Janssen Research & Development

Statistical Analysis Plan (Week 52 Database Lock)

A Randomized Phase 2a, Double-blind, Placebo-controlled, Parallel-group, 2-arm, Multicenter Study to Assess the Efficacy and Safety of SIMPONI® to Arrest β-cell Loss in Type 1 Diabetes

Protocol CNTO148DML2001; Phase 2a

SIMPONI® (golimumab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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ABBREVIATIONS

ADA	American Diabetes Association
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	hepatitis B core antibody
ARC	Anticipated Event Review Committee
AS	ankylosing spondylitis
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCG	Bacille Calmette-Guérin
BG	blood glucose
BSA	body surface area
CD	Crohn's Disease
CDC	Centers for Disease Control and Prevention
CDE	certified diabetes educator
CL/F	apparent total systemic clearance
CMV	cytomegalovirus
CRF	case report form(s) (paper or electronic as appropriate for this study)
DBL	data base locks
DKA	diabetic ketoacidosis
DMC	Data Monitoring Committee
EBV	Epstein-Barr virus
eDC	electronic data capture
eDiary	electronic diary
FDA	Food and Drug Administration
GAD-65	Glutamic acid decarboxylase
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	Human leukocyte antigen
HPV	human papillomavirus
IAC	Interim Analysis Committee
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	instructions for use
IL	interleukin-
IND	Investigational New Drug
IRB	Institutional Review Board
IWRS	interactive web response system
LQC	lowest quantifiable concentration
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MMTT	Mixed-meal Tolerance Test
MS	multiple sclerosis
MTX	methotrexate
NAb	neutralizing antibody
NONMEM	NONlinear Mixed Effects Modeling

NPH	Neutral Protamine Hagedorn
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PE	physical examination
PFS-U	UltraSafe Passive® Delivery System assembled with PFS
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PsA	psoriatic arthritis
PsO	psoriasis
q2w	every 2 weeks
q4w	every 4 weeks
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SIPPM	Study Site Investigational Product and Procedures Manual
SLE	systemic lupus erythematosus
SUSAR	suspected unexpected serious adverse reaction
T1D	type 1 diabetes
TB	tuberculosis
TE	target engagement
TNFα	tumor necrosis factor alpha
UC	ulcerative colitis
ULN	upper limit of normal
V/F	apparent volume of distribution

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the analysis of efficacy, safety, pharmacokinetics, and immunogenicity of golimumab in the CNTO148DML2001 study. This SAP is specific to the Week 52 database lock (DBL).

1.1. Trial Objectives

Primary Objectives

The primary objective is to determine if golimumab can preserve β-cell function in children and young adults with newly diagnosed T1D.

Secondary Objectives

- To evaluate the impact of golimumab on measures of diabetes control in this subject population.
- To evaluate the off-therapy durability of golimumab on measures of diabetes control in this subject population.
- To determine the safety and tolerability of golimumab in children and young adults with T1D.
- To evaluate the pharmacokinetics (PK) and immunogenicity of golimumab in this specific subject population with T1D.

Exploratory Objectives

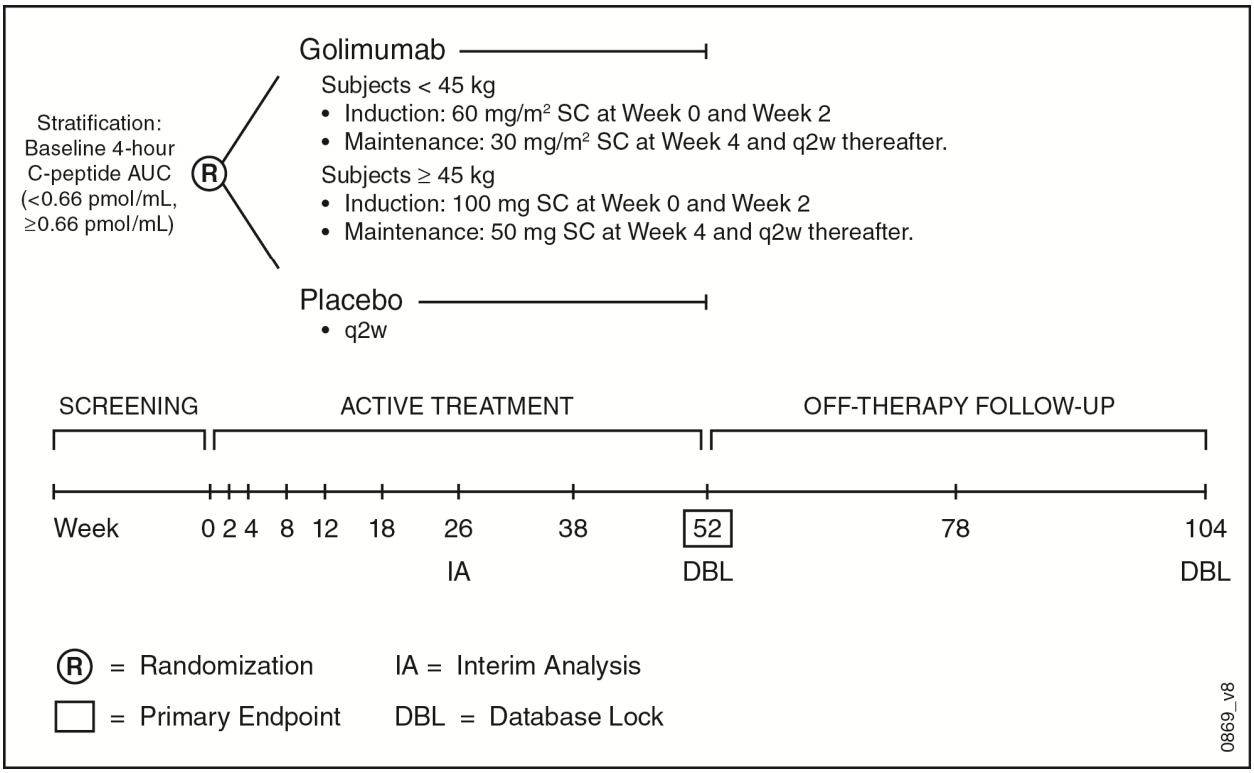
Exploratory objective is to evaluate how golimumab impacts immunologic profiles and indicators of β-cell stress, and the correlation with efficacy and safety endpoints in this study.

