Targeting the cause of neurodegenerative and autoimmune diseases

February 2019
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GeNeuro’s mission

To develop therapies that improve the life of patients with neurodegenerative and autoimmune diseases

• Leveraging the biology of human endogenous retroviruses (HERVs) to stop key causal factors associated with these disorders

• The HERV field is a new frontier pioneered by GeNeuro since 2006, based on 15 years of R&D at Institut Mérieux and INSERM

• Demonstrated benefit of blocking a causal factor in an autoimmune disease in a Phase IIb clinical trial in Multiple Sclerosis
**Human Endogenous Retroviruses (HERVs)**

**Ancestral retroviral genomic (DNA) insertions**

**HERV elements are latent in human genome**
- Represent approximately 8% of total human genome
- Genetic transposition leads to variable copy number, with non-ubiquitous copies in individuals
- HERVs are normally latent but may be de-repressed and transcribed to produce viral proteins

**Missing link between viral infections and poorly understood autoimmune / neurodegenerative diseases**
- Strong epidemiology data associates environmental viruses with diseases such as MS and T1D
- However environmental viruses do not appear to play a direct role in their development
- These viruses may de-repress HERV proteins upon infection of permissive cells
- Pathogenic HERV proteins have been implicated as causal factors in autoimmune / neurodegenerative diseases

Sources:
- Regulatory evolution of innate immunity through co-option of endogenous retroviruses; Science, Vol. 351, Issue 6277
- Discovery of unfixed endogenous retrovirus insertions in diverse human populations. Proc Natl Acad Sci U S A. 2016
- Human Endogenous Retrovirus Type W Envelope Protein Inhibits Oligodendroglial Precursor Cell Differentiation; Ann Neurol. 2013;74(5)A
Viruses triggering HERV Proteins and link to disease
Examples of pHERV Env mediated diseases

Suspected transactivating viruses and affected organs

- Pathogenic HERV proteins found at high levels in affected organs
- Pathogenicity is generally mediated by (abnormally expressed) viral envelope proteins – pHERV Env
- pHERV Env directed toxicities found in:
  - Microglia
  - OPCs
  - Pancreatic beta islet cells
  - Neurons
  - Schwan cells
  - Others…

Herpesviridae

**Suspected transactivating viruses and affected organs**

- **HERV-W**
  - CNS Gray Matter
    - CMV, Toxoplasma...
    - Inflammatory Psychoses
    - 40-60 % of cases?
  - CNS White Matter
    - EBV, HSV1, HHV6, VZV,...
    - Multiple Sclerosis
    - 75-100% of cases

- **HERV-K**
  - Motor neurons
    - Neurotropic viruses,…
    - Sporadic ALS
  - Synovial membrane
    - RA
  - Peripheral Nerves
    - CMV, ...
    - CIDP
    - ~ 50% of cases ?
  - Pancreas
    - Enteroviruses, Coxackie viruses ... 
    - Type 1 Diabetes
    - 50-60 % of cases ?
  - Other Diseases ?
    - (Systemic lupus, psoriasis, etc.)

Recent data validates GeNeuro’s platform approach against pathogenic HERV proteins

- Positive results of 270-patient RRMS Phase IIb study funded by Servier,
  - Consistent benefit with temelimab at highest dose on three key markers of neurodegeneration linked to disease progression
  - Results strongly supported by preclinical evidence and mode of action rationale

  ➢ Clear positioning against the key unmet medical need in MS: disease progression

- Successful Phase IIa in T1D

- Launch of the pHERV-K monoclonal antibody program against ALS, in partnership with NIH

- Wide application potential in other autoimmune and degenerative diseases
## 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>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Temelimab</strong> Multiple Sclerosis</td>
<td>270 patients / 50 centers in the RRMS indication / Completed March 2018</td>
<td>Planning next stage developments based on positive neurodegeneration 48-week results</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2. <strong>Temelimab</strong> Type 1 Diabetes</td>
<td>Safety &amp; signal finding Phase IIa</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Launched April 2017 / 6-month data Sept. 2018, full 12-month data 2Q2019</td>
<td></td>
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</tr>
<tr>
<td>3. <strong>Temelimab</strong> Pharmacology</td>
<td>Phase 1c study on 24 healthy controls with doses up to 110 mg/kg / results end 2018</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>4. <strong>Temelimab</strong> CIDP</td>
<td>ODD granted by the US FDA</td>
<td>Planning discussions with FDA to design a proof-of-concept study</td>
<td></td>
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<tr>
<td>5. New anti HERV-W Ab Inflammatory Psychosis</td>
<td>R&amp;D collaborations with Academic labs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. <strong>Anti-HERV-K ALS</strong></td>
<td>R&amp;D Agreement with NIH in ALS</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

