Abstract 1803
Poster P0239

Temelimab for prevention of neurodegeneration: preclinical safety profile and design of the ProTEct-MS (temelimab following rituximab in RMS) study

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Disclosures

F. Piehl has received research grants from Genzyme, Merck KGaA and UCB, and fees for serving as Chair of DMC in clinical trials with Parexel.
G. Kornmann is an employee of GeNeuro.
B. Cree has received personal compensation in the past 36 months for consulting for Abbvie, Akili, Alexion, Biogen, EMD Serono, Novartis, and TG Therapeutics.
HP Hartung has received honoraria for consulting and serving on steering and data monitoring committees from Bayer Healthcare, Biogen, Celgene Receptos, GeNeuro SA, MedDay, MedImmune, Merck, Novartis, Roche, Sanofi Genzyme, and TG Therapeutics with permission by the rector of Heinrich-Heine-Universität Düsseldorf.
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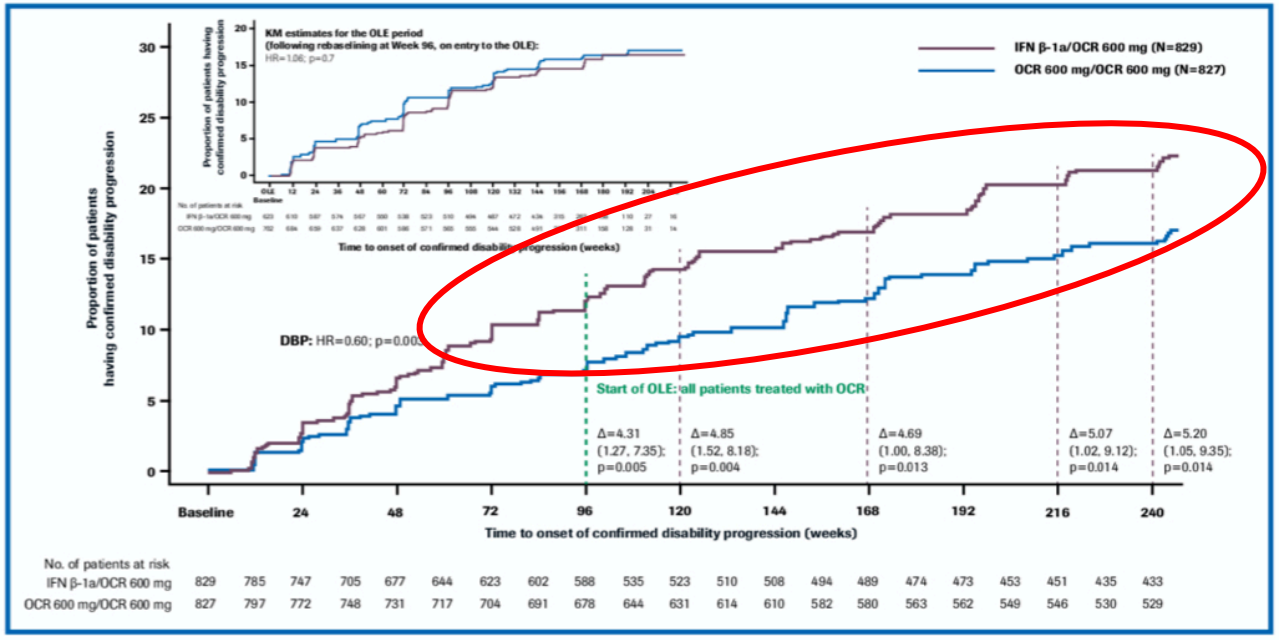
B. Buffet is an employee of GeNeuro.
N. Berthuy is an employee of GeNeuro.
J. Leja-Jarblad is an employee of Immuneed AB.
G. Törnqvist is an employee of Immuneed AB.
J. Medina is an employee of GeNeuro.
P. Küry performed consultancy work for GeNeuro and is supported by the Stifterverband/Novartisstiftung.
T. Rückle is an employee of GeNeuro.
D. Leppert is CMO of GeNeuro; he has received personal compensation for consulting and speaking, and travel reimbursement from Quanterix, Roche, Novartis, Orion, GeNeuro and Sanofi.

