To make temelimab available to ALL MS patients

- Disease progression
- Relevant to all disease forms
- Excellent safety profile

Tackle two of the core mechanisms of disability progression
Progression starts from the beginning of MS
Temelimab has no negative impact on immune system
A strong pipeline to leverage and extract full value of HERV technology
## First mover in HERV-mediated diseases

<table>
<thead>
<tr>
<th>Program</th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Phase IIb</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>1. <strong>Temelimab</strong></td>
<td></td>
<td>Planning next stage developments based on positive neurodegeneration 96-week results</td>
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<tr>
<td>Multiple Sclerosis</td>
<td></td>
<td>CHANGE-MS : 270 patients in RRMS indication - completed 03/2018</td>
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<tr>
<td>CHANGE-MS / ANGEL-MS</td>
<td></td>
<td>ANGEL-MS : 219 patients extension - Completed 03/2019</td>
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<tr>
<td>Karolinska/ASC trial</td>
<td></td>
<td>Phase II study in Non-Active Progressive / Launch planned Q1 2020</td>
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<tr>
<td>2. <strong>Anti-HERV-K</strong></td>
<td></td>
<td>R&amp;D Agreement with NIH, IND submission planned by 1H2021</td>
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<tr>
<td>ALS</td>
<td></td>
<td>Preclinical program underway, candidate humanized</td>
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<tr>
<td><strong>Other opportunities</strong></td>
<td></td>
<td><strong>Subject to ad-hoc funding / partnering</strong></td>
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<tr>
<td>3. <strong>Temelimab</strong></td>
<td></td>
<td>Safety &amp; signal finding Phase IIa, completed 05/2019</td>
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<tr>
<td>Type 1 Diabetes</td>
<td></td>
<td>New study subject to development of temelimab in MS</td>
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<tr>
<td>4. <strong>Temelimab</strong></td>
<td></td>
<td>ODD granted by the US FDA</td>
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<tr>
<td>CIDP</td>
<td></td>
<td>No study planned presently.</td>
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<tr>
<td>5. New anti HERV-W Ab</td>
<td></td>
<td>Research collaborations with Academic labs, murine candidate selected</td>
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<td></td>
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<tr>
<td>Inflammatory Psychosis</td>
<td></td>
<td>No study at present without ad-hoc non-dilutive funding</td>
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</table>
ALS program: The NIH initiated and evidenced the HERV-K concept

- NINDS developed a transgenic mouse that expresses HERV-K Env in the brain and spinal cord (neurons)

![HERV-K transgenic vs Wild type](image)

- The phenotype of the transgenic mouse mimics signs and symptoms of clinical ALS

![Reduced life span, Motor neuron functionality, Clasping behavior](image)

ALS program planned to initiate clinical trials in 2021

• Research partnership in 2017, extended in 2019, with the National Institute of Neurological Disorders and Stroke (NINDS), part of the U.S. National Institutes of Health (NIH)
  • GeNeuro provides antibodies designed to block the activity of HERV-K envelope protein
  • NINDS tests antibodies in cellular and animal models of HERV-K associated ALS
  • Results validate the potential of GeNeuro’s anti pHERV-K antibodies as a new therapeutic approach against ALS

• Following successful results of the research partnership with NIH in ALS models, GeNeuro has signed in October 2018 an exclusive worldwide license with the NIH covering the development rights of an antibody program to block the activity of pHERV-K Env, a potential key factor in the development of ALS

GeNeuro is executing on the preclinical development of the lead antibody, aiming at IND by 1H2021
RAINBOW-T1D Summary
Successful study, opening way to early-onset T1D trials

• 12 month study with a 6-month double blind period and a 6-month extension with all patients on temelimab, including patients previously on placebo

• Excellent safety / tolerability of temelimab observed over one year

• Positive temelimab pharmacodynamic observations at 6 months are confirmed in the second period

• No conclusions possible on C-peptide, insulin consumption and HbA1C: small cohort size from a late onset adult population, well treated with low insulin needs, stable during trial

• Study completes its objective of demonstrating safety and pharmacodynamic response in adult T1D patients, opening door to further development in larger early-onset pediatric population
Rainbow T1D Week 48 PD Outcomes - Hypoglycemia
Confirmed decrease of hypoglycemic episodes