1.2. Trial Design

This is a Phase 2a randomized, double-blind, placebo-controlled, parallel-group, multicenter, study of golimumab in children and young adults with new onset T1D. Confirmation of the autoimmune nature of T1D in subjects will be determined by positivity of at least one T1D-associated autoantibody. Subjects must also show evidence of residual endogenous β-cell function, defined by a C-peptide level of ≥0.2 pmol/mL from a 4-hour MMTT at study screening, and be able to be randomized within 28 days of screening and 100 days of diagnosis.

A diagram of the study design is provided below and as depicted in **Error! Reference source not found.**, approximately 81 subjects will be randomly assigned in a 2:1 ratio to receive golimumab or matching placebo therapy and be stratified based on a C-peptide AUC of <0.66 pmol/mL or ≥0.66 pmol/mL from a 4-hour MMTT conducted at study screening. Following screening, subjects must be randomized within 28 days. Following randomization there will be a 52-week treatment period with study agent followed by a 52-week off-therapy follow-up period. Two planned database locks (DBLs) will occur, at Week 52 and at Week 104.

Figure 1: Schematic Overview of the Study



Efficacy assessments will be performed according to the Schedules of Activities. Serum samples for PK, immunogenicity, and exploratory assessments will be collected at the timepoints shown in the Time and Events Schedule in the protocol.

An independent Data Monitoring Committee (DMC) will be commissioned to continually assess the safety of study subjects. The DMC will evaluate an interim analysis based on 4-hour C-peptide AUC in response to an MMTT after at least 60% of subjects complete their Week 26 MMTT assessment. The primary goal of this interim analysis is to obtain an early read on treatment effect to facilitate planning of future studies.

1.3. Statistical Hypotheses for Trial Objectives

The primary hypothesis to be tested in this study is that golimumab is superior to placebo in maintaining β-cell function in children and young adults with newly diagnosed T1D as measured by MMTT-stimulated 4-hour C-peptide AUC at Week 52.

1.4. Sample Size Justification

This study is designed to enroll approximately 81 subjects in order to have sufficient power to detect a difference between the golimumab groups and the placebo group for the primary efficacy endpoint. The rationale for the study sample size is based on the hypothesis tests for the primary efficacy endpoint.

The sample size calculation is based on the primary endpoint, an MMTT 4-hour C-peptide AUC at Week 52. Due to skewed C-peptide AUC data, normalizing transformation of log (AUC +1) is

applied for sample size assessment. The method has been well accepted and used in numerous clinical studies. Based on published data, a common standard deviation (SD) of log (AUC+1) of 0.215 is assumed, and the back-transformed means for 4-hour C-peptide AUC are assumed to be 0.385 and 0.635 for the placebo and golimumab groups respectively, ie the expected treatment difference (back-transformed) is 0.25. Based on these assumptions, with 81 subjects (54 on golimumab and 27 on placebo), there is 90% power to detect a treatment difference with a 2-sided significance level of 0.05 through a 2-sample t-test.

1.5. Randomization and Blinding

1.5.1 Randomization

Central randomization will be implemented in this study. Approximately 81 subjects who meet all enrollment criteria and have all Day 1 procedures performed will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by, or under the supervision of, the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified on subject baseline C-peptide AUC (<0.66 pmol/mL, ≥0.66 pmol/mL) derived from the 4-hour MMTT conducted at screening. The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study agent kit for the subject. Members of the study site will have unique user and personal identification numbers to contact the IWRS and must provide relevant subject details to uniquely identify the subject.

1.5.1. Blinding

This will be a randomized, double-blind, placebo-controlled study. To maintain the study blind, the study agent container will have a multipart label containing the study name, study agent number, reference number, and other information on each part. The label will not identify the study agent in the container. However, if it is necessary for a subject's safety, the study blind may be broken and the identity of the study agent ascertained. The study agent number will be entered in the case report form (CRF) when the study agent is administered. The study agents will be identical in appearance and will be packaged in identical containers.

The investigator will not be provided with randomization codes. The codes will be maintained within IWRS, which has the functionality to allow the investigator to break the blind for an individual subject.

Data that may potentially unblind the treatment assignment will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all subjects have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific

emergency treatment/course of action would be dictated by knowing the treatment status of the subject. In such cases, the investigator may in an emergency determine the identity of the treatment by contacting the IWRS. It is recommended that the investigator contact the sponsor or its designee if possible to discuss the particular situation before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented by the IWRS in the appropriate section of the electronic case report form (eCRF), and in the source document.

The documentation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner so as to not unblind the treatment assignment to the subject, the study site, or sponsor personnel. The investigator is also advised not to reveal the study treatment assignment to the subject, the study site, or sponsor personnel.

Subjects who have had their intervention assignment unblinded by the investigator will not be eligible to receive further study intervention, but should continue to complete scheduled evaluations.

An independent DMC will monitor the safety of the study in an unblinded subject-level fashion on a regular basis and whenever deemed necessary. In addition, the Sponsor Medical Monitor will review safety data in a blinded manner as the study is ongoing.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

Nominal visits will be used for all by visit analyses.

2.2. Analysis Sets

2.2.1. Efficacy Analysis Set(s)

Unless otherwise specified, all analyses will use the full analysis set, which is defined below.

- **The full analysis set** includes all randomized subjects who take at least one dose (complete or partial) of study agent.
- **The per-protocol (PP) analysis set** will consist of the full analysis set who complete 52 weeks of treatment (as described above) and have no major protocol deviations that may affect the interpretation of the primary efficacy endpoint.
- **The extended efficacy analysis set** includes all randomized subjects in this study and an additional 45 placebo subjects from three external trials. The three Immune Tolerance Network (ITN) funded trials had similar eligibility criteria and trial set-up.[1,2,3] To match population in the study, only those aged between 6 and 21 will be included in the analysis.

Efficacy data will be analyzed according to the randomization assignment regardless of the actual treatment received.

2.2.2. Safety Analysis Set

The safety analysis set includes all randomized subjects who received at least 1 (partial or complete) dose of study agent, i.e., the treated population. In this study, the safety analysis set is the same as the full analysis set.

In the safety analyses, subjects will be analyzed according to the treatment they actually received, regardless of the treatments they are randomized to. More details are provided in Section 6.

