CHANGE-MS
End-of-Study (Week 48) Results

Phase 2b Study in RRMS

ECTRIMS 2018

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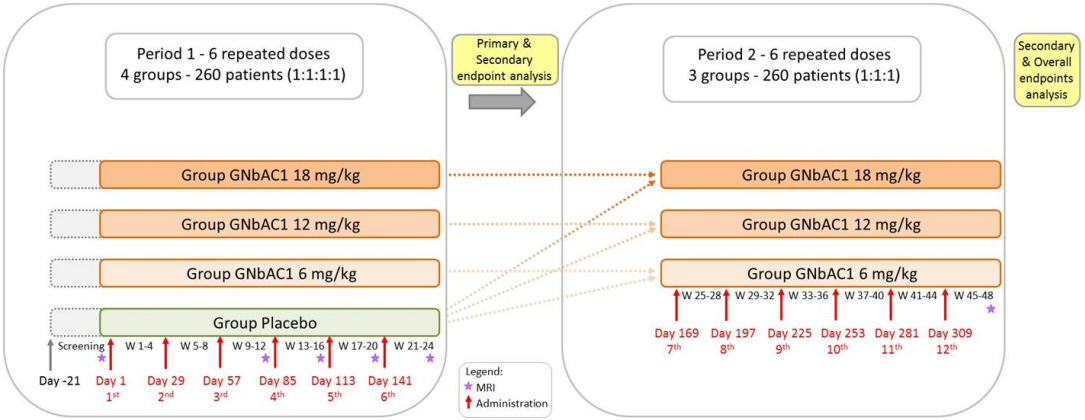
Clinical trial of anti-pHERV-W Env hu-mAb (GNbAC1) in RRMS

- Double-blind, placebo-controlled, Ph2b study
- 270 patients with RRMS according to 2010 revised McDonald criteria*
- 4 parallel groups: GNbAC1 6 mg/kg, 12 mg/kg, 18 mg/kg, placebo
- 2 periods:
  - Weeks 1-24: 3 active dose groups vs. placebo
  - Weeks 25-48: placebo patients re-randomized into 3 active dose groups
  - Patients, investigators, MRI reading center remained blinded to treatment assignment



*Polman CH et al. Ann Neurol. 2011; 69:292-302

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Patient Disposition – Analysis Sets

Period 1 group: Analysis set	6 mg/kg n = 67 (%)	12 mg/kg n = 67 (%)	18 mg/kg n = 67 (%)	Placebo n = 69 (%)	Overall n = 270 (%)
Randomized Set	67 (100.0)	67 (100.0)	67 (100.0)	69 (100.0)	270 (100.0)
Full Analysis Set	67 (100.0)	65 (97.0)	65 (97.0)	66 (95.7)	263 (97.4)
Per Protocol Set	60 (89.6)	60 (89.6)	63 (94.0)	65 (94.2)	248 (91.9)
Safety Set	67 (100.0)	66 (98.5)	67 (100.0)	68 (98.6)	268 (99.3)
Completed Period 1	60 (89.6)	60 (89.6)	62 (92.5)	65 (94.2)	247 (91.5)
Full Analysis Set Entering Period 2	**81 (21 from placebo)**	**82 (22 from placebo)**	**84 (22 from placebo)**	**Entering dose ← ← ← groups**	**247 (91.5)**

Week-48 Anti-neuroinflammation Outcomes

Modest benefit on MRI markers of neuroinflammation

- Primary endpoint at 6 months:
  - Non-significant reduction in cumulative number Gd+ lesions on brain MRI scans of Weeks 12, 16, 20 and 24*
- Post-hoc analyses at 6 months:
  - Trend seen on MRI markers of neuroinflammation markers at highest dose in active patients at Week 24*
- From Month 6 to Month 12:
  - For most MRI markers of neuroinflammation, all groups significantly improved with no significant separation between treatment groups
- Unlikely to translate into clinically relevant results at the doses tested