<table>
<thead>
<tr>
<th>Adjusted mean number of hypoglycemic episodes per patient</th>
<th>Temelimab/temelimab (N=31 out of 43**)</th>
<th>Placebo/temelimab (N=14 out of 21**)</th>
<th>Rate ratio</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double-blind Period</td>
<td>2.09</td>
<td>2.92</td>
<td>0.75</td>
<td>0.0001</td>
</tr>
<tr>
<td>Extension Period</td>
<td>1.88</td>
<td>2.07</td>
<td>0.91</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Group treated by temelimab 12 months:

- Reduction of frequencies of hypoglycemia under temelimab in first 6-month (-28%, p<0.0001 vs placebo),
- Further reduction of 10% in the second 6 month period

Group switching to temelimab from placebo:

- Reduction of hypoglycemia frequency in this group vs the previous placebo period (-29%), reaching the level of reduction observed with temelimab in the first 6 months of treatment

* Poisson regression analysis

** Patients who continued in the Open-Label period

January 2020
Good basis for growth
The GeNeuro team

Jesús Martin-Garcia | MBA
Chief Executive Officer – Co-founder

Strong track-record in creating value in high technology start-ups
More than 20 years of experience as founder and investor in successful startups
MBA from Harvard Business School

Dr. François Curtin | MD, MPhil, MBA
Chief Operating Officer & Acting Chief Medical Officer

15 years experience in MS, in charge of R&D and clinical development
Clinical expertise at Merck Serono, previously at Swissmedic (“Swiss FDA”)
MD from Geneva Medical School & MBA from Warwick Business School

Dr. Hervé Perron | PhD, HDR
Chief Scientific Officer – Co-founder

Made the initial key discoveries in the field of human endogenous retroviruses while at INSERM and bioMérieux
Has published over 120 peer-reviewed papers and patents, mostly on HERVs
PhD in virology and a professorial thesis in neuroimmunology

Dr. Thomas Rückle | PhD, PMP
Chief Development Officer

Over 20 years experience in translational science
Preclinical and early clinical expertise at Merck Serono & MMV. As project director, led several projects from lead to Phase II clinical proof of concept
PhD in Organic Chemistry

Miguel Payró
Chief Financial Officer

Experience in international groups & expertise as CFO of a Swiss listed company in the medical sector
Previously CFO of Groupe Franck Muller & Unilabs, among others
Degree in business administration from the University of Geneva
Broad and strong IP supporting first mover advantage

- Mérieux Group & GeNeuro worked for more than 25 years in the HERV field
- 16 families of patents in HERV-W*, including the following 3 broad categories:
- **Key granted patents on temelimab filed from 2008 (NCE) to 2014 (on progression)**
  Strong IP development strategy to continue protecting temelimab beyond 2034 (2039 w. SPC)

  - **SEP 16 family**
    Background including sequences
  - **TLR4 family**
    Antibody strategy against target
  - **MSRV* ligand family**
    Product patents & disease areas

Existing IP portfolio & constant efforts to protect new discoveries place GeNeuro in a strong competitive position

- **New anti pHERV-K patent, co-owned with and in-licensed from NIH**
  
  * previous name of pHERV-W Env
Financial Summary

Share capital as of Sept. 2019

- Eclosion²: 43.4%
- Institut Mérieux Group (through GNEH SAS): 33.9%
- Public: 12.5%
- Management & Treasury shares: 1.6%
- Servier: 8.6%

Note: excludes stock options, representing a maximum 6.9% dilution, with an average exercise price of €10.38 per share

P&L and cash balance (in € ‘000)

<table>
<thead>
<tr>
<th></th>
<th>3Q 2019</th>
<th>1H 2019</th>
<th>FY 2018</th>
<th>FY 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Income</td>
<td>-</td>
<td>-</td>
<td>7,463</td>
<td>14,949</td>
</tr>
<tr>
<td>R&amp;D Expenses</td>
<td>n.d.</td>
<td>(2,535)</td>
<td>(10,930)</td>
<td>(16,161)</td>
</tr>
<tr>
<td>G&amp;A</td>
<td>n.d.</td>
<td>(1,796)</td>
<td>(4,686)</td>
<td>(4,597)</td>
</tr>
<tr>
<td>Operating loss</td>
<td>n.d.</td>
<td>(4,319)</td>
<td>(8,089)</td>
<td>(5,740)</td>
</tr>
<tr>
<td>Cash &amp; Equivalents</td>
<td>8M</td>
<td>9,992</td>
<td>8,961</td>
<td>26,602</td>
</tr>
</tbody>
</table>
Capturing the full value of the HERV platform