Background

Even highly effective disease-modifying therapies, have limited effect on MS disease progression ⇒ need for anti-neurodegenerative drugs

Figure 4. Time to onset of CDP for at least 24 weeks during the DBP and OLE periods



Without imputation. ITT population. Pooled OPERA I and OPERA II population; DBP clinical cut-off dates: 2 April 2015 and 12 May 2015, respectively; OLE clinical cut-off date: 5 February 2018.
Data shown up to Week 240, the last visit all ongoing patients completed.
CDP, confirmed disability progression; DBP, double-blind period; HR, hazard ratio; IFN, interferon; ITT, intention-to-treat; KM, Kaplan-Meier; OCR, ocrelizumab; OLE, open–label extension.

DBP: double-blind phase; OLE open label extension

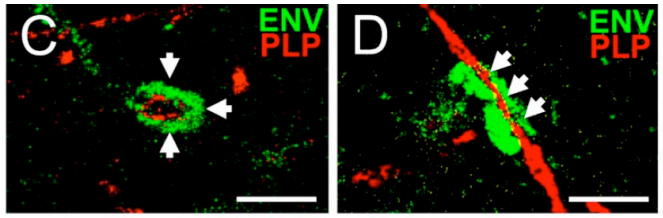
- High efficacy disease-modifying therapies for MS can induce an almost complete suppression of acute disease activity (relapses, formation of new lesions, enlarging of lesions); this is specifically the case for anti-CD20 therapies
- However, these drugs have little impact on progression, and may delay clinical worsening only indirectly, i.e. via their anti-inflammatory mode of action
- Neurodegenerative processes may be driven by chronic-active lesions / slowly expanding lesions, leading to Wallerian degeneration, as well as brain-diffuse mechanisms affecting the integrity of myelin
- Novel therapeutic approaches are needed to modify neurodegenerative processes directly, i.e. within the CNS

Hauser SL et al., ECTRIMS Online Library. Hauser S. 10/10/18; 228434; P590
Long-term reduction of relapse rate and confirmed disability progression after 5 years of ocrelizumab treatment in patients with relapsing multiple sclerosis

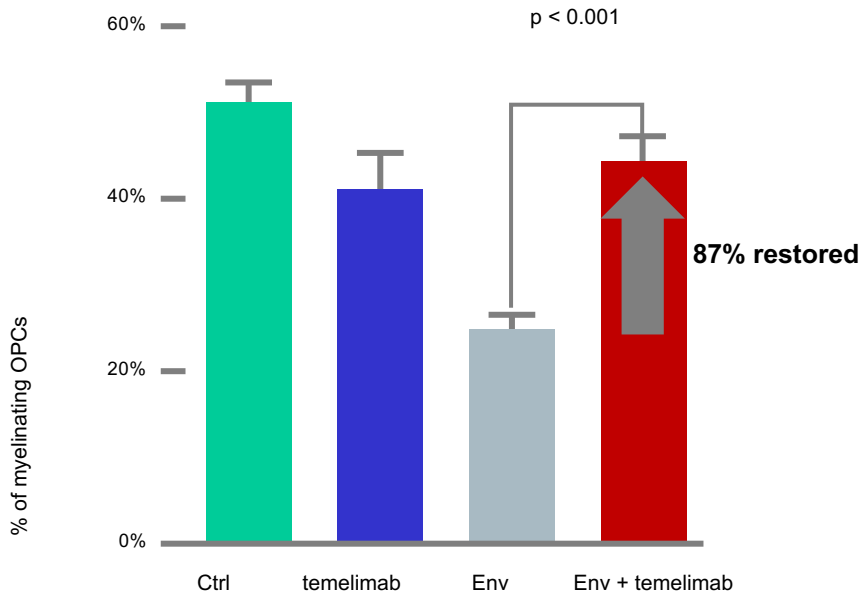
Background

Temelimab neutralizes HERV-W-ENV mediated damage through microglia and oligodendrocyte precursor cells (OPCs)

The envelope protein of the human endogenous retrovirus type W (HERV-W-ENV) is expressed in chronic active MS lesions. Preclinical models have shown that HERV-W ENV activates microglia, prevents maturation of oligodendrocyte precursor cell and leads to neuronal death.



