CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Placebo Controlled Trial, Examining the Safety, Tolerability, Pharmacodynamic Effects and Pharmacokinetics of Temelimab Following Rituximab Treatment in Patients with Relapsing Forms of Multiple Sclerosis (RMS)

- *ProTEct-MS*

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List of used acronyms and abbreviations

Ab	Antibody
ADA	Anti drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ARR	Annual relapse rate
AST	Aspartate aminotransferase
CA	Competent Authorities
CC	Cerebral Cortex
CNS	Central nervous system
CRO	Contract research organization
CSF	Cerebrospinal fluid
CSP	Clinical study protocol
CRF	Case report form
DBP	Diastolic blood pressure
DMT	Disease modifying therapies
DSMB	Data Monitoring Safety Board
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
eCRF	Electronic case report form
EDSS	Expanded disability status scale
EMA	European Medicines Agency
Env	Envelope protein
EQ-5D	EuroQol five dimension scale
FLAIR	Fluid-attenuated inversion recovery
FPCBP	Female patient of childbearing potential
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
HBc / HBs	Hepatitis B virus core / surface
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HERV	Human endogenous retrovirus
pHERV-W Env	Pathogenic Human endogenous retrovirus W envelope protein

HIV	Human immunodeficiency virus
hsCRP	High-sensitivity C-reactive protein
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IRS	Interactive response system
ISF	Investigator site file
IV	Intravenous
LOCF	last observation carried forward
LP	Lumbar puncture
mAb	Monoclonal antibody
MedDRA	Medical dictionary for regulatory activities
MPA	Medical Products Agency
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MS	Multiple sclerosis
MSRV	Multiple sclerosis-associated endogenous retrovirus
MTR	Magnetization transfer
NAWM	Normal-appearing white matter
NBGLM	Negative binomial generalized linear model
NfL	Neurofilament light chain
ODRS	Overall Disability Response Score
OPC	Oligodendrocyte precursor cell
PCBP	Partners of childbearing potential
pHERV	Pathogenic human endogenous retrovirus
PK	Pharmacokinetics
PT	Preferred Term
PMP	Procreative male patient
PMS	Progressive multiple sclerosis
PPMS	Primary progressive multiple sclerosis
REMyDI	Rapid estimation of myelin for diagnostic imaging
QoL	Quality of life
RMS	Relapsing multiple sclerosis
RRMS	Relapsing remitting multiple sclerosis
SAE	Serious adverse event

SAP	Statistical analysis plan
SDMT	Symbol Digit Modalities Test
SERA	Swedish Ethical Review Authority
SOC	System Organ Class
SPMS	Secondary progressive multiple sclerosis
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse events
TNF	Tumor necrosis factor
T25FW	Timed 25-foot walk
ULN	Upper limit of normal range
WHO	World Health Organization
9-HPT	9-Hole Peg Test

