Neuroprotective effects of temelimab in relapsing-remitting Multiple Sclerosis patients extend to 96 weeks

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Context

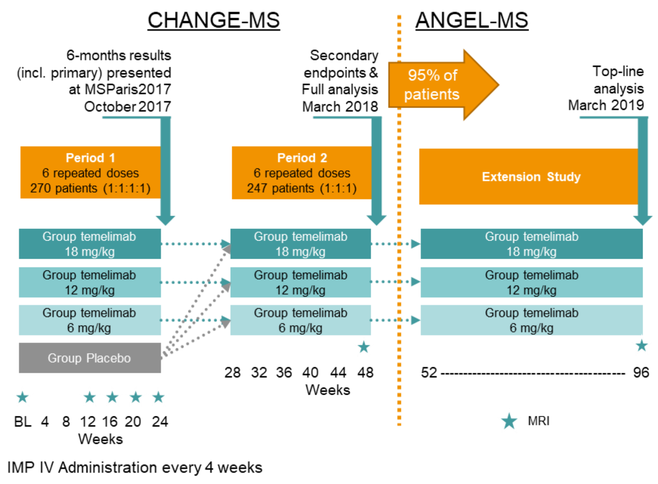
Emerging epidemiological, neuropathological and neuropharmacological data implicate the pathogenic form within a human endogenous retrovirus family, HERV-W, and its envelope protein (pHERV-W Env), in the development of multiple sclerosis (MS). pHERV-W Env is expressed in regions of active demyelination within MS lesions and activates the toll-like Receptor 4 (TLR4), a key driver of innate immunity that is expressed on macrophages/microglia, endothelial cells of the blood-brain barrier, and transiently on oligodendrocyte precursor cells (OPCs) during maturation. pHERV-W induces impairment of remyelination and also inflammation and neurodegeneration mediated by microglia activation[1-3]. *Ex vivo*, pHERV-W Env induces the release of pro-inflammatory cytokines in cultured peripheral blood mononuclear cells (PBMC)[4]. p-HERV-W Env inhibits OPC maturation by a direct interaction with TLR4 receptors transiently expressed on OPCs, which are essential for remyelination[2]. *In vitro*, the pHERV-W Env-induced inhibition of OPC maturation can be rescued with an anti-pHERV-W Env monoclonal antibody (temelimab)[5,6]. pHERV-W Env-mediated microglial polarization also contributes to direct axonal damage leading to neurodegeneration in MS[3].

Temelimab (INN, previously referenced by its Company code GNbAC1) is a recombinant, immunoglobulin (Ig) G4/subclass kappa, humanized monoclonal antibody (mAb) that selectively binds with high affinity (Kd = 2.2 nM) to the extracellular domain of pHERV-W Env[7]. Efficacy of temelimab has been firstly assessed in the GNC-003 (CHANGE-MS) study by examining the cumulative number of gadolinium (Gd)-enhancing T1 lesions from Week 12 to Week 24 in the temelimab groups (6, 12, and 18 mg/kg) compared with the placebo group. No significant reductions in cumulative Gd-enhancing lesions were seen between any temelimab dose group compared with the placebo group at Week 24. Week 48 analyses examined secondary, MRI-based efficacy endpoints relating to disease progression and neuroprotection. These included: number of new qualifying T1-hypointense lesions at Week 48, brain atrophy as measured by percentage change volume of whole brain and other specific cerebral structures, and change in magnetisation transfer ratio (MTR) in pre-defined regions of interest in normal-appearing white matter and cerebral cortex. The temelimab 18 mg/kg treatment group consistently showed evidence for target engagement on these MRI-based measures, correlating to or predicting disease progression in MS versus the Comparator Group (defined as the group of patients originally randomised to placebo) at Week 48. Importantly, these benefits were not driven by a significant anti-neuroinflammatory effect. This poster presents results of the GNC-004 (ANGEL-MS) study, extension of the CHANGE-MS study.

Study design

ANGEL-MS is an international, multicenter Phase-2b study in Relapsing-Remitting Multiple Sclerosis (RRMS) patients who had completed the CHANGE-MS Phase-2b study. This trial is a 3-arm study with the objective of demonstrating the long-term safety and efficacy of repeated doses of temelimab in terms of magnetic resonance imaging outcomes, relapse rate, disability and disease progression.

Patients and site staff remained dose-blinded. The study was early terminated after one year due to loss of funding following termination of a partnership.



Main Selection Criteria & Patient Disposition

Inclusion criteria: patients who had completed study CHANGE-MS, had tolerated the study drug according to the investigator's opinion, and could have benefitted from receiving long-term treatment with temelimab. Exclusion Criteria included pregnancy, emergence of any disease diagnosis during the course of study CHANGE-MS that was not MS and could better explain the patient's neurological signs and symptoms, and forbidden concomitant medications.

