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 p**H**ERV-W Env **AN**tagonist **G**NbAC1 for **E**fficacy in **MS** **(CHANGE-MS)**

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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

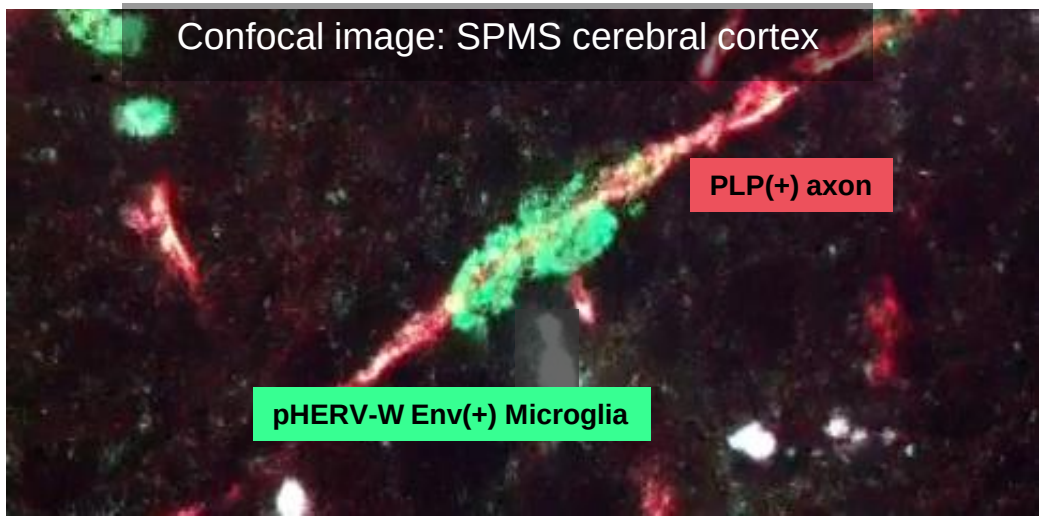
- François Curtin, Herve Porchet and Robert Glanzman are employees of GeNeuro S.A.

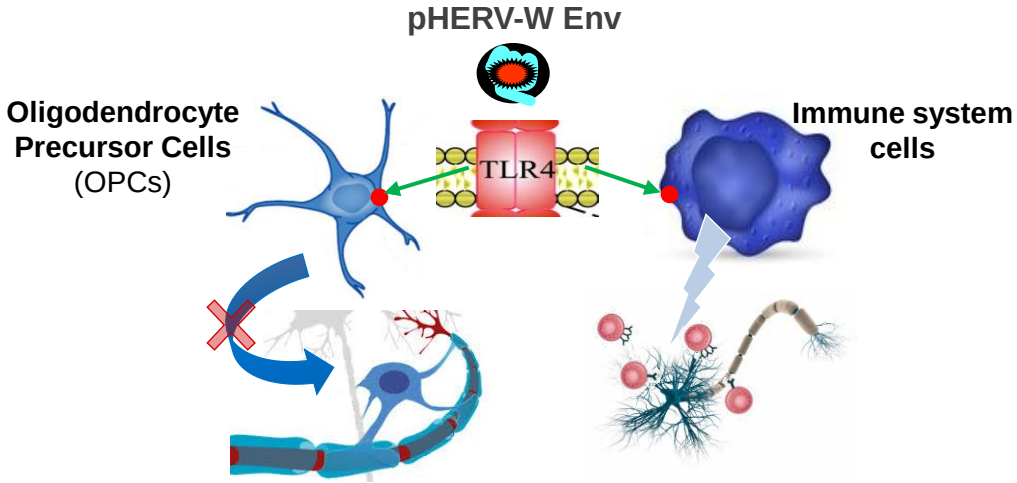
- Hans-Martin Schneble and Estelle Lambert are employees of Servier

