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Author

Curtin, Francois, Champion, Bernard, Davoren, Peter, Duke, Sally, Ekinci, Elif, Gilfillan, Chris, Morbey, Claire, Nathow, Thomas, O'Moore-Sullivan, Trisha, O'Neal, David, Roberts, Adam, Stranks, Stephen, Stuckey, Bronwyn, Vora, Parind, Malpass, Sam, Lloyd, David, Maestracci-Beard, Nicole, Buffet, Benedicte, Kornmann, Gabrielle, Bernard, Corinne, Porchet, Herve, Simpson, Richard

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Curtin Francois (Orcid ID: 0000-0002-4570-1850)
Bernard Corinne (Orcid ID: 0000-0001-9436-1912)

A Safety and Pharmacodynamics Study of Temelimab, an anti-HERV-W-Env Monoclonal Antibody, in Type 1 Diabetes Patients

Francois Curtin MD[1,2,+], Bernard Champion MD[3], Peter Davoren MD[4], Sally Duke MD[5], Elif I Ekinci MD[6], Chris Gilfillan MBBS PhD[7], Claire Morbey MD[8], Thomas Nathow MD[9], Trisha O'Moore-Sullivan MD[10], David O'Neal MD[11], Adam Roberts MD[12], Stephen Stranks MD[13], Bronwyn Stuckey MD[14], Parind Vora MD[15], Sam Malpass MSc[16], David Lloyd PhD[16], Nicole Maëstracci-Beard PhD[1], Bénédicte Buffet PhD[1], Gabrielle Kornmann PharmD PhD[1], Corinne Bernard PhD[1], Hervé Porchet MD[1,17], Richard Simpson DM[7]

Affiliation

1 GeNeuro SA, chemin Pré-Fleuri 3, CH 1228 Plan-les-Ouates/Geneva, Switzerland
2 Division of Clinical Pharmacology and Toxicology, Rue Perret-Gentil, University of Geneva, Geneva, Switzerland
3 Macquarie University, Faculty of Medicine and Health Sciences, Suite 407, Level 4, Department of Clinical Medicine, F10A Building, 2 Technology Place, Macquarie University NSW 2109, Australia
4 Gold Coats Hospital, Diabetes and Endocrinology, 1 Hospital Blvd, Southport QLD 4215, Australia
5 Royal North Shore Hospital, Department of Diabetes, Endocrinology and Metabolism, Level 3, Acute Services Building, St Leonards NSW 2065, Australia
6 Department of Medicine, Austin Health and The University of Melbourne, Level 1 Centaur Building, 300 Waterdale Rd, Heidelberg Heights VIC 3081, Australia
7 Eastern Clinical Research Unit, Eastern Health and Monash University Level 2, 5 Arnold St, Box Hill VIC 3128, Australia
8 AIM Centre, Level 1, 41 Llewellyn Street, Merewether NSW 2291, Australia
9 Ipswich Research Institute, Suite 5D, 10 Churchill St, Ipswich QLD 4305, Australia
10 Mater Hospital, Level 6, Duncombe Building, Raymond Terrace, South Brisbane QLD 4101, Australia
11 St. Vincent's Hospital, Department of Medicine, 4th Floor, Clinical Sciences Building, 29 Regent Street, Fitzroy VIC 3065, Australia
12 Barwon Health, Department of Endocrinology, Myers House, PO Box 281, Geelong VIC 3220, Australia
13 Southern Adelaide Diabetes & Endocrine Services, Flinders Medical Centre Bedford Park SA 5042, Australia
14 Keogh Institute for Medical Research, 1st Floor C Block, Queen Elizabeth II Medical Centre, Hospital Avenue, Nedlands WA 6009, Australia
15 Lyell McEwin Hospital, Division of Medicine, Haydown Road, Elizabeth Vale SA 5112, Australia
16 Southern Star Research Pty Ltd, Gordon NSW 2072 Australia
17 Department of Pharmacology; University of Pretoria; Pretoria, South Africa

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[+] Corresponding authors: François Curtin, MD, Address: GeNeuro SA, 3, chemin Pré-Fleuri, CH-1228 Plan-les-Ouates, Geneva, Switzerland; email address: fc@geneuro.com

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ABSTRACT (words 251)

Aims

Type 1 diabetes (T1D) is characterized by a loss of β-cell function resulting in insulin deficiency. The pathogenic human endogenous retrovirus type W envelope (pHERV-W-Env) protein is associated with T1D and may play a role in the loss of β-cells. Temelimab is a monoclonal antibody neutralizing pHERV-W-Env and we report its first study in T1D patients.

Material and Methods

This double blind placebo-controlled randomized clinical trial recruited adult T1D patients within 4 years post-diagnosis and remaining C-peptide secretion. Sixty four patients were randomized (2:1) to monthly temelimab 6 mg/kg or placebo during 24 weeks followed by a 24-week open-label extension during which all patients received temelimab. The primary objective was the safety and tolerability of temelimab. The secondary objective was to assess pharmacodynamics (PD) response such as C-peptide levels, insulin use, glycated hemoglobin (HbA1c), hypoglycemia and auto-antibodies.

Results

Temelimab was well tolerated without any group difference in the frequency or severity of adverse events. Concerning exploratory endpoints, there was no difference in the levels of C-peptide, insulin use or HbA1c between treatment groups at Weeks 24 and 48. The frequency of hypoglycemia events was reduced with temelimab ($p=0.0004$) at Week 24 and the level of anti-insulin antibodies was lower with temelimab ($p<0.01$), the other auto-antibodies did not differ between groups.

Conclusions

Temelimab appeared safe in T1D patients. Pharmacodynamics signals (hypoglycemia and anti-insulin antibodies) under temelimab were observed. Markers of β-cell functions were not modified by treatment. These results need to be further explored in younger T1D patients with earlier disease onset.