* results not adjusted for multiplicity, data presented at MSParis 2017

Week-48 Anti-neuroinflammation Outcomes

Non-significant reduction in new T2 lesions at Week 48

Number of new / enlarging T2 lesions from Week 24 to Week 48

Groups	Mean (Median)	Treatment Ratio	Standard Error	P-value
18 mg/kg ($N^{\pm}$ = 250)	3.83 (2.0)	0.85	0.19	0.480
Comparator* ($N^{\pm}$ = 301)	4.49 (3.0)	n/a	n/a	n/a

*Comparator Group = originally randomized placebo group
$^{\pm}$N = number of new T2 lesions
$^{\pm}$ Analysis limited to lesions ≥ 3 mm in diameter
Treatment comparison ratio < 1 indicates benefit of Treatment versus Comparator
Negative Binomial GLM fitted in SAS using PROC GENMOD
Including factors for treatment and presence of T1 lesions at Baseline

Week-48 Anti-neurodegeneration Outcomes

Significant 63% reduction in new T1-Black Holes vs. Comparator

Number of new T1 Black Holes from Week 24 to Week 48

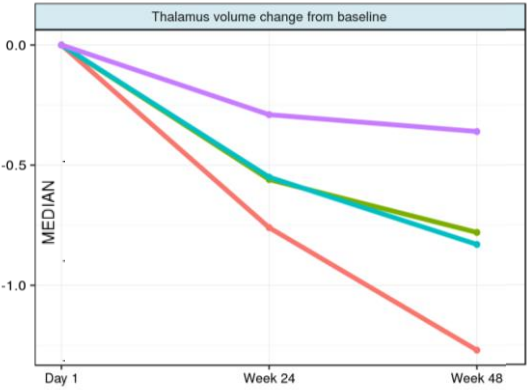
Groups	Mean (Median)	Treatment Ratio	Standard Error	P-value
18 mg/kg (N± = 18)	0.28 (0)	0.37	0.15	*0.014*
Comparator* (N± = 60)	0.75 (0)	n/a	n/a	n/a

*Comparator Group = originally randomized placebo group
±N = number of new T1 Black Holes from Week 24
± Analysis limited to lesions ≥ 3 mm in diameter
Treatment comparison ratio < 1 indicates benefit of Treatment versus Comparator
Negative Binomial GLM fitted in SAS using PROC GENMOD
Including factors for treatment and presence of T1 lesions at Baseline

Week-48 Anti-neurodegeneration Outcomes

Reduced CNS volume loss versus the Comparator Group

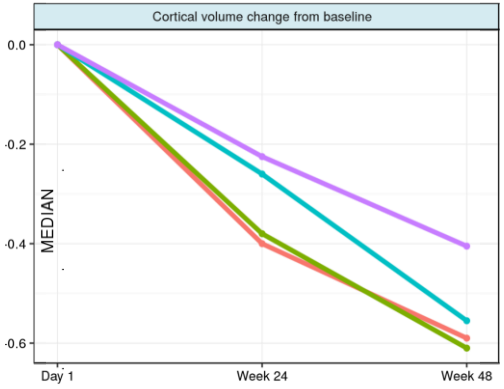
Thalamus



Group	Median % reduction at week 48	Relative reduction Median volume
Comparator	-1.27	
18mg/kg	-0.36	**72%**

Dose response* p=0.014

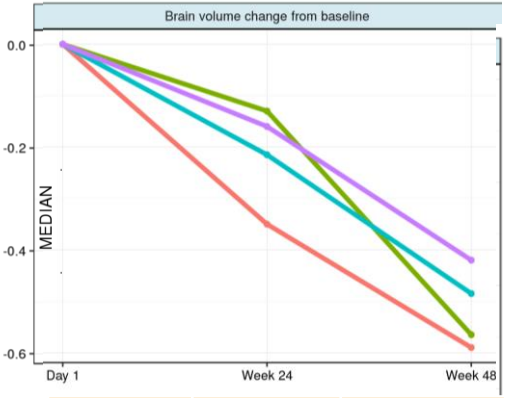
Cerebral cortex



Group	Median % reduction at week 48	Relative reduction median volume
Comparator	-0.59	
18mg/kg	-0.41	**31%**

