A causal approach to changing the course of neurodegenerative diseases

December 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 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

• Approach validated through results on Multiple Sclerosis disease progression markers in a Phase IIb clinical trial
Clear path to deliver the full value of its technology and assets

**Multiple Sclerosis**
- Positive results of temelimab on the key markers of neurodegeneration linked to disease progression in 1-yr 270-patient RRMS Phase IIb and 1-yr extension
- Clear development path against non-active progression, key unmet medical need in MS, with next study on target population at the Karolinska’s Academic Specialist Center

**Amyotrophic Lateral Sclerosis**
- Preclinical development in partnership with the NIH, planning IND for 1H2021

**Other HERV-Mediated diseases**
- Successful Phase IIa in T1D, opening door for trials in juvenile population
- FDA’s Orphan Drug designation for CIDP
- Preclinical candidates for Inflammatory Psychoses
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
• Environmental viruses do not appear to play a direct role in disease development
• They can activate HERV genes upon infection of permissive cells
• Pathogenic HERV proteins have been suggested as potential 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

**Transactivating viruses in affected organs**

**HERV-W**
- CNS Gray Matter
  - CMV, Toxoplasma...
  - Inflammatory Psychoses
  - 40-60 % of cases?

**HERV-K**
- CNS White Matter
  - EBV, HSV1, HHV6, VZV,...
  - Multiple Sclerosis
  - 75-100% of cases

**Peripheral Nerves**
- CMV, ...
- CIDP
- ~ 50% of cases?

**Motor neurons**
- Neurotropic viruses,…
- Sporadic ALS

**Synovial membrane**
- ?
- RA

**Pancreas**
- Enteroviruses, Coxsackie viruses …
- Type 1 Diabetes
- 50-60 % of cases?

**Other Diseases ?**
- (Systemic lupus, psoriasis, etc.)

- Pathogenic HERV proteins found at high levels in affected organs

- Pathogenicity is generally mediated by (abnormally expressed) viral envelope proteins – pHERV Env W, K...

- pHERV Env directed toxicities found in:
  - Microglia
  - OPCs
  - Pancreatic beta islet cells
  - Motor Neurons
  - Schwan cells
  - Others…

CNS Gray Matter
- CMV, Toxoplasma…
- Inflammatory Psychoses
- 40-60 % of cases?

CNS White Matter
- EBV, HSV1, HHV6, VZV,…
- Multiple Sclerosis
- 75-100% of cases

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- CIDP
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Synovial membrane
- ?
- RA

Pancreas
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- 50-60 % of cases?

Other Diseases ?
- (Systemic lupus, psoriasis, etc.)

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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 to 2014**
    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*
Temelimab mode of action in MS
2.5 million MS patients worldwide
$21.8 bn market in 2018

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**: Infrequent inflammation, chronic axonal degeneration gliosis.

<table>
<thead>
<tr>
<th>Time since onset of disease</th>
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<tbody>
<tr>
<td><strong>Inflammation</strong></td>
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<tr>
<td>Inflammation mediated by adaptive immunity (B and T lymphocytes)</td>
</tr>
<tr>
<td><strong>Axonal loss</strong></td>
</tr>
<tr>
<td>Neuronal damage mediated by innate immunity (activated microglia) and accelerated by hampered remyelination (oligodendrocyte precursor cells)</td>
</tr>
</tbody>
</table>

Adapted from Compston et al., The Lancet 2002.

- RRMS: Relapsing-Remitting MS; SPMS: Secondary Progressive MS

November 2019
The unmet medical need in MS is the progression of the disease

MS at first diagnosis (Post CIS)

Relapsing-remitting 85%
Primary progressive 10%
Progressive relapsing 5%

Existing MS drugs address inflammation and relapses

Patient evolution

8 out of 10 people who are diagnosed with relapsing-remitting MS develop secondary progressive MS

Secondary progressive

No drugs preventing accumulation of disability over time

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Known drivers of multiple sclerosis and existing therapeutic agents

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

Target of most DMTs
• α-CD20s mAbs
• S1P1/n agonists
• α-integrin mAb
• etc.