February 2019
Part 1

GeNeuro development in MS
2.5 million MS patients worldwide
$22.3bn market in 2017

MS is a life-long inflammatory and degenerative disorder of the central nervous system

- Brain impairment
  - Vision, cognition, motor coordination, equilibrium

- Spinal cord impairment
  - Walking, strength, sensation, sexuality, bowel / bladder control

- Disease onset mainly occurs in young adults
- Female to male ratio is 2:1
- Mean prevalence about 1/1000

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

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)

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Adapted from Compston et al., The Lancet 2002
**Known drivers of multiple sclerosis**

**Adaptive Immunity**

T- and B-cells are selectively recruited to the CNS

**Detrimental circle of events:**
- Tissue damage: release of antigens to the periphery,
- which in turn primes new immune responses in the lymphoid tissue,
- followed by the invasion of lymphocytes into the CNS. (autoimmunity)

**Innate Immunity**

Infiltrating Macrophages and CNS residential Microglia

**Driver of MS disease progression**
- Promote T/ B cells response.
- Release of proinflammatory cytokines, chemokines, NO radicals and glutamate
- Direct damage on axons

**Repair**

Dysfunctional Oligodendrocyte Precursor Cells (OPCs)

**Remyelination is altered**
- by dysfunctional OPCs
The unmet need in MS:

**Adaptive Immunity**

T- and B-cells are selectively recruited to the CNS

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

**Innate Immunity**

Infiltrating Macrophages and CNS residential Microglia

**No approved drugs**

**Repair**

Dysfunctional Oligodendrocyte Precursor Cells (OPCs)

**No approved drugs**
Current treatment paradigm focuses on relapse control

Reductions of relapse rate by leading MS drugs (in published clinical trials)

<table>
<thead>
<tr>
<th>ABCRs(1)</th>
<th>Orals and intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avonex MSCRG</td>
<td>2017 sales = $9.2bn (42%)</td>
</tr>
<tr>
<td>Copaxone CMSSG</td>
<td>2017 sales = $12.4bn (56%)</td>
</tr>
<tr>
<td>Betaseron MSSG</td>
<td>18%</td>
</tr>
<tr>
<td>Rebif Prisms</td>
<td>29%</td>
</tr>
<tr>
<td>Aubagio Tower</td>
<td>31%</td>
</tr>
<tr>
<td>Tecfidera Define</td>
<td>33%</td>
</tr>
<tr>
<td>Gilenya Freedoms</td>
<td>36%</td>
</tr>
<tr>
<td>Tysabri AFFIRM</td>
<td>53%</td>
</tr>
<tr>
<td>Ocrevus Phase II</td>
<td>55%</td>
</tr>
<tr>
<td>18%</td>
<td>68%</td>
</tr>
<tr>
<td>29%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Currently approved drugs target immune pathways
Associated impact on immune system & potential side effects

(1) ABCR = Avonex-Betaseron-Copaxone-Rebif
Critical unmet medical need
MS inevitably leads to progressive disability

MS at first diagnosis (Post CIS)

Relapsing-remitting: 85%
Primary progressive: 15%

Few drugs for progressive forms of the disease

Patient evolution
80% of people who are diagnosed with RRMS develop secondary progressive MS

Secondary progressive

No drugs prevent conversion from RRMS to SPMS

Sources: National MS Society; Atlas of MS 2013; NIH estimates.
Objective: develop a new treatment effective for disease progression

Immune-modulating therapies

GeNeuro’s Main focus

Inflammation

Neurodegeneration

RRMS ——— SPMS ——— PPMS

“The greatest remaining challenge for multiple sclerosis is the development of treatments incorporating neuroprotection and remyelination to treat and ultimately prevent the disabling, progressive forms of the condition.”