2.2.3. Pharmacokinetics Analysis Set

The pharmacokinetics evaluable (PKE) analysis set includes treated subjects (who received at least 1 injection) who have sufficient PK samples for analysis.

Pharmacokinetics analyses will be performed using the PKE analysis set.

2.3. Baseline Measurements

The baseline measurement of a parameter is defined as the closest measurement taken prior to or on the same day as the Week 0 administration except otherwise specified.

2.4. Definition of Subgroups

To evaluate the consistency in the key efficacy over demographics, baseline characteristics, prior and baseline medication use, subgroup analyses will be performed when sample sizes are permitted (at least 5 subjects for each treatment group within a subset). The subgroups include, but are not limited to, the following:

Baseline demographics:

- Sex (male, female)
- Baseline Age (<12, 12-18, ≥18)
- Baseline weight (<45kg, ≥45kg)

Baseline disease characteristics:

- Subjects positive to at least one diabetes-related autoantibody: 1, >1-<=3 and >3
- Baseline HbA1c categories: ≤6.5%, >6.5%
- Baseline C-peptide AUC: <0.66 pmol/mL or ≥0.66 pmol/mL
- Baseline insulin usage by quantiles
- Number of days since diagnosis of T1D: < 60 days or ≥ 60 days

In addition, subgroup analyses defined by Human Leukocyte Antigen (HLA)-DR3 presence/absence, and HLA-DR4 presence/absence will be explored for selected endpoints (See Section 5.5.2).

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

An independent DMC will review safety and efficacy data periodically. Safety review starts once the first 10 subjects complete their week 12 visits. Efficacy review takes place at interim analysis when at least 60% of subjects complete their Week 26 MMTT assessment. After each review, the DMC is to make recommendations regarding the continuation of the study as planned or, in the event that any unanticipated concerning safety events or issues occur, placing the study on hold or stopping the study. In addition, the DMC roles and responsibilities, and the general procedures (including communications) are defined and documented in the DMC charter developed by the sponsor detailing the safety data monitoring and efficacy data review to be conducted by the DMC.

An administrative interim analysis was performed when at least 60% of subjects complete their Week 26 MMTT assessment. The interim endpoint of interest is the MMTT-stimulated 4-hour C-peptide AUC. A mixed model for repeated measures (MMRM) was fitted on the post-baseline log(AUC+1) data. Similar analyses were conducted on the extended interim analysis set to leverage the external placebo subject data. All adverse event data up to the interim analysis cut-off date was also reviewed in the interim analysis. Refer to interim analysis SAP for interim analysis details.

After interim analysis review, the committee recommended the efficacy analysis supporting the IA be provided by the SSG for review in subsequent scheduled DMC meetings before study unblinding. The objective was to re-evaluate the observation at IA. The details regarding these reviews were provided in the DMC SAP and DMC Charter.

4. SUBJECT INFORMATION

Unless specified otherwise, full analysis set will be used for the subject information analyses and subjects will be analyzed according to the treatment group to which they were randomized at Week 0, regardless of the treatment they actually received. The number of subjects in each analysis set will be summarized by treatment group and overall.

Simple descriptive statistics, such as mean, median, standard deviation, interquartile range, maximum, and minimum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data and no formal statistical analyses for treatment comparisons will be performed. In addition, subject listings will also be used to present the data.

4.1. Demographics and Baseline Characteristics

Demographic (age, race, sex, height, weight and BMI) and baseline characteristic variables will be summarized by randomized treatment groups and overall (all treatments pooled together) for

all subjects randomized. Descriptive statistics (N, mean, SD, median, and range) will be provided for continuous variables at baseline as well as the number and percentage of subjects for categorical variables.

Baseline disease characteristics to be summarized will include but not limited to: number of days since diagnosis of T1D, fasting blood glucose prior MMTT, 4-h peak C-peptide, 4-h C-peptide AUC, 2-h C-peptide AUC, HbA1C, insulin use unit per day, and subjects positive to at least one diabetes-related autoantibody.

In addition, the number and percentage of subjects in the following categories will be summarized by treatment group:

- Age :<12 years, 12-18 years, >18 years
- Weight: <45 kg, ≥45 kg
- Number of positive diabetes-related autoantibodies: 1, >1-≤3 and >3
- Type of positive diabetes-related autoantibody: GAD-65, IA-2, ZnT8, ICA, and insulin
- Baseline $HbA_{1c:}$ ⩽6.5%, >6.5%
- Number of days since diagnosis of T1D: < 60, ≥60

4.2. Disposition Information

Subjects who discontinued study agent prior to Week 52 along with the reasons for discontinuation will be summarized by treatment group. In addition, subjects who terminated study participation prior to Week 52 along with the reasons for termination will be summarized by treatment group for all subjects who received at least one administration of study agent.

4.3. Treatment Compliance

Study agent compliance will be summarized descriptively through Week 52 for the safety analysis set. Number of subjects by randomized treatment versus actual treatment will be presented in a summary table.

4.4. Extent of Exposure

The number and percentage of subjects receiving study agent will be summarized by treatment group for the safety analysis set. Descriptive statistics will be presented for the following parameters:

- Number of administrations
- Total duration of exposure

Total duration of exposure is defined as the time lapses between the first and last study admissions.

4.5. Protocol Deviations

Major protocol deviations will be tabulated by treatment group as defined in the following categories:

- Entered but did not satisfy criteria
- Developed withdrawal criteria but not withdrawn
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

4.6. Prior and Concomitant Medications

Prior medications will be summarized by the number of subjects taking pre-specified categories of by treatment group. Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study agent. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study agent, including those that were started before and continued after the first dose of study agent. Concomitant medications will be listed.

5. EFFICACY

5.1. Methods of Analysis

All efficacy analyses will be performed on the full analysis set unless otherwise specified. The full analysis set includes all randomized subjects who have received at least 1 dose of study agent. The primary efficacy endpoint will be analyzed by using a mixed model for repeated measures (MMRM). Assessment of the primary efficacy endpoint on the PP analysis set will be conducted as the supportive analysis.

5.2. Analysis Specifications

5.2.1. Level of Significance

Unless otherwise specified, all statistical testing procedures will be performed at a 2-sided significance level of 0.05.

