Review of week-24 results

GNC-003: an international, double-blind, randomized, placebo-controlled phase IIb trial to assess the efficacy, safety and pharmacokinetics of GNbAC1 in patients with relapsing remitting multiple sclerosis

Clinical trial assessing the pHERV-W Env ANtagonist GNbAC1 for Efficacy in MS (CHANGE-MS)

Hans-Peter Hartung, François Curtin, Hans-Martin Schneble, Herve Porchet, Robert Glanzman, Estelle Lambert, Krzysztof Selmaj, on behalf of the GNC-003 investigators, Frederik Barkhof

ClinicalTrials.gov Identifier: NCT02782858
Authors’ Disclosures

• Hans-Peter Hartung:
  • Consulting, speaking and serving on steering committees from Bayer Healthcare, Biogen, GeNeuro, MedImmune, Merck, Novartis, Opexa, Receptos Celgene, Roche, Sanofi Genzyme and Teva, with approval by the Rector of Heinrich-Heine-University.

• Frederik Barkhof:
  • Consultancies: IXICO, Biogen-IDEC, Apitope Ltd, GeNeuro, Genzyme-Sanofi, Jansen Research, Roche, Novartis, Merck-Serono,
    • TEVA, Bayer-Schering Pharma
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    • NIHR UCLH Biomedical Research Centre (BRC), ECTRIMS-MAGNIMS
  • Board Memberships: Radiology, Multiple Sclerosis Journal, Neurology, Eur Radiology, Brain
  • Speakers Bureaus: IXICO, Biogen-IDEC

• Krzysztof Selmaj, on behalf of the GNC-003 investigators

• François Curtin, Herve Porchet and Robert Glanzman are employees of GeNeuro S.A.

• Hans-Martin Schneble and Estelle Lambert are employees of Servier
Human Endogenous Retroviruses (HERVs)
Ancestral retroviral genomic insertions

- HERV elements are latent in human genome
  - Represent approximately 8% of human genome

- Pathogenic HERV-W envelope protein (pHERV-W Env) is associated with Multiple Sclerosis
  - Found in active MS lesions on monocytes and microglia
  - Viral infections (EBV) may de-repress and trans-activate pHERV-W Env expression

- pHERV-W Env: potent agonist of toll-like receptor 4
  - Pro-inflammatory immune activation
  - Inhibits oligodendrocyte precursor cell (OPC) maturation through nitrosative stress

Regulatory evolution of innate immunity through co-option of endogenous retroviruses; Science, Vol. 351, Issue 6277

Human Endogenous Retrovirus Type W Envelope Protein Inhibits Oligodendroglial Precursor Cell Differentiation; Ann Neurol. 2013;74(5)
The neutralizing antibody GNbAC1 abrogates HERV-W envelope protein-mediated oligodendroglial maturation blockade; Mult Scler. 2015 Aug;21(9)

GNbAC1
Blocks Env-induced nitrosative stress in OPCs: rescues myelin expression

- 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

*MBP: Myelin Basic Protein; marker of OPC maturation
GNC-003 (CHANGE-MS)

Study Overview

- International, randomized, 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
- $^{10}$ 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

Week 24
$^{10}$/2$^{0}$ endpoints

Week 48
2$^{0}$/overall endpoints

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

- Group GNbAC1 18 mg/kg
- Group GNbAC1 12 mg/kg
- Group GNbAC1 6 mg/kg
- Group Placebo

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

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

MRI

IMP Administration
# GNC-003 (CHANGE-MS)