Prof. Alan J Thompson, Lancet 2018; 391: 1622–36
## Drugs in development that 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>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
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

pHERV-W Env protein is expressed in chronic active MS lesions

- In progressive plaques, pHERV-W Env is expressed in the demyelinating border composed of activated microglia.

A - Chronic plaque with microglial line (myelin in brown)

B - The line of microglia is highly activated (HLA-DR+++).

C - Env is expressed in this microglial line only

D - Activated and migrating microglial cells are strongly positive for Env

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**

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

**drives OPC mediated remyelination failure**

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 et al. presentation at the 2018 Charcot Conference
pHERV-W Env fuels microglial cell mediated neurodegeneration in MS

**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, Küry et al. presentation at Charcot Conference, Nov 2018
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-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 (GNbAC1) rescues myelin expression by blocking Env-induced nitrosative stress in 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

Phase IIb trial (CHANGE-MS): Efficacy in RRMS patients at 1 year

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

- 1° Endpoint: Cumulative # Gd+ lesions on brain MRI scans at weeks 12, 16, 20 and 24 versus placebo

- Remyelination and neuroprotection endpoints: brain atrophy, black holes, change in MTR in NAWM, cerebral cortex

- In Period 2, the control group is composed of patients originally randomized to placebo. Dose-effect analyzed by Spearman correlation coefficient

**CHANGE-MS**

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

**ANGEL-MS**

- Secondary endpoints & Full analysis
  - March 2018

- 92% of patients

**MRI**

- IMP Administration

<table>
<thead>
<tr>
<th>Weeks</th>
<th>BL</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
</tr>
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<tbody>
<tr>
<td>Group temelimab 18 mg/kg</td>
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<tr>
<td>Group temelimab 12 mg/kg</td>
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<tr>
<td>Group temelimab 6 mg/kg</td>
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<td></td>
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<tr>
<td>Group Placebo</td>
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</tbody>
</table>

**Extension Study**

- Group temelimab 18 mg/kg
- Group temelimab 12 mg/kg
- Group temelimab 6 mg/kg

<table>
<thead>
<tr>
<th>Weeks</th>
<th>28</th>
<th>32</th>
<th>36</th>
<th>40</th>
<th>44</th>
<th>48</th>
<th>52</th>
<th>144</th>
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</thead>
<tbody>
<tr>
<td>MRI</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IMP Administration</td>
<td></td>
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</tbody>
</table>
Overview of CHANGE-MS 48-week results

• Modest benefit on MRI markers of neuroinflammation
  • 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 (measure of remyelination)

• Continued excellent safety and tolerability
  • Opens the door for possible increase in dose, and/or
  • Combination with powerful anti-inflammatory agents
Marked reduction of brain atrophy measures

**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><strong>72%</strong></td>
</tr>
</tbody>
</table>

*Dose effect* $p=0.014$

**Cerebral cortex**

<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><strong>31%</strong></td>
</tr>
</tbody>
</table>

*Dose effect* $p=0.045$

**Whole brain**

<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>-0.42</td>
<td><strong>29%</strong></td>
</tr>
</tbody>
</table>

*Dose effect* $p=0.079$

* Dose-effect analyzed by Spearman correlation coefficient

February 2019
Consistent benefit with temelimab seen in non-active population is a key asset

Change in volume in non-active population*

- Appears to confirm that the effect of temelimab on its target cells (OPC and microglia) and is not confounded by adaptive immunity
- Appears to confirm that, in state of reduced T/B cell activity, temelimab could effectively target neurodegeneration and promote regeneration.
- Opens door for co-therapy temelimab with DMTs to address the inflammatory component in MS

* defined as patients without Gd+ activity at baseline

Source: Kremer et al. presentation at the 2018 Charcot Conference
Reduction in the number of new T1 hypointense lesions (Black Holes) at month 12 with 18mg/kg

Median reduction between 18mg/kg group and control group in new larger T1 Black Holes* = 63% (p=0.014)

* T1 hypointense lesion > 14mm³ volume
Reduction of the transformation of T1Gd+ lesions at baseline into new T1Black Holes at week 48

