Stopping neurodegenerative and autoimmune diseases

December 2017
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GeNeuro’s mission

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

• Through 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.

• Initially focusing on Multiple Sclerosis and Type 1 Diabetes, both in Phase II clinical trials
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 these diseases
- 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

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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

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*The enemy within: dormant retroviruses awaken*
Engel & Hiebert, Nature Medicine, 2010
Viruses triggering HERV Proteins and link to disease
Examples of pHERV Env mediated diseases

Suspected transactivating viruses and affected organs

- HERV-W
- HERV-K

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

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

Motor neurons
Neurotropic viruses,...
Sporadic ALS

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

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

### 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>GNbAC1</strong>&lt;br&gt;Multiple Sclerosis – RRMS&lt;br&gt;Multiple Sclerosis – SPMS</td>
<td>270 patients / 50 centers in the RRMS indication / Data expected 1Q2018</td>
<td><strong>Partnership (ex-US &amp; Japan)</strong>&lt;br&gt;Review possible options after 48-week results</td>
<td></td>
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</tr>
<tr>
<td>2. <strong>GNbAC1</strong>&lt;br&gt;Type1D</td>
<td>Proof-of-concept Phase IIa</td>
<td>Launched April 2017 / Data expected 3Q2018</td>
<td></td>
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</tr>
<tr>
<td>3. <strong>GNbAC1</strong>&lt;br&gt;CIDP</td>
<td>Proof-of-concept Phase IIa trial in preparation</td>
<td></td>
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<tr>
<td>4. Other Anti HERV-W products &amp; approaches&lt;br&gt;Inflammatory Psychosis</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>5. Other anti-HERV approaches&lt;br&gt;(HERV-K in ALS)</td>
<td>R&amp;D Agreement with NIH in ALS</td>
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</table>

December 2017
On path to deliver the full potential of GeNeuro’s anti-HERV approach

• First treatment against a suspected causal factor of MS and T1D

• Positive results in PMS Phase IIa showing safety and early clinical benefit on progression

• Validating €360m partnership with Servier in MS, retaining US rights

• Fully recruited, ongoing 270-patient RRMS Phase IIb,
  • Top line 6-month results communicated 3Q17
  • Promising 6-month analyses data presented at MSParis2017 in October 2017
  • Full 12-month results / analyses in 1Q2018

• T1D Phase IIa ongoing, results expected 3Q18

• Wide application potential in other autoimmune and degenerative diseases
Part 1

GeNeuro development in MS
2.5 million MS patients worldwide
$21.5bn market in 2016

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

December 2017
Current treatment paradigm focuses on relapse control

Reductions of relapse rate by leading MS drugs

<table>
<thead>
<tr>
<th>ABCRs(1)</th>
<th>Orals and intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016 sales = $9.8bn (46%)</td>
<td>2016 sales = $10.9bn (51%)</td>
</tr>
</tbody>
</table>

(1) ABCR = Avonex-Betaseron-Copaxone-Rebif

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

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

Secondary progressive
No drugs prevent conversion from RRMS to SPMS

Presence of pathogenic HERV-W Env (pHERV-W Env) in the brain

- Pathogenic pHERV-W Env is highly expressed in MS patients
  - Found in 100% of MS brain lesions
  - Also found in 75% of patients’ blood
  - Expression in the brain correlates with lesion activity
  - Detected in areas of active demyelination from earliest to latest stages of disease


pHERV-W Env positive infiltrating perivascular macrophages in early demyelinating lesion
Van Horssen et al., MS & Related Disorders 2016
pHERV-W Env’s mode of action in MS: fueling inflammation AND neurodegeneration

Env interacts with TLR4 receptors

- Release of pro-inflammatory cytokines...
- ...causing attacks by the immune system
- Remyelination process blocked
- Neurodegeneration
- Neuroinflammation

GeNeuro’s GNbAC1 targets pHERV-W Env, to act on inflammation AND neurodegeneration.