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





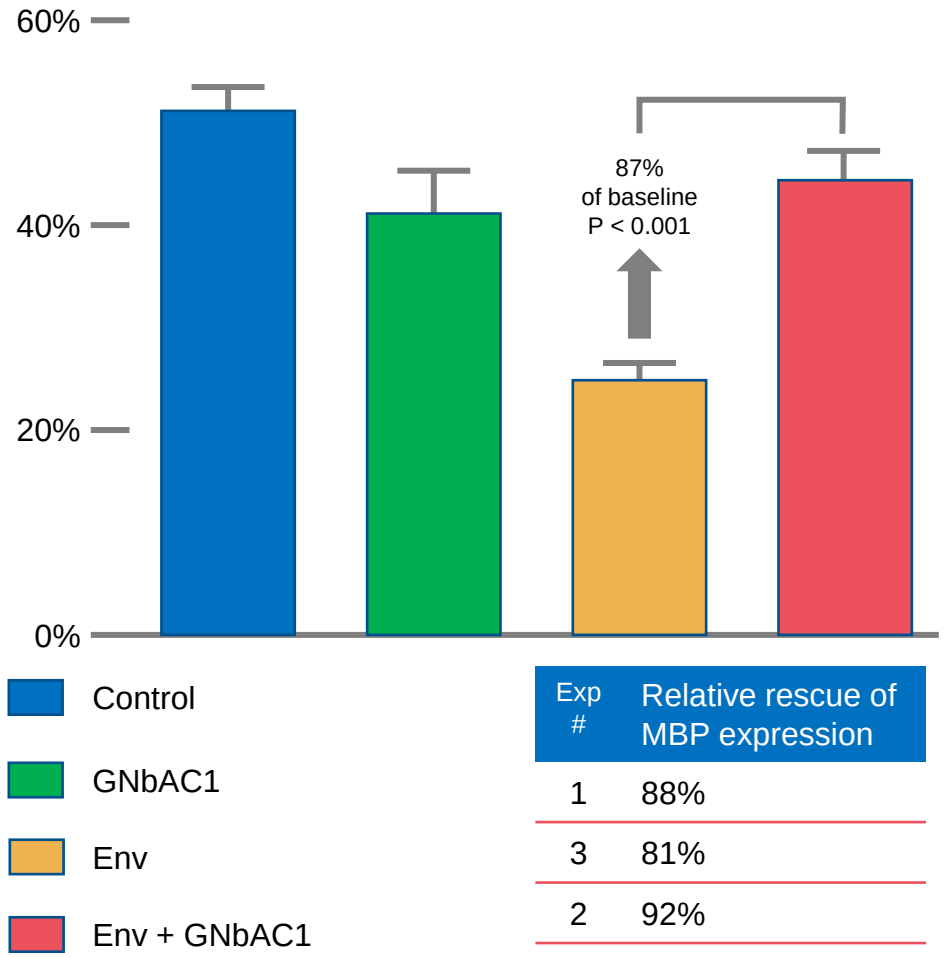
Regulatory evolution of innate immunity through co-option of endogenous retroviruses; Science, Vol. 351, Issue 6277

Human Endogenous Retrovirus Type W Envelope Protein Inhibits Oligodendroglial Precursor Cell Differentiation; Ann Neurol. 2013;74(5)