Number of patients with T1Gd+ lesions at baseline

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Control Group T1Gd+ lesions transformed into T1BHs at week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Group</td>
<td>33</td>
<td>58%</td>
</tr>
<tr>
<td>Temelimab 18mg/kg</td>
<td>23</td>
<td>30%</td>
</tr>
</tbody>
</table>

In patients with transformation, percentage of Baseline T1Gd+ lesions that transformed into T1BHs at week 48

- Control Group: 50%
- Temelimab 18mg/kg: 45%

Patients with T1Gd+ lesions transformed into new T1BHs at week 48

- Control Group: 58%
- Temelimab 18mg/kg: 30%

Reduction: 47%
Reduction of the transformation of non-enhancing T2 lesions at baseline into new T1Black Holes at week 48

Number of patients with non-enhancing T2 lesions at baseline

Patients with T1Gd+ lesions transformed into new T1BHs at week 48

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Temelimab 18mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=64</td>
<td>36%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>- 41%</td>
<td></td>
</tr>
</tbody>
</table>

In patients with transformation, percentage of baseline non-enhancing T2 lesions that transformed into T1BHs at week 48

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>Temelimab 18mg/kg</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>2.8%</td>
<td>2.3%</td>
</tr>
<tr>
<td></td>
<td>-20%</td>
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</tbody>
</table>
## Stabilization of MTR Signal at 48 weeks

### Normal Appearing White Matter (PV) Bands

<table>
<thead>
<tr>
<th>Change in MTR signal (% units)</th>
<th>WEEK 24*</th>
<th>WEEK 48</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>PV Band 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18mg/kg</td>
<td>0.68</td>
<td>0.28</td>
</tr>
<tr>
<td>Placebo / 6-12-18mg</td>
<td>-0.35</td>
<td>-0.58</td>
</tr>
<tr>
<td>18mg vs. Placebo / 6-12-18mg</td>
<td>1.03</td>
<td>0.188</td>
</tr>
<tr>
<td>PV Band 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18mg/kg</td>
<td>0.64</td>
<td>0.30</td>
</tr>
<tr>
<td>Placebo / 6-12-18 mg</td>
<td>-0.32</td>
<td>-0.64</td>
</tr>
<tr>
<td>18mg vs. Placebo / 6-12-18 mg</td>
<td>0.96</td>
<td>0.188</td>
</tr>
<tr>
<td>PV Band 3</td>
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<tr>
<td>18mg/kg</td>
<td>0.66</td>
<td>0.34</td>
</tr>
<tr>
<td>Placebo / 6-12-18 mg</td>
<td>-0.28</td>
<td>-0.61</td>
</tr>
<tr>
<td>18mg vs. Placebo / 6-12-18 mg</td>
<td>0.94</td>
<td>0.194</td>
</tr>
</tbody>
</table>

* Recalculated with the same number of qualifying MTR scans at 48 weeks
12 months safety
No safety or tolerability issues

<table>
<thead>
<tr>
<th></th>
<th>Temelimab 6 mg/kg N=88</th>
<th>Temelimab 12mg/kg N=90</th>
<th>Temelimab 18 mg/kg N=89</th>
<th>Overall N=267</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Serious-related AE*</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>AE leading to early termination</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>AE leading to death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Macroscopic hematuria: resolved

February 2019
Findings in CHANGE-MS are supported by GeNeuro’s preclinical knowledge to date

Clinical observations

- Reduction of Brain Atrophy
- Reduction in new T1 Black Holes
- Benefit on Magnetization Transfer Ratio
- Modest benefit on inflammation, not driving the effect on markers associated with disease progression
- Promising a safe treatment option against neurodegeneration in all forms of MS

Supporting pre-clinical rationale

- Neurodegeneration directly reduced by
  - effectively 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 myelination capacity - the key precursor cells in remyelination processes.
- 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

Sources:
Next steps for temelimab development in MS

Finalize Phase Ic study at higher doses (up to 110 mg/kg) – 1Q2019
- Allowing testing front-loading or higher doses up to 4g

Analysis of ANGEL-MS results – 1Q2019
- 92% of CHANGE-MS patients enrolled in the ANGEL-MS continuation study
- Over 100 patients treated for 2 years

Ongoing partnering discussions for temelimab in MS
- Servier has returned all rights to GeNeuro following strategic and geographic reorientation
- Wide options for combinations with existing DMTs

GeNeuro is also planning optimal study to continue development
- Based on CHANGE-MS and ANGEL-MS results, GeNeuro may run confirmatory trial to find optimal dose in target progressive population, contributing to product registration file
Part 2

GeNeuro development in T1D
Overview of Type 1 Diabetes

- Type 1 Diabetes is a **chronic disease** associated with autoimmunity that results from the destruction of pancreas’ insulin-producing beta cells.