## Baseline Demographics

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Age</th>
<th>Sex</th>
<th>Relapses 1 Yr Prior</th>
<th>Duration of MS Yrs</th>
<th>Baseline EDSS</th>
<th>% Active * Gad+</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mg/kg</td>
<td>38</td>
<td>64%</td>
<td>1.2</td>
<td>5.6</td>
<td>2.9</td>
<td>58%</td>
</tr>
<tr>
<td>12 mg/kg</td>
<td>39</td>
<td>70%</td>
<td>1.4</td>
<td>6.0</td>
<td>3.2</td>
<td>48%</td>
</tr>
<tr>
<td>18 mg/kg</td>
<td>38</td>
<td>51%</td>
<td>1.3</td>
<td>5.4</td>
<td>3.3</td>
<td>38%</td>
</tr>
<tr>
<td>Placebo</td>
<td>36</td>
<td>73%</td>
<td>1.3</td>
<td>3.7</td>
<td>3.0</td>
<td>49%</td>
</tr>
</tbody>
</table>

* ≥ 1 Gad+ lesion on Baseline brain MRI scan: Per Protocol-like Set
# 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 12 mg/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></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><strong>Primary Endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Gad+ lesions</td>
<td>Week 12 - 24</td>
<td># of lesions</td>
<td>510</td>
<td>407</td>
</tr>
<tr>
<td></td>
<td>Mean (Med)</td>
<td>P value</td>
<td>8.4 (2.0)</td>
<td>6.9 (2.0)</td>
</tr>
<tr>
<td></td>
<td>p = 0.539</td>
<td>p = 0.704</td>
<td>p = 0.481</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% change in whole brain volume</td>
<td>Baseline – week 24</td>
<td>Mean (Med)</td>
<td>-0.32 (-0.13)</td>
<td>-0.35 (-0.22)</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td></td>
<td>p = 0.539</td>
<td>p = 0.704</td>
</tr>
<tr>
<td># of relapses</td>
<td>Baseline – week 24</td>
<td># of lesions</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td></td>
<td>p = 0.492</td>
<td>p = 0.217</td>
</tr>
<tr>
<td>Total Gd+ lesions</td>
<td>Week 24</td>
<td>Mean (Med)</td>
<td>2.7 (1.0)</td>
<td>2.3 (0)</td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td></td>
<td>p = 0.103</td>
<td>p = 0.907</td>
</tr>
</tbody>
</table>

Secondary endpoints include: total # new/enlarging T2 / CUAL / T1 BH; T2 / T1 BH volume, ARR, EDSS, MSFC, MSQOL-54
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>Treatment</th>
<th>Rate Ratio</th>
<th>P-value</th>
<th>Rate Ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6mg/kg</td>
<td>0.988</td>
<td>0.970</td>
<td>6mg/kg</td>
<td>0.434</td>
</tr>
<tr>
<td>12mg/kg</td>
<td>0.918</td>
<td>0.805</td>
<td>12mg/kg</td>
<td>0.475</td>
</tr>
<tr>
<td>18mg/kg</td>
<td>0.567</td>
<td>0.129</td>
<td>18mg/kg</td>
<td>0.311</td>
</tr>
</tbody>
</table>

* Had at least 1 Gd+ lesion on their Baseline brain MRI scan
+ No adjustment for multiplicity was made
† Combined Unique Active lesions
Magnetization Transfer Ratio (MTR) in MS patients
Evidence for Myelin damage in NAWM and cerebral cortex

- MTR is reduced 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 magnetisation 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
Individual NAWM bands show an absolute increase of
≈ 2 MTR percentage units, with statistical trends in favor of
GNbAC1 at 18 mg/kg

<table>
<thead>
<tr>
<th>BAND</th>
<th>GNbAC1</th>
<th>Δ MTR BL to Week 24 (%units)</th>
<th>P value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6mg/kg</td>
<td>-0.280</td>
<td>0.814</td>
</tr>
<tr>
<td>1</td>
<td>12mg/kg</td>
<td>0.679</td>
<td>0.554</td>
</tr>
<tr>
<td>1</td>
<td>18mg/kg</td>
<td>2.177</td>
<td>0.060</td>
</tr>
<tr>
<td>2</td>
<td>6mg/kg</td>
<td>-0.262</td>
<td>0.820</td>
</tr>
<tr>
<td>2</td>
<td>12mg/kg</td>
<td>0.632</td>
<td>0.567</td>
</tr>
<tr>
<td>2</td>
<td>18mg/kg</td>
<td>2.064</td>
<td>0.064</td>
</tr>
<tr>
<td>3</td>
<td>6mg/kg</td>
<td>-0.278</td>
<td>0.806</td>
</tr>
<tr>
<td>3</td>
<td>12mg/kg</td>
<td>0.586</td>
<td>0.588</td>
</tr>
<tr>
<td>3</td>
<td>18mg/kg</td>
<td>2.014</td>
<td>0.066</td>
</tr>
</tbody>
</table>