5.2.1.1. Multiplicity Adjustment for Testing Procedures

To control for multiplicity in the primary endpoint analysis and major secondary endpoint analyses, the hypothesis testing will be conducted in a hierarchical manner with the test on the primary analysis first and the tests on major secondary analyses next. The success of any major secondary analysis, i.e., p-value < 0.05, is contingent upon the success of the primary statistical analysis. Hochberg approach will be applied within major secondary endpoint analyses.

Nominal p-values will be reported for all other efficacy endpoints.

5.2.2. Data Handling Rules

The following missing data handling rules will be applied to the analyses in this study. For the analyses of change from baseline for a given efficacy parameter, only subjects who have both baseline and at least one post-baseline measurement for that parameter will be included.

5.2.2.1. Missing Data

Unless otherwise specified, in situations with the presence of missing data (e.g. lost to follow-up, missed study visit) the following rules will apply:

Missing baseline value: No imputation will be performed for missing baseline values.

Subjects missing values for any subgroup parameters (defined in Section 2.4) at baseline will be excluded from the subgroup analysis.

Continuous endpoints:

- In general, no imputation will be performed for missing post-baseline continuous values. Missing data will be adjusted for in the statistical model (i.e. Mixed effect Model Repeated Measures)

- In several sensitivity analyses of the primary endpoint, missing C-peptide AUC value will be imputed through linear extrapolation. More specifically, missing log(AUC+1) value will be imputed through a random effect model with time (continuous), age, treatment, and treatment by time interaction as fixed effects, and intercept and slope at subject level as random factors.

- Multiple Imputation (MI) is applied in one sensitivity analysis of the primary endpoint.

Binary endpoints:

- In general, subjects with missing observations of interest at a visit will be regarded as non-responders for that visit.

- When evaluating sustained response status for C-peptide AUC, if a subject presents one or more intermittent missing C-peptide AUC value, then the response statuses at visits prior to and after the miss value(s) will be referred to. If the subject is a responder at both visits, the he/she will be regarded as a responder at the missing visit. If the subject is a responder at the visit prior to the missing value and a non-responder at the visit after missing value(s), then the subject becomes a non-responder at the first missing visit. If all C-peptide AUC values after a visit are missing, then the response status for those missing visits is set to be non-responder.

Time-to endpoints:

- For time-to peak C-peptide < 0.2 pmol/mL, in case of intermittent missing measurement, if both the previous value and the next observed value are ≤ 0.2, then the missing value id regarded as ≤0.2. Otherwise, treat the first missing value above 0.2.

- Similarly, for time-to loss of remission (remission duration), in case of intermittent missing measurement, if both the previous and the next observed value are ≤ 9 (in remission), then the missing value is regarded to be ≤9. Otherwise, treat the first missing value above 9.

5.2.3. General Analysis Method

Data summaries will be provided for each treatment group. Statistical comparisons will be made between active and placebo treatment groups.

Descriptive statistics such as mean, median, standard deviation, minimum, and maximum will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Recurrence data will be summarized by mean as well as counts and percentages. Median will be reported for time to event variables. Graphical data displays (e.g., mean plots, Kaplan-Meier curves, and forest plots) will be used to support the presentation of data.

5.3. Primary Efficacy Endpoint

5.3.1. Definition

The primary endpoint is the MMTT-stimulated 4-hour C-peptide AUC at Week 52.

Four-hour C-peptide AUC is calculated as the standardized trapezoidal summation. It is calculated as the AUC based on available c-peptide concentration values from the MMTT divided by the time span between 0 minute (baseline) and the time associated with last available c-peptide concentration. The 4-hour MMTT should take 250 minutes to perform with blood samples collected at 11 time points: – 10, 0, 15, 30, 60, 90, 120, 150, 180, 210, and 240 minutes. As the peak concentration is expected to be within 60 to 180 minutes, the AUC value is considered invalid and set to missing if no C-peptide concentration is measured during this time period (60 minutes through 180 minutes, inclusive).

5.3.2. Analysis Methods

In the primary efficacy analysis, data from all randomized subjects will be analyzed according to their assigned treatment group regardless of the actual treatment received. The primary efficacy analyses are based on the full analysis set. To address the primary objective of the study, the primary endpoint will be analyzed by using a MMRM based on restricted maximum likelihood. No missing data handing rules will be utilized for this analysis. The model will be based on a normalizing transformation of log(AUC+1). The analysis will use post-baseline log(AUC+1) as the response variable and will include the fixed, categorical effects of treatment, time, gender and treatment-by-time interaction, as well as the continuous, fixed covariates of baseline,

baseline-by-time and age. The baseline will be in log(AUC+1) scale as well. An unstructured covariance will be used to model the within-patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom and adjust standard errors. The treatment comparison at Week 52 in terms of the least square mean difference and the 2-sided 95% confidence interval (CI) will be estimated based on this model. Descriptive statistics and estimates from the above model will be presented on the back-transformed scale. Specifically, the back-transformed mean is the geometric-like mean derived through exp(y)-1, where y = log(AUC+1). For transparency and completeness, descriptive statistics on the raw scale will be presented as well. Nominal p-values for treatment comparison will be provided for reference.

In addition, the estimated LS means of change from baseline in log(AUC+1) scale over time as well as the corresponding 60% and 95% CI from the mixed effect model will be provided by treatment group. Plot of Mean treatment difference at week 52 in change from baseline in log(AUC+1) scale will be also provided. Plot of mean 4-h C-peptide AUC by treatment group will be shown over time as well as plot of the individual 4-h C-peptide AUC over time.

5.3.2.1. Subgroup Analysis for the Primary Endpoint

The treatment difference of the primary endpoint by each subgroup factor listed in Section 2.3 will be explored and presented through forest plots. Subgroup analysis will not be performed on the sensitivity analyses described below.

5.3.2.2. Sensitivity Analysis

To test the robustness of the primary analysis results, sensitivity analyses will be conducted. The following sensitivity analyses will be performed:

In sensitivity analysis 1, the primary endpoint will be analyzed using the same model as in the primary analysis on **per-protocol population,** which is defined as all subjects in the full analysis set with exclusion of subjects identified by the study physician according to the blinded list of subjects with major protocol deviations that may potentially confound the primary efficacy endpoint.

In the sensitivity analysis 2, a random effect model will be fit with log(AUC+1) at all time points (including baseline) as the response variable, age, gender, time (continuous variable), treatment and treatment by time interaction as fixed effects, interception and slope as random effects. As time is a continuous effect, the study day of the C-peptide collection is used as time. No missing imputation is needed.