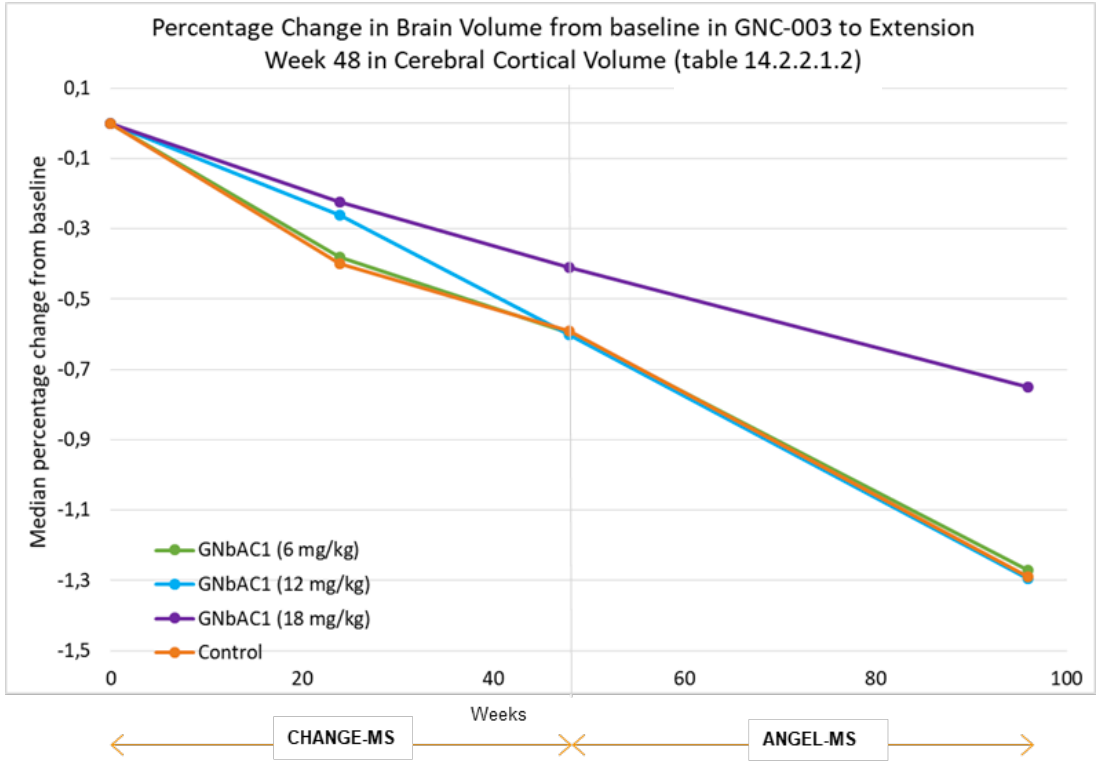
Human endogenous retroviruses (HERVs) are "archeological remnants" of infections in our ancestors that were absorbed into the human genome.
Single-layer confocal imaging showing that HERV-W-ENV-positive cells completely wrap around PLP-positive axons (C and D: arrows).