- **Oligodendrocyte Precursor Cells (OPCs)**
- **pHERV-W Env**
- **GNbAC1**: Humanized Monoclonal Antibody, IgG4
- **Immune cells**
- **Stop Env interaction with TLR4 receptors**
- **Neutralize a source of inflammation**
- **Restart remyelination process**

**Neurodegeneration**

**Neuroinflammation**
Objective: develop a new first line MS treatment relevant to all disease forms & stages

Potential benefits of GNbAC1

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop disease progression in all active MS forms</td>
<td>Enable myelin repair mechanism</td>
</tr>
<tr>
<td>Reduce number of relapses in RRMS</td>
<td>Neutralize pro-inflammatory protein present in MS plaques and on activated immune cells</td>
</tr>
<tr>
<td>GNbAC1</td>
<td>pHERV-W Env has no physiological function</td>
</tr>
<tr>
<td></td>
<td>No negative impact on immune system</td>
</tr>
</tbody>
</table>
### A well-crafted partnership in MS with Servier

**GeNeuro retains US rights**

<table>
<thead>
<tr>
<th>1</th>
<th><strong>Option agreement</strong></th>
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<tbody>
<tr>
<td></td>
<td>Option payment of €37.5 million</td>
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<tr>
<td></td>
<td>Ongoing Phase IIb trial in MS led by GeNeuro</td>
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<tr>
<td></td>
<td>Post Phase IIb option to license GNbAC1 in MS <strong>ex-USA and Japan</strong></td>
</tr>
<tr>
<td></td>
<td>Exercised in December 2015 its option to buy 8.6% of GeNeuro for €15 million</td>
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<tr>
<td></td>
<td>Launch of ANGEL-MS study, fully funded by Servier</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>2</th>
<th><strong>Licensing agreement</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Global Phase III financed by Servier</td>
</tr>
<tr>
<td></td>
<td>Up to €325 million in development and sales milestones</td>
</tr>
<tr>
<td></td>
<td>Tiered royalties on future sales up to mid-teens</td>
</tr>
<tr>
<td></td>
<td>Right of first negotiation on GNbAC1 in other indications in Servier territories</td>
</tr>
</tbody>
</table>

**GeNeuro retains rights for US & Japan (67% of WW MS) and other GNbAC1 indications**
GNbAC1 rescues myelin expression by blocking Env-induced nitrosative stress in OPCs:

- Recombinant, humanized IgG4-kappa mAb
- PK approx. dose linear, Half-life ≈ 1 month
- Binds with high affinity to pHERV-W Env (IC50 = 5.8 nM)
- Blocks pHERV-W Env activation of TLR4
- Rescues MBP* expression in OPCs

![Graph showing relative rescue of MBP expression](graph.png)

*MBP: Myelin Basic Protein; marker of OPC maturation

The neutralizing antibody GNbAC1 abrogates HERV-W envelope protein-mediated oligodendroglial maturation blockade; Mult Scler. 2015 Aug;21(9)

Data presented at MSParis2017; Late Breaking News
GNbAC1 human tolerance confirmed in Phase I

Phase Ia:
33 healthy adult subjects, placebo-controlled single ascending doses of GNbAC1 from 0.15mg/kg to 6.00mg/kg

Excellent safety profile
• Excellent tolerability
• No adverse events were observed
• No immunogenicity

Monthly administration
• PK is dose linear
• Half-life of 19-26 days

Phase Ib:
21 healthy adult subjects, placebo-controlled single ascending doses of GNbAC1 from 6 to 36 mg/kg

Documented availability in the brain
• High penetration in CSF with a ratio of 0.3%-0.4% in CSF / serum concentrations

Phase IIa patients characteristics & study design

### Patients
- 10 patients
- Treated in Basel and Geneva
- 2 cohorts of patients with different doses
- 9 out of 10 patients had progressive MS

- Inclusion criteria: EDSS up to 6.5
- Exclusion of patients with any other treatment
- No pHERV-W level requirements

### Design
- Single-blind, placebo-controlled dose-escalating randomized study
- Followed by two 6-month open-label extensions
- 12 administrations of GNbAC1 every 4 weeks

### Patients EDSS (mean)

<table>
<thead>
<tr>
<th>Patients</th>
<th>EDSS (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRMS (n=1)</td>
<td>2.5</td>
</tr>
<tr>
<td>PPMS (n=3)</td>
<td>5.0</td>
</tr>
<tr>
<td>SPMS (n=6)</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Source: Derfuss et al., MS Journal, 2014.
Positive results in Phase IIa

1. Strong safety
   - Good safety profile over 1 year after repeated administrations
   - Preserved immune system and TLR4 function
   - No induction of immunogenicity
   - No infusion-related reactions or hypersensitivity

2. Monthly administration
   - GNbAC1 needs 25-37 elimination days half-life in patients
   - Compatible with a 4-week administration schedule