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INTRODUCTION

Type 1 diabetes (T1D) is characterized by a progressive loss of β-cell function resulting in absolute insulin deficiency in most cases, due to an autoimmune destruction of these cells in the pancreatic islets of Langerhans. Despite recent advances in technology, including closed loop systems, normal glycemic control has not been achieved in T1D patients. Furthermore, despite drug development efforts focusing on immunosuppression and immunomodulation to preserve the β-cells from immune-mediated destruction,[1] there are currently no approved disease modifying treatments for T1D.[2]

There is a large heterogeneity of immunopathogenic and cytotoxic mechanisms involved in T1D, reflected by varying levels of functional β-cell reserve, different types of auto-antibodies or of immune pancreatic infiltrations,[3] which makes the development of disease modifying treatments particularly challenging. The pathogenesis of T1D has an autoimmune component involving innate immunity, notably the activation of Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4) systems,[4] and dysregulated humoral and cellular adaptive immune responses.

Among possible factors associated with T1D, the role of human endogenous retroviruses (HERV) has been suggested.[5] HERV are part of mobile genetic elements and are composed of different genes and originate from exogenous retrovirus sequences that have been incorporated into germ-line cells deoxyribonucleic acid (DNA), and represent about 8% of the human genome. Among HERV families, several have been potentially implicated in the development of human autoimmune diseases.[6] The pathogenic HERV type W envelope (pHERV-W Env) protein has been found in the blood of 60% of patients with T1D and appears to be expressed in the pancreas of 75% of patients who died from T1D.[5] pHERV-W Env displays pro-inflammatory properties mediated through TLR4 activation[7] and is cytotoxic to β islet cells, which express TLR4 receptor. In a transgenic mouse model expressing pHERV-W Env, a dysregulation of glucose metabolism accompanied by insulitis was observed.[5] Interestingly, a possible link of endogenous retroviral activation, but with

other strains than HERV-W, has also been recently proposed to be involved in the pathogenic mechanism of non-obese diabetic (NOD) mice.[8]

Temelimab, previously known as GNbAC1, is a humanized immunoglobulin (Ig) G4 monoclonal antibody which targets pHERV-W Env.[9] Temelimab administration has been shown to reverse pHERV-W Env induced inhibition of insulin secretion *in vitro* on primary human Langherhans islets.[5,10] Therefore, the neutralization of pHERV-W Env by Temelimab may be efficient in T1D in patients with remaining insulin secretion capacity by preserving β islet cell function without impairing the immune system. Temelimab has been tested in six previous clinical trials in healthy volunteers and multiple sclerosis (MS) patients, showing a favorable safety profile of temelimab and promising signs of neuroprotection in MS patients.[11]

The current study (GNC-301 or RAINBOW T1D) was a multicenter, randomized, double-blind, placebo controlled trial of temelimab administered 4-weekly for 24 weeks, followed by an open-label treatment of temelimab for additional 24 weeks. The primary objective of this study was the assessment of the safety and tolerability of temelimab in adult T1D patient with detectable c-peptide in serum[12] and secondary objectives were the exploration of pharmacodynamics (PD) response to temelimab.

MATERIAL AND METHODS

Design

This was a double-blind, placebo-controlled randomized study, which was performed in male and female adult subjects with onset of T1D within the last 4 years and detectable C-peptide serum levels. After a screening period of up to 28 days (Days -28 to 0), subjects were randomized into two treatment groups, receiving 6 consecutive double-blind administrations of temelimab 6 mg/kg or placebo at 4-week intervals for 24 weeks. Drug administration at Day 1, Day 29, Day 57, Day 85, Day 113 and Day 141 was done on an

outpatient basis as an hour-long infusion. Study assessments were performed during these visits. Subjects were required to stay in the clinic for 1 hour after the end of infusion for observation. At the end of the double-blind period, subjects were offered to continue in an open-label extension phase where all subjects received temelimab 6 mg/kg at 4-week intervals for an additional 24-week period with a follow up visit 4 weeks after the last infusion and a follow-up phone call performed 5 months after the last treatment to check for pregnancy in subjects or their partners. The design of the study has already been published.[10]

Participants

Participants were males or females patients of 18 to 55 years of age diagnosed with T1D in the 4 years prior to the study with a peak stimulated C-peptide greater than 0.2 nmol/L during a mixed meal tolerance test (MMTT), performed during the screening period (without an insulin bolus). The MMTT was the liquid Ensure® Plus (13.8 g of protein, 10.8 g of fat, 44.4 g of carbohydrates, 330 kcal, 220 ml, Abbott Laboratories). We postulated that, despite a possible already significant disease duration, pHERV-Env would still be expressed and the presence of remaining C peptide secretion would be sufficient to detect a protective effect of temelimab. Participants had to fulfill the protocol inclusion criteria requesting that patient would be "diagnosed with type 1 diabetes in the 4 years prior to signed informed consent", and positive for at least one diabetes associated auto-antibody [insulin, glutamicacid-decarboxylase-65 (GAD-65), tyrosine phosphatase-related antigen 2 (IA-2), zinc transporter 8 (ZnT8) or islet-cell antibody (ICA)]. The diagnosis of T1D was established by a diabetologist/endocrinologist. No further guidelines were provided regarding this diagnosis. They had to be between 18 to 55 years of age and have body weights between 40 and 100 kg. Subjects could not be on any of the following prohibited treatments during the study: β-cell stimulants e.g. sulphonylureas, glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase-IV (DPP-IV) inhibitors, insulin sensitisers e.g. metformin, thiazolidinedione or immunomodulatory drugs including systemic, but not topical or inhaled steroids. Subjects

on any of the prohibited drugs at screening could wash out these drugs over three months. Subjects had to be willing and able to follow all study procedures and assessments according to the protocol and they had to have daily access to an internet-connected device (smartphone, tablet, laptop or PC) and be willing and able to use an electronic study diary. All subjects were required to use an effective form of contraception during the trial if sexually active. Subjects had to provide written informed consent to participate prior to any trial procedure as shown by dated signature on the subject consent form.

Product

Temelimab is a recombinant humanized IgG4 monoclonal antibody which blocks pHERV-W Env.[9] Temelimab solution was diluted into an infusion bag containing 5% of glucose solution allowing the administration of 100 mL. During the double-blind period, subjects randomized to the placebo arm received 100 mL of placebo solution as an IV infusion over one hour. Placebo solution was diluted into an infusion bag containing 5% of glucose solution allowing the administration of 100 mL.

