# A High-dose Pharmacokinetic Study of a New IgG4 Monoclonal Antibody Temelimab/GNbAC1 Antagonist of an Endogenous Retroviral Protein pHERV-W Env

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## ABSTRACT

**Purpose:** Temelimab/GNbAC1 is a humanized immunoglobulin G4 monoclonal antibody antagonist of the human endogenous retrovirus W envelope protein, which is associated with multiple sclerosis (MS) pathophysiology and possibly with other autoimmune disorders. Human endogenous retrovirus W envelope protein is expressed in the central nervous system of patients with MS, and sufficient amount of temelimab must reach the target. The safety of very high dosages of temelimab should be tested to support further clinical trials in MS.

**Methods:** This randomized, placebo-controlled, dose-escalation study evaluated the safety and pharmacokinetic profile of temelimab in 24 healthy volunteers after a single intravenous infusion at doses of 36, 60, 85, and 110 mg/kg administered sequentially.

**Findings:** Temelimab was well tolerated, with no particular adverse drug reactions at any dose. The maximal dose of 110 mg/kg could be administered, and no antidrug antibodies were induced. After administration of 36−110 mg/kg, mean temelimab $C_{max}$ increased from 859 to 2450 μg/mL, and AUC values increased from 319,900 to 1,030,000 μg·h/mL. There was an approximate dose-proportional increase in exposure, similar to observations at lower doses.

**Implications:** The favorable data in terms of safety and pharmacokinetic variables support temelimab use at high doses in future MS trials to optimally neutralize the temelimab target in the central nervous system. ClinicalTrials.gov identifier: NCT03574428. (*Clin Ther*. 2019;41:1737−1746) © 2019 Published by Elsevier Inc.

**Key words:** clinical trial, GNbAC1, monoclonal antibody, pharmacokinetics, safety, temelimab.

## INTRODUCTION

It has been shown that an envelope protein of endogenous retroviral origin (pHERV-W Env) is involved in the pathophysiological process of multiple sclerosis (MS) and type 1 diabetes.[1,2] pHERV-W Env interacts with the toll-like receptor 4 receptor; this interaction in the brain stimulates the microglial cells, which produce reactive oxygen and nitrogen species as well as pro-inflammatory cytokines, leading to myelin destruction and subsequent degeneration. Furthermore, pHERV-W Env blocks the maturation process of oligodendrocyte precursor cells, necessary for remyelination.[3−5] Blocking the pHERV-W Env target could therefore be an excellent etiologic approach to protect against neurodegeneration.[6] Because pHERV-W Env also appears to be expressed in certain patients with type 1 diabetes, a similar therapeutic approach is currently being investigated in this disease.[7]

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To explore the effects of targeting pHERV-W Env in humans, the monoclonal antibody (mAb) temelimab (previously designated as GNbAC1), which selectively binds with high affinity to the extracellular domain of the pHERV-W Env, was selected for clinical development. Temelimab is a recombinant humanized mAb of the immunoglobulin G4 (IgG4)/kappa isotype, the development of which has been reviewed elsewhere.[1] Recently, a clinical trial involving 270 patients with relapsing-remitting MS found that the brain atrophy rate could be decreased with temelimab in a dose-dependent manner and that the relative volume reduction was decreased from 29% for the whole brain to 72% for the thalamus compared with the control group.[8] These findings were supported by the observation of a decrease in the number of new hypointense T1 lesions, as well as by the preservation of the magnetic transfer ratio in the group receiving the 18-mg/kg temelimab dose, a series of observations that strongly support a neuroprotective effect of temelimab in patients with MS. These data suggest that, in MS, temelimab 18 mg/kg may be a minimally effective dose for neuroprotection, and it is possible that higher temelimab dosages may induce therapeutic effects of higher magnitude. This conclusion is notably based on the observation that only a relatively low percentage of the temelimab serum concentration is found in the cerebrospinal fluid (CSF) of healthy volunteers as well as in the CSF of patients receiving temelimab, varying between 0.1% and 0.4%.[8–10] Furthermore, temelimab at a high dose (up to 36 mg/kg) and during repeated administrations is very well tolerated without inducing any specific adverse events.[8–11] Therefore, to ensure optimal cerebral target access and to maximize the benefit–risk of the product, the investigation of dosages of temelimab >18 mg/kg monthly was planned during the confirmatory phase of temelimab clinical development in MS.