In sensitivity analysis 3, an analysis of covariance (ANCOVA) model with log(AUC+1) at Week 52 as the response variable, baseline log(AUC+1) and age as covariates, and treatment as a fixed factor will be performed. Missing data handling strategy of multiple imputation will be implemented Missing values will be imputed through Markov chain Monte Carlo (MCMC)

method. The analysis results based on each of the N = 10 imputed datasets will be pooled together to estimate treatment effects and test treatment difference at Week 52.

In sensitivity analysis 4, an analysis of covariance (ANCOVA) model with log(AUC+1) at Week 52 as the response variable, baseline log(AUC+1), gender and age as covariates, and treatment as fixed factors will be performed. Missing data handling strategy of linear extrapolation will be implemented.

In sensitivity analysis 5, comparing change from baseline in 4-hour C-peptide AUC by using non-parametric method rank analysis of covariance. For subjects with missing Week 52 value, the missing measurement will be imputed with linear extrapolated value.

In sensitivity analysis 6, constrained Longitudinal Analysis will be applied with log (AUC+1) including baseline as the response variable, the fixed, categorical effects of treatment, time, and treatment-by-time interaction, as well as the fixed covariate of age.

In sensitivity analysis 7, a similar model as in the primary analysis will be applied with covariates identified by a stepwise regression model on C-peptide AUC in log (AUC+1) scale at Week 52. The covariates in the stepwise regression will include sex, race (white, or not white), number of positive T1D related autoantibodies (≤ 3, >3), age, baseline weight, baseline HbA1c, number of days since diagnosis at randomization, and baseline C-peptide AUC in log (AUC+1) scale. For subjects with missing Week 52 value, the missing measurement will be imputed with linear extrapolated value.

5.4. Secondary Endpoints

The secondary endpoints are:

- Change from baseline in insulin use in units per kilogram body weight per day at Week 52.
- Change from baseline in HbA1c at Week 52.
- Hypoglycemic event rates (defined as blood glucose levels of ≤70mg/dL or clinical sequelae consistent with severe hypoglycemia in the absence of a BG reading) through Week 52.

This section outlines the definition and analyses of these major secondary endpoints. Data from all subjects in full analysis set will be included and analyzed according to the randomized treatment groups.

5.4.1. Definition

5.4.1.1. Insulin use in units per kilogram body weight per day

According to the protocol, subjects are to record daily the type and amount of insulin they have used during the 7-day period immediately preceding each study visit. As the target visit date and actual visit date can be different, insulin entry is available on eDiary during a 10-day period prior

to a scheduled visit. insulin use in units per kilogram body weight per day at a visit is calculated as the average of daily weight-adjusted total insulin usage during an 8-day period immediately preceding to a visit. A subject must have at least 3 daily insulin use records within the 8-day window prior to a visit for this calculation. Otherwise, the insulin usage will be regarded as missing for that visit.

Considering that subjects must have at least 5 days of daily insulin use recorded within the 7 days immediately preceding randomization, insulin use for a sensitivity analysis is defined. In this calculation, insulin use at a visit is calculated as the average of at least 5 days of recorded available data within 7-day period immediately preceding to the visit. If 3 or more days' data are missing during the 7-day period, then the value for that visit will be regarded missing.

5.4.1.2. Hypoglycemia event

This study uses the ADA suggested classification of hypoglycemia to guide the collection of episodes of asymptomatic and/or symptomatic hypoglycemia. Hypoglycemic events are collected through eDiary and are reviewed by investigators through hypoglycemic reconciliation form.

A hypoglycemic event is defined as either a biochemically confirmed hypoglycemic episode (ie, concurrent fingerstick glucose or plasma glucose ≤70 mg/dL (3.9 mmol/ L)), and/or a severe hypoglycemic event, as reported on eDiary, as follows.

- Biochemically documented hypoglycemia episode: a hypoglycemic episode with a concurrent reported glucose value of ≤70 mg/dL (3.9 mmol/ L), regardless of whether the episode is associated with symptoms (symptomatic hypoglycemia) or not (asymptomatic hypoglycemia).
- Severe hypoglycemic episode: a hypoglycemia episode that is considered an event requiring assistance of another person for support which may include administration of carbohydrates or glucagon. Such events do not need to have a documented blood glucose reading to be classified clinically as a severe hypoglycemic event.

Any events occurred within 1 hour are considered as one episode to avoid double-counting. The associated BG will be the minimum of those events within 1 hour. Summary and analysis of hypoglycemia events will be based on the manual algorithm.

On the hypoglycemia event reconciliation form, investigators are asked if they agree with eDiary captured hypoglycemia episode. If they agree that a hypoglycemia episode is indeed an event, then they will determine if it is a new episode or a continuation of a previous episode. This definition is applied in a sensitivity analysis of hypoglycemia event rates.

5.4.2. Analysis Methods

5.4.2.1. The change from baseline in insulin use and HbA1c at Week 52

Change from baseline in insulin use and change from baseline in HbA1c will be analyzed with an MMRM model based on a restricted maximum likelihood (REML) approach. The analysis will be based on observed data and will include the fixed, categorical effects of gender, treatment, time, and treatment-by-time interaction, as well as the continuous, fixed covariates of baseline and baseline-by-time interaction. An unstructured covariance will be used to model the within subject errors. The treatment comparisons will be made between Golimumab and placebo at Week 52 and significance tests will be based on the difference between the Least-Squares means. No missing imputation will be applied. Treatment effect in these endpoints will be estimated by the difference between the treatment groups along with their associated 95% confidence intervals.

5.4.2.2. Hypoglycemia event rate at Week 52

The number of hypoglycemia events per subject from the first study agent administration through Week 52 will be compared between treatment groups by using a Poisson regression model with treatment as fixed factor, baseline HbA1c and age as covariates, and the study participation through week 52 in logarithm as an offset variable. Hypoglycemia event rate will be estimated for each treatment group and the ratio of the rates and its and its 95% CI will be estimated as well.

5.4.2.3. Subgroup Analyses for Major Secondary Endpoints

The treatment difference of the major secondary endpoints by each subgroup factor listed in Section 2.3 will be explored and presented through forest plots. Subgroup analyses will not be performed on the endpoints defined for sensitivity analyses.