Primary endpoint: Safety

The primary endpoint was related to safety and tolerability: serious adverse events (SAE) and adverse events (AE). In addition, physical examination, vital signs (blood pressure, heart rate, respiratory rate and temperature), clinical laboratory values (hematology, chemistry, coagulation) including hepatic enzymes, bilirubin, alkaline phosphatase (AP), urea, creatinine, high-sensitivity C reactive protein (hsCRP) and cholesterol were recorded as well as urinalysis. These endpoints were assessed at each visit. Human anti-temelimab antibodies were assessed at baseline, weeks 12, 24, 36 and 48.

Exploratory endpoints: Pharmacodynamics

Endpoints related to T1D were assessed: Glycated hemoglobin (HbA1c) blood level; C-peptide level as assessed by area under the concentration curve $(AUC)_{0\text{-}2h}$, during two hours following a standardized MMTT, plasma concentration at 90 minutes (C_{90min}) and maximum

concentration (C_{max}); fasting and post-prandial (2 hours) blood glucose; daily use of insulin (total units) normalized by body weight and percentage of subjects not requiring insulin. Hypoglycemic episodes were classified per protocol according to the 2013 American Diabetes Association (ADA)/Endocrine Society Classification of Hypoglycaemic Episodes[13] (see also Figure A in Supplementary Appendix). Patients were asked to perform self-monitoring blood glucose (SMBG) and to record hypoglycemic episodes in the electronic diary. No specific guidelines regarding SMBG were provided, beyond usual practice for the patient. In particular, no "end of one event" was defined (for the vast majority of hypoglycemic episodes, there was not more than one episode per day. In a few instances, two or three hypoglycaemic episodes were noted on the same day, 1.5 to 6 hours apart. In very rare instances, several hypoglycaemic episodes, classified as "Documented symptomatic hypoglycaemia", were entered on the same day). In addition autoimmune diabetic biomarkers were measured every 12 weeks: anti-GAD-65 antibody; anti-ICA antibody; anti-insulin antibody; anti-ZnT8 antibody; anti-IA-2 antibody.

Other exploratory endpoints

The exploratory endpoints which were assessed were the pHERV-W-Env mRNA biomarkers extracted from peripheral blood mononuclear cells (PBMC) and analysed by reverse transcription at weeks 12 and 24 – quantitative Polymerase Chain Reaction (RT-qPCR). pHERV-W Env mRNA values were expressed as calibrated normalized relative quantity (CNRQ) values. Other markers for autoimmune disorders possibly associated were measured every 12 weeks: anti-thyroglobulin antibodies, anti-thyroperoxidase (TPO) antibodies, anti-transglutaminase antibodies, total Immunoglobulin A (IgA) and anti-21-hydroxylase antibodies.

Statistical analysis

Determination of Sample Size

The total planned sample size was 60: it was not based on a formal statistical assessment. This number of subjects was considered sufficient to achieve the primary safety objectives of the study.

Data analysis

The general analytical approach was descriptive in nature as the primary objective was safety. For continuous variables, descriptive statistics included the number of non-missing values, mean, standard deviation (SD) and/or median. For categorical variables, descriptive statistics included frequency counts and percentages per category. Mixed-model-repeat-measures (MMRM) analyses was used to compare the changes in HbA1c and C-peptide between both treatment groups for Baseline to Week 24 and Baseline to Week 48. The model included baseline as a covariate and factors for treatment group, visit and interaction between treatment group and visit. The rates of hypoglycemic events were compared between both treatment groups using Poisson regression. Hypoglycemic events were graphically summarized as the mean number of hypoglycemic events (with SD) versus study weeks for both groups. For C-peptide, insulin use, HbA1c, hypoglycemia, data were graphically presented according to treatments in the double-blind and open-label periods: patients receiving temelimab during the double-blind period and discontinuing thereafter, patients receiving temelimab during both periods, patients receiving placebo during the double-blind period and discontinuing thereafter, patients receiving placebo during the double-blind period and temelimab during the open-label period. Analyses of covariance (ANCOVA) of the change from baseline in autoantibodies at Weeks 24 and 48 were performed, containing baseline values and treatment group.

Planned Analyses

An interim analysis was performed following the completion of the double-blind period of the study (Week 24). The Week 24 interim analysis was conducted following the soft-locking of all data associated with the double-blind period of the study. The final analysis was done

at Week 48 comparing the temelimab/temelimab group versus the placebo/temelimab group. For Week 24 and for Week 48 analyses, only completer analyses were done, no imputation was done in case of missing data. Thirty two statistical tests of hypothesis were performed for the exploratory pharmacodynamics endpoints between Week 24 and 48. As these were exploratory analyses, no adjustment for multiple testing was performed systematically (for exploratory purpose, the statistically significant p-values were corrected for multiple tests (n=32) by Bonferroni correction).

Ethics

This study was carried out according to the Declaration of Helsinki, the Good Clinical Practice GCP) (International Council for Harmonization of technical requirements for Human Use (ICH) GCP E6 (R2, as adopted in Australia) and the Australian National Statement on Ethical Conduct in Human Research (2007 – updated in May 2015). The study was approved by the local and central ethics committees and notified to the Australian Therapeutics Goods Administration (TGA).

RESULTS

Patient disposition

Due to parallel enrollment at different sites, a total of 64 subjects, more than the planned 60 patients, were enrolled in the study, with 43 subjects randomly assigned to active treatment and 21 subjects randomly assigned to placebo (Figure 1). Three subjects were discontinued from the study during the double-blind period (2 active and 1 placebo), all due to withdrawal of consent for personal reasons. A total of 45 subjects participated in the open-label period (Figure 1). The study was initially planned to be a 24-week double-blind study only. After starting the study, it was decided to extend it to 48 weeks by adding a 24-week open-label period. Patients were asked thereupon to sign a new informed consent to

enter into the “open label” study. About a third declined this extension, because of time “off-work” (corresponding to about 1 day per month) requested monthly by the travel to the sites and study procedures. Thirty-one of these subjects were from the temelimab treatment group and 14 from the placebo group during the double-blind period. Three subjects were discontinued from the study during the open-label period (2 subjects from the temelimab/temelimab group and 1 subject from the placebo/temelimab group). A summary of subject demographics and disease characteristics is presented in Table 1: the age of subjects in the temelimab and placebo groups was well matched, the proportion of males to females was greater in the placebo group. All subjects had Caucasian origins, except for three subjects in the temelimab/temelimab group who had Asian origins. There were no differences between groups for weight, height, body mass index (BMI), daily insulin and HbA1c, with slightly higher C peptide values 90 minutes after MMTT in the placebo group. The proportion of patients having less than 1 year of disease duration was a slightly higher in the placebo group, and the proportion of patients having 3-4 years of disease duration was slightly higher in the temelimab group.