1. Synopsis

EudraCT number:	2019-004822-15
Title:	A Randomized, Double-Blind, Placebo Controlled Trial, Examining the Safety, Tolerability, Pharmacodynamic Effects and Pharmacokinetics of Temelimab Following Rituximab Treatment in Patients with Relapsing Forms of Multiple Sclerosis (RMS)
Study code:	GNC-401
Development Phase:	IIa
Short Rationale:	Temelimab, a humanised, IgG4-κ monoclonal antibody represents a novel therapeutic approach for degenerative features of Multiple Sclerosis (MS). Preclinical studies have shown that the envelope protein of the pathogenic human endogenous retrovirus type W (pHERV-W Env) activates microglia into pro-inflammatory phenotype. Furthermore, in the presence of pHERV-W Env, oligodendrocyte precursor cells (OPCs) will not mature into functional oligodendrocytes, thereby preventing optimal remyelination. Temelimab inhibits these effects in preclinical models, both in vitro and in vivo. The postulated mode of action of temelimab is to neutralise pHERV-W Env and hence to prevent the pHERV-W Env induced pro-inflammatory activation of microglia, and to preserve OPC maturation. Both these cell types are key cellular targets in neurodegeneration of MS that eventually manifests as disease progression/disability worsening independent of relapse activity and lesion formation. Therefore, temelimab, is expected to address an unmet medical need for patients suffering from MS. In neuropathological studies, pHERV-W Env was found in chronic active MS lesions, which are considered a main driver of progression in MS and may persist despite current standard disease modifying therapies. Temelimab has been studied in Phase 2b clinical studies in two-hundred-seventy (270) relapsing-remitting MS (RRMS) patients for up to 96 weeks. In these studies, temelimab showed neuroprotective effects, as documented by: • reduction in volume loss in whole brain, cerebral cortex and thalamus, • reduction in T1 hypointense (T1 Black Hole) lesion number and volume, • stabilization of magnetization transfer ratio (a magnetic resonance imaging (MRI) measure of myelin integrity) in both normal-appearing white matter and cerebral cortex, over 96 Weeks. However, no clinically-relevant effects were observed with temelimab as monotherapy on MRI measures of neuroinflammation in RRMS patients. Phase 2 clinical trial data with rituximab in RRMS patients demonstrated highly significant effects on neuroinflammation, which is seen even years after cessation of treatment. In contrast, rituximab failed to demonstrate a statistically significant effect on disease progression in Primary progressive multiple sclerosis (PPMS).

Although rituximab is not approved by the European Medicines Agency (EMA) for any form of MS, rituximab has become the most frequent disease modulatory treatment in Sweden for MS, based on positive results obtained in several real world cohorts.

Therefore, the introduction of temelimab treatment, in relapsing MS (RMS) patients who have been treated with rituximab, and hence experience sustained reduction of relapse activity and lesion formation is postulated to have a significant additional beneficial effect on disease progression.

In all preclinical as well as clinical studies to date, temelimab has shown to be well tolerated with no apparent safety signal either at repeated doses over two years in RRMS, or at single doses in healthy human volunteers as high as 110 mg/kg.

In addition, no drug-drug interactions are expected with the staggered administration of temelimab after rituximab, based on data from human ex vivo models.

This proposed clinical Phase 2a study will be performed in patients with RMS who have been receiving rituximab off-label, as per local clinical practice guidelines for at least 12 months. In this study temelimab is administered subsequently to rituximab therapy, i.e. no co-administration of rituximab and temelimab is done in this study.

Primary objective:

- To assess the safety and tolerability of temelimab following intravenous (IV) administration of 18 mg/kg, 36 mg/kg or 54 mg/kg, in patients with RMS who have been treated with rituximab for at least 1 year.

Secondary objective:

- To determine the pharmacodynamic effects of temelimab on neuroprotection and remyelination based on neuroimaging.

Exploratory objectives:

- To assess the clinical and cognitive effects of temelimab (including physical disability)
- To assess the effect of temelimab on quality of life
- To assess the effects of temelimab on exploratory neuroimaging endpoints associated with neuroprotection and remyelination.
- To assess the effects of temelimab on fluid biomarkers associated to myelin integrity, target and immune function
- To determine the PK characteristics of temelimab following repeated IV administration (including CSF distribution) and immunogenicity

Study design:

This is a randomized, double-blind, placebo-controlled Phase IIa clinical study, assessing safety, tolerability, pharmacodynamic effects and pharmacokinetics of temelimab, administered at three different dose levels (18 mg/kg or 36 mg/kg or 54 mg/kg).

The study will consist of a Screening period of a maximum duration of up to 3 weeks (Days -21 to -1) and a treatment period of 48 weeks. On Day 1 all patients who meet eligibility criteria may be randomized (randomization ratio 1:1:1:1) into:

- the placebo group
- the 18 mg/kg group

- the 36 mg/kg group
- the 54 mg/kg group

When the first eight (8), patients randomized into either placebo, 18, 36 or 54 mg/kg group respectively, have achieved ≥2 months (8 weeks) of exposure to IMP, formal review by an independent Data Safety Monitoring Board (DSMB) of all of the available safety data from the study will be performed.