Dose response* p=0.045

Whole brain



Group	Median % reduction at week 48	Relative reduction median volume
Comparator	-0.59	
18mg/kg	-0.42	**29%**

Dose response* p=0.079

Placebo/GNbAC1 (6, 12 or 18 mg/kg) — GNbAC1 (12 mg/kg)/GNbAC1 (12 mg/kg)

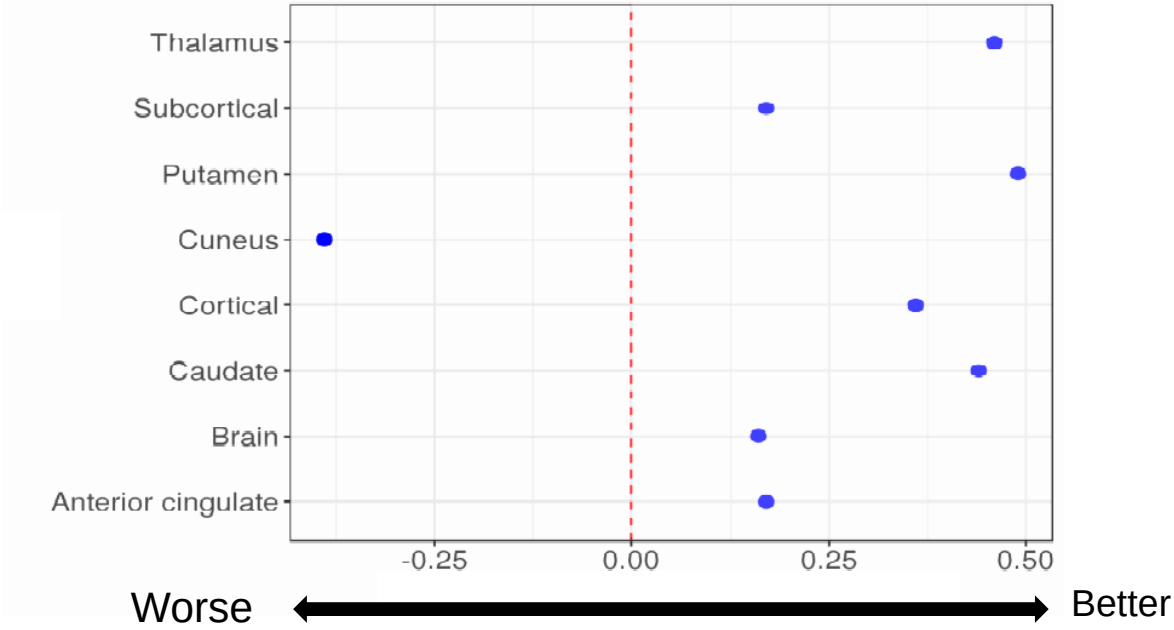
GNbAC1 (6 mg/kg)/GNbAC1 (6 mg/kg) — GNbAC1 (18 mg/kg)/GNbAC1 (18 mg/kg)