Progression independent of relapse activity (PIRA)
CNS resident Microglia and Macrophages

No approved drugs

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

No approved drugs
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


pHERV-W Env positive microglial/monocytic cells in MS lesions
Kremer et al., under revision
pHERV-W Env protein is expressed in progressive 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 - pHERV-W Env is expressed in the microglial line only

D - Activated and migrating microglial cells are strongly positive for pHERV-W 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, Gruchot et al. PNAS May 2019
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, 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
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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 ($K_d = 2.2 \text{ nM}$)
- Blocks pHERV-W Env activation of TLR4
- Rescues MBP* expression in OPCs

*MBP: Myelin Basic Protein; marker of OPC maturation


December 2019
Temelimab 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)

**ANGEL-MS**

- **Secondary endpoints & Full analysis**
  - March 2018
- **Extension Study**
  - 92% of patients

**Administration:** IMP IV every 4 weeks

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December 2019
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
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 Week 48 in Cerebral Cortical Volume
   - Median % Change From Baseline (1.5)
   - Weeks 0 20 40 60 80 100
   - Groups:
     - Control
     - 6mg/kg
     - 12mg/kg
     - 6mg/kg
   - Median % reduction at week 48 in ANGEL-MS
     - Control (1.29) 42%
     - 6mg/kg (1.27) 41%
     - 12mg/kg (0.75) 63%
   - Dose effect p=0.058(1)

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

   - CC Band 2 (Dose effect p=0.035)(1)
   - Change in Mean MTR signals (% units)
     - Baseline
     - ANGEL-MS Week 48
     - 1.000 0.768
     - (1.000) (1.239)
     - (2.000) (1.244)
   - Groups:
     - GNbAC1 18mg/kg
     - GNbAC1 12 mg/kg
     - GNbAC1 6 mg/kg
     - Control

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

   - (not computed at week 96 for technical reasons)
   - Black Holes
     - New larger Black Holes
     - 18mg
     - 12mg
     - 6mg
     - Placebo
   - Median reduction between 18mg/kg group and control group in new larger T1 Black Holes(3) = 63%
   - (p=0.014)

4. **Very well tolerated drug**

   - # of Patients (%)
     - 18 mg/kg (N=77)
     - 12 mg/kg (N=68)
     - 6 mg/kg (N=74)
   - Adverse Events (AEs)
     - 34 (44.2%)
     - 32 (47.1%)
     - 33 (44.6%)
   - Serious Adverse Events (SAEs)
     - 5 (6.5%)
     - 1 (1.5%)
     - 6 (8.1%)
   - Serious Related AEs
     - 3 (3.9%)
     - 0
     - 0
   - AEs Leading to Study Discontinuation
     - 2 (2.6%)
     - 1 (1.5%)
     - 1 (1.4%)
   - Fatality(4)
     - 1 (1.3%)
     - 0
     - 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.
Continued reduction Thalamic atrophy
Original CHANGE-MS Groups

Dose effect* p=0.038

<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

December 2019
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* p=0.03

**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>
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</table>

*Dose effect* p=0.04

* Dose-effect analyzed by linear regression model
Continued reduction of Cortex atrophy
Original CHANGE-MS Groups

**CHANGE-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>-0.59</td>
<td></td>
</tr>
<tr>
<td>18mg/kg</td>
<td>-0.41</td>
<td>31%</td>
</tr>
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</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>
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</table>

Dose effect* p=0.058

* Dose-effect analyzed by linear regression model

December 2019
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
December 2019
Reduction in the number and volume of new T1 hypointense lesions (Black Holes) through CHANGE-MS and ANGEL-MS

CHANGE-MS Week 48

Mean Number of Qualifying BH Lesions* (95% CI)

<table>
<thead>
<tr>
<th>Group</th>
<th>New Qualifying BH</th>
</tr>
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<tbody>
<tr>
<td>18mg/kg</td>
<td></td>
</tr>
<tr>
<td>12mg/kg</td>
<td></td>
</tr>
<tr>
<td>6mg/kg</td>
<td></td>
</tr>
<tr>
<td>Control Group</td>
<td></td>
</tr>
</tbody>
</table>

-63% (p=0.014)

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>

-59% (p=0.12)

**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

* T1 hypointense lesion ≥ 14mm³ volume
Reduction in risk of lesions at baseline transforming into new T1 Black Holes at CHANGE-MS Week 48

**Proportion of patients with T1Gd+ lesions at baseline**

- **Control Group**: N=33, 58%
- **Temelimab 18mg/kg**: N=23, 30%

Proportion of patients with T1Gd+ lesions transformed into new T1 BHs at week 48: 48%