Primary endpoint safety

During the double-blind period, the percentage of subjects experiencing at least one treatment emergent adverse event (TEAE) was equivalent between the temelimab and placebo groups (Table 2). The most frequent adverse events were nasopharyngitis and upper respiratory tract infections with a slightly higher frequency in the group of patients receiving temelimab during both periods. Overall, subjects in the temelimab group reported fewer TEAEs considered related to study drug compared to the placebo group. A higher proportion of subjects in the placebo group experienced TEAEs and related TEAEs at each intensity grade compared to subjects in the temelimab group. In the subjects that participated in both the double-blind and open-label periods of the study, the proportion experiencing at least one TEAE was equivalent between the temelimab/temelimab and

placebo/temelimab groups. The proportion of subjects that experienced a TEAE of severity Grade 3+ was notably higher in the placebo/temelimab group compared to the temelimab/temelimab group, as was the proportion of subjects experiencing a TEAE considered related to study treatment. There were no death nor other significant adverse events associated with temelimab use, and there were no changes or interruptions to study drug dosing due to TEAEs considered related to temelimab. One subject withdrew from the study due to a TEAE considered related to temelimab (migraine). There were no serious adverse events reported that were considered related to temelimab.

Temelimab use was not associated with any trends in changes to safety laboratory parameters, nor were there any major changes in vital signs, physical examination findings, or ECG assessments. Concomitant medication usage did not appear to increase with temelimab use in either study period.

There was 1 subject from the temelimab group who was positive for human anti-temelimab antibodies at baseline but became negative at further tests, with no subjects from either group returning a positive result at any other time point during the study.

Exploratory pharmacodynamics Results:

C-peptide, HbA1c, Insulin use

Mean (±SD) $AUC_{0\text{-}2h}$ values for C peptide is given in Figure 2A and 2B at Week 24 and at Week 48 respectively. There were no statistically significant temelimab effects, particularly no impairment, as demonstrated for the C-peptide $AUC_{0\text{-}2h}$ observed during the double-blind and open-label periods and a large SD was observed. In the subjects that switched from placebo to temelimab treatment at Week 24, there was a decrease in mean C-peptide $AUC_{0\text{-}2h}$ from Week 24 onwards. In the temelimab/temelimab group, the mean decrease in C-peptide $AUC_{0\text{-}2h}$ over time appeared to be steady from Week 12 through to Week 48. Similar absence of noticeable differences between groups and over time could be observed for C_{90min} and C_{max}.

Mean HbA1c values, over time and by treatment group, are given in Figure 2C and 2D at Week 24 and at Week 48. There were no differences in mean HbA1c values over time for both the temelimab and the placebo groups in the double-blind period and for the temelimab/temelimab and placebo/temelimab groups during the open-label period. The groups of patients with placebo or temelimab, who did not continue the open label period had on average high HBA1c values but did not differ between them.

The mean insulin use values over time are presented in Figure 2E and 2F at Week 24 and at Week 48 respectively. There was no major difference in mean insulin use between the temelimab and placebo groups in the double-blind period and between the temelimab/temelimab and the placebo/temelimab groups during both periods apart from some variability in the patients receiving placebo during the first period and then discontinuing study.

None of the mixed models for these 3 endpoints showed any statistically significant effect of the treatment at Weeks 24 or 48.

Hypoglycemic episodes

In general, subjects that received placebo during the double-blind period reported more hypoglycemic episodes than subjects that received temelimab during the double-blind period. This was mainly driven by asymptomatic hypoglycemic episodes which represented the most numerous category of hypoglycemia. The Poisson regression comparing the overall rate of hypoglycemic episodes throughout the double-blind period showed a significantly lower rate of hypoglycemic events in the temelimab treatment group (2.09, 95%CI 1.41-3.09) compared with the placebo group (2.92, 95%CI 1.66-5.13), which was statistically significantly different by Poisson regression (p=0.0004) (By applying a Bonferroni correction, the corrected p-value is 0.013). This trend was still seen in the open-label period with 1.88 episodes (95%CI 1.16-3.04) in the temelimab/placebo group vs 2.07 (95%CI 1.08-3.96) but the difference was no longer statistically significant with all patients being under treatment

(p=0.82). Figure B presents the hypoglycemic episodes in the treatment groups is the Supplementary Appendix.

Auto-antibodies and HERV-W-Env mRNA

Table 3 shows the mean concentrations of the anti-insulin antibody by group in the study. At baseline the mean level of this antibody was lower in the temelimab group compared to the placebo group. At Week 24, in the group treated by temelimab, the levels decreased which was not the case in the placebo group: the differences adjusted for baseline was statistically significant (p=0.010) (By applying a Bonferroni correction, the corrected p-value is 0.32). The difference remained statistically significant at Week 48 between the temelimab/temlimab and the placebo/temelimab groups (p=0.009) (By applying a Bonferroni correction, the corrected p-value is 0.29).

For the anti-GAD-65 antibody, at Screening, more subjects in the temelimab group (14.0%) had a negative anti-GAD-65 antibody concentration compared to the placebo group [n=1 (4.8%)] (see Table A of the Supplementary Appendix). At Week 24, there were no major changes in either group and at the commencement of the open-label treatment (Week 24), more subjects in the temelimab/temelimab group (14.6%) had no anti-GAD-65 antibody compared to the placebo/temelimab group (10.0%), without much modification at Week 48.