* Dose response analyzed by Spearman Rank Correlation Coefficient

Week-48 Anti-neurodegeneration Outcomes

Consistent Benefit in Reducing Atrophy in Non-active Population

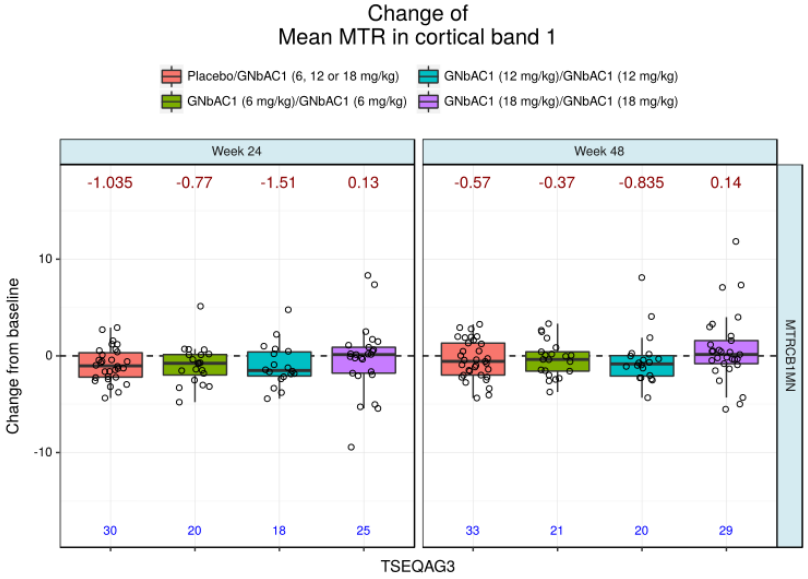
% Median Change in Volume in Non-active Population* versus Comparator



* *defined as patients without Gd+ activity at baseline

Week-48 Anti-neurodegeneration Outcomes

MTR benefit in NAWM and Cortical Bands vs Comparator Group



Week-48 Anti-neurodegeneration Outcomes

MTR benefit in Normal Appearing White Matter (PV) Bands vs Comparator Group

		WEEK 24		WEEK 48	
Change in MTR signal (% units)		**Mean**	**Median**	**Mean**	**Median**
PV Band 1	18mg/kg	0.68	0.28	0.128	-0.265
	Placebo / 6-12-18mg	-0.35	-0.58	-0.855	-1.01
		Gain vs. placebo	**P value**	**Gain vs. placebo / 6-12-18mg**	**P value**
	18mg vs. Placebo / 6-12-18mg	**1.03**	**0.188**	**0.98**	**0.271**
PV Band 2	18mg/kg	0.64	0.30	0.179	-0.155
	Placebo / 6-12-18 mg	-0.32	-0.64	-0.763	-0.94
		Gain vs. placebo	**P value**	**Gain vs. placebo / 6-12-18mg**	**P value**
	18mg vs. Placebo / 6-12-18 mg	**0.96**	**0.188**	**0.94**	**0.277**
PV Band 3	18mg/kg	0.66	0.34	0.223	-0.145
	Placebo / 6-12-18 mg	-0.28	-0.61	-0.712	-0.91
		Gain vs. placebo	**P value**	**Gain vs. placebo / 6-12-18mg**	**P value**
	18mg vs. Placebo / 6-12-18 mg	**0.94**	**0.194**	**0.94**	**0.269**

Week-48 safety outcomes

No safety or tolerability issues

	GNbAC1 **6 mg/kg N=88**	GNbAC1 **12mg/kg N=90**	GNbAC1 **18 mg/kg N=89**	Overall **N=267**
SAE	3	4	1	8
Serious-related AE*	0	1	0	1
AE leading to early termination	2	2	2	6
AE leading to death	0	0	0	0

* Macroscopic hematuria: resolved

CHANGE-MS Week-48 Results

Conclusions

First clinical trial to show efficacy with a specific anti-HERV therapy in MS

- Consistent benefit on MRI measures associated with disease progression
  - Reduction in new T1 Black Hole formation from Week 24 to Week 48
  - Reduction of brain volume loss
  - Improvement in Magnetization Transfer Ratio in NAWM and cerebral cortex
- Anti-neurodegeneration benefits consistently seen in non-active population
- Modest benefits on MRI markers of neuroinflammation
  - Not likely to translate into clinical benefit as monotherapy, at doses tested
- Continued safety and tolerability
  - Allows for future studies with increased dose and/or in combination with DMTs

Provides clinical support for pre-clinical findings of pHERV-W Env toxicity

Further development in non-active, progressive populations is warranted