- Open options for development going forward in MS
  - Partnering discussions ongoing
  - Registration supporting/enabling trial in patients with disability progression in the absence of relapses

- Open options for development in other indications, with ad-hoc funding/partners
  - Phase IIb in T1D in a juvenile population
  - Program for anti pHERV-W new monoclonal antibody against inflammatory psychosis
A causal approach to changing the course of neurodegenerative diseases

Jesús Martin-Garcia | CEO
jmg@geneuro.com
Tel: +41 22 552 4800
www.geneuro.com
Temelimab Phase II clinical results in MS
Phase IIb trial (CHANGE-MS followed by ANGEL-MS)

Efficacy in RRMS patients at 6 months, 1 year and 2 years

- International, randomized, double-blind, placebo-controlled Phase 2b study in RRMS patients + extension

- Primary Endpoint: Cumulative # Gd+ lesions on brain MRI scans at weeks 12-24

- After 24 weeks, the control group is composed of patients originally randomized to placebo.

- Remyelination and neuroprotection endpoints at 48 weeks and at week 96 in extension study

---

**CHANGE-MS**

- **Period 1**
  - 6 repeated doses
  - 270 patients (1:1:1:1)

- **Period 2**
  - 6 repeated doses
  - 247 patients (1:1:1)

- **Extension Study**
  - Group temelimab 18 mg/kg
  - Group temelimab 12 mg/kg
  - Group temelimab 6 mg/kg

---

**ANGEL-MS**

- **Secondary endpoints & Full analysis**
  - March 2018

- **92% of patients**

---

**MRI**

- Administration: IMP IV every 4 weeks
ANGEL-MS: extension study to CHANGE-MS assessing safety & efficacy of temelimab in RRMS patients

- 219 patients from CHANGE-MS entered ANGEL-MS (92% of completers)
  - Early termination was a result of Servier’s decision to opt-out
  - 154 patients (70%) completed 96 weeks or more across the combined studies
  - Approximately 90% of patients completed at least 86 weeks

- All patients remained on active therapy; patients, investigators and MRI reading center remained blinded to dose/original randomization group

- Delays in study start-up led to dose interruptions between the trials
  - > 80% missed ≥ 1 dose; ≈ 50% missed ≥ 2 doses and ≈ 20% missed ≥ 3 doses

- Analysis strategy:
  - As per SAP, original randomization groups: 18, 12 and 6mg/kg & Control Group (defined as patients originally randomized to placebo in CHANGE-MS, and re-randomized to active treatment after 6 months)
  - Several sensitivity analyses performed:
    - (1) by dose groups (placebo patients placed into the active dose group they were re-randomized to)
    - (2) by exposure (separating quartiles by total exposure to temelimab, irrespective of body weight);
    - (3) separating 18mg/kg against all other treatments
  - No adjustments were performed for multiple testing
CHANGE-MS and ANGEL-MS 48-week results position temelimab’s against disease progression in MS

- No clinically relevant benefit on MRI markers of neuroinflammation
  - Primary endpoint on the reduction of number of Gd+ lesions at Week 24 not met
  - All groups substantially improved from Week 24 to Week 48
  - No significant differences across groups

- Consistent benefit with temelimab at highest dose on key markers of neurodegeneration, linked to disease progression
  - Reduction of Brain Atrophy (thalamus, cerebral cortex, deep gray matter and whole brain)
  - Reduction in T1 Black Holes (marker of permanent tissue damage)
  - Benefit seen on Magnetization Transfer Ratio (MTR - measure of remyelination)

- Temelimab’s effect is independent from the inflammatory activity experienced by the patients during the study

- First encouraging signals of neuroprotection translating into clinical benefits at 96 weeks

- Continued excellent safety and tolerability
  - Opens the door for possible increase in dose, and/or
  - Combination with powerful anti-inflammatory agents
Continued reduction Thalamic atrophy
Original CHANGE-MS Groups