The independent DSMB will meet thereafter every 4 months and review all of the available safety data.

All patients will receive double-blind IV infusions of study drug (temelimab 18 mg/kg, 36 mg/kg, 54 mg/kg or matching placebo), via monthly IV infusions for up to Week 44. All patients will be observed for 6 hours following completion of the first administration of IMP infusion and at least 2 hours following completion of the subsequent IMP infusions (second to twelfth). Intra-patient dose escalation of temelimab is not permitted.

Study population: Patients with RMS who have been treated with rituximab for at least 1 year and who meet inclusion/exclusion criteria.

Number of subjects: 40 patients with RMS will be randomized and enrolled (30 temelimab at three dose levels (18, 36 or 54 mg/kg) and 10 placebo)

Inclusion criteria:

1. The subject has given written informed consent to participate in the study
2. Current diagnosis of RMS, based on the McDonald 2017 criteria[1]
3. Having received treatment with rituximab, as per local clinical routine for at least 12 months prior to the Screening Visit
4. Having received their last dose of rituximab not more than 8 weeks and not less than 4 weeks before Randomization (Study Day 1)
5. Having B-cell count < Lower limit of detection (LLOD) (<$0.01*10^{-9}$ $CD19^{+}$ cells/ L)
6. Having expanded disability status scale (EDSS) 2.5 – 5.5 inclusive at Screening
7. 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.
8. Brain Magnetic resonance imaging (MRI), lesion burden with >9 T2 cerebral lesions (assessed within the last 24 months)
9. Stable clinical presentation of MS for 30 days prior to Screening e.g. no relapse, no acute neurological exacerbation.
10. Age range from 18 to 55 years (both inclusive)
11. Body weight between 40 – 100 kg (both ranges are inclusive)
12. No disease modifying therapies (DMTs) other than rituximab, within 12 months of Screening

13. No contraindication to Biomarker assessments: brain Magnetic resonance imaging (MRI), blood/serum collection and cerebrospinal fluid (CSF) collection
14. Agreeing to undergo two lumbar puncture
15. Be willing and able to follow all study procedures and assessments according to the study protocol
16. Female patients of childbearing potential (FPCBP) or procreative male patients (PMP), willing to use highly effective contraceptive methods throughout the study duration and at least until 5 months after the last study treatment. The investigators must inform the participant about the risks not to use an effective method of birth control during the course of the study and they should discuss with the participant the most appropriate method.
    - FPCBP means female patients who are neither menopausal (for a minimum of at least 2 years), nor underwent irreversible surgical procedures leading to permanent infertility like bilateral tubal occlusion or hysterectomy;
    - PMP means male patients who have a female partner of childbearing potential and who are not vasectomized (vasectomy to have been a minimum of 10 weeks ago) or underwent other surgical procedures leading to permanent infertility;
    - Partners of childbearing potential (PCBP) means female partners of a PMP who are neither menopausal (for a minimum of at least 2 years), nor underwent irreversible surgical procedures leading to permanent infertility like tubal ligation or hysterectomy;
    - FPCBP and PMP, as well as non-pregnant PCBP, must use an effective method of birth control, as described below, (additional local requirements may apply) throughout the study and for at least 5 months after the last dose of study treatment:
        - For FPCBP or PCBP, highly effective methods of birth control refer to those which result in a low failure rate (i.e. less than 1% per year), when used consistently and correctly, such as combined hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), some intra uterine devices (IUDs), intrauterine hormone-releasing system (IUS), true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant), or male partner sterilization (vasectomy to have been a minimum of 10 weeks ago);
        - For PMP, the barrier method of contraception, condom is considered as acceptable

Exclusion criteria:

1. Current diagnosis of primary progressive MS (PPMS)
2. Any disease other than MS (e.g. myelitis and /or bilateral optic neuritis) that could better explain the patient's signs and symptoms
3. Usage of any of the following medications prior to the Screening visit:
    a) Any usage of interferon beta, glatiramer acetate, IV immunoglobulin (IVIG), dimethyl fumarate or teriflunomide within 12 months prior to Screening,
    b) Any history of exposure to mitoxantrone, cladribine, alemtuzumab, cyclophosphamide, systemic cytotoxic therapy, total lymphoid irradiation, and/or bone marrow transplantation at any time,
    c) Any usage of natalizumab within 24 months prior to Screening,
    d) Any usage of highly potent immune modulating therapy, such as: ocrelizumab, ofatumumab, fingolimod, siponimod, ozanimod or anti-cytokine therapy, plasmapheresis or azathioprine within 12 months prior to Screening,
    e) Any usage of any experimental treatment if not washed out for ≥ 5 half-lives or ≥ 12 months (whichever is longer), except rituximab which is allowed before the study.
4. CTCAE Grade 2 or greater lymphopenia
5. Any major medical or psychiatric disorder that would affect the capacity of the patient to fulfill the requirements of the study, including:
    a) Diagnosis or history of schizophrenia
    b) Current diagnosis of moderate to severe bipolar disorder, major depressive disorder, major depressive episode, history of suicide attempt, or current suicidal ideation
    c) Current or past (within the last 2 years) alcohol or drug abuse
6. History or presence of serious or acute heart disease such as uncontrolled cardiac dysrhythmia or arrhythmia, uncontrolled angina pectoris, cardiomyopathy, or uncontrolled congestive heart failure (NYHA class 3 or 4)
7. Known inability to undergo an MRI scan
8. Contraindications to the use of glucose 5% infusion
9. Inability to follow study instructions, or complete study assessments, as defined by the protocol
10. Any history of cancer with the exceptions of basal cell carcinoma and/or carcinoma *in situ* of the cervix, and only if successfully treated by complete surgical resection, with documented clean margins and any medically unstable condition as determined by the investigator
11. Legal incapacity or limited legal capacity
12. Pregnant or breastfeeding women

13. History of, or positive serology for viral hepatitis B not explained by vaccination (see table)

Serological Hepatitis B status	HBsAg	Anti-HBc Ab	Anti-HBs Ab	eligible
• No history	-	-	-	yes
• Vaccination	-	-	+	yes
• Past (resolved) infection	-	+	+	no
• Acute infection / chronic carrier	+	+/-	-	no
• Doubtful case	-	+	-	no

14. History of, or positive serology for viral hepatitis C or human immunodeficiency virus (HIV) at any time

15. Abnormal liver function tests: AST or ALT > 2 times upper limit of normal range (ULN), or conjugated bilirubin > 2 times ULN, or AP or GGT > 3 times ULN

16. Positive pregnancy test at any time

    A FPCBP cannot be included in the study if any of the following occurs:

    - The urine dipstick pregnancy test indicates a positive result and the pregnancy has not yet been ruled out by the subsequent blood test
    - No urine dipstick pregnancy test has been performed
    - The urine dipstick pregnancy test indicates a negative result, but an early pregnancy (≤ 2 weeks from conception) is suspected by the investigator based on anamnestic or clinical elements and cannot be ruled out by further investigations

Investigational product(s), dosage, administration:

Temelimab 18 mg/kg, 36 mg/kg, 54 mg/kg or matching placebo will be given as monthly (4-weekly) intravenous (IV) infusions over 48 weeks (12 administrations in total).