- Represents 5-10% of total diabetes cases (est. >4-6 million worldwide)

- Prevalence of T1D is approximately 1 in 300 in the US by 18 years of age.

- 85% of all T1D diabetes cases have an onset in people under 20 years-old

- Treatments focused on managing glycaemia by insulin injections

- $6.6bn worldwide sales in 2013; Market growth driven by approval of T2D drugs for T1D (GLP-1s RAs and SGLT-2 inhibitors )

Sources: NIH - Genetics Home reference; JDRF.org; WHO; Endocrinol Metab Clin North Am. D. Maahs et al., 2010
T1D Unmet medical needs
No disease modifying therapies available today

Several debilitating complications associated with insulin replacement, a life-long treatment

- Insulin replacement therapies are not satisfactory over the long term
- >50% of adults with T1D have an A1C >8%
- Severe consequences of poor glucose level control include renal, ophthalmic, cardiac, vascular and nervous system dysfunctions and deficiencies
- Significant risk of coma and death by hyperglycemia or hypoglycemia

Preservation of remaining insulin production: a potential efficient way to act on the cause of the disease

- Residual β-cell function may prevent ketoacidosis for many years
- Preservation of endogenous insulin production is the best prognosis against T1D co-morbidities
- Early diagnosis: understanding pathophysiology of T1D and early diagnosis with a biomarker could facilitate T1D treatment and possibly preserve pancreatic function

Data support the hypothesis of a causal role of pHERV-W Env in T1D

- Found in the pancreas of over 70% of T1D patients post-mortem. About 60% in blood.
- Dose dependent disruption of insulin production in vitro by pHERV-W Env
- Induction of hyperglycemia and hypoinsulinemia by pHERV-W Env protein in young HERV-W env transgenic mice
- Preliminary results showing that Coxsackie virus type B 4E2 strain upregulates pHERV-W Env expression

Sources: An ancestral retroviral protein identified as a therapeutic target in type-1 diabetes, S. Levet et al., JCI Insights, September 2017; JDRF/nPOD 2017 Meeting, Fort Lauderdale, USA. ADA 2017 meeting, San Diego, USA.
RAINBOW-T1D: Main Study Features

• Randomized, placebo-controlled (for the double blind period) phase 2a study
• 64 male and female patients, 18–55 years, with T1D diagnosed in the 4 years prior to signed ICF
• Peak stimulated C-peptide of ≥ 0.2nmol/L; HbA1c < 9%; >1 diabetes-associated auto-antibody
• 2 parallel groups: temelimab 6 mg/kg, placebo; 2 periods:
  • Weeks 1-24: 1 active dose group vs. placebo – Double Blind Period
  • Weeks 25-48: 1 active dose group – Open Label Period
## Week 24 Safety Outcomes

*No safety issues over 24 weeks*

<table>
<thead>
<tr>
<th></th>
<th>Temelimab 6 mg/kg (N=43)</th>
<th>Placebo (N=21)</th>
<th>Overall (N=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse events (SAEs)</strong></td>
<td>1&lt;sup&gt;1&lt;/sup&gt;</td>
<td>3&lt;sup&gt;2&lt;/sup&gt;</td>
<td>4</td>
</tr>
<tr>
<td><strong>Serious related AEs</strong></td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total AEs n (ratio)</strong></td>
<td>89 (2.1)</td>
<td>47 (2.2)</td>
<td>136</td>
</tr>
<tr>
<td><strong>AEs leading to early termination</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>AEs leading to death</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>1</sup> Viral Illness  
<sup>2</sup> Viral Gastroenteritis, Occipital Headache, Headache
Less frequent hypoglycemic episodes in active group