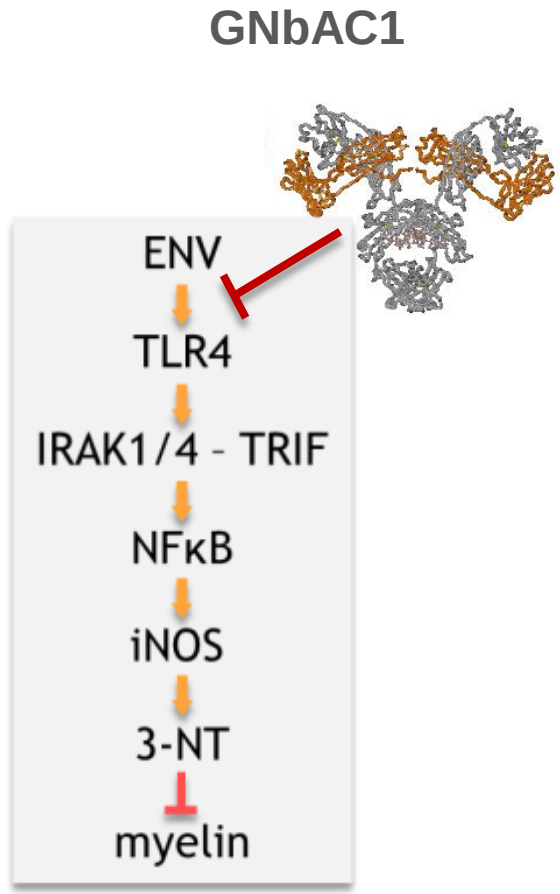
GNbAC1

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



Exp #	Relative rescue of MBP expression
1	88%
3	81%
2	92%
4	88%
5	87%

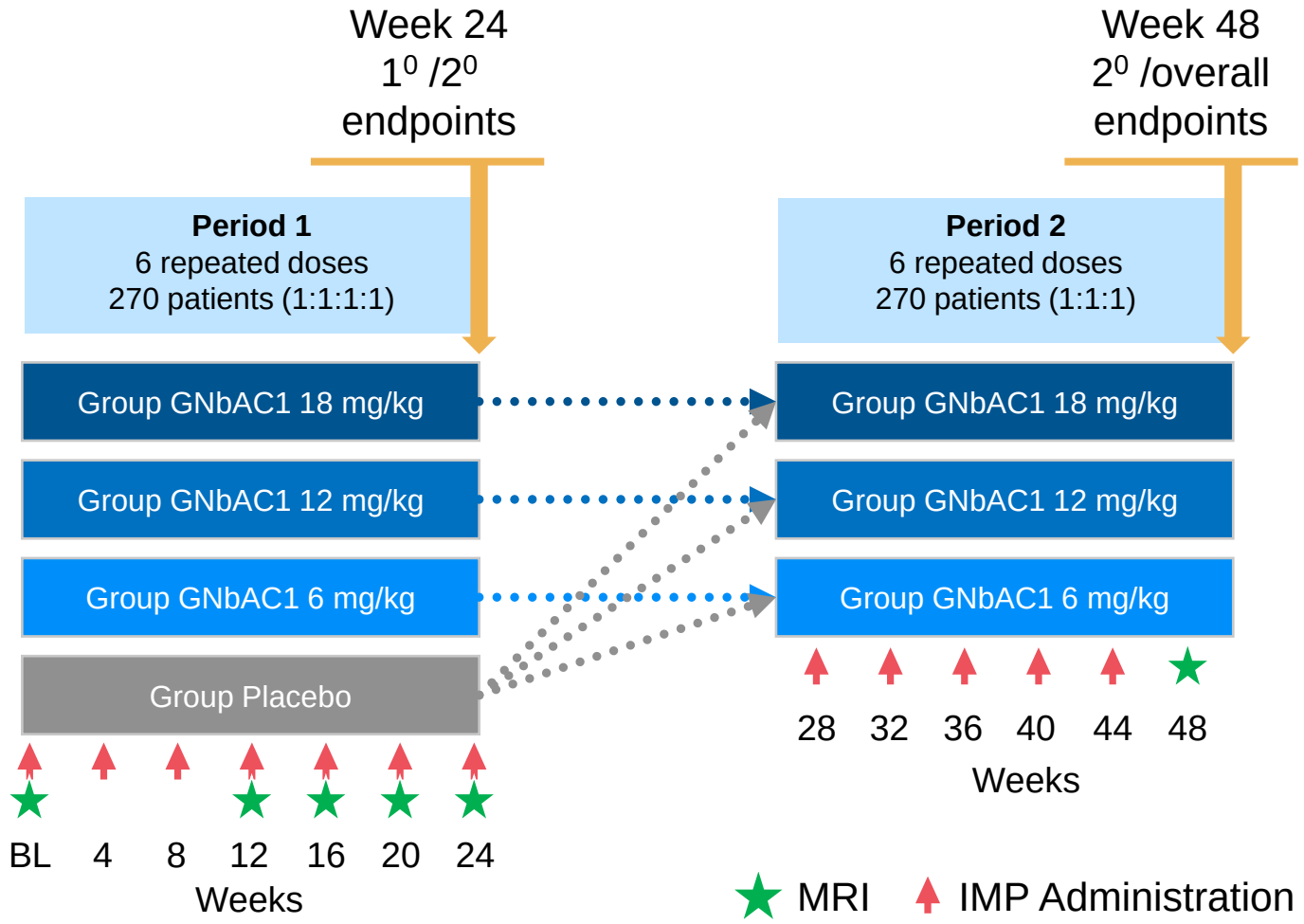


*MBP: Myelin Basic Protein; marker of OPC maturation

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

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
- 1^0 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



GNC-003 (CHANGE-MS)