Following the first two Phase I clinical trials,[9,11] the goals of the current new double-blind, placebo-controlled dose escalation pharmacokinetic (PK) study were therefore to assess the safety and tolerability profile of single high doses of temelimab in healthy subjects up to 110 mg/kg IV with a higher infusion rate as well as to confirm the PK parameters observed at lower doses, particularly dose linearity. The highest dose that has been tested in patients with MS in a Phase IIb study was 18 mg/kg given intravenously once a month with the first evidence of effect on surrogate markers of neurodegeneration.[8] Monthly doses up to 60 mg/kg IV are envisaged in a future MS dose-finding clinical trial. Indeed, based on this first evidence of efficacy, the indirect estimates of the target load in the central nervous system (CNS) and the report of a CSF/plasma concentration ratio of temelimab of 0.2% in patients with MS (not increased compared with that observed in healthy subjects),[11] these observations suggest that up to a 3 time increase in dosage should be tested in patients with MS. Because the accumulation ratio is ~1.7 calculated after monthly administration with an estimated average $t_{½}$ of 28 days, and because a linear PK profile is assumed for temelimab, it was necessary to assess the tolerance and the PK variables of doses up to 110 mg/kg of temelimab after single intravenous administration to cover the doses envisaged in future MS trials. We present here the results of this study.

## SUBJECTS AND METHODS

### Trial Design

This Phase I, double-blind, placebo-controlled, parallel-group, dose-escalating randomized study was designed to assess and compare the safety and tolerability, PK profile, and immunogenicity of temelimab administered as a single dose at 4 different dose levels (36, 60, 85, and 110 mg/kg). The study was double-blind to avoid bias in the collection and evaluation of data during its conduct.

After a screening period of up to 21 days, a minimum of 24 healthy male volunteers were to receive temelimab or placebo across 4 cohorts. Each cohort consisted of 6 subjects receiving temelimab or placebo in a 2:1 ratio. Subjects underwent dosing during a 2-day confinement period at the study center. After discharge from the study center, there was a further 55-day follow-up period requiring a total of 4 ambulatory visits to site occurring on days 8 (±1 day), 15 (±1 day), 29 (±3 days), and 57 (±3 days) postinfusion.

Dosing was to be staggered within each cohort, with a minimum of 24 h between sentinel dosing of 2 subjects and each successive group of 2 subjects within each cohort. There was a minimum 3-day period between the last infusion in cohort 1 and the first infusion in cohort 2, and a minimum of 28 days

between the last infusion in cohorts 2 and 3 and the first infusion in cohorts 3 and 4, respectively. Intrapatient dose escalation was not permitted. Dose escalation between cohorts was determined by a Safety Review Committee after assessment of safety data (all cohorts) and review of PK data for $C_{max}$ and AUC from time zero to day 28 (extrapolated from AUC from time zero to day 15) to assess PK linearity (cohorts 3 and 4).

### Inclusion and Exclusion Criteria

Subjects were eligible if they met the following criteria: (1) healthy male volunteers as determined by medical history, physical examination, vital signs, ECG, and laboratory test results at screening, and confirmed at baseline, who have signed the informed consent form; (2) age between 18 and 55 years inclusive; (3) negative urine drug screen for psychotropic drugs or drugs of abuse (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiates, phencyclidine, tetrahydrocannabinol, and tricyclic antidepressants); (4) venous access suitable for blood sampling; (5) systolic blood pressure $\geq$100 and $\leq$ 150 mm Hg and diastolic blood pressure $\geq$50 and $\leq$ 95 mm Hg, and pulse rate $\geq$45 and $\leq$ 100 beats/min (blood pressure and pulse were measured after 3 min of rest in a sitting or lying down position); (6) body mass index $\geq$18.0 and $\leq$ 30.0 kg/m$^2$ and body weight $\geq$50 and $\leq$ 100 kg, both inclusive; (7) adequate contraception with the use of condoms during the entire period of the study and for a minimum of 5 months after investigational product administration; and (8) ability to communicate well with the investigator and be willing to comply with all study assessments and adhere to the protocol schedule throughout the study.