- *Temelimab* is a recombinant, humanized IgG4-κ mAb
- PK approximately dose linear, half-life ≈ 1 month
- Binds with high affinity to HERV-W-ENV (K_d = 2.2 nM)
- Blocks HERV-W-ENV activation of TLR4
- **Left:** rescues myelin basic protein (MBP) expression in OPCs

Kremer et al. MSJ 2015, Göttle et al. Glia 2019, Kremer et al., PNAS 2019

Results of CHANGE-MS and ANGEL-MS phase 2 studies with *temelimab* in MS



Hartung HP et al., ECTRIMS2019, P1379

- Efficacy of *temelimab* as monotherapy has been assessed in CHANGE-MS (core study) and ANGEL-MS (extension study) studies in RRMS.
- The primary endpoint was not met (reduction of cumulative number of gadolinium(Gd)-enhancing T1 lesions from week12-24 in temelimab groups (6,12, and18mg/kg) compared with placebo).
- However, patients originally randomised to temelimab 18mg/kg in CHANGE-MS showed evidence for relative improvements in MRI-based neurodegenerative outcomes such as brain volumes, MTR and blackholes during CHANGE-MS and ANGEL-MS, compared to all other groups.
- The extension study demonstrated that temelimab is safe to use and well tolerated for a prolonged period.

These data suggest a possible neuroprotective effect of temelimab and support further clinical development towards a treatment for progression of MS-disability.
Because temelimab has no significant anti-inflammatory effect, combination with a highly effective DMT, such as an anti-CD20-antibody, to protect against new focal neuroradiological disease activity is likely needed to properly explore temelimab's tissue protective, anti-neurodegenerative effect: *this represents the rational for the ProTEct-MS study* [1].

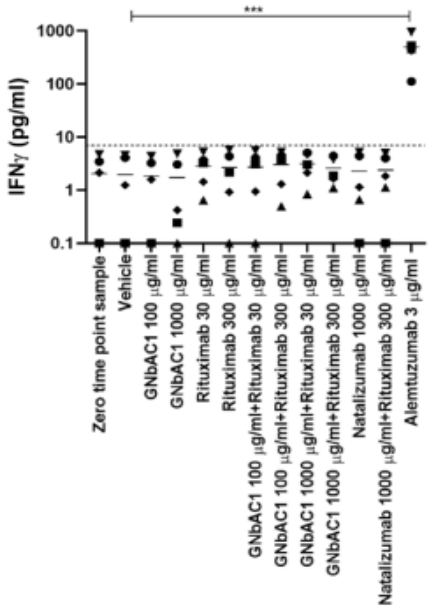
1. ClinicalTrials.gov Identifier: NCT04480307

Background

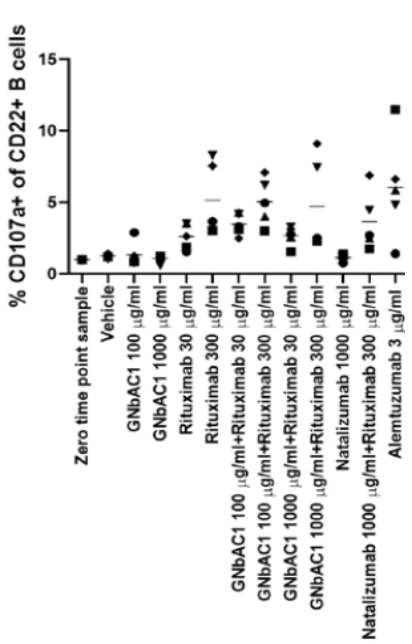
Ex *vivo* model of co-administration of *temelimab* and rituximab (RTX)[1]: *No evidence of interaction in immune assays*[2]

Human ex vivo models representing human circulation (whole blood loop model) and lymph node-like conditions (high-density PBMCs) (five donors)