3. Early signs of clinical benefit
   - Statistically significant decline of pHERV-W Env biomarkers
   - GNbAC1 patients:
     - Are radiologically stable after 1 year (no new lesions nor increase in existing ones)
     - Have stable EDSS scores over 1 year (> to published data in progressive MS trials)
CHANGE-MS Phase IIb trial: confirm GNbAC1’s efficacy
Full results 1Q2018

- International, randomized, double-blind, placebo-controlled Phase 2b study
- RRMS patients, 18 – 55
- EDSS 0 – 5.5
- 1 attack in the prior year or 1 Gd+ lesion within 3 months of screening, concomitant DMTs not allowed
- 1° Endpoint: Total # Gd+ lesions on brain MRI scans at weeks 12, 16, 20 and 24
- Remyelination endpoints: change in MTR in NAWM, cerebral cortex and lesions

6-months results (including primary) presented at MSParis2017 October
Secondary endpoints & Full analysis Q1 2018
Summary of CHANGE-MS 24-week results

**Restart remyelination process**
- Strong increase in MT signal in NAWM and in Cortex already visible at 24 weeks

**Neutralize a source of inflammation**
- Failed primary of cumulative number of new Gd+ lesions
- Statistically significant reduction of lesions in active population at week 24 (post-hoc)

**GNbAC1**
Humanized Monoclonal Antibody, IgG4

+ Excellent safety and tolerability

**Neurodegeneration**

**Neuroinflammation**
GNC-003 (CHANGE-MS) week 24 safety results

No safety or tolerability issues over 24 weeks

<table>
<thead>
<tr>
<th></th>
<th>GNbAC1 6 mg/kg N=67</th>
<th>GNbAC1 12mg/kg N=66</th>
<th>GNbAC1 18 mg/kg N=67</th>
<th>Placebo N=68</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-week completers</td>
<td>60 (90%)</td>
<td>59 (90%)</td>
<td>64 (95%)</td>
<td>66 (97%)</td>
</tr>
<tr>
<td>SAE</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Serious-related AE*</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AE leading to early termination</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</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
**GNC-003 (CHANGE-MS) week 24 efficacy results**

No effect on inflammatory measures over weeks 12 - 24

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>GNbAC1 6 mg/kg</th>
<th>GNbAC1 12 mg/kg</th>
<th>GNbAC1 18 mg/kg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Gd+ lesions</td>
<td>Week 12 - 24</td>
<td># of lesions</td>
<td>Mean (Med)</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>510</td>
<td>8.4 (2.0)</td>
<td>p = 0.539</td>
</tr>
<tr>
<td></td>
<td></td>
<td>407</td>
<td>6.9 (2.0)</td>
<td>p = 0.704</td>
</tr>
<tr>
<td></td>
<td></td>
<td>339</td>
<td>5.3 (1.0)</td>
<td>p = 0.481</td>
</tr>
<tr>
<td></td>
<td></td>
<td>666</td>
<td>10.1 (1.5)</td>
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<table>
<thead>
<tr>
<th>Secondary Endpoints</th>
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</table>

Secondary endpoints include: total # new/enlarging T2 / CUAL / T1 BH; T2 / T1 BH volume, ARR, EDSS, MSFC, MSQOL-54

<table>
<thead>
<tr>
<th>% change in whole brain volume</th>
<th>Baseline – week 24</th>
<th>Mean (Med)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GNbAC1 6 mg/kg</td>
<td>-0.32 (-0.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>p = 0.539</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GNbAC1 12 mg/kg</td>
<td>-0.35 (-0.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>p = 0.704</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GNbAC1 18 mg/kg</td>
<td>-0.24 (-0.16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>p = 0.480</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>-0.34 (-0.35)</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th># of relapses</th>
<th>Baseline – week 24</th>
<th>Mean (Med)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GNbAC1 6 mg/kg</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>P value</td>
<td>p = 0.492</td>
<td>p = 0.217</td>
</tr>
<tr>
<td>GNbAC1 12 mg/kg</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>P value</td>
<td>p = 0.291</td>
<td>p = 0.291</td>
</tr>
<tr>
<td>GNbAC1 18 mg/kg</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>Placebo</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Gd+ lesions</th>
<th>Week 24</th>
<th>Mean (Med)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GNbAC1 6 mg/kg</td>
<td>2.7 (1.0)</td>
<td>p = 0.103</td>
<td></td>
</tr>
<tr>
<td>GNbAC1 12 mg/kg</td>
<td>2.3 (0)</td>
<td>p = 0.907</td>
<td></td>
</tr>
<tr>
<td>GNbAC1 18 mg/kg</td>
<td>2.0 (0)</td>
<td>p = 0.083</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>4.1 (0)</td>
<td></td>
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</tbody>
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Data presented at MSParis2017; Late Breaking News
GNC-003 (CHANGE-MS) week 24 post-hoc analyses