Parameter	Statistic	Temelimab (6 mg/kg) (N=74)	Temelimab (12 mg/kg) (N=68)	Temelimab (18 mg/kg) (N=77)	Overall (N=219)
Age at Baseline (years)	Mean (SD)	38.0 (10.09)	39.8 (9.13)	39.4 (8.66)	39.1 (9.29)
Gender Male Female	N (%)	 22 (29.7) 52 (70.3)	 20 (29.4) 48 (70.6)	 33 (42.9) 44 (57.1)	 75 (34.2) 144 (65.8)
EDSS	Mean (SD)	2.90 (1.269)	3.05 (1.231)	3.31 (1.504)	3.09 (1.351)
Duration of MS at Screening for CHANGE-MS (years)	Mean (SD)	5.59 (6.138)	5.95 (4.875)	5.37 (5.250)	5.15 (5.171)

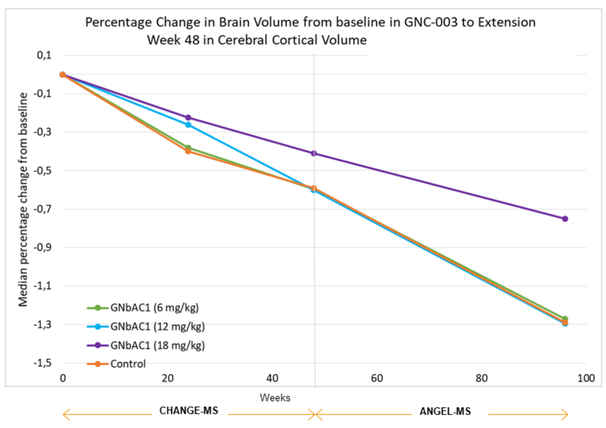
Patients with RRMS who completed the CHANGE-MS study were included, from 43 centers across 12 countries. Overall, 220 patients from CHANGE-MS entered ANGEL-MS (95% of completers), with 75 patients enrolled in the temelimab 6 mg/kg treatment group, 68 enrolled in the temelimab 12 mg/kg treatment group, and 77 enrolled in the temelimab 18 mg/kg treatment group.

		Temelimab (6 mg/kg) (N=74)	Temelimab (12 mg/kg) (N=68)	Temelimab (18 mg/kg) (N=77)	Overall (N=219)
All Enrolled Patients	N	75	68	77	220
Safety Set	N (%)	74 (100.0)	68 (100.0)	77 (100.0)	219 (100.0)*
Completed Week 48	N (%)	34 (46%)	38 (56%)	44 (57%)	116 (53%)

*one patient was enrolled in ANGEL-MS but did not receive any injection

Efficacy

- Decrease of atrophy rate of CNS volumes with statistically significant dose-trend



CHANGE-MS

Group	Median % reduction at week 48	Relative reduction of atrophy
Control	-0.59	
18mg/kg	-0.41	31%

Dose effect* p=0.045

ANGEL-MS

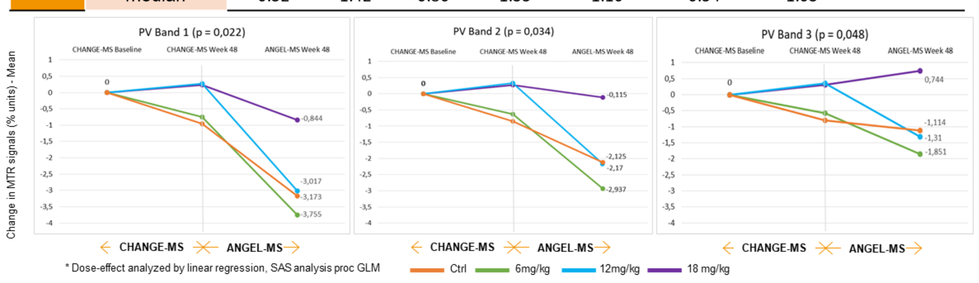
Group	Median % reduction at week 48	Relative reduction of atrophy
Control	-1.29	42%
6mg/kg	-1.27	41%
12mg/kg	-1.29	42%
18mg/kg	-0.75	

Dose effect* p=0.058

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

- Magnetisation Transfer Ratio (MTR) signal preserved or increased with temelimab 18mg/kg

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



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

- Lower increase of T1 lesions volume with temelimab 18mg/kg

	18 mg/kg	12 mg/kg	6 mg/kg	Control	P-value
New or newly enlarged T1 hypointense lesions from ANGEL-MS baseline median number (interquartile range)	1.5 (0-4)	2.0 (0-4)	2.0 (0-4)	2.0 (0-5)	0.74*