<table>
<thead>
<tr>
<th>Frequency count over the Double blind phase</th>
<th>Temelimab (N=43)</th>
<th>Placebo (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of hypoglycemic episodes per patient</td>
<td>13.3</td>
<td>17.6</td>
</tr>
<tr>
<td>Treatment effect (p value)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Hypoglycemic episodes, over time, per treatment group
Week 24 PD Outcomes – Insulin use and C-Peptide

Stable without difference between groups

Insulin use over time by treatment group

C-Peptide Cmax over time by treatment group

February 2019
RAINBOW-T1D Week 24 Summary

First study of Anti-HERV-specific treatment in T1D

• Excellent safety / tolerability profile of temelimab

• Well controlled population, well treated with low insulin needs, which remained stable during the trial

• Interesting pharmacodynamic signs with temelimab on:
  • Decrease of hypoglycemic episodes
  • Decrease of anti-insulin antibody

But small cohort size and low occurrence of events do not allow for any efficacy conclusions

• Final results at Week 48 in early 2Q2019

• Opens the path to further Phase II development in larger T1D populations, notably pediatric
Part 3

GeNeuro development in ALS
HERV-K Env is upregulated in ALS, and toxic to neurons

- HERV-K (HML-2) is significantly higher expressed in brain tissue of ALS patients than healthy controls or other neurological disorders.

- Expression of HERV-K in neurons is toxic.

- Genetic investigations reveal that there is dysregulation of HERV-K in a subset of patients with sporadic ALS.

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

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

Reduced life span
Motor neuron functionality
Clasping behavior

Status of the ALS project

• Research partnership in 2017 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 has launched the preclinical development of the lead antibody, aiming at IND by mid-2020
Part 4

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

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. Robert Glanzman | MD
Chief Medical Officer

Over 20 years of clinical, medical affairs and clinical development experience in MS
13 years as Medical Affairs/Clinical Development Leader at Pfizer, Novartis and Roche. Global Development Lead for Ocrelizumab Phase III
MD with Residency in Neurology from the University of Michigan

Miguel Payré
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 patents on temelimab filed from 2008 to 2014
  - 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 December 2018

P&L and cash balance (in € ‘000)

<table>
<thead>
<tr>
<th></th>
<th>FY 2018</th>
<th>1H 2018</th>
<th>FY 2017</th>
<th>FY 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Income</td>
<td>7,348</td>
<td>7,348</td>
<td>14,949</td>
<td>5,918</td>
</tr>
<tr>
<td>R&amp;D Expenses</td>
<td>n.a.</td>
<td>(7,491)</td>
<td>(16,161)</td>
<td>(14,419)</td>
</tr>
<tr>
<td>G&amp;A</td>
<td>n.a.</td>
<td>(2,319)</td>
<td>(4,597)</td>
<td>(5,535)*</td>
</tr>
<tr>
<td>Operating loss</td>
<td>n.a.</td>
<td>(2,429)</td>
<td>(5,740)</td>
<td>(14,037)</td>
</tr>
<tr>
<td>Cash &amp; Equivalents</td>
<td>9,000**</td>
<td>17,315</td>
<td>26,602</td>
<td>34,489</td>
</tr>
</tbody>
</table>

Notes: * 2016: includes €1,801k of IPO-related fees  
** : plus €7.5 mln line of credit facility with GNEH SAS established Dec. 2018

Note: excludes stock options and performance-based option units, representing a maximum 6.5% dilution, with an average exercise price of €11.65

February 2019
Value enhancing milestones in early 2019

- Phase Ic testing higher doses of temelimab for further development 1Q2019
- ANGEL-MS (2 year results) 1Q2019
- Partnership discussions on temelimab in MS
- T1D Phase IIa full 12-month results 2Q2019
Capturing the full value of the HERV platform

• Cash to deliver on ongoing programs
  - MS: ANGEL-MS results – Phase Ic testing safety of higher doses of temelimab
  - T1D: 12-month results of RAINBOW trial with temelimab
  - ALS: preclinical development of new monoclonal antibody against pHERV-K

• Open options for development going forward in MS
  - Partnering discussions ongoing
  - Confirmatory trial to find optimal dose in target progressive population, potentially supporting registration

• Open options for development in other indications, alone or with partners
  - Phase IIb in T1D in a juvenile population
  - IND for anti pHERV-W new monoclonal antibody planned for mid-2020
Targeting the cause of neurodegenerative and autoimmune diseases

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