Evidence for delayed onset of anti-inflammatory effect in active patients† at 18 mg/kg

- Potential benefit appears at week 24
- Consistent across MRI endpoints
- 18 mg/kg dose consistently numerically superior
- Statistical separation with 18 mg/kg by week 24*

<table>
<thead>
<tr>
<th>Ratio of number of Gd+ lesions/pt/scan versus placebo</th>
</tr>
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<tbody>
<tr>
<td>GNbAC1</td>
</tr>
<tr>
<td>Rate Ratio</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>6mg/kg</td>
</tr>
<tr>
<td>12mg/kg</td>
</tr>
<tr>
<td>18mg/kg</td>
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</table>

† Had at least 1 Gd+ lesion on their Baseline brain MRI scan
* No adjustment for multiplicity was made
¶ Combined Unique Active Lesions

Data presented at MSParis2017; Late Breaking News
Magnetization Transfer Ratio (MTR) in MS patients
Recent studies point to myelin damage in NAWM and cerebral cortex

- In MS patients, MTR is reduced versus healthy controls throughout normal-appearing white matter (NAWM) and cerebral cortex
- Pathological gradient of MTR loss: worst at CSF interfaces, worse in SPMS than RRMS
- Gradient of MTR loss suggests CSF-mediated pathogenesis

Investigation of outer cortical magnetization transfer ratio abnormalities in multiple sclerosis clinical subgroups; Mult Scler. 2014 Sep;20(10)
Magnetization transfer ratio measures in normal-appearing white matter show periventricular gradient abnormalities in multiple sclerosis; Brain. 2015 May;138(Pt 5):1239-46
GNC-003 (CHANGE-MS) week 24 MTR analyses - NAWM Evidence for remyelination with GNbAC1 18 mg/kg in NAWM vs. placebo

Individual NAWM bands show a positive increase of MTR, with statistical trends in favor of G NbAC1 at 18mg/kg

Pathological gradient of MTR loss confirmed by data in CHANGE-MS

<table>
<thead>
<tr>
<th>GNbAC1 dose</th>
<th>N</th>
<th>BAND</th>
<th>Mean (%units)</th>
<th>Median (%units)</th>
<th>Δ mean, BL to Week 24 (%units)</th>
<th>P value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>55</td>
<td>1</td>
<td>-0.705</td>
<td>-0.71</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>-0.656</td>
<td>-0.75</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>3</td>
<td>-0.610</td>
<td>-0.67</td>
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</tr>
<tr>
<td>6mg/kg</td>
<td>41</td>
<td>1</td>
<td>-0.986</td>
<td>-0.72</td>
<td>-0.281</td>
<td>0.814</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>-0.919</td>
<td>-0.63</td>
<td>-0.263</td>
<td>0.820</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>-0.888</td>
<td>-0.54</td>
<td>-0.278</td>
<td>0.806</td>
</tr>
<tr>
<td>12mg/kg</td>
<td>48</td>
<td>1</td>
<td>-0.026</td>
<td>-0.33</td>
<td>0.679</td>
<td>0.554</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>-0.024</td>
<td>-0.29</td>
<td>0.632</td>
<td>0.567</td>
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<td>-0.024</td>
<td>-0.36</td>
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<tr>
<td>18mg/kg</td>
<td>47</td>
<td>1</td>
<td>1.472</td>
<td>0.21</td>
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<td>1.404</td>
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GNC-003 (CHANGE-MS) week 24 MTR analyses - Cortex
Evidence for remyelination with GNbAC1 18 mg/kg in cerebral cortex vs. placebo

Pathological gradient of MTR loss confirmed by data in CHANGE-MS

Individual NAWM bands show a positive increase of MTR, with statistical trends in favor of GNbAC1 at 18mg/kg

<table>
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<tr>
<th>GNbAC1 dose</th>
<th>N</th>
<th>BAND</th>
<th>Mean (%units)</th>
<th>Median (%units)</th>
<th>Δ mean, BL to Week 24 (%units)</th>
<th>P value vs. placebo</th>
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<td>Placebo</td>
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<td>6mg/kg</td>
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<td>1.572</td>
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<td>1.479</td>
<td>0.42</td>
<td>2.052</td>
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</table>
ANGEL-MS: 2-year extension open to CHANGE-MS patients