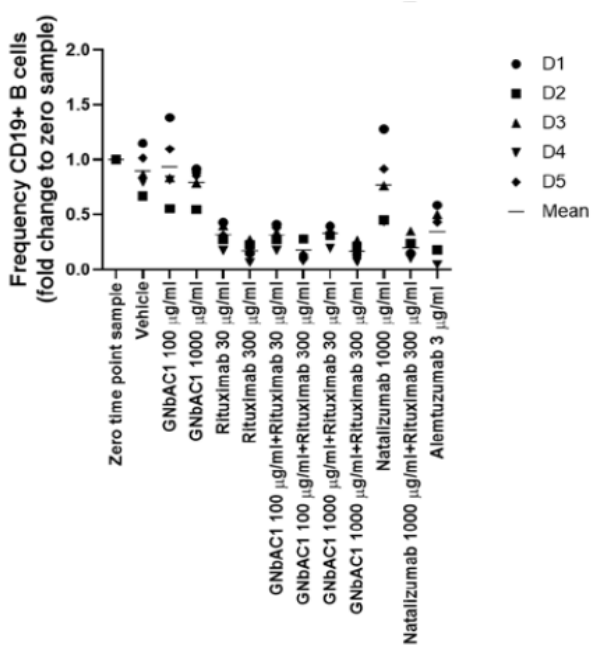
Cytokine release (IFNγ)



B cells activation



B cells viability

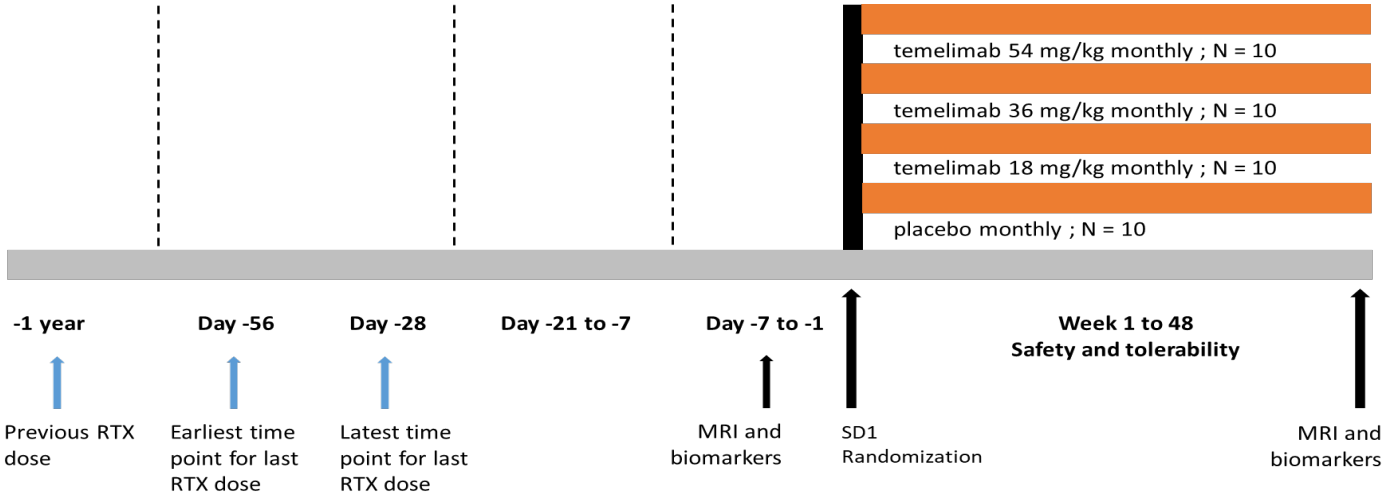


- Temelimab (GNbAC1, up to 1000µg/ml) is overall comparable to vehicle and reference antibody, natalizumab for PLT counts, WBC counts, cytokine levels (IFNγ, IL2, IL6, IL8, TNFα), cellular activation, cell viability for all five donors.
- Co-administration of temelimab (GNbAC1, up to 1000µg/ml) with RTX (up to 300µg/ml) did not affected its mode of action as cellular binding, cellular activation, B cell depletion, and cytokine levels were comparable to levels seen in groups with rituximab alone suggesting that co-administration of temelimab with RTX did not affect the safety and functionality profile of rituximab.