Study endpoints:

Primary endpoints:

- Overall Summary of Adverse Events
- AEs by Primary SOC and PT
- SAE by Primary SOC and PT
- Physical Examination: Shift from Baseline to worst post-dose result by Body System
- ECG Interpretation: Change from Baseline to Week 48 and Summary Statistics for change from Baseline to Week 48
- Vital Signs: Summary Statistics For Change From Baseline By Follow-Up Visit

- Concomitant Medications by WHO ATC Level Class 1 and WHO ATC Level Class 2
- Hematology: Normal Range Shifts from Baseline by Follow-Up visit
- Clinical Chemistry (including C-reactive protein): Normal Range Shifts from Baseline by Follow-Up Visit -Safety Set
- Coagulation: Normal Range Shifts from Baseline by Follow-Up Visit - Safety Set
- Urinalysis: Normal Range Shifts from Baseline by Follow-Up Visit

Secondary endpoints:

- 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

Exploratory endpoints

- An "Overall Disability Response Score" (ODRS) which takes into consideration EDSS, T25FW, dominant and non-dominant 9-HPT, accounting for Worsening and Improvement on Respective Components from Baseline to Week 48
- Event of relapse, as measured by time to relapse and annual relapse rate (ARR)
- Change in Symbol Digit Modalities Test (SDMT) Score at Week 48 compared to Baseline
- Change in Quality of Life (EQ-5D) at Week 48 compared to Baseline.
- Number of new T2 lesions at Week 48
- Change in cortical thickness at week 48 compared to baseline
- Change in REMyDI myelin fraction in lesions at week 48 compared to baseline
- Change in REMyDI myelin fraction in NAWM at week 48 compared to baseline
- Change in intra-lesional axonal density at week 48 compared to baseline as measured with multi-shell diffusion
- Change in NAWM axonal density at week 48 compared to baseline as measured with multi-shell diffusion
- Change in axonal density, MTR, REMyDI myelin fraction in rim lesions (as part of slowly expanding lesions) vs non-rim lesions at week 48 compared to baseline

- Change in levels of neurofilament-light chain protein (NfL) in serum at Week 48 compared to baseline (Day 1)
- Change in levels of neurofilament-light chain protein in CSF at Week 48 compared to baseline (Day 1)
- Change in levels of proteins or gene expression related to MS or the target of temelimab (pHERV-W ENV), in blood at Week 48 compared to Baseline and in CSF at Week 46 compared to Baseline
- Change in levels of immunoglobulin (Ig) levels in blood (including Total Ig, IgG, IgM, and IgA isotypes) at Week 48 compared to baseline (Day 1)
- Pharmacokinetics (PK) in serum of repeated doses of temelimab at Weeks 4, 24, 46 and 48
- Levels of temelimab in CSF at D15 post last study drug administration (Week 46)
- Antidrug antibodies (ADA) in serum of repeated doses of temelimab at pre dose Day 1, Weeks 4, 24, 46 and 48 (or, in case of early termination, at the study discontinuation visit)

Study period: Q2 2020 (First Patient First Visit)– Q4 2021 (Last Patient Last Visit)

2. Statistics

Statistical analysis will be performed by eXYSTAT SAS. A Statistical Analysis Plan (SAP), and associated templates for Tables, Listings and Figures, will be written and signed before the database lock and study unblinding. These specifications will detail the implementation of all the planned statistical analyses in accordance with the main characteristics stated in this protocol.

2.1. Analysis population

Randomized Set (RS): All patients to whom a therapeutic treatment was randomly assigned using IRS. Patients will be analyzed in their randomization group whatever the treatment they received

Safety Set (SS): All patients having taken at least one dose of IMP. Patients will be affected to the group of treatment they received.

2.2. Statistical methods

2.2.1. General considerations

The following descriptive statistics will be provided depending on the nature of considered data:

- **Qualitative data:** number of observed values, number and percentage of patients per class;
- **Quantitative data:** number of observed values, mean and standard deviation, median, first and

third quartiles, minimum and maximum;
- **Survival data (time to event occurrence or to censoring):** total number of patients, total number and percentage of patients having an event, number of patients at risk, number of patients with censored data, number of patients with event of interest.

The type I error will be set at α = 5% two-sided.