For the anti-IA2 antibody, at screening, the number of subjects that had a normal anti-IA2 antibody concentration in the temelimab (48.8%) and placebo groups (42.9%) was similar. At the commencement of the open-label period (Week 24), the number of subjects with a normal anti-IA2 antibody concentration in the temelimab/temelimab group (56.1%) was slightly higher compared to the placebo/temelimab group (50.0%); at Week 48, there were no changes in either group.

For the anti-ICA antibody, all subjects in both treatment groups had a normal (negative) anti-ICA antibody concentrations at Baseline and during the whole study.

For the anti-ZnT8 antibody, at Screening, the number of subjects that had a normal anti-ZnT8 antibody concentration in temelimab group was 46.5% and placebo group 47.6% was similar, this was similar at Week 24, the percentages moved to 48.8% in the temelimab/temelimab group and to 50.0% in the placebo/temelimab group; without much modification at Week 48.

The other auto-antibodies for other autoimmune disorder did not show difference between groups.

The pHERV-W-Env mRNA by RT-qPCR for the first 24 weeks is presented by treatment groups in Figure C of the Supplementary Appendix. There were no clear trend differences between the groups. Stratified analyses of the C-peptide, HbA1c and Insulin use by level of expression of pHERV-W Env mRNA at baseline did not show meaningful differences (data not shown).

DISCUSSION

The primary objective of this study was to demonstrate the safety and tolerability of temelimab in adult T1D patients with detectable c-peptide in serum. It was important to establish safety in this specific patient population and the results obtained here are in line with the favorable temelimab safety profile obtained so far over the long term (up to two-years) in multiple sclerosis patients[13] or at very high dose (up to 110 mg/kg).[15] This is probably due to the pHERV-W Env target antigen, which does not appear to play any physiological role,[9] and the absence of any known impact of temelimab on the immune system. This observation is reassuring and opens the way to further clinical trials with temelimab in particular in the pediatric population with early disease onset.

The difference in the frequency of hypoglycemic episodes was in favor of temelimab during the first double-blind period and this difference disappeared in the open-label period when all patients were treated with temelimab, due to a decrease of hypoglycemic episodes in the placebo patients who switched then to temelimab. This might suggest that there was a better glycemic control during temelimab treatment, but this needs to be confirmed in further temelimab studies. However, in this patient population, there was no evidence of an impact of temelimab treatment on the usual parameters measuring β -islet cell capacity, such as C-peptide or insulin use, or long-term glycemic control such as HbA1c concentration. There was also a large variability in the level of these parameters, knowing that there may be sub-populations of responders as it can be seen for anti-CD3 monoclonal antibodies such as teplizumab or otelixizumab.[16,17] Subgroup analyses on demographic or disease characteristics did not identify a typical population of responders in this study. In particular, the stratification by the level of expression of pHERV-W Env RNA at baseline did not show that the RNA Env level at baseline was predictive of a better response to the treatment. Also, the expression of pHERV-W-Env mRNA did not seem to be particularly modified by the presence of the protein antagonist temelimab. It is unknown whether the level of RNA expression in PBMC has any relationship to the level of the protein expression in the

pancreas,[5] and the small sample size limits the capacity to identify subgroups large enough to draw statistical conclusions.

The apparent effect of the treatment on the anti-insulin antibody is intriguing. The other auto-antibodies do not show particular response to the treatment. Such a differential effect had been observed in the T1D population when treated with rituximab, a powerful immunosuppressor:[18] in this study, it was observed that rituximab, an anti-CD20 monoclonal antibody, suppressed anti-insulin antibody with no or minor effects on anti-GAD65, insulinoma-associated protein 2 and ZnT8. It is unclear whether the decrease in the level of anti-insulin antibodies observed here is a sign of a modification in the auto-immune process, a decrease of the immune response against exogenous insulin or simply a chance finding (the baseline values between groups were already different at baseline) and it should be highlighted that temelimab, contrary to rituximab, is not impacting the immune system.

Among limitations of the study, multiple testing on PD endpoints were performed and therefore chance findings for the parameters which appeared statistically significantly different between groups cannot be ruled out. Also a very heterogeneous T1D population was recruited for this safety trial to ensure a broad coverage of all different types of patients in terms of safety. In terms of pharmacodynamics, such a heterogeneity was possibly a limitation to detect efficacy signals. The heterogeneity of the population in terms of age and duration of disease may be an explanation for the absence of results on C-peptide or insulin use as it has been seen with immunomodulators.[19] For example the dynamic of the C-peptide decline is not linear over time[20] and may respond differently to treatment. It cannot be excluded either that the follow-up of the trial (1 year) was too short and that the disease duration up to 4 years prior to inclusion was too long to detect a therapeutic action with temelimab. Indeed the expected mode of action of this neutralizing antibody should take a longer time to translate into an assessable PD response, at least longer compared to some response observed with immunomodulators. When used for MS, temelimab shows

neuroprotective effects but only after 1 year of treatment[14] while classical immunomuldators in MS induce measurable therapeutic response after a few weeks.[21]

In conclusion, temelimab appeared safe in the T1D population, thereby reinforcing the safety findings collected so far with this drug in healthy volunteers and in MS patients. The PD results were mixed with signs of response in hypoglycemia reduction and anti-insulin antibody levels whereas C-peptide or insulin use were not affected with the treatment. Certainly these results deserve further confirmation, as well as a better understanding of the exact role of pHERW-Env in the pathogeny of T1D. The definitive response on the interest of the anti-HERV-W Env approach in this new indication should rely on a clinical study including a much more homogeneous population including children or young adults with disease duration of only a few weeks, as it appears that a very early start is the key for successful therapeutic effects as suggested by recent teplizumab trial results.[22]

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Conflict of Interest

F Curtin, C Bernard, H Porchet, G Kornmann, N Beart are employees of GeNeuro SA.

S Malpass, D Lloyd are or were employees of Southern Star Research Pty Ltd.

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Figure Legends

Figure 1: Consort diagram with patient flow into the study.

