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

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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 neurogeneration mediated by microglia activation1-5. Ex vivo, pHERV-W Env induces the release of pro-inflammatory cytokines in cultured peripheral blood mononuclear cells (PBMC)1-5. p-HERV-W Env inhibits OPC maturation by a direct interaction with TLR4 receptors transiently expressed on OPCs, which are essential for remyelination2. In vitro, the pHERV-W Env-mediated inhibition of OPC maturation can be rescued with an anti-pHERV-W Env monomolecular antibody (temelimab)6-9. pHERV-W Env-mediated microparticle polarization also contributes to direct axonal damage leading to neurodegeneration in MS10.

Temelimab (IMN, previously referred to its Company code GNC001) is a recombinant, immunoglobulin (lg)4/subclass kappa, humanized monoclonal antibody (mAb) that selectively binds with high affinity (Kd = 2.2 nM) to the extracellular domain of pHERV-W Env. 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 randomized to placebo) at Week 48. Importantly, these benefits were not driven by a significant pro-inflammatory effect. This poster presents results of the GNC-004 (ANGEL-MS) study, extension of the CHANGE-MS study.

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 benefited 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.

Study design

ANGEL-MS is an international, multicenter Phase-2b study in Relapsing-Remitting Multiple Sclerosis (RRMS) patients who had completed the CHANGE-MS study. ANGEL-MS was 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.

Efficacy

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

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

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

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

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 (%)

- Treatment emergent adverse events (TEAEs) 33 (46.6%) 32 (47.4%) 34 (44.2%)

- Serious adverse events (SAEs) 5 (6.1%) 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 (1.1%)

Most commonly reported Adverse Events

- Infections/Infections related to temelimab

- Musculoskeletal

- Nervous system

Conclusion

Findings in CHANGE-MS and ANGEL-MS are consistent with previously observed data.

- Reduction of Brain Atrophy

- Beneficial on Magnatisation Transfer Ratio

- Informational does not appear to alter the effective effect as monitored with disease progression

Clinical observations

- Neurodegeneration directly related to intracerebral lesions and to disease progression, the former type is, for example, in progressive MS, repothesized to be slow growth processes possibly related to 

- Neurodegeneration induced by activation of microglia/macrophage and/or GPC expression/activation - the key process that may be modulated by temelimab or other classes of neuroprotective agents

- No direct effect on TLR4 expression and activity, nor compromising dopamine integrity

- Excellent proof-of-concept safety package based on in vivo and in vitro (animal) data, for immunologically driven adverse effects of temelimab

Supporting pre-clinical rationales

References

1. Perron et al, Plas One 2013


3. Kremer et al, PMAS, 2019


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.

Patients and RRMS patients who completed the CHANGE-MS study were included, from 43 centers across 12 countries. Overall, 220 patients from CHANGE-MS entered ANGEL-MS (55% 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.

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