The treatment effect (temelimab versus placebo) will be estimated as well as its precision: estimate of the difference, standard error (SE) of the estimate and two-sided 95% confidence interval (CI) of the estimate.

In case of formal comparison between treatment groups, the two-sided p-value associated with the treatment effect will also be provided.

All inferential analyses are considered as exploratory in order to have a first estimation of treatment effect. Consequently, no method to handle with multiplicity issues is needed.

2.2.2. Study patients:

Demographic data and other baseline characteristics will be described by treatment group, to assess their comparability, and overall in the RS population. The main patients' characteristics will also be described for SS population.

Disposition of patients, including reasons for withdrawal, protocol deviations, extent of exposure and treatment compliance, as well as concomitant treatments will be described in the RS population.

2.2.3. Safety analysis

Safety and tolerability of temelimab and placebo will be assessed in each treatment group in the safety population.

AE summaries will include all AEs starting on or after study day 1 (i.e. on the day of or following the day of first study treatment administration) and starting before the end of study visit, i.e. 4 weeks after the date of last study treatment administration.

A Summary of AEs (number and % of patients, number of AEs) and summarized by System Organ Class (SOC) and Preferred Term (PT) will be tabulated by treatment group and overall for patients with:

- at least one treatment-emergent adverse event (TEAE),
- at least one related treatment-emergent adverse event (TEAE),
- at least one severe treatment-emergent adverse event (TEAE),
- at least one severe related treatment-emergent adverse event (TEAE),
- at least one serious TEAE,
- at least one serious TEAE related to the study treatment,
- a TEAE leading to treatment discontinuation,
- a related TEAE leading to treatment discontinuation,
- a TEAE leading to death.

AEs will be summarized by presenting the number and percentage of patients having at least one AE and by number of AEs, overall and by treatment group. Data will be presented by SOC and PT using the latest version of MedDRA. A patient with multiple occurrences of the same PT will be counted only once in the AE category.

Separate AE summaries will be presented by SOC, PT, and severity. In the summaries presented by severity, all AEs will be pooled. Specific tables will summarize related AEs to temelimab.

Written narratives will be produced for all SAEs.

Adverse events/SAEs occurring after signing the Inform Consent Form (ICF) but before starting study treatment, including those observed in patients included but never treated with the IMP, will be listed separately from those occurring after treatment start.

Adverse events/SAEs occurring after 4 weeks after the date of last study treatment administration will be also listed separately.

Laboratory data analysis:

The summaries will include all laboratory assessments collected during the study.

All laboratory values will be converted into SI units and will have a severity grade calculated using appropriate common terminology criteria for AEs (NCI CTCAE, version 4.03). A listing of laboratory values will be provided by laboratory parameter and by patient. A separate listing will display notable laboratory abnormalities (i.e. newly occurring CTCAE Grade 3 or 4 laboratory toxicities). The frequency of these notable laboratory abnormalities will be displayed by parameter.

Shift tables using CTCAE grades to compare baseline to the worst post-baseline value will be produced for all relevant safety measures as described in the statistical analysis plan. Note that for parameters with two directions abnormalities (hypo/hyper), two tables will be presented.

The shift tables using Normal Range Shifts from Baseline will be also produced for all safety measures as described in the section 4.3.

Vital signs and physical examination

Vital signs and physical examination will be described, in terms of value at baseline, value at each post-baseline visit; as well as in terms of change from baseline to each post baseline visit. For physical Examination: Shift from Baseline to Worst Post dose Result by Body System will be provided.

Other safety data

Other safety data (e.g. 12-lead electrocardiogram, concomitant medication use) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical procedures performed in order to explore the data will be used only to highlight any comparisons that may warrant further consideration. Change from Baseline by Follow-Up Visit and Summary Statistics for Change from Baseline By Follow-Up Visit will be provided.

10.2.4 Efficacy analyses

Each secondary endpoint will be described by treatment group in the RS population.