Figure 2: Mean values (±SD) of C-peptide (area under the curve, $AUC_{0\text{-}2h}$) in temelimab and placebo groups during double blind period (A) and over the whole study in patients receiving temelimab in the double-blind period and discontinuing thereafter, in patients receiving temelimab in both periods, in patients receiving placebo in the double-blind period and discontinuing thereafter and in patients receiving placebo in the double-blind period and temelimab in the open-label period (B). Daily insulin use (±SD) in temelimab and placebo groups during double blind period (C) and over the whole study in patients receiving temelimab in the double-blind period and discontinuing thereafter, in patients receiving temelimab in both periods, in patients receiving placebo in the double-blind period and discontinuing thereafter and in patients receiving placebo in the double-blind period and temelimab in the open-label period (D). HbA1c levels (±SD) in temelimab and placebo groups during double blind period (E) and over the whole study in patients receiving temelimab in the double-blind period and discontinuing thereafter, in patients receiving temelimab in both periods, in patients receiving placebo in the double-blind period and discontinuing thereafter and in patients receiving placebo in the double-blind period and temelimab in the open-label period (F).

Supplementary Appendix

Figure A: Classification of hypoglycemia in the trial

Figure B: Mean (±SD) number of hypoglycemia episode by time in patients receiving temelimab in the double-blind period and discontinuing thereafter, in patients receiving temelimab in both periods, in patients receiving placebo in the double-blind period and discontinuing thereafter and in patients receiving placebo in the double-blind period and temelimab in the open-label period.

Figure C: pHERV-W-Env mRNA level by treatment group in the double blind period.

Figure 1

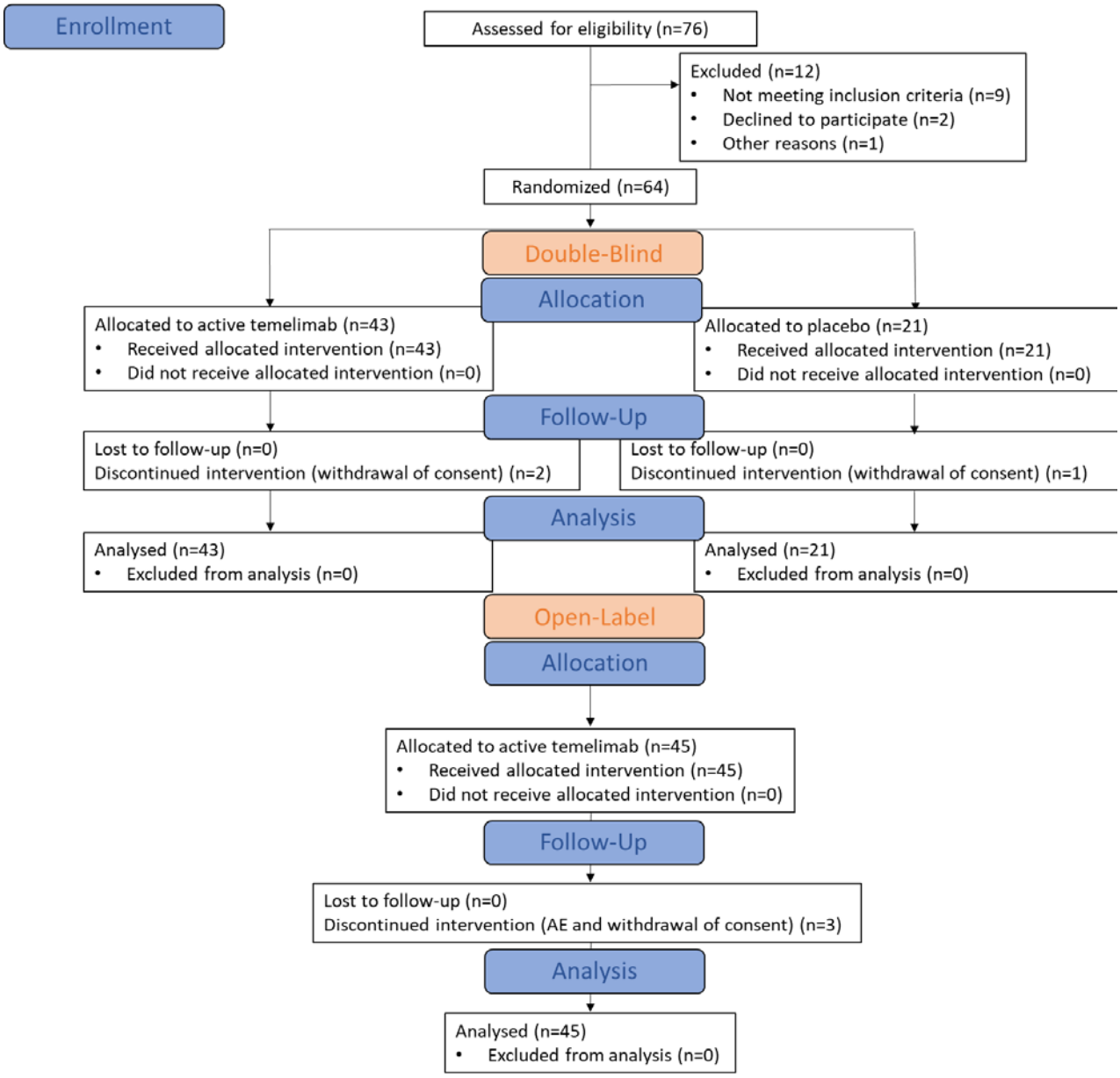
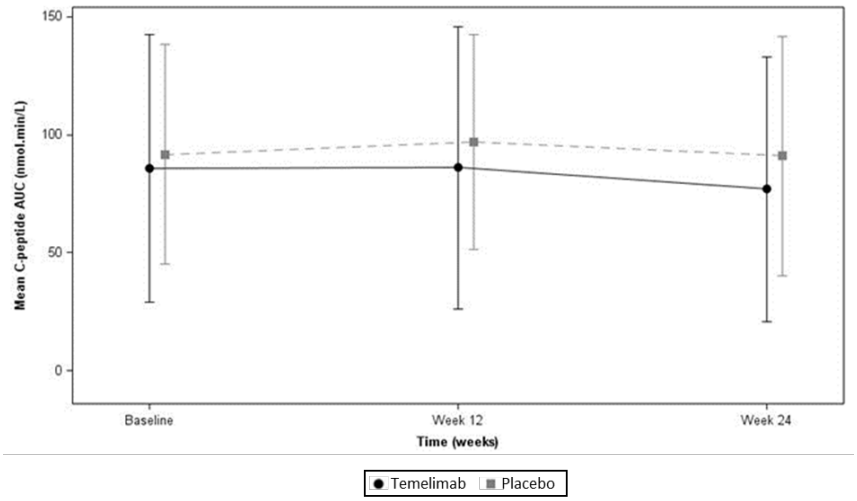