Baseline Demographics

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

* ≥ 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

Number of patients (%)

	GNbAC1 6 mg/kg N=67	GNbAC1 12 mg/kg N=66	GNbAC1 18 mg/kg N=67	Placebo N=68
24 week completers	60 (90%)	59 (90%)	64 (95%)	66 (97%)
SAE	1	1	0	2
Serious-related AE*	0	1	0	0
AE leading to early termination	2	1	1	0
AE leading to death	0	0	0	0

* Macroscopic hematuria: resolved

GNC-003 (CHANGE-MS) week 24 efficacy results

No effect on inflammatory measures over weeks 12 - 24

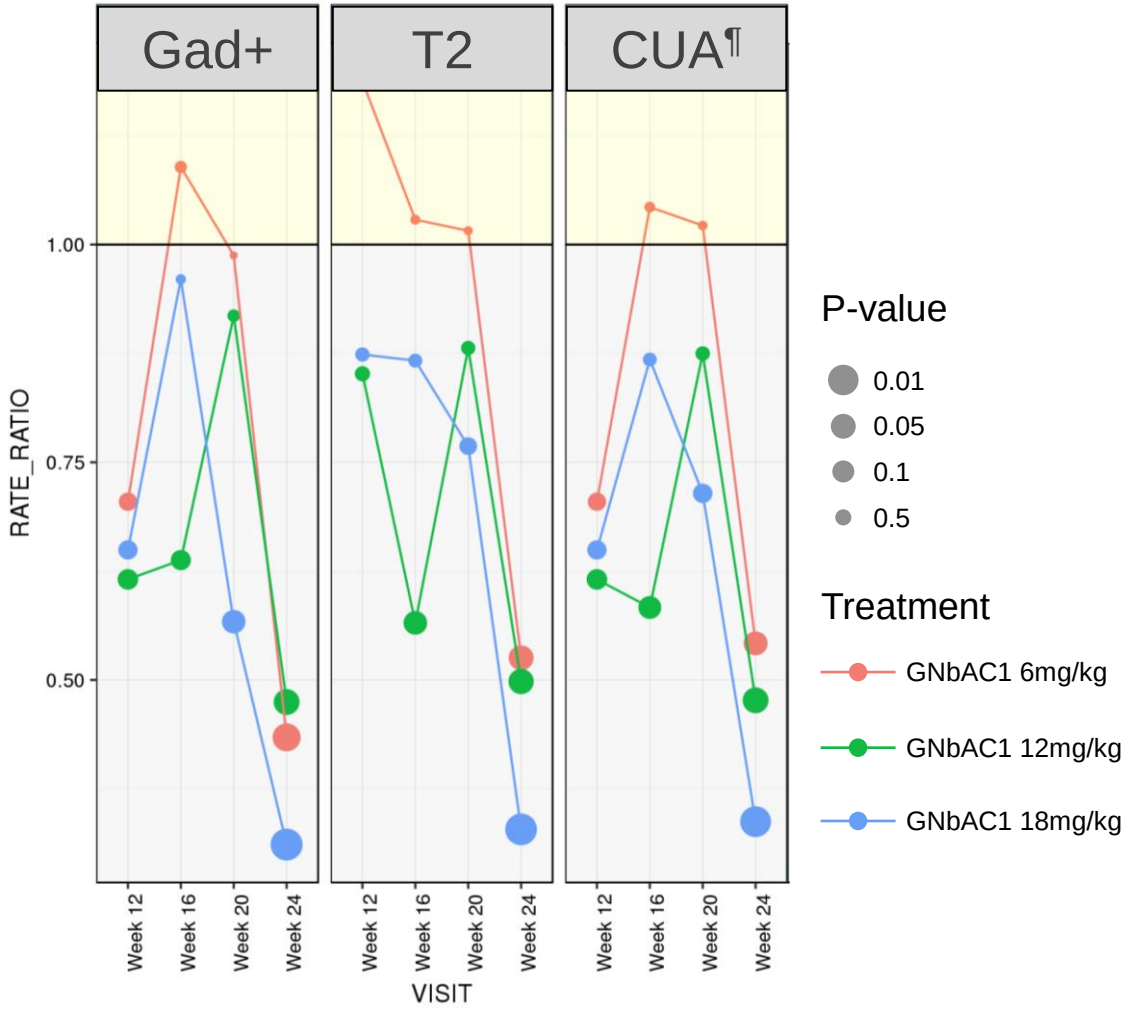
			GNbAC1 6 mg/kg	GNbAC1 12mg/kg	GNbAC1 18 mg/kg	Placebo
Primary Endpoint						
Total Gad+ lesions	Week 12 -24	# of lesions	510	407	339	666
		Mean (Med) P value	8.4 (2.0) p = 0.539	6.9 (2.0) p = 0.704	5.3 (1.0) p = 0.481	10.1 (1.5)
Secondary Endpoints Secondary endpoints include: total # new/enlarging T2 / CUAL / T1 BH; T2 / T1 BH volume, ARR, EDSS, MSFC, MSQOL-54						
% change in whole brain volume	Baseline – week 24	Mean (Med)	-0.32 (-0.13)	-0.35 (-0.22)	-0.24 (-0.16)	-0.34 (-0.35)
# of relapses	Baseline – week 24		18 p = 0.492	21 p = 0.217	21 p = 0.291	15
Total Gd+ lesions	Week 24	Mean (Med) P value	2.7 (1.0) p = 0.103	2.3 (0) p = 0.907	2.0 (0) p = 0.083	4.1 (0)