5.5. Other Efficacy Variables

Other efficacy variables include, but are not limit to the following:

C-peptide and proinsulin:

- MMTT-stimulated 4-hour C-peptide AUC over time.
- MMTT-stimulated 2-hour C-peptide AUC over time.
- peak MMTT-stimulated C-peptide over time.
- Fasting proinsulin over time.
- Fasting proinsulin /c-peptide ratio over time.
- The proportion of subjects with MMTT-stimulated 4-hour C-peptide AUC response over time

- The proportion of subjects with peak MMTT-stimulated C-peptide ≥ 0.2 pmol/mL over time.
- Time to peak MMTT-stimulated C-peptide <0.2 pmol/mL.

Hypoglycemia episodes

- Number of hypoglycemia episodes through Week 52 by quarter.
- Number of hypoglycemia episodes by American Diabetes Association (ADA) categorization[4]: symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, and ADA-defined severe hypoglycemia.

Insulin

- Change from baseline in insulin use in units per kilogram body weight per day over time.
- Proportion of subjects with insulin free over time.

HbA1c

- Change from baseline in HbA1c levels over time.
- Proportion of subjects reaching HbA_{1c} goal of <7% over time.
- Proportion of subjects reaching HbA_{1c} goal of <6.5% over time.
- Proportion of subjects with HbA_{1c} <7%, <6.5% and ≤5.7% at week 52.

Remission score

- Summary of Remission score over time
- Number of subjects in remission over time
- The proportion of subjects in remission among those in remission at baseline
- Remission duration among those in remission at baseline
- Number the subjects reached remission among those not in remission at baseline

Subjects with C-peptide response and in remission

- The proportion of subject with C-peptide response and in remission over time

T1D related auto-antibodies

- The proportions of subjects with positive T1D related auto-antibodies by count and type

5.5.1. Definitions

5.5.1.1. C-peptide responder

Subjects with decrease from baseline in 4-hour C-peptide AUC no more than 5% are defined as C-peptide responders.

5.5.1.2. Remission

Remission score is Insulin dose-adjusted HbA1c (IDDAA1c). It is defined as the summation of HbA1c value in percent and 4 times the average daily insulin usage/kg. A remission score ≤ is categorized as in remission.

5.5.1.3. Subjects with C-peptide response and in remission

Specifically, subjects with C-peptide response and in remission are referred to those with percent change from baseline in 4-hour C-peptide AUC >= -5% and a remission score ≤9 at a visit.

5.5.2. Analysis Methods

All analyses for other endpoints will be based on full analysis set unless otherwise specified.

For continuous endpoints, summary statistics (mean, standard deviation, median, IQ range, and range) will be presented by treatment group. For categorical endpoints, frequency counts and percentages will be presented by treatment group. Graphic presentations will be provided for some endpoints.

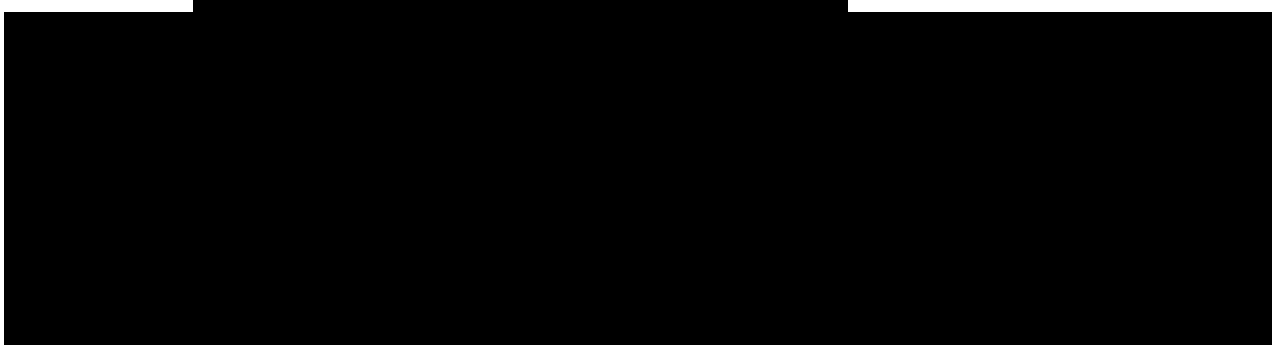
Treatment comparisons are presented for selected variables. Continuous endpoints will be analyzed using a mixed model repeated measures model to test the difference between treatment groups if deemed reasonable. Binary endpoints will be analyzed using a logistic regression in general. In case of complete separation, Chi-square test will be adopted. The hazard ratio for time to event data will be estimated using the Cox proportional hazards model and its 95% confidence interval will be calculated. The proportional hazards assumption will be verified with appropriate methods (e.g. log-minus-log plots) as part of the analysis. The survival curves will be estimated using Kaplan-Meier estimates.

Proportions of C-peptide responders at Week 52, subjects in remission at Week 52, and subjects who are C-peptide responders and in remission at Week 52 will be presented in subgroups defined by HLA-DR3 presence/absence and HLA-DR4 presence/absence. Forest plots will be created to represent treatment comparison in each of the subgroups.

There is no multiplicity adjustment for other efficacy endpoint analysis.

5.6. Exploratory Efficacy Analyses

5.6.1. [redacted]



5.6.2. [redacted]

[redacted]

6. SAFETY

Unless otherwise stated, all safety analyses will be based upon the safety analysis set. No formal statistical comparison is planned.

Safety will be assessed by summarizing the incidence and type of AEs and examining changes in laboratory parameters (hematology and chemistry) and vital signs. There will be no imputation of missing values for clinical laboratory test results, vital sign measurements in the safety analyses.

In the safety analyses, subjects will be analyzed according to the treatment they actually received, regardless of the treatments they are randomized to. More specifically, if a subject only received one study agent, either golimumab or placebo, he/she will be analyzed under the treatment received. In rare situations of erroneous study agent switch, if a subject started to receive golimumab but with a wrong dose of placebo in the middle, the subject will be summarized in golimumab group. If a subject started to receive placebo but with a wrong dose of golimumab, the subject will be summarized under placebo until receiving golimumab and then under golimumab. The safety information of any subjects with wrong dosing will be listed.