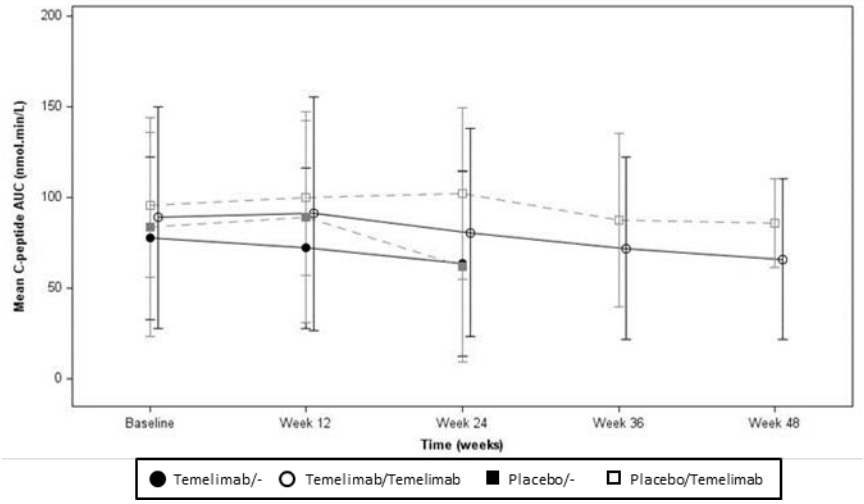
Figure 2.

A) Mean (±SD)

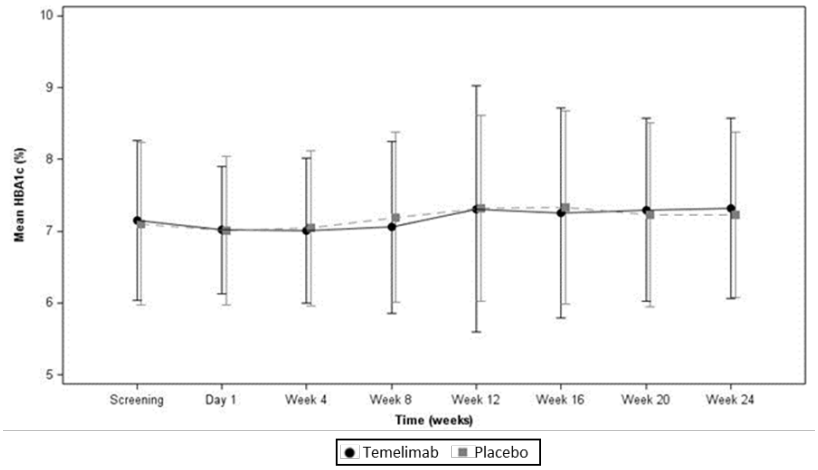
a. C-Peptide $AUC_{0\text{-}2h}$ during the double-blind period



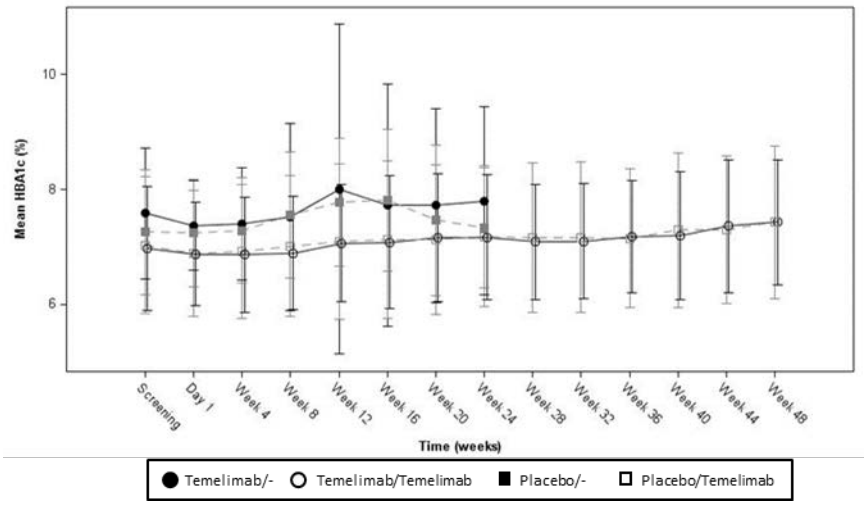
B) Mean (±SD) C-Peptide $AUC_{0\text{-}2h}$ during the whole study



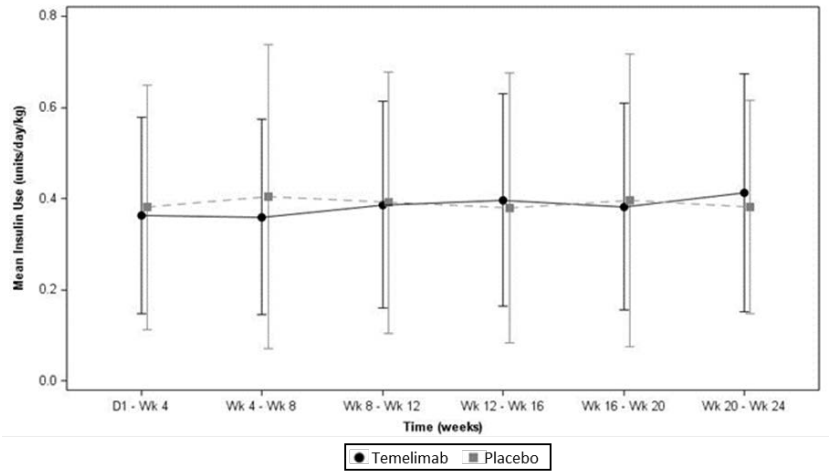
C) Mean (±SD) HbA1c during the double-blind period