- 96-week, long-term, open-label extension to CHANGE-MS
- Maintains patient access
- Generates long-term data for GNbAC1 on Safety, Efficacy and Quality of Life

**CHANGE-MS: dose finding**
Placebo-control to week 24

- Group GNbAC1 18 mg/kg vs placebo
- Group GNbAC1 12 mg/kg vs placebo
- Group GNbAC1 6 mg/kg vs placebo

**ANGEL: single dose**
Open-label Rx

Group GNbAC1 optimal dose

Week 24

Period 1  Period 2

96 weeks
Next steps for development in MS

Assess Phase IIb 48-week results on
• Safety and tolerability
• Inflammatory endpoints
• Remyelination endpoints
• Biomarkers

Define path forward in terms of population to treat
• RRMS, and/or
• Progressive forms of MS
• MS subgroups
• Identification of responders based on biomarkers

Define path forward in terms of possible comparators / combinations
• As a single agent against comparator, and/or
• In combination with existing DMTs
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
- Data from worldwide epidemiologic studies indicate that the incidence of T1D has been increasing by 2–5% p.a.

Source: NIH - Genetics Home reference ; JDRF.org ; WHO; Endocrinol Metab Clin North Am. D. Maahs et Al. 2010
$6.6bn worldwide sales in 2013

Treatments focused on managing glycaemia by insulin injections

Market growth driven by approval of T2D drugs for T1D (GLP-1s RAs and SGLT-2 inhibitors)

Products in clinical development include
- Immunomodulators
- Beta-cell growth factors
- Artificial pancreas

Source: GlobalData PharmaPoint report 2015
T1D Unmet medical needs
No disease modifying therapies available today

Efficient management of glucose levels

- 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 at diagnosis

- 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 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

Source: 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.
Type 1 Diabetes: Phase IIa with GNBAC1 in T1D

Placebo controlled randomized Phase IIa on GNBAC1 with 60 recently diagnosed adults

- One cohort (6 mg/kg), randomized 2:1 against placebo, repeated administration over 6 months
- Patients diagnosed with T1D during the last 4 years
- With a residual insulin production measured based on C-peptide levels
- Age: from 18 yrs to 45 yrs (the inclusion of pediatric patients has been ruled out)

Primary end-point: safety in this new population

Secondary end-points:

- Link between response and pHERV-W Env biomarkers
- Efficacy measures to assess maintenance of insulin production (C-peptide)
- Other T1D-related biomarkers such as insulin consumption, glycaemia, anti-beta cells antibodies
- Pharmacokinetics and Pharmacodynamics

December 2017
Next steps for development in T1D

RAINBOW – ongoing Phase IIa trial in Australia
• FPFV 2Q2017
• LPFV end 4Q2017
• Results by 3Q2018

Review of RAINBOW Results
• Safety and tolerability in this new population
• GNbAC1 impact on T1D clinical measures
• Relationship between response and levels of pHERV-W Env biomarkers

Discussion with the regulatory authorities for further development
• Pivotal Phase IIb/III in adults
• Pediatric development plan

December 2017
Part 3

Creating value in other indications
Develop new approach against CIDP

Pathology
- CIDP is a neuroinflammatory and demyelinating disorder affecting peripheral nerves, often referred as “the peripheral multiple sclerosis”
- Different forms with relapsing/remitting or progressive presentations

Rationale for pHERV-W Env as a causal factor
- HERV-W Env mRNA and protein are over-expressed in PBMC and serum of 40-50% of CIDP patients
- HERV-W Env proteins are expressed in affected peripheral nerves in CIDP patients
- pHERV-W Env induces release of inflammatory IL6 and CXCL10 in Schwann cells, two cytokines which are over-expressed in peripheral nerves, CSF and serum of CIDP patients

Market
- Est. 5 to 7 cases per 100,000 have CIDP in Europe or America; for the USA, the population of patient is estimated between 20,000 to 25,000 patients
- CIDP is an Orphan Disease
- Treatments today are based on corticosteroids, high dose of IVIG or plasmapheresis

Development stage
- Ongoing collaborations with University Hospitals in France, Switzerland and Germany (Créteil, Lausanne, Dusseldorf)
- Scientific Advice with EMA supporting launch of a clinical program in CIDP