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*

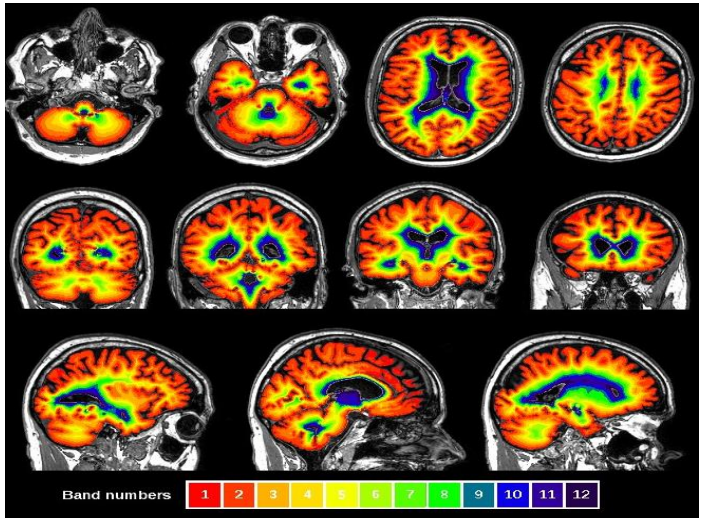
Ratio of number of Gd+ lesions/pt/scan versus placebo					
GNbAC1	**Week 20**		**GNbAC1**	**Week 24**	
	Rate Ratio	P-value		Rate Ratio	P-value
6mg/kg	0.988	0.970	6mg/kg	0.434	0.034
12mg/kg	0.918	0.805	12mg/kg	0.475	0.069
18mg/kg	0.567	0.129	18mg/kg	**0.311**	**0.008**

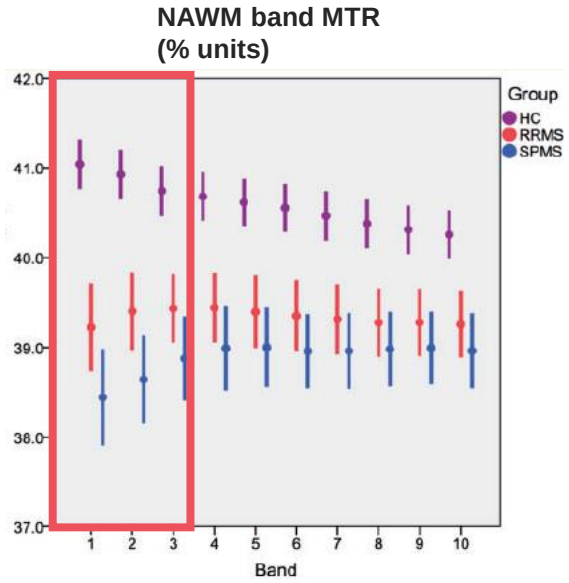


⁺ Had at least 1 Gd+ lesion on their Baseline brain MRI scan
• No adjustment for multiplicity was made
¶ Combined Unique Active lesions