D) Mean (±SD) HbA1c during the whole study



E) Mean (±SD) Insulin use during the double-blind period



F) **Mean (±SD) Insulin use during the whole study**

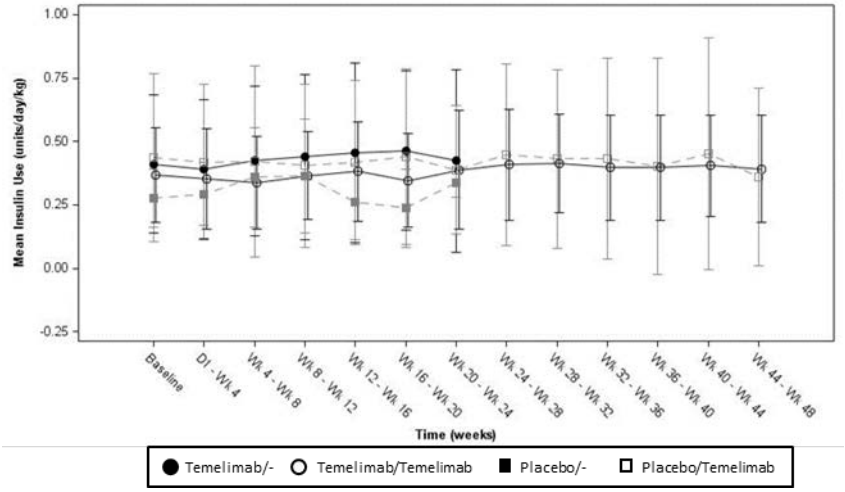


Table 1. Demographic Characteristics for patients at baseline

	Temelimab (N=43)	Placebo (N=21)	Overall (N=64)
Age at Screening (years)			
Mean (SD)	31.4 (10.2)	34.9 (10.1)	32.6 (10.2)
Sex [n (%)]			
Male	25 (58.1)	14 (66.7)	39 (60.9)
Female	18 (41.9)	7 (33.3)	25 (39.1)
Race [n (%)]			
White	40 (93.0)	21 (100.0)	61 (95.3)
Asian	3 (7.0)	0	3 (4.7)
Height (cm)			
Mean (SD)	174.5 (8.3)	173.1 (8.2)	174.0 (8.2)
Weight (kg)			
Mean (SD)	76.21 (13.72)	75.94 (11.58)	76.12 (12.97)
BMI (kg/m^2)			
Mean (SD)	25.08 (4.52)	25.25 (2.82)	25.14 (4.02)
Daily insulin (units/day/kg)			
Mean (SD)	0.379 (0.214)	0.359 (0.290)	0.381 (0.235)
HbA1c (%)			
Mean (SD)	7.15 (1.12)	7.10 (1.13)	7.13 (1.11)
90-min MMTT stimulated C-peptide			
Mean (SD)	0.89 (0.57)	1.01 (0.54)	0.93 (0.56)
Disease duration in years [n (%)]			
0-1	17 (39.5)	11 (52.4)	28 (43.8)
1-2	10 (23.3)	5 (23.8)	15 (23.4)
2-3	5 (11.6)	2 (9.5)	7 (10.9)
3-4	9 (20.9)	3 (14.3)	12 (18.8)
Not specified but <4	2 (4.7)	-	2 (3.1)

Abbreviations: Number of subjects (n), standard deviation (SD), body mass index (BMI), minutes (min), Mixed Meal Tolerance Test (MMTT)

Table 2. Frequently Reported Treatment Emergent Adverse Events (observed in 2 or more subjects within any treatment group) by System Organ Class and Preferred Term

	Temelimab/- N=12		Temelimab/Temelimab N=31		Placebo/- N=7		Placebo/Temelimab N=14		Total N=64	
System Organ Class/Preferred Term TEAE	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)
ALL BODY SYSTEMS										
Abdominal pain	0	0	4	4 (12.9)	1	1 (14.3)	1	1 (7.1)	6	6 (9.4)
Nausea	1	1 (8.3)	3	3 (9.7)	3	2 (28.6)	0	0	7	6 (9.4)
Chest Pain	0	0	1	1 (3.2)	0	0	2	2 (14.3)	3	3 (4.7)
Gastroenteritis	0	0	2	2 (6.5)	0	0	1	1 (7.1)	3	3 (4.7)
Nail Bed Infection	0	0	0	0	0	0	2	2 (14.3)	2	2 (3.1)
Nasopharyngitis	4	3 (25.0)	6	5 (16.1)	0	0	2	2 (14.3)	12	10 (15.6)
Upper Respiratory Tract Infection	3	3 (25.0)	21	16 (51.6)	1	1 (14.3)	6	4 (28.6)	31	24 (37.5)
Glycosylated hemoglobin increased	2	2 (16.7)	0	0	0	0	0	0	2	2 (3.1)
Headache	3	1 (8.3)	14	5 (16.1)	1	1 (14.3)	2	1 (7.1)	20	8 (12.5)
Hypoaesthesia	0	0	2	2 (6.5)	1	1 (14.3)	0	0	3	3 (4.7)
Parasthesia	0	0	2	2 (6.5)	0	0	0	0	2	2 (3.1)

	Temelimab/- N=12		Temelimab/Temelimab N=31		Placebo/- N=7		Placebo/Temelimab N=14		Total N=64	
System Organ Class/Preferred Term TEAE	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)
Presyncope	0	0	2	2 (6.5)	0	0	0	0	2	2 (3.1)
Anxiety	0	0	2	2 (6.5)	0	0	0	0	2	2 (3.1)
Oropharyngeal pain	1	1 (8.3)	3	3 (9.7)	0	0	0	0	4	4 (6.3)

Abbreviations: Number of subjects (n), treatment emergent adverse event (TEAE)

Table 3. Mean anti-insulin autoantibody levels by period and treatment group

	Temelimab/Temelimab		Placebo/Temelimab		
	Actual value	**Absolute change from baseline**	**Actual value**	**Absolute change from baseline**	**ANCOVA-p**
Baseline	7.89		11.51		
Week 24	6.22	-2.02	14.13	2.05	0.010
Week 48	5.14	-3.62	14.19	0.62	0.009

ANCOVA: analysis of covariance