Evidence for remyelination with GNbAC1 18 mg/kg in NAWM vs. placebo
GNC-003 (CHANGE-MS) week 24 MTR analyses - Cortex
Evidence for remyelination with GNbAC1 18 mg/kg in cerebral cortex vs. placebo

<table>
<thead>
<tr>
<th>BAND</th>
<th>GNbAC1</th>
<th>Δ MTR BL to Week 24 (%units)</th>
<th>P value vs. placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>6mg/kg</td>
<td>-0.252</td>
<td>0.832</td>
</tr>
<tr>
<td>3</td>
<td>12mg/kg</td>
<td>0.587</td>
<td>0.605</td>
</tr>
<tr>
<td>3</td>
<td>18mg/kg</td>
<td>2.167</td>
<td>0.059</td>
</tr>
<tr>
<td>2</td>
<td>6mg/kg</td>
<td>-0.251</td>
<td>0.829</td>
</tr>
<tr>
<td>2</td>
<td>12mg/kg</td>
<td>0.555</td>
<td>0.617</td>
</tr>
<tr>
<td>2</td>
<td>18mg/kg</td>
<td>2.109</td>
<td>0.060</td>
</tr>
<tr>
<td>1</td>
<td>6mg/kg</td>
<td>-0.282</td>
<td>0.807</td>
</tr>
<tr>
<td>1</td>
<td>12mg/kg</td>
<td>0.545</td>
<td>0.622</td>
</tr>
<tr>
<td>1</td>
<td>18mg/kg</td>
<td>2.052</td>
<td>0.066</td>
</tr>
</tbody>
</table>

Individual cortical bands also show an absolute increase of ≈ 2 MTR percentage units with statistical trends in favor of GNbAC1 at 18mg/kg
GNC-003 (CHANGE-MS) week 24 results

Summary

Excellent safety and tolerability through 24 weeks

Effect of GNbAC1 on inflammatory measures:
- No effect on any MRI measure of inflammation from weeks 12 – 24 at any dose
- No effect on clinical measures through 24 weeks
- Post-hoc evidence for effect in active patients at week 24 at highest dose (18 mg/kg)

Effect of GNbAC1 18 mg/kg on measures of remyelination:
- NAWM and cerebral cortex:
  - Individual NAWM and cortical bands show dose-dependent trends in favor of GNbAC1 vs. placebo
  - Increase of ≈ 2 MTR percentage units across NAWM and cortical bands for 18mg/kg at week 24
  - MTR lesion analyses inconclusive for week 12 - 24. Week 48 data may be more informative.

GNC-003 is ongoing:
- Week 48 data on inflammation, remyelination, biomarkers and clinical measures - available Q1 2018
Acknowledgements

GNC-003 Scientific Steering Committee:
Chair: Hans-Peter Hartung, F.R.C.P.
Members: Sandra Vukusic, M.D., Ph.D., Maria Pia Sormani, Ph.D., Tobias Derfuss, M.D., Bruce Cree, M.D., Ph.D., Frederik Barkhof, MD, Ph.D.

Data Safety Monitoring Board:
Chair: Andreas Steck  M.D.
Members: François Montestruc, Ph.D., Jules Desmeules, M.D., Ph.D.

Servier:
Alliance Partner for GNbAC1 development in Multiple Sclerosis

Worldwide Clinical Trials

BioClinica and Queen Square MS Trial Office

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