Magnetization Transfer Ratio (MTR) in MS patients

Evidence for Myelin damage in NAWM and cerebral cortex





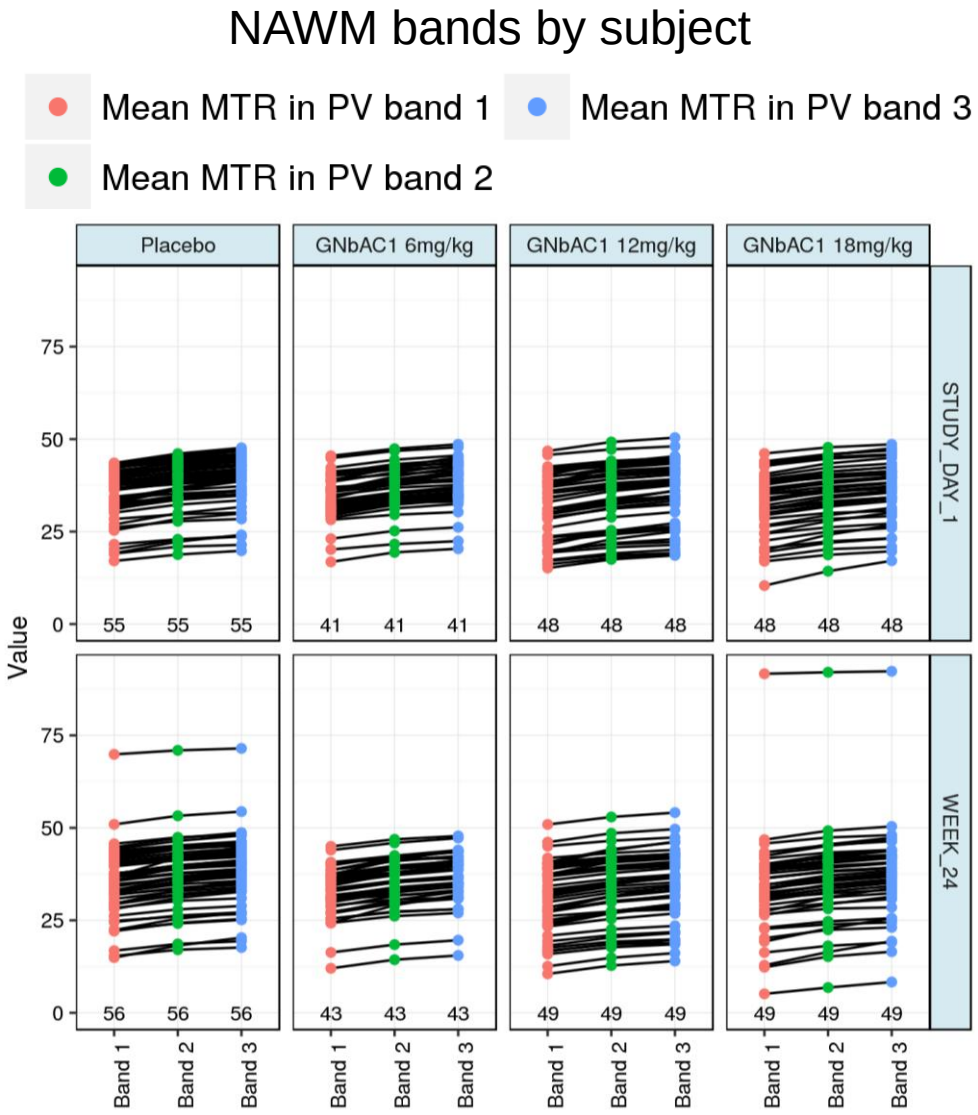
NAWM segmented into concentric periventricular one-voxel thick bands

- 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
Delineation of cortical pathology in multiple sclerosis using multi-surface magnetization transfer ratio imaging; Neuroimage Clin. 2016; 12: 858–868