### Study Drug

Temelimab is a recombinant DNA-derived humanized mAb that selectively binds with high affinity to the extracellular domain of pHERV-W Env. Temelimab is a full-length antibody of the IgG4/kappa subclass with a molecular weight of ~147,000 Da. The antibody was humanized via an in silico design based on the amino acid sequence of a murine antibody that binds to pHERV-W Env. As an IgG4, it does not activate antibody-dependent cell-mediated cytotoxicity nor complement-dependent cytotoxicity; to stabilize the interchain disulfide bridges of the IgG4 molecule, its hinge region has been modified.[1] Temelimab is produced by fermentation in a Chinese hamster ovary cells suspension culture, using a qualified master cell bank. The placebo used in the study was the vehicle of the temelimab drug product.

Temelimab/placebo was administered as a single dose by intravenous infusion at an infusion speed of 18 mg/kg per hour for the sentinel group receiving 36 mg/kg (2 h) and at an infusion speed of 36 mg/kg for the remaining 4 subjects dosed at 36 mg/kg (1 h) and those dosed at 60 mg/kg (1 h and 40 min), 85 mg/kg (2 h and 22 min), and 110 mg/kg (3 h and 3 min) within respective infusion volumes of 200, 333, 472, and 611 mL. Temelimab/placebo was diluted into an infusion bag containing 5% glucose solution. Study drug was administered via an intravenous infusion because this is the intended clinical route of administration of temelimab. The prepared solution for infusion was stored at room temperature and used within 4−9 h after dose preparation.

### Laboratory Evaluations and Monitoring

Blood and urine samples were collected for clinical laboratory evaluations at specific times during the study and when judged to be clinically appropriate. High-sensitivity C-reactive protein vital signs (sitting/lying down blood pressure and pulse, respiratory rate, and body temperature) were determined. Twelve-lead triplicate ECG recordings were taken at screening and on days −1, 1, 2, 29 (±3 days), and 57 (±3 days) or at discontinuation. Continuous ECG monitoring was performed during infusion and up to 4 h after the end of the infusion.

Blood samples for temelimab PK parameters were taken on day 1 up to 60 min' preinfusion; at 5 min before the end of infusion; and at 2, 4, and 6 h (±10 min) after the infusion end. On day 2 at 24 h' (±10 min) postinfusion start, PK blood samples were also drawn. PK samples were also taken at the ambulatory visits on days 8 (±1 day), 15 (±1 day), 29 (±3 days), and 57 (±3 days) or at the discontinuation visit.

### PK Assessments

PK parameters were determined from the serum concentrations of temelimab by using

noncompartmental analysis. The following PK parameters were determined: (1) $AUC_{0-last}$, calculated by using linear-trapezoidal integration; (2) $AUC_{0-\infty}$, calculated as $AUC_{0-last} + C_{last}/\lambda_z$, where $C_{last}$ is the last quantifiable concentration and $\lambda_z$ is the terminal phase elimination rate constant; (3) $C_{max}$; (4) $T_{max}$; (5) the terminal elimination $t_{½}$ calculated as $Ln(2)/\lambda_z$; (6) the mean residence time (MRT), calculated as the area under the first moment curve from time 0 extrapolated to infinity divided by $AUC_{0-\infty}$; (7) the total body clearance (CL) calculated as dose/$AUC_{0-\infty}$; (8) the volume of distribution based on the terminal phase calculated as dose/($\lambda_z \times AUC_{0-\infty}$); and (9) the volume of distribution at steady state, calculated as MRT × CL. The analysis of temelimab was grounded on a competitive electrochemiluminescence (ECL)-based immunoassay using an anti-idiotypic mAb (Mab1E4F7H6) against temelimab as capture antibody.[12]

### Immunogenicity

Blood samples to measure human anti-temelimab antibodies were taken at day −1 and at day 57 (±3 days) to determine the immunogenic potential of temelimab. The screening for binding antibodies against temelimab was performed by using ECL with a bridging format. Temelimab was labeled with biotin and with Sulfo-Tag (Meso Scale Diagnostics, LLC, Rockville, Maryland), respectively. Both labeled preparations bind to anti-temelimab antibodies. This complex was immobilized on streptavidin-coated ECL-specific microtiter plates and was detected by using the ECL technique via the Sulfo-Tag (Ru) label. This approach is based on the bridging format, enables the detection of all isotypes, and is species independent. Affinity-purified monoclonal anti-idiotypic temelimab antibodies served as controls.[12] Positive samples were quasi-quantified by repeated analysis in dilution.