Faucard et al EBioMedicine 6 (2016) 190–198

Develop new approach against ALS

Pathology
- Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord
- 60% of the people with ALS are men and 93% of patients are Caucasian

Rationale for HERV-W Env as a causal factor
- HERV-K proteins are expressed in the brains of ALS patients
- HERV-K Env was observed in the anterior horn of the spinal cord, the site of lower motor neurons that degenerate in ALS
- HERV-K Env expression induces toxicity in human motor neurons
- Signs of motor dysfunction observed in transgenic mice expressing HERV-K Env

Market
- 6,000 people in the U.S. are diagnosed with ALS each year. As many as 20,000 Americans have the disease at any given time.
- No cure today. Current treatments modestly extend life span and manage patient comfort (median survival time from onset is 20 to 48 months)

Development stage
- Partnership with the National Institute of Neurological Disorders and Stroke (NINDS), part of the U.S. National Institutes of Health (NIH)
- GeNeuro provides antibodies to block the activity of HERV-K envelope protein
- NINDS tests antibodies in cellular and animal models of HERV-K associated ALS
- Goal: to achieve preclinical proof-of-concept of this novel therapeutic avenue addressing ALS pathogenesis

Sources: “Human endogenous retrovirus-K contributes to motor neuron disease”, Li et al, Sci Transl Med. 2015 Sep 30; ALS Association (www.alsa.org)
Develop new approach against Inflammatory Psychosis

Pathology

- Inflammatory psychosis include schizophrenia and bipolar disorder observed in patients presenting an inflammatory syndrome marked with a increase in C-reactive protein
- Symptoms include hallucinations, delusions, paranoïa leading to social withdrawal, BD is characterized by episodes of agitation and elation or depression

Rationale for HERV-W Env as a causal factor

- HERV-W Env and Gag proteins are increased in the PBMC and serum of 50% to 60% of patients with SCZ and BD correlated with an increase of C-reactive protein
- HERV-W genes and proteins are expressed in the cortex of patients with psychotic disorders
- Demyelination due to HERV-W Env could participate to the neuropsychiatric dysfunction
- HERV-W triggered by Influenza, Herpes or T gondii – germs epidemiologically associated with SCZ

Market

- About 1% of the population worldwide suffers from psychotic disorders
- No curative treatments exist today: antipsychotic drugs or mood stabilizers are symptomatic treatments but frequently these drugs do not prevent mental handicap and social withdrawal, at the price of severe side effects

Development stage

- Ongoing collaborations with research centers in France (Créteil and Bordeaux) on epidemiological studies and animal models of psychotic disorders

Leverage HERV platform to develop other product candidates

- 26 families of HERVs identified to date
- Scientific literature suggests HERV families are involved in numerous pathologies
- Better and increasing understanding of their roles in diseases (first HERV & Disease congress held in Lyon in May 2015)
- Second HERV & Disease Congress in March 2017 in Washington DC

- GeNeuro is leveraging its first mover advantage to create a HERV platform to develop disruptive treatments for numerous additional diseases

Source: van der Kuyl AC - Retrovirology (2012)
Part 4

Strong 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

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 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

December 2017
Broad and strong IP supporting first mover advantage

- Mérieux Group & GeNeuro worked for more than 25 years in the HERV field
- Built a strong intellectual property portfolio
- 16 families of patents, including the following 3 broad categories:
- Key patents on GNbAC1 **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

* : previous name of pHERV-W Env
Financial Summary

Share capital as of October 2017

P&L and cash balance (in € '000)

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<th>FY</th>
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<td>Revenue</td>
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<td>(5,535)</td>
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<td>Operating Income (loss)</td>
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<td>(14,037)</td>
<td>(4,323)</td>
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<td>Cash &amp; Equivalents</td>
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<td>34,489</td>
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Notes: excludes stock options and performance-based option units, representing a maximum 6% dilution

Notes: * 2016: includes €1,801k of IPO-related fees
Multiple value enhancing milestones in the next twelve months, leading to Phase II results

- Full recruitment of Phase IIa trial of GNbAC1 in T1D by end of 2017
- LPLV Phase IIb clinical trial in MS by January 2018
- Analysis of 48-week Phase IIb results, 1Q2018
- US IND & opening Phase II trial in Secondary Progressive MS patients
- New anti-pHERV antibodies (e.g. ALS, inflammatory psychosis)
- T1D Phase IIa results 3Q2018
Stopping neurodegenerative and autoimmune diseases

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Tel: +41 22 552 4800