**Proportion of patients with non-enhancing T2 lesions at baseline**

- **Control Group**: N=64, 36%
- **Temelimab 18mg/kg**: N=61, 21%

Proportion of patients with non-enhancing T2 lesions transformed into new T1 BHs at week 48: 42%

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

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<thead>
<tr>
<th></th>
<th>WEEK 48 ANGEL-MS</th>
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<tbody>
<tr>
<td></td>
<td><strong>Change in MTR signal from CHANGE-MS BL (% units)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>18 mg</strong> <strong>12 mg</strong> <strong>6 mg</strong> <strong>Control</strong> <strong>Gain 18 vs 12</strong> <strong>Gain 18 vs 6</strong> <strong>Gain 18 vs Ctrl</strong> <strong>Trend p</strong>*</td>
</tr>
<tr>
<td><strong>NAWM Band 1</strong></td>
<td>mean: -0.84, -3.02, -3.76, -3.17, 2.18, 2.91, 2.33, 0.022</td>
</tr>
<tr>
<td></td>
<td>median: -1.83, -3.55, -3.39, -3.52, 1.72, 1.56, 1.69</td>
</tr>
<tr>
<td><strong>NAWM Band 2</strong></td>
<td>mean: -0.12, -2.17, -2.94, -2.13, 2.05, 2.82, 2.01, 0.034</td>
</tr>
<tr>
<td></td>
<td>median: -0.99, -2.70, -2.16, -2.65, 1.71, 1.17, 1.66</td>
</tr>
<tr>
<td><strong>NAWM Band 3</strong></td>
<td>mean: 0.74, -1.31, -1.85, -1.11, 2.05, 2.60, 1.86, 0.048</td>
</tr>
<tr>
<td></td>
<td>median: -0.32, -1.42, -0.86, -1.35, 1.10, 0.54, 1.03</td>
</tr>
</tbody>
</table>

* Dose-effect analyzed by linear regression, SAS analysis proc GLM

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### Temelimab preserves myelin integrity over 96 weeks

Cerebral Cortex - Original CHANGE-MS Groups

#### WEEK 48 ANGEL-MS

<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>
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<tbody>
<tr>
<td>CC Band 2 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>CC Band 2 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>CC Band 3 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>CC Band 3 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>CC Band 4 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>CC Band 4 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

---

December 2019
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 $p=0.27$

Lower probability for confirmed disability progression observed - Original CHANGE-MS Groups

<table>
<thead>
<tr>
<th>% of patients with 12-week confirmed worsening in neurological disability from CHANGE-MS baseline to week 48 ANGEL-MS</th>
<th>18 mg/kg</th>
<th>12 mg/kg</th>
<th>6 mg/kg</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.8</td>
<td>4.8</td>
<td>8.3</td>
<td>9.1</td>
</tr>
</tbody>
</table>
## Encouraging signs of clinical benefit on Timed 25-Foot Walk

Original CHANGE-MS groups and Sensitivity analyses

### Timed 25-foot walk – Original CHANGE-MS Groups

<table>
<thead>
<tr>
<th>Dose</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>% of patients with worsening ≥ 20%</td>
<td>2.4</td>
<td>23.1</td>
<td>13.3</td>
<td>10.2</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

### Timed 25-foot walk – By Dose Groups

<table>
<thead>
<tr>
<th>Dose</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>% of patients with worsening ≥ 20%</td>
<td>3.6</td>
<td>16.9</td>
<td>15.0</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### Timed 25-foot walk – By 18 vs Others

<table>
<thead>
<tr>
<th>Dose</th>
<th>18 mg/kg</th>
<th>Others</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of patients with worsening ≥ 20%</td>
<td>2.4</td>
<td>15.0</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Fisher exact test**
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.
Efficacy findings are supported by preclinical data

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

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.” (“naSPMS”)

FDA has confirmed to GeNeuro what it considers naSPMS patients (Sept 2019)

• Clinical: definition on non-active progressive MS
  “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”
"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…

Sources: EvaluatePharma, Annual reports of companies active in MS
December 2019

$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
~30% of MS population
Very high impact on quality of life
Highest unmet medical need
# Drugs in late 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>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
The strong results pave the way for the continued development against MS 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
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 neuroprotection biomarkers at higher doses of temelimab versus placebo
High unmet medical need with multiple options for Phase III development