6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE starting at or after the initial administration of study agent through the end of the trial is considered to be treatment emergent. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be

considered to be treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date.

All reported treatment-emergent adverse events will be included in the analysis. Treatment-emergent adverse events (TEAEs) by system organ class and preferred term (ie, number and proportion of subjects with one or more TEAEs within a system organ class) will be summarized by treatment group.

The following TEAE summary tables will be provided:

- Any TEAEs
- TEAEs by severity
- Serious treatment-emergent adverse event (SAEs)
- Reasonably related TEAEs
- Frequent TEAEs
- TEAEs leading to study agent discontinuation
- Injection site reactions
- TEAEs of special interest such as hypoglycemia events, infections, tuberculosis, malignancies

These summary tables will provide the count and percentage of subjects with 1 or more of the specified AEs by treatment group, and by system-organ class/preferred term respectively.

In order to support the additional assessment of particular categories of adverse events, addition summary is done on selected adverse events. The number and percent of subjects with the following selected TEAEs will be summarized by treatment group:

In addition to the summary tables, listings of subjects with the following AEs will be provided:

- Death
- Serious TEAEs
- TEAEs leading to discontinuation of study agent
- Hypoglycemia episodes reported as TEAEs
- Key Safety findings including malignancies, opportunistic infections, a new autoimmune disease or worsening of an existing autoimmune disease, and so forth.

6.2. Clinical Laboratory Tests

Clinical laboratory values are to be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 (see Table 4). The laboratory data to be summarized are as follows:

Hematology Panel

-hemoglobin -white blood cell (WBC) count with differential

-hematocrit -platelet count

Serum Chemistry Panel

-sodium -calcium

-potassium -phosphate

-chloride -albumin

-bicarbonate -total protein

-blood urea nitrogen (BUN) -total and direct bilirubin

-creatinine -aspartate aminotransferase (AST)

-glucose -alanine aminotransferase (ALT)

-alkaline phosphatase

Additional Laboratory Tests

- C-reactive protein

- CD4 T-cell count

-CMV and EBV DNA PCR

-Lipids (cholesterol, HDL, LDL, Triglycerides)

The following clinical laboratory data analyses will be performed:

- Descriptive summary of the observed values and changes from baseline over time through Week 52.
- Descriptive summary of maximum NCI-CTCAE toxicity grade for postbaseline laboratory values through Week 52 for parameters listed in Table .
- Shift tables, using normal reference ranges, will also be presented for those laboratory parameters at each visit on which the laboratory tests are scheduled.
- Descriptive summary of maximum postbaseline measurement through Week 52 for ALT, AST and alkaline phosphatase and total bilirubin relative to ULN.
- Listings of subjects with any abnormal postbaseline laboratory values of CTCAE grade ≥2 will also be provided.

The baseline value for a subject is the value closest to but prior to the first dose of study agent (Week 0). Shift tables summarize the number of subjects with low, normal, and high values

(determined by the laboratory normal ranges) at the post baseline visit for each of the classifications of low, normal, and high at baseline.

Table 4: Grading Criteria for Clinical Laboratory Tests [CTCAE Version 4.03]

Hematology Tests		**Criteria**			
Test	**Direction**	**1**	**2**	**3**	**4**
Hemoglobin (g/L)	Decrease	≥100 - <LLN	≥80 - <100.0	≥65 - <80	<65
Neutrophils (10^9/L)	Decrease	≥1.5 - <LLN	≥1.0 - <1.5	≥0.5 - <1.0	<0.5
Platelets (10^9/L)	Decrease	≥75.0 - <LLN	≥50.0 - <75.0	≥25.0 - <50.0	<25.0
Total WBC count (Leukocytes 10^9/L)	Decrease	≥3.0 - <LLN	≥2.0 - <3.0	≥1.0 - <2.0	<1.0
Lymphocytes (10^9/L)	Decrease	≥0.8 - <LLN	≥0.5 - <0.8	≥0.2 - <0.5	<0.2
Chemistry Tests		**Criteria**			
Test	**Direction**	**1**	**2**	**3**	**4**
ALT	Increase	>ULN - ≤3.0 xULN	>3.0 xULN - ≤5.0 xULN	>5.0 xULN - ≤20.0 xULN	>20.0 xULN
AST	Increase	>ULN - ≤3.0 xULN	>3.0 xULN - ≤5.0 xULN	>5.0 xULN - ≤20.0 xULN	>20.0 xULN
Albumin (g/L)	Decrease	≥30 - <LLN	≥20 - <30	<20	
Alkaline Phosphatase	Increase	>ULN - ≤2.5 xULN	>2.5 xULN - ≤5.0 xULN	>5.0 xULN - ≤20.0 xULN	>20.0 xULN
Bilirubin (total)	Increase	>ULN - ≤1.5 xULN	>1.5 xULN - ≤3.0 xULN	>3.0 xULN - ≤10.0 xULN	>10.0 xULN
Calcium (mmol/L)	Increase	>ULN - ≤2.9	>2.9 - ≤3.1	>3.1 - ≤3.4	>3.4
Calcium (mmol/L)	Decrease	[Albumin ≥40 g/L or missing and calcium ≥2.0 - <LLN]; or [Albumin < 40 g/L and (calcium – 0.8 x (albumin – 40)) ≥2.0 - <LLN]	[Albumin ≥40 g/L or missing and calcium ≥1.75 - <2.0]; or [Albumin < 40 g/L and (calcium – 0.8 x (albumin – 40)) ≥1.75 - <2.0]	[Albumin ≥40 g/L or missing and calcium ≥1.5 - <1.75]; or [Albumin < 40 g/L and (calcium – 0.8 x (albumin – 40)) ≥1.5 - <1.75]	[Albumin ≥40 g/L or missing and calcium <1.5]; or [Albumin < 40 g/L and (calcium – 0.8 x (albumin – 40)) <1.5]
Creatinine	Increase	>ULN - ≤1.5 xULN	>1.5 xULN - ≤3.0 xULN	>3.0 xULN - ≤6.0 xULN	>6.0 xULN
Phosphate (mmol/L)	Increase	>ULN - ≤5.5	>5.5 - ≤6.0	>6.0 - ≤7.0	>7.0
Phosphate (mmol/L)	Decrease	≥0.8 - <LLN	≥0.6 - <0.8	≥0.3 - <0.6	<0.3
Potassium (mmol/L)	Increase	>ULN - ≤5.5	>5.5 - ≤6.0	>6.0 - ≤7.0	>7.0
Potassium (mmol/L)	Decrease	≥3.0 - <LLN		≥2.5 - <3.0	<2.5
Sodium (mmol/L)	Increase	>ULN - ≤150	>150 - ≤155	>155 - ≤160	>160
Sodium (mmol/L)	Decrease	≥130 - <LLN		≥120 - <130	<120

6.3. Vital Signs

Descriptive statistics (N, mean, standard deviation, median, and range) will be reported for systolic and diastolic blood pressure (SBP and DBP) and pulse at each scheduled time point for absolute value and for change from baseline. In addition, a listing of subjects with abnormal vital signs (temperature, respiration rate, pulse rate, diastolic blood pressure and systolic blood pressure) will be presented with change from baseline vital sign values.