For exploratory analyses, Frequentist and Bayesian methodologies will be used.

For the frequentist approach change from baseline at Week 48 will be analyzed using a non-parametric ANCOVA including baseline and treatment as factors.

For all analyses, estimate of treatment effect (temelimab versus placebo), its SE and 95% CI, as well as the associated p-value will be provided.

In addition, exploratory Bayesian analysis will be done using a non-informative prior on mean and standard error. The Posterior probability that the change from baseline at Week 48 is <0 will be provided for each dose and for placebo with its 95% credible interval (measure of Bayesian precision).

An alternative Bayesian version of the T-test: Bayesian Estimation Supersedes the t-test (BEST) developed by (Kruschke, 2012) will also be used[74]. The difference of the change in lesion volume between each dose and placebo and the posterior probability that Delta versus placebo is >0 will be provided . If these posterior probabilities are > 80%, temelimab could be considered as interesting for future development.

Those probabilities will also be provided for the other measurements of change.

For sensitivity analyses, the same analyses will be performed comparing pooled dose with placebo.

10.2.5 Exploratory analyses

10.2.5.1 PK interpretation

Standard PK parameters such as minimum serum concentrations (C_{min}) and, accumulation factor, will be derived. The PK parameters will be described by treatment groups to make an initial assessment of dose linearity/proportionality.

Descriptive statistics (mean, standard deviation, median, min, max, variation coefficient) will be performed on CSF and serum concentrations of temelimab and PK parameters. Data will be evaluated by standard summary statistics and additional descriptive methods including individual data listings and plots of individual and group data. Further population PK analysis is envisaged based on the collected data.

10.2.5.2 Exploratory analyses

Each exploratory endpoint will be described by treatment group in the RS population.

Same Frequentist and Bayesian methodologies will be used.

For frequentist approach change from baseline at Week 48 will be analyzed using a non-parametric ANCOVA including baseline and treatment as factors.

Time to first relapse will be analyzed by Kaplan-Meier method and the associated log-rank test.

For the number of new T2 lesions, each dose will be compared to placebo using a Negative Binomial Generalized Linear Model (NBGLM) studying treatment effect and adjusted for baseline and treatment.

2.3. Determination of sample size

The total sample size (N=40) is not based on a formal statistical assessment. This number of subjects is considered sufficient to achieve the primary safety objective of the study which will be based on a descriptive evaluation of safety data, in addition the difference dosage and placebo will allow to assess any variations in terms of severity or frequency or adverse events between the doses.

For the secondary endpoints the sample size was assessed as follows:

Results from MTR% (peri-ventricular bands) in the GNC-004 study are:

- 0.84%±4.84 in the 18 mg/kg dose (n=23)
- -3.17%±2.05 for placebo (n=26)

Simulation on SAS© Version 9.4 and on R software have been performed in order to explore the capability of the study to detect a signal of efficacy.

The table below gives the power according to several hypotheses for the 40 patients.

Table 3. Power and posterior probabilities simulations with alpha 5% two-sided

Temelimab (n=10)		Placebo (n=10)		Delta Temelimab Placebo		Power for at least one dose superior to placebo	Power for pooled doses versus placebo	Posterior P(at least one dose with delta>0)>95%	Posterior P(pooled doses with delta>0)>95%
Mean	Std	Mean	Std	Mean	Std	Non parametric Sign test		MCMC simulations	
-0.84	4.84	-3.17	2.05	2.33	5.26	52%	63%	78%	90%
-0.5	4	-3	2	2.5	4.47	67%	83%	88%	95%
0	4	-3	2	3	4.47	80%	94%	96%	>95%
1	4	-3	2	4	4.47	95%	>95%	>95%	>95%

With 10 patients per group, -3%±2 for placebo and 0%±4 for temelimab, the study has 80% power to show a statistically significant (5% two-sided) difference for at least one dose. The power is higher than 80% for the comparison of pooled dose (n=30) versus placebo.