**Phase III options**

- **As a monotherapy or on top of existing DMTs**
  - As monotherapy, in non-active progressive MS patients, as clear regulatory entry point; 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 combination with existing anti-inflammatory drugs
  - Objective to slow-down / prevent progression on treated Relapsing MS patients (rendered “non-active” by their anti-inflammatory treatment)
Despite progresses made, the need to address disease progression remains a huge opportunity

ORATORIO trial of Ocrevus in PPMS patients
Primary Endpoint: Time to Confirmed Disability Progression for ≥12 Weeks

Risk Reduction: 24%
HR (95% CI): 0.76 (0.59, 0.98)
p=0.0321

Objective for drugs targeting progression

Source: X. Montalban et al., New England Journal of Medicine, Jan 2019; Adapted from X. Montalban et al., Presentation at Charcot 2019
Ultimate objective in MS
To make temelimab available to ALL MS patients

- Tackle two of the core mechanisms of disability progression
- Progression starts from the beginning of MS
- Temelimab has no negative impact on immune system

- Disease progression

- Relevant to all disease forms

- Excellent safety profile
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>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Temelimab</strong> &lt;br&gt;Multiple Sclerosis</td>
<td>Planning next stage developments based on positive neurodegeneration 96-week results</td>
<td>CHANGE-MS : 270 patients / 50 centers in RRMS indication - completed March 2018</td>
<td>ANGEL-MS : 219 patients extension - Completed March 2019</td>
<td>Karolinska Phase II study in Non-Active Progressive / Launch planned Q1 2020</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>3. <strong>Temelimab</strong> &lt;br&gt;Type 1 Diabetes</td>
<td>Safety &amp; signal finding Phase IIa</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>4. <strong>Temelimab</strong> &lt;br&gt;CIDP</td>
<td>ODD granted by the US FDA</td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>5. <strong>Anti-HERV-K</strong> &lt;br&gt;ALS</td>
<td><strong>R&amp;D Agreement with NIH, IND submission planned by 1H2021</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. <strong>New anti HERV-W Ab</strong> &lt;br&gt;Inflammatory Psychosis</td>
<td>Research collaborations with Academic labs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</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  Wild type

  chAT + motor 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


December 2019
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

December 2019
Part 4

Good basis for growth
<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Experience/Qualifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jesús Martin-Garcia</td>
<td>MBA, Chief Executive Officer – Co-founder</td>
<td>Strong track-record in creating value in high technology start-ups</td>
</tr>
<tr>
<td>Dr. François Curtin</td>
<td>MD, MPhil, MBA, Chief Operating Officer &amp; Acting Chief Medical Officer</td>
<td>15 years experience in MS, in charge of R&amp;D and clinical development</td>
</tr>
<tr>
<td>Dr. Hervé Perron</td>
<td>PhD, HDR, Chief Scientific Officer – Co-founder</td>
<td>Made the initial key discoveries in the field of human endogenous retroviruses while at INSERM and bioMérieux</td>
</tr>
<tr>
<td>Dr. Thomas Rückle</td>
<td>PhD, PMP, Chief Development Officer</td>
<td>Over 20 years experience in translational science</td>
</tr>
<tr>
<td>Miguel Payró</td>
<td>Chief Financial Officer</td>
<td>Experience in international groups &amp; expertise as CFO of a Swiss listed company in the medical sector</td>
</tr>
<tr>
<td></td>
<td></td>
<td>More than 20 years of experience as founder and investor in successful startups</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical expertise at Merck Serono, previously at Swissmedic (“Swiss FDA”)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Has published over 120 peer-reviewed papers and patents, mostly on HERVs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Preclinical and early clinical expertise at Merck Serono &amp; MMV. As project director, led several projects from lead to Phase II clinical proof of concept</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experience in international groups &amp; expertise as CFO of a Swiss listed company in the medical sector</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Previously CFO of Groupe Franck Muller &amp; Unilabs, among others</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Degree in business administration from the University of Geneva</td>
</tr>
</tbody>
</table>
Financial Summary

Share capital as of Sept. 2019

- 43.4% Institut Mérieux Group (through GNEH SAS)
- 33.9% Public
- 12.5% Management & Treasury shares
- 8.6% Inst. Mérieux Group (through GNEH SAS)

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>

December 2019
Capturing the full value of the HERV platform

- Cash to deliver on ongoing programs – funded through 3Q 2020
  - MS: partnership discussions and preparation of clinical development plans
  - 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 non-active 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 end-2020
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