Percentage Change in Brain Volume from baseline CHANGE-MS to ANGEL-MS Week 48 in Thalamus

<table>
<thead>
<tr>
<th>Group</th>
<th>Median % reduction at week 48</th>
<th>Relative reduction of atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>-1.27</td>
<td></td>
</tr>
<tr>
<td>18mg/kg</td>
<td>-0.36</td>
<td>72%</td>
</tr>
</tbody>
</table>

Dose effect* p=0.014

<table>
<thead>
<tr>
<th>Group</th>
<th>Median % reduction at week 48</th>
<th>Relative reduction of atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>-3.24</td>
<td>43%</td>
</tr>
<tr>
<td>6mg/kg</td>
<td>-2.31</td>
<td>19%</td>
</tr>
<tr>
<td>12mg/kg</td>
<td>-1.70</td>
<td>-9%</td>
</tr>
<tr>
<td>18mg/kg</td>
<td>-1.86</td>
<td></td>
</tr>
</tbody>
</table>

Dose effect* p=0.038

* Dose-effect analyzed by linear regression model
Continued reduction Thalamic atrophy
Sensitivity analysis by Dose and by Exposure

**BY DOSE**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median % reduction at week 48 in ANGEL-MS</th>
<th>Relative reduction of atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>6mg/kg</td>
<td>-2.7</td>
<td>-</td>
</tr>
<tr>
<td>12mg/kg</td>
<td>-2.3</td>
<td>17%</td>
</tr>
<tr>
<td>18mg/kg</td>
<td>-1.9</td>
<td>30%</td>
</tr>
</tbody>
</table>

* Dose-effect analyzed by linear regression model

**BY EXPOSURE**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median % reduction at week 48 in ANGEL-MS</th>
<th>Relative reduction of atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 MIN</td>
<td>-2.3</td>
<td>-</td>
</tr>
<tr>
<td>G4 MAX</td>
<td>-1.6</td>
<td>30%</td>
</tr>
</tbody>
</table>
Continued reduction of Cortex atrophy
Original CHANGE-MS Groups

**Percentage Change in Brain Volume from baseline CHANGE-MS to ANGEL-MS Week 48 in Cerebral Cortical Volume**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median % reduction at week 48</th>
<th>Relative reduction of atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>-0.59</td>
<td></td>
</tr>
<tr>
<td>18mg/kg</td>
<td>-0.41</td>
<td>31%</td>
</tr>
</tbody>
</table>

Dose effect* p=0.045

**ANGEL-MS**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median % reduction at week 48</th>
<th>Relative reduction of atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>-1.29</td>
<td>42%</td>
</tr>
<tr>
<td>6mg/kg</td>
<td>-1.27</td>
<td>41%</td>
</tr>
<tr>
<td>12mg/kg</td>
<td>-1.29</td>
<td>42%</td>
</tr>
<tr>
<td>18mg/kg</td>
<td>-0.75</td>
<td></td>
</tr>
</tbody>
</table>

Dose effect* p=0.058

* Dose-effect analyzed by linear regression model
Consistent benefit with temelimab seen in non-active population is a key asset

Median change in volume in non-active population* in CHANGE-MS 18mg/kg versus Control Group

- Effects of temelimab on OPCs and microglia are not due to immune modulation
- Suggests temelimab monotherapy could effectively target neurodegeneration and promote regeneration in non-active populations
- Suggests temelimab as adjunct to highly-effective DMTs for all forms of active MS

* defined as patients without Gd+ activity at baseline

Source: H.P. Hartung et al, ECTRIMS 2018 Presentation
Reduction in the number and volume of new T1 hypointense lesions (Black Holes) through CHANGE-MS and ANGEL-MS

**CHANGE-MS Week 48**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Number of Qualifying BH Lesions* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18mg/kg</td>
<td>-63% (p=0.014)</td>
</tr>
<tr>
<td>12mg/kg</td>
<td></td>
</tr>
<tr>
<td>6mg/kg</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
</tr>
</tbody>
</table>