### Sample Size and Statistics

Sample size considerations for this study were based on the usual sample size for safety assessment in Phase I studies. Designs ranging from 4 subjects on active drug and 2 subjects on placebo per dose level to 6 subjects on active drug and 3 subjects on placebo per dose level are usually implemented.

The general analytical approach for all end points was descriptive in nature. All summaries present the data according to treatment group. Summary statistics are presented for the PK data by using arithmetic means and %CV. The noncompartmental analysis was performed by using the validated R package, maNCA. The package and associated code were written in R version 3.2 or higher. Data management, computation of summary statistics, and graphical analyses were performed by using R version 3.2 or higher (R Development Core team, 2018).

### Ethics Approval

Before initiation of the study, the protocol, the patient informed consent form, and other relevant study documentation were approved in writing by the Bellberry Human Research Ethics Committee (Eastwood, South Australia). Amendments to the protocol and other relevant study documents were reviewed and approved in the same manner before being implemented. This study was conducted according to the Declaration of Helsinki, the Notes for Guidance on Good Clinical Practice (2000) (CPMP/ICH/135/95), and the Principles of the International Conference on Harmonisation Good Clinical Practice (R2) (as adopted in Australia) and the National Statement on Ethical Conduct in Human Research (2007 [updated in May 2016]). All subjects enrolled in this study had signed the informed consent form before any study procedures were performed.

## RESULTS

### Study Population

Twenty-four subjects entered the study in accordance with the protocol and the treatment randomization (temelimab, n = 16; placebo, n = 8) (Figure 1); all subjects completed the study as per protocol. The 4 dose levels of temelimab (36, 60, 85, and 110 mg/kg IV) were studied as planned, and the maximal dose of 110 mg/kg was reached.

Seventeen subjects were white, 6 were Asian, and 1 was classified as other; they were aged between 18 and 36 years, both inclusive; the mean (SD) age was 24.5 (5.0) years, the mean height was 176 (7.0) cm, and the mean weight at screening was 73.5 (10.7) kg. Table I summarizes the demographic data according to treatment groups. The mean age and body mass index were relatively similar for subjects across all treatment groups. All subjects satisfied the inclusion