Vital sign parameters will be considered abnormal by using the criteria listed below.

Markedly Abnormal Blood Pressure by Age and Gender

Age (years)	Male		Female	
	Systolic BP (≥ value)	Diastolic BP (≥ value)	Systolic BP (≥ value)	Diastolic BP (≥ value)
6	105	68	104	68
7	106	70	106	69
8	107	71	108	71
9	109	72	110	72
10	111	73	112	73
11	113	74	114	74
12	115	74	116	75
13	117	75	117	76
14	120	75	119	77
15	120	76	120	78
16	120	78	120	78
17	120	80	120	78
≥ 18	120	80	120	80

Note: Age here is the calculated age at visits (when lab samples are taken).

Markedly Abnormal Heart Rates by Age

Age (years)	Abnormal low value (less than)	Abnormal high value (greater than)
6- <11	65	115
11- <16	55	110

16- <21	55	105
21 and older	45	85

7. CLINICAL PHARMACOLOGY

7.1. Pharmacokinetics

Pharmacokinetics (PK) samples for measuring serum golimumab concentrations will be collected from all subjects at the specified visits as shown in the schedule of events of the protocol. All PK evaluations will be based on the subjects who receive at least 1 injection of golimumab (PKE analysis set). No imputation for missing concentration data will be performed.

The data analysis of serum golimumab concentrations includes the following:

- Summary of serum golimumab concentrations at each visit by treatment group
- Summary of serum golimumab concentrations at each visit by age group (≥ 6 to < 12 Years, ≥ 12 to < 21 Years)
- Summary of serum golimumab concentrations by treatment group and by body weight quartiles
- Summary of serum golimumab concentrations by treatment group and by body weight category (< 45 kg, ≥45 kg)
- Proportion of subjects without detectable serum golimumab concentration at each visit by treatment group
- Median serum golimumab concentrations plotted over time by treatment group

In addition, the relationship between serum golimumab concentrations, and antibody to golimumab status, safety and efficacy may be explored using graphical displays.

For summary statistics of serum golimumab concentrations, concentration values below the lower limit of quantification will be treated as zero. Once a subject meets one of the following dosing deviation criteria, the subject's data will be excluded from the by-visit data analyses from that point onwards.

Dosing deviation criteria:

- Discontinue SC study agent administration

- Skipped an SC administration
- Received an incomplete/incorrect SC dose
- Received an incorrect SC study agent
- Received and additional SC dose

In addition, if a subject has an administration more than 7 days earlier or later than the scheduled dosing date, the concentration data collected between such a dosing visit and the subsequent dosing visit will be excluded from the by-visit data analyses. For the Week 26 visit, if the PK sampling time deviates more than 3 days earlier or later than the scheduled date, the PK concentration at this visit will be excluded from the by-visit data analyses. Additional exclusions for incongruous PK data to be implemented based on Janssen SOP-07948v2.

Population PK analyses may be performed to characterize the population PK parameters based on the available golimumab concentration data obtained through the Week 52 visit. The population pharmacokinetic approach will also be used to identify and quantify any significant covariates such as demographic characteristics (including but not limited to body weight, ethnic origin, sex, and age) and concomitant medications that have substantial impact on the population pharmacokinetics of golimumab in subjects with T1D. A detailed analysis plan for population PK analysis will be developed separately, and a stand-alone technical report will be written to summarize the results of the population PK analysis.

PK Analyses Presentation

PK analyses will be summarized through Week 52:

For the analyses, a subject is included in one and only one treatment group on the basis of the treatment regimen followed. The description of the treatment group is as follows:

- Golimumab q2w

7.2. Immunogenicity

Blood samples will be collected to examine the formation of antibodies to golimumab at the specified visits as shown in the schedule of events of the protocol. For subjects who discontinue SC study agent administrations, samples will be collected at their 2 months safety follow-up visit. All immunogenicity evaluations will be based on the subjects who receive at least 1 injection of study agent (Safety analysis set).

For the analyses, a subject is included in one and only one treatment group on the basis of the treatment regimen followed. The description of the treatment groups are as follows:

- Golimumab q2w

The data analysis of antibodies to golimumab includes the following:

- The antibody status (positive, negative) of subjects will be summarized by golimumab treatment groups. For subjects who discontinue SC study agent administrations and complete 2 months safety follow-up, a listing of their antibody status will be presented.

- The relationship between antibody to golimumab status and efficacy evaluations will be assessed at Week 52: C-peptide AUC by antibody to golimumab status and treatment group.

- The relationship between antibody to golimumab status and safety will be assessed at Week 52: Injection-site reactions by antibody to golimumab status and treatment group.

- Onset and duration of antibody formation

- Table and figure of serum golimumab concentrations by antibody to golimumab status.

7.3. Pharmacodynamics

Summary statistics of total and free TNFα values and change from baseline will be evaluated. TNFα values below the lower limit of quantification will be treated as zero.

PD Analyses Presentation

PD analyses will be summarized through the Week 52:

For the analyses, a subject is included in one and only one treatment group on the basis of the treatment regimen followed. The description of the treatment groups are as follows:

- Golimumab q2w

7.4. Pharmacokinetic/Pharmacodynamic Relationships

The relationship between serum golimumab and pharmacodynamic markers may be explored. Scatter plots of serum golimumab concentrations versus TNFα (total and free), fasting blood glucose, plasma glucose, HbA1c, insulin and c-peptide may be generated. If PK/PD modeling is performed, the results will be reported in an independent technical report.

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