* T1 hypointense lesion ≥ 14mm³ volume

**ANGEL-MS Week 96**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median percent increase in T1 hypointense lesion volume**</th>
</tr>
</thead>
<tbody>
<tr>
<td>18mg/kg</td>
<td>8.7%</td>
</tr>
<tr>
<td>12mg/kg</td>
<td>9.2%</td>
</tr>
<tr>
<td>6mg/kg</td>
<td>14.5%</td>
</tr>
<tr>
<td>Control Group</td>
<td>21.3%</td>
</tr>
</tbody>
</table>

**The set-up of ANGEL-MS did not allow to differentiate acute and chronic T1-hypointense lesions, therefore data not directly comparable to CHANGE-MS measure of chronic lesions**
Reduction in risk of lesions at baseline transforming into new T1Black Holes at CHANGE-MS Week 48

Proportion of patients with T1Gd+ lesions at baseline

Control Group | Temelimab 18mg/kg
---|---
N=33 | N=23
Proportion of patients with T1Gd+ lesions transformed into new T1 BHs at week 48
58% | 30%
- 48%

Proportion of patients with non-enhancing T2 lesions at baseline

Control Group | Temelimab 18mg/kg
---|---
N=64 | N=61
Proportion of patients with non-enhancing T2 lesions transformed into new T1 BHs at week 48
36% | 21%
- 42%

January 2020
Temelimab preserves myelin integrity over 96 weeks
Normal Appearing White Matter - Original CHANGE-MS Groups

<table>
<thead>
<tr>
<th>Change in MTR signal from CHANGE-MS BL (% units)</th>
<th>18 mg</th>
<th>12 mg</th>
<th>6 mg</th>
<th>Control</th>
<th>Gain 18 vs 12</th>
<th>Gain 18 vs 6</th>
<th>Gain 18 vs Ctrl</th>
<th>Trend p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NAWM Band 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>-0.84</td>
<td>-3.02</td>
<td>-3.76</td>
<td>-3.17</td>
<td>2.18</td>
<td>2.91</td>
<td>2.33</td>
<td>0.022</td>
</tr>
<tr>
<td>median</td>
<td>-1.83</td>
<td>-3.55</td>
<td>-3.39</td>
<td>-3.52</td>
<td>1.72</td>
<td>1.56</td>
<td>1.69</td>
<td></td>
</tr>
<tr>
<td><strong>NAWM Band 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>-0.12</td>
<td>-2.17</td>
<td>-2.94</td>
<td>-2.13</td>
<td>2.05</td>
<td>2.82</td>
<td>2.01</td>
<td>0.034</td>
</tr>
<tr>
<td>median</td>
<td>-0.99</td>
<td>-2.70</td>
<td>-2.16</td>
<td>-2.65</td>
<td>1.71</td>
<td>1.17</td>
<td>1.66</td>
<td></td>
</tr>
<tr>
<td><strong>NAWM Band 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>0.74</td>
<td>-1.31</td>
<td>-1.85</td>
<td>-1.11</td>
<td>2.05</td>
<td>2.60</td>
<td>1.86</td>
<td>0.048</td>
</tr>
<tr>
<td>median</td>
<td>-0.32</td>
<td>-1.42</td>
<td>-0.86</td>
<td>-1.35</td>
<td>1.10</td>
<td>0.54</td>
<td>1.03</td>
<td></td>
</tr>
</tbody>
</table>

* Dose-effect analyzed by linear regression, SAS analysis proc GLM
Temelimab preserves myelin integrity over 96 weeks
Cerebral Cortex - Original CHANGE-MS Groups

<table>
<thead>
<tr>
<th>Change in MTR signal from CHANGE-MS BL (% units)</th>
<th>18 mg</th>
<th>12 mg</th>
<th>6 mg</th>
<th>Control</th>
<th>Gain 18 vs 12</th>
<th>Gain 18 vs 6</th>
<th>Gain 18 vs Ctrl</th>
<th>Trend p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CC Band 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>0.77</td>
<td>-1.24</td>
<td>-1.24</td>
<td>-1.01</td>
<td>2.01</td>
<td>2.01</td>
<td>1.78</td>
<td>0.035</td>
</tr>
<tr>
<td>median</td>
<td>0.00</td>
<td>-0.89</td>
<td>-0.73</td>
<td>-0.96</td>
<td>0.89</td>
<td>0.73</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td><strong>CC Band 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>0.63</td>
<td>-1.40</td>
<td>-1.42</td>
<td>-1.19</td>
<td>2.03</td>
<td>2.06</td>
<td>1.82</td>
<td>0.033</td>
</tr>
<tr>
<td>median</td>
<td>-0.01</td>
<td>-0.97</td>
<td>-1.07</td>
<td>-1.20</td>
<td>0.96</td>
<td>1.06</td>
<td>1.19</td>
<td></td>
</tr>
<tr>
<td><strong>CC Band 4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>0.44</td>
<td>-1.76</td>
<td>-1.78</td>
<td>-1.54</td>
<td>2.20</td>
<td>2.22</td>
<td>1.98</td>
<td>0.024</td>
</tr>
<tr>
<td>median</td>
<td>0.13</td>
<td>-1.11</td>
<td>-1.12</td>
<td>-1.41</td>
<td>1.24</td>
<td>1.25</td>
<td>1.54</td>
<td></td>
</tr>
</tbody>
</table>