GNC-003 (CHANGE-MS) week 24 MTR analyses - NAWM

Evidence for remyelination with GNbAC1 18 mg/kg in NAWM vs. placebo

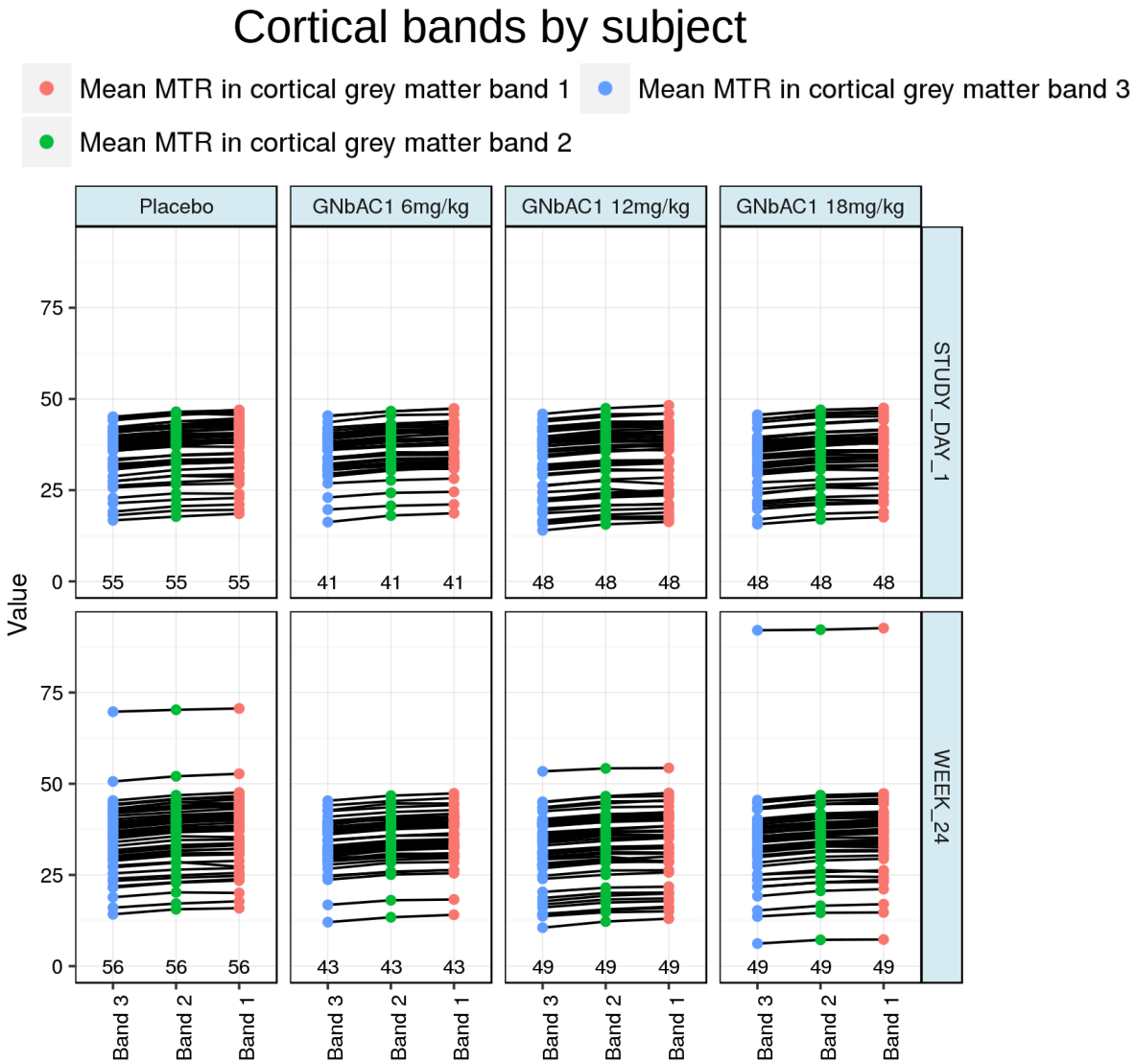


BAND	GNbAC1	Δ MTR BL to Week 24 (%units)	P value vs. placebo
1	6mg/kg	-0.280	0.814
1	12mg/kg	0.679	0.554
1	18mg/kg	**2.177**	**0.060**
2	6mg/kg	-0.262	0.820
2	12mg/kg	0.632	0.567
2	18mg/kg	**2.064**	**0.064**
3	6mg/kg	-0.278	0.806
3	12mg/kg	0.586	0.588
3	18mg/kg	**2.014**	**0.066**

Individual NAWM bands 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 MTR analyses - Cortex

Evidence for remyelination with GNbAC1 18 mg/kg in cerebral cortex vs. placebo



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

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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