	18 mg/kg	12 mg/kg	6mg/kg	Control
CHANGE-MS Baseline T1 hypo-intense lesion median volume (mm3)	1857	1269	1124	900
Median hypointense lesion volume changes from CHANGE-MS baseline	162	117	163	192
Median percent increase in T1 hypointense lesion volume	8.7	9.2	14.5	21.3
Pairwise comparisons vs Control, p-values**	0.12	0.80	0.41	

*Non parametric analysis SAS Proc NPAR1WAY
**Analysis of covariance on rank transformed data

- Timed 25 Foot Walk Test : less frequent worsening with temelimab 18mg/kg

Timed 25-foot walk – Original CHANGE-MS Groups	18 mg/kg	12 mg/kg	6 mg/kg	Control	P-value**
Percentage of patients with worsening ≥ 20% in the Timed 25-Foot Walk Test compared to CHANGE-MS Baseline*	2.4	23.1	13.3	10.2	0.03

Timed 25-foot walk – By Dose Groups	18 mg/kg	12 mg/kg	6 mg/kg	P-Value**
Percentage of patients with worsening ≥ 20% in the Timed 25-Foot Walk Test compared to CHANGE-MS Baseline*	3.6	16.9	15.0	0.04

Timed 25-foot walk – By 18 vs Others	18 mg/kg	Others	P-value**
Percentage of patients with worsening ≥ 20% in the Timed 25-Foot Walk Test compared to CHANGE-MS Baseline*	2.4	15.0	0.03

*Fifteen patients with extreme walking disability removed from analysis – for whom the test was almost impossible to perform – excluded patients distributed equally across treatment groups

**Fisher exact test

Safety

Temelimab was safe and well tolerated up to the highest dose tested. No differences were observed between treatment groups in number, maximum intensity, or seriousness of AEs, and most AEs were not treatment-related. Only 2 patients tested positive for anti-temelimab antibodies during the study.

Overall Summary of Adverse Events

Number of patients (%)	Temelimab 6 mg/kg (N=74)	Temelimab 12 mg/kg (N=68)	Temelimab 18 mg/kg (N=77)
Treatment emergent adverse events (TEAEs)	33 (44.6%)	32 (47.1%)	34 (44.2%)
Serious adverse events (SAEs)	6 (8.1%)	1 (1.5%)	5 (6.5%)
Serious related AEs	0	0	3 (3.9%)
AEs leading to study discontinuation	1 (1.4%)	1 (1.5%)	2 (2.6%)
Fatal TEAEs	0	0	1 (1.3%)

Most commonly reported Adverse Events

MedDRA Primary SOC Preferred Term	Temelimab 6 mg/kg no of patients (%)	Temelimab 12 mg/kg no of patients (%)	Temelimab 18 mg/kg no of patients (%)
Infections/infestations	16 (21.6%)	17 (25.0%)	25 (32.5%)
Nasopharyngitis	5 (6.8%)	6 (8.8%)	6 (7.8%)
Upper respir. tract infection	2 (2.7%)	3 (4.4%)	6 (7.8%)
Musculoskeletal (mainly diverse pains potentially related to MS)	7 (9.5%)	5 (7.4%)	5 (6.5%)
Investigations (diverse lab abnormalities)	5 (6.8%)	5 (7.4%)	6 (7.8%)
Nervous system	5 (6.8%)	5 (7.4%)	5 (6.5%)
Headache	3 (4.1%)	3 (4.4%)	4 (5.2%)

Conclusion

Findings in CHANGE-MS and ANGEL-MS are consistent with preclinical knowledge to date:

Clinical observations

- **Reduction of Brain Atrophy**
- **Reduction in formation of new T1 Black Holes**
- **Benefit on Magnetization Transfer Ratio**
- **Inflammation does not appear to drive the effect the effect on markers associated with disease progression**

Supporting pre-clinical rationale

- **Neurodegeneration directly reduced** by
  - effectively **acting on** proinflammatory **microglia**, the key immune cells in Progressive MS, responsible for lesion growth
- **Neuroregeneration enabled** by
  - rescuing the negative impact of pHERV-W Env on **OPC** myelination capacity - the key precursor cells in remyelination processes.
- **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

Patients originally randomised to temelimab 18 mg/kg in CHANGE-MS continued to show evidence for relative improvements in MRI-based neurodegenerative outcomes such as brain volumes, MTR and black holes during ANGEL-MS compared to all other groups.

This extension study demonstrated that temelimab is safe to use and well tolerated for a prolonged period.

These data support a neuroprotective effect of temelimab and support further clinical trials with temelimab in MS, particularly in progressive forms.

References

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