* Dose-effect analyzed by linear regression, SAS analysis proc GLM
Lower probability of 12-week confirmed disability progression in the 18 mg/kg group, but not reaching statistical significance:

- Survival Wilcoxon overall test $p=0.34$
- Log-rank overall test $p=0.45$
- Hazard ratio 18mg/kg vs control = 0.50, pairwise comparison $p=0.27$
Encouraging signs of clinical benefit on Timed 25-Foot Walk
Original CHANGE-MS groups and Sensitivity analyses

<table>
<thead>
<tr>
<th>Timed 25-foot walk – Original CHANGE-MS Groups</th>
<th>18 mg/kg</th>
<th>12 mg/kg</th>
<th>6 mg/kg</th>
<th>Control</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients with worsening ≥ 20% in the Timed 25-Foot Walk Test compared to CHANGE-MS Baseline*</td>
<td>2.4</td>
<td>23.1</td>
<td>13.3</td>
<td>10.2</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timed 25-foot walk – By Dose Groups</th>
<th>18 mg/kg</th>
<th>12 mg/kg</th>
<th>6 mg/kg</th>
<th>P-Value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients with worsening ≥ 20% in the Timed 25-Foot Walk Test compared to CHANGE-MS Baseline*</td>
<td>3.6</td>
<td>16.9</td>
<td>15.0</td>
<td>0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Timed 25-foot walk – By 18 vs Others</th>
<th>18 mg/kg</th>
<th>Others</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients with worsening ≥ 20% in the Timed 25-Foot Walk Test compared to CHANGE-MS Baseline*</td>
<td>2.4</td>
<td>15.0</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Fifteen outliers (patients with extreme walking disability) removed from analysis – excluded patients distributed equally across treatment groups

**Fisher exact test

January 2020
Temelimab was safe and well tolerated over two years

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>18 mg/kg (N=77)</th>
<th>12 mg/kg (N=68)</th>
<th>6 mg/kg (N=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Events (AEs)</td>
<td>34 (44.2%)</td>
<td>32 (47.1%)</td>
<td>33 (44.6%)</td>
</tr>
<tr>
<td>Serious adverse events (SAEs)</td>
<td>5 (6.5%)</td>
<td>1 (1.5%)</td>
<td>6 (8.1%)</td>
</tr>
<tr>
<td>Serious related AEs</td>
<td>3 (3.9%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs leading to study discontinuation</td>
<td>2 (2.6%)</td>
<td>1 (1.5%)</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Fatality*</td>
<td>1 (1.3%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Patient had previously voluntarily exited the study; the Investigator considered the event as unrelated.
Clinical observations

- Reduction of Brain Atrophy
- Reduction in new T1 Black Holes
- Benefit on Magnetization Transfer Ratio
- Effects on markers associated with disease progression not due to immune modulation
- Promising a novel treatment option against neurodegeneration in all forms of MS

Supporting pre-clinical data

- Neurodegeneration reduced by directly acting on proinflammatory microglia, the key immune cells in PMS, responsible for lesion growth and exacerbation
- Neuroregeneration enabled by rescuing the negative impact of pHERV-W Env on OPC maturation - the key cells in the remyelination process.
- No direct effect on T/B lymphocytes and thereby not compromising adaptive immunity
- Excellent preclinical safety package based on a stabilized IgG4 backbone, low immunogenicity and a linear PK at all doses


January 2020