1. Collaboration Immuneed AB
2. Fletcher et al, Int Immunopharmacol, 2018 & Romer et al, Blood, 2011

ProTEct-MS (*temelimab* following RTX in relapsing forms of MS (RMS): *Study design*

Primary objective: to assess safety and tolerability of iv temelimab in patients with RMS treated with RTX
Secondary objective: to determine the pharmacodynamic effects of temelimab on neuroprotection and remyelination based on innovative neuroimaging techniques[1], as well as biomarkers studies (exploratory objectives)



- Patients with RMS who have been treated with RTX for ≥1y
- Randomized, double-blind, parallel group, placebo-controlled phase IIa trial
- Temelimab will be given in monthly iv infusions for 48 weeks (12 administrations in total).
- 3 doses (18 mg/kg or 36 mg/kg or 54 mg/kg)
- ClinicalTrials.gov Identifier: NCT04480307, has started in June 2020

Primary Endpoints (Safety)	*Secondary Endpoints*
• Adverse events • Clinical Laboratory tests • Vital signs • Physical examination • 12-lead ECG	• Change in magnetization transfer (MTR) in periventricular normal-appearing white matter (NAWM) at week 48 compared to baseline • Change in magnetization transfer (MTR) in cerebral cortex at week 48 compared to baseline • Change in T1 lesion volume at week 48 compared to baseline • Change in T2 lesion volume at week 48 compared to baseline • Change in brain parenchymal volume fraction at week 48 compared to baseline • Change in thalamic volume fraction at week 48 compared to baseline

1. Ouellette et al, Ann Neurol 2020

ProTEct-MS (*temelimab* following RTX in RMS) study:
Inclusion / Exclusion criteria

Key inclusion criteria:

- Diagnosis of RMS, based on the McDonald 2017 criteria (Thomson et al, 2017)
- Having received treatment with RTX, as per local clinical routine for at least 12 months prior to the Screening Visit (not more than 8 weeks and not less than 4 weeks before Randomization (Study Day 1))
- Having expanded disability status scale (EDSS) 2.5 – 5.5 inclusive at Screening
- Present clinical worsening in one or more neurological domains as assessed by EDSS, ambulatory function as assessed by 6MWT or T25FW, cognitive functioning as assessed by SDMT or increased need of walking aids or pharmacological/procedures for bowel and bladder functions over the last year
- Brain MRI: lesion burden with >9 T2 cerebral lesions (assessed within the last 24 months)
- Age range from 18 to 55 years (both inclusive)
- Female patients of childbearing potential or procreative male patients, willing to use highly effective contraceptive methods throughout the study duration and at least until 5 months after the last study treatment

Key exclusion criteria:

- Diagnosis of primary progressive MS
- Previous use within 12 months prior to Screening with interferon beta, glatiramer acetate, IV immunoglobulin (IVIG), dimethyl fumarate or teriflunomide, ocrelizumab, ofatumumab, fingolimod, siponimod, ozanimod or anti-cytokine therapy, plasmapheresis or azathioprine
- Any history of exposure to mitoxantrone, cladribine, alemtuzumab, cyclophosphamide, systemic cytotoxic therapy, total lymphoid irradiation, and/or bone marrow transplantation
- Any usage of natalizumab within 24 months prior to Screening
- Any history of cancer with the exceptions of resected basal cell carcinoma and/or carcinoma in situ of the cervix
- Pregnant or breastfeeding women

Conclusions

- Combination therapy with an anti-inflammatory and an anti-neurodegenerative drug may be needed to successfully target disability worsening in MS patients

- Preclinical safety experiments of the drug combination showed no evidence against the use of *temelimab* following RTX in humans.

- ProTEct-MS study patients represent a RMS cohort with progression in absence of relapse activity (PIRA)[1], i.e. whose present clinical condition is stable under RTX therapy, enabling proper exploration of *temelimab's* suggested attenuating effects on continued local nerve and myelin damaging inflammation without interference by acute inflammatory activity driven by the adaptive immune system

1. Kappos et al, JAMA Neurol 2020

Acknowledgments

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