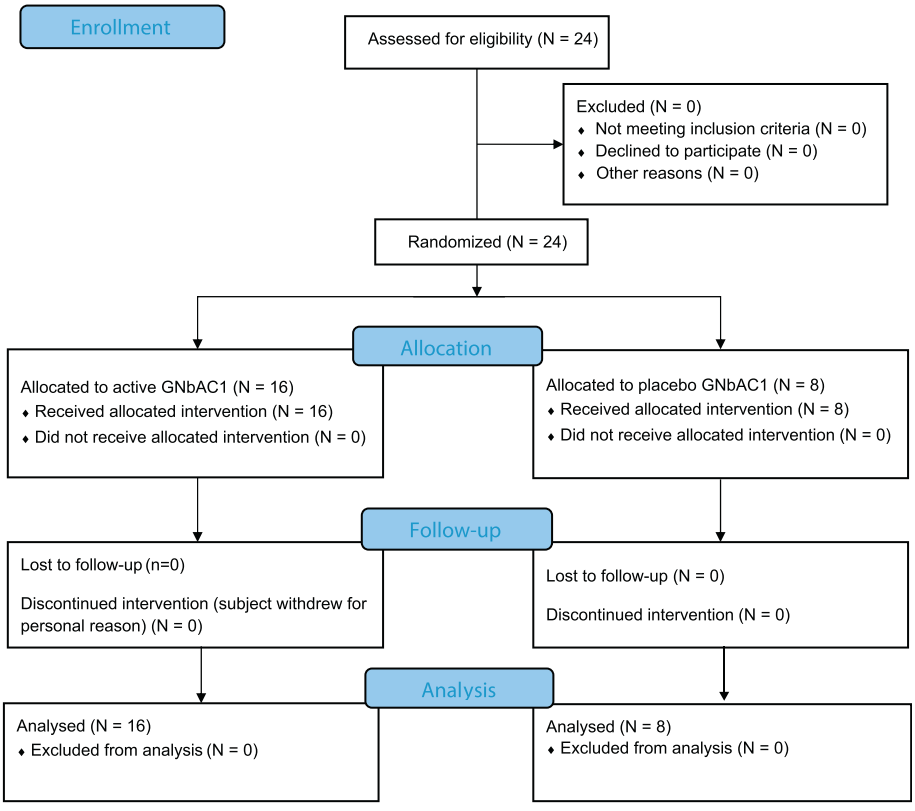


Figure 1. Study flow diagram according to CONSORT recommendations.

Table I. Summary of screening demographic data according to dose groups. Values are given as arithmetic mean (SD).

| Characteristic | Placebo (n = 8) | Temelimab | | | |
|---|---|---|---|---|---|
| | | 36 mg/kg (n = 4) | 60 mg/kg (n = 4) | 85 mg/kg (n = 4) | 110 mg/kg (n = 4) |
| Age, y | 23.8 (4.2) | 26.3 (4.5) | 25.0 (6.6) | 25.3 (8.1) | 22.8 (3.0) |
| Height, cm | 175.4 (7.2) | 176.5 (3.0) | 179.3 (6.2) | 174.8 (12.4) | 174.3 (5.9) |
| Weight, kg | 76.0 (13.6) | 76.8 (10.7) | 76.2 (4.6) | 70.2 (10.6) | 65.6 (7.7) |
| Body mass index, kg/m$^2$ | 24.6 (3.2) | 24.7 (4.0) | 23.8 (2.9) | 22.9 (1.5) | 21.6 (2.6) |

criteria before entry into the study. There were no findings of clinical concern in the medical history for any subjects. In addition, there were no baseline signs and symptoms of clinical concern before dosing for any subjects. The results of the urinary screening for drugs of abuse, of alcohol detection in breath, and of serologic tests at screening indicated that all subjects were suitable for inclusion in the study.

## Safety and Tolerability

Twenty-four subjects received a single infusion of temelimab or placebo (Figure 1). Single doses of

temelimab were well tolerated when administered at dose levels of 36, 60, 85, or 110 mg/kg. Treatment-emergent adverse events are summarized in Table II. All adverse events were mild or moderate in severity. No serious adverse events were reported, and no subjects were withdrawn as a result of adverse events. Overall, 24 treatment-emergent adverse events were reported by 12 subjects. Six adverse events were reported by 4 subjects who had received placebo. The most commonly reported adverse events belonged to the system organ classes "respiratory, thoracic, and mediastinal disorders" and "nervous system disorders." Two adverse events (lymphadenopathy and headache) in 2 of the subjects receiving temelimab 85 mg/kg were considered to have a possible relation to study drug. No infusion site reactions were observed in the study. No particular modifications were observed in any treatment group concerning blood or chemistry parameters, notably high-sensitivity C-reactive protein. No changes in vital signs or ECG data apparently related to the study drug were observed.

### PK Profile

The mean serum concentration time curves are presented in Figure 2. Temelimab exhibited a biphasic elimination profile with quantifiable concentrations observed for all subjects up to day 57.

Table II. Adverse events according to dose groups (number of subjects with an adverse event) indicated by preferred term.

| System Organ Class Preferred Term | Placebo (n = 8) | Temelimab | | | |
|---|---|---|---|---|---|
| | | 36 mg/kg (n = 4) | 60 mg/kg (n = 4) | 85 mg/kg (n = 4) | 110 mg/kg (n = 4) |
| Blood and lymphatic system disorders | 0 | 0 | 0 | 1 | 0 |
| Lymphadenopathy | 0 | 0 | 0 | 1 | 0 |
| Ear and labyrinth disorders | 0 | 0 | 1 | 0 | 0 |
| Ear pain | 0 | 0 | 1 | 0 | 0 |
| Infections and infestations | 1 | 0 | 1 | 1 | 1 |
| Upper respiratory tract infection | 1 | 0 | 1 | 1 | 1 |
| Injury, poisoning, and procedural complications | 0 | 0 | 2 | 0 | 0 |
| Limb injury | 0 | 0 | 1 | 0 | 0 |
| Posttraumatic pain | 0 | 0 | 1 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | 0 | 0 | 1 | 0 | 0 |
| Neck pain | 0 | 0 | 1 | 0 | 0 |
| Nervous system disorders | 1 | 0 | 1 | 2 | 0 |
| Dizziness | 0 | 0 | 0 | 1 | 0 |
| Headache | 1 | 0 | 1 | 2 | 0 |
| Respiratory, thoracic, and mediastinal disorders | 2 | 0 | 0 | 1 | 2 |
| Cough | 0 | 0 | 0 | 1 | 0 |
| Oropharyngeal pain | 1 | 0 | 0 | 0 | 1 |
| Rhinorrhoea | 0 | 0 | 0 | 0 | 1 |
| Sinus congestion | 0 | 0 | 0 | 0 | 1 |
| Throat irritation | 1 | 0 | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | 1 | 0 | 0 | 0 | 0 |
| Rash, pruritic | 1 | 0 | 0 | 0 | 0 |
| Skin irritation | 1 | 0 | 0 | 0 | 0 |

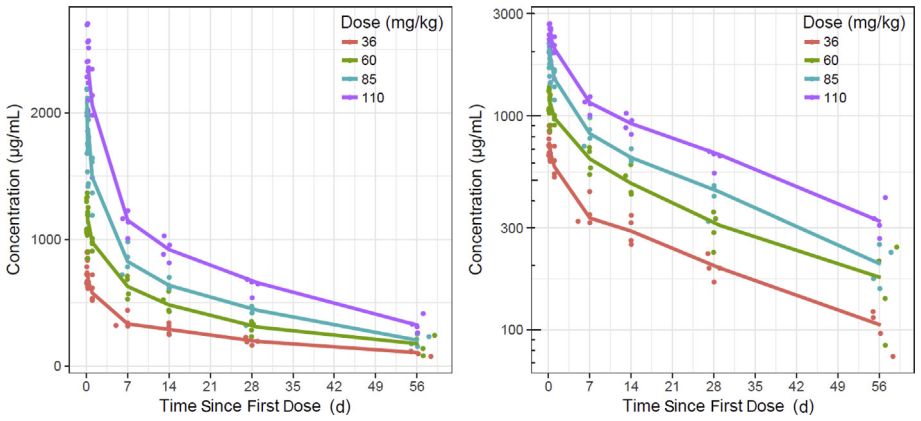


Figure 2. Temelimab median serum pharmacokinetic profiles according to dose group.

Variability in the PK profiles between subjects was low to moderate (Table III). Temelimab peak concentrations were observed at a median time of ~2–6 h. After administration of 36–110 mg/kg, mean (SD) temelimab $C_{max}$ increased from 859 (150) µg/mL to 2450 (300) µg/mL, whereas $AUC_{0-last}$ values increased from 319,900 (38,420) µg · h/mL to 1,030,000 (96,630) µg · h/mL. The mean clearance was estimated between 0.0059 and 0.0077 L/h, with a mean estimated MRT between 29 and 37 days (698 h and 899 h, respectively). The mean elimination $t_{½}$ was 22–28 days (536–672 h) with a low volume of distribution estimated in the range of 5.3–6.4 L comparable to the volume of distribution at steady state (estimates ranged between 4.9 and 5.7 L). The variability in the PK parameters between dosing cohorts was generally low (%CV <22%).

Dose-normalized exposure metrics $C_{max}$ and $AUC_{0-\infty}$ for temelimab according to dose are also presented in Table III. The dose-normalized exposure metrics $C_{max}$ and $AUC_{0-\infty}$ (divided by dose) were generally comparable across the dose range, with 95% CIs of means computed for $C_{max}$ and $AUC_{0-last}$ overlapping clearly across the different dosages. These results support an approximate dose-proportional increase in exposure.

### Immunogenicity

There was no evidence of antibody production against temelimab throughout the entire study period. Two subjects were positive at baseline, but the antibody titers became negative during treatment. The data indicate that single ascending intravenous infusions of temelimab did not induce an antibody response in healthy subjects.

## DISCUSSION

We report here the results of a PK study testing very high doses of the IgG4 mAb temelimab, the first mAb targeting an endogenous retroviral protein, pHERV-W Env, which is associated with MS and type 1 diabetes. Motivated by the need to increase the dose of temelimab in the CNS, the expected site of expression of the target in MS,[5] this analysis is the third Phase I study with this mAb. In this study, which tested single intravenous doses of temelimab up to 110 mg/kg in a single administration with high-speed infusion, the safety profile of temelimab remained favorable, as previously reported with lower doses.[9,10] The adverse events were essentially related to minor upper respiratory tract disorders and headache. There was no evidence of any specific events (including no infusion reactions or hypersensitivity) or any increase in frequency or severity of adverse events even at very high doses of temelimab. Based on the data, one can conclude that a single intravenous administration of temelimab is well tolerated and safe in healthy subjects up to a dose of 110 mg/kg. This favorable safety profile, even at a very high dose, is probably associated with the high specificity of temelimab to a target with unknown physiological function. No antidrug antibodies were observed during treatment, which is

Table III. Arithmetic mean (%CV) of the pharmacokinetic parameters of temelimab according to doses after a single infusion with dose-normalized values for $C_{max}$ and AUC.

| Parameter | Temelimab | | | |
|---|---|---|---|---|
| | 36 mg/kg (n = 4) | 60 mg/kg (n = 4) | 85 mg/kg (n = 4) | 110 mg/kg (n = 4) |
| $AUC_{0-last}$, μg·h/mL | 319,900 (12.0) | 533,200 (15.2) | 713,000 (14.1) | 1,030,000 (9.4) |
| $AUC_{0-\infty}$, μg·h/mL | 348,000 (–) | 500,000 (–) | 769,500 (12.2) | 1,190,000 (–) |
| $AUMC_{0-\infty}$, μg·$h^2$/mL | 280,300,000 (–) | 281,800,000 (–) | 536,400,000 (9.4) | 929,000,000 (–) |
| $C_{max}$, μg/mL | 859 (17.5) | 1273 (11.3) | 2022 (11.8) | 2450 (12.3) |
| $T_{max}$, h* | 2.53 (0.93–4.98) | 2.64 (1.58–3.68) | 2.58 (2.52–4.60) | 6.35 (5.32–9.37) |
| $\lambda_z$, $h^{-1}$ | 0.001 (9.3) | 0.001 (18.5) | 0.001 (2.2) | 0.001 (8.0) |
| $t_{½}$, d | 28.0 (0.4) | 22.3 (0.7) | 22.6 (0.1) | 26.8 (0.3) |
| MRT, d | 37.4 (0.4) | 31.0 (0.9) | 29.1 (0.1) | 35.7 (0.4) |
| CL, L/h | 0.0067 (19.3) | 0.0077 (21.4) | 0.0068 (0.69) | 0.0059 (8.7) |
| $V_z$, L | 6.42 (13.8) | 5.80 (11.3) | 5.31 (1.3) | 5.46 (2.4) |
| $V_{ss}$, L | 5.95 (13.6) | 5.74 (8.3) | 5.37 (14.3) | 4.91 (5.8) |
| Dose-normalized $AUC_{0-last}$, μg·h/mL† | 8886 (1045)† | 8887 (1319)† | 8388 (1158)† | 9364 (860)† |
| Dose-normalized $AUC_{0-\infty}$, μg·h/mL | 9667 | 8333 | 9053 | 10,818 |
| Dose-normalized $C_{max}$, μg/mL† | 23.9 (4.1)† | 21.2 (2.4)† | 23.8 (2.8)† | 22.3 (2.7)† |

$AUMC_{0-\infty}$ = area under the first moment curve from time 0 extrapolated to infinity; CL = total body clearance; MRT = mean residence time; $V_{ss}$ = volume of distribution at steady state; $V_z$ = volume of distribution based on the terminal phase.

* Median (minimum–maximum).

† Mean normalized for dose (95% CI).

supported by the current absence of immunogenicity observed thus far in other clinical trials.[8–11]

The amount of temelimab used in the current study is among the highest dosages of mAb administered in clinical trials. Other examples of very-high-dose administration can be found with opicinumab, an IgG1 mAb for the treatment of MS administered up to doses of 100 mg/kg in single and multiple ascending dose studies[13]; PRX002, an IgG1 mAb antagonist of the alpha-synuclein in Parkinson disease tested in multiple ascending doses up to 60 mg/kg[14]; or in infectiology with MHAA4549A, an IgG1 mAb-neutralizing influenza A hemagglutinin tested in single ascending dose studies up to 10,800 mg equivalent to doses in the range of 150 mg/kg.[15] The results of these studies indicate a generally good tolerance of these mAbs even when administered at a very high dose, with the exception of rare hypersensitivity reactions; the current temelimab results are in line with these observations, less the occurrence of hypersensitivity.

The observed PK profile of temelimab is similar to previous observations after single- or repeated-dose administrations of the mAb. Mean $t_{1/2}$ values ranged from 22 to 28 days, which are similar to what had been observed after single administration at a lower dose.[9,11] Mean clearance by dose ranged from 0.0059 to 0.0077 L/h or 1.9–2.5 mL/d per kilogram when normalized for the average weight of the study subjects: these results are similar to the ones obtained at doses of 6–36 mg/kg.[9] The observed arithmetic mean volume of distribution according to dose ranged from 5.3 to 6.4 L/kg, similar to the volume of distribution previously observed and corresponding to the relatively small volume of distribution known with other mAbs.[16] Following what had already been observed at lower doses,[9,11] the exposure to temelimab increased approximately in a dose-proportional fashion. Taking into account the available small sample size, one can conclude that there is a dose proportionality of temelimab PK values in healthy subjects at high doses, as observed at lower doses. Although the target is not expressed in healthy subjects,[1] its expression in patients with MS at the level of the CNS, behind the blood–brain barrier, does not seem to significantly modify temelimab PK parameters, notably the dose propotionality[10,17].

The infusion speed of the mAb after dosing of the sentinel subjects was 36 mg/kg per hour (ie, 200 mL/h). This finding represents a high load of immunoglobulins but remains below the amount of immunoglobulins that are administered with intravenous immunoglobulin cocktails used for certain autoimmune disorders or immunoglobulin deficiencies for which infusion recommendations are between 60 and 120 mg/kg per hour and that can even reach 840 mg/kg per hour.[18] Despite this high quantity, no infusion reaction or hypersensitivity with temelimab was observed during the trial. This finding is important for the practicality of future clinical trials.

## CONCLUSIONS

Single doses of temelimab were well tolerated by the healthy male study subjects up to a dosage of 110 mg/kg IV. The dose-proportional PK profile in the tested dose range was in line with the PK data obtained at lower dosages. Recent trial results show that temelimab at a dose of 18 mg/kg had a positive effect on surrogate markers of neurodegeneration[8] and suggest that higher dosages may be even more beneficial to patients, although target engagement studies are not yet available in patients. The positive observations of this trial are essential for the future development of temelimab, and they introduce the possibility of high-dose temelimab administration in MS studies to bind optimally to the intra-CNS pHERV-W Env target expressed in MS.

## CONFLICTS OF INTEREST

Dr. Porchet, Mrs. Vidal, Dr. Kornmann, and Dr. Curtin are employees of GeNeuro SA; Mrs. Malpass was an employee of Southern Star Research Plc. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

The sponsor and its employees (ie, the authors) were responsible for the design of the study; the collection, analysis, and interpretation of the data; writing the report; and submitting the report.

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The authors contributed in the following manner: Dr. Porchet, conceptualization, methodology, and review; Mrs. Vidal, project administration, supervision, and review; Dr. Kornmann, project administration and review; Mrs. Malpass,

investigation, project administration, and review; and Dr. Curtin, conceptualization, methodology, review, and writing.

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