**Janssen Research & Development ***

**Clinical Protocol**

# SIMPONI® to Arrest β-cell Loss in Type 1 Diabetes

**T1GER**

**Protocol CNTO148DML2001; Phase 2a**
**Amendment 3**

**SIMPONI® (golimumab)**

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This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

**Status:** Approved
**Date:** 23 August 2019
**Prepared by:** Janssen Research & Development, LLC
**EDMS number:** EDMS-ERI-113134249, 4.0

**GCP Compliance:** This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Amendment 3 | 22 Aug 2019 |
| Amendment 2 | 09 May 2016 |
| Amendment 1 | 02 Jun 2016 |
| Original Protocol | 26 Apr 2016 |

### Amendment 3 (22 August 2019)

**Overall Rationale for the Amendment:** Subsequent to the granting of a single patient investigational new drug for a subject who had shown an increase in C-peptide at Week 52 and who had an insulin dose-adjusted HbA1c (IDAA1c) score less than 9, the Data Monitoring Committee recommended to re-start active treatment for other subjects showing a similar response profile.

| **Section number and Name** | **Description of Change** | **Brief Rationale** |
|---|---|---|
| Time and Events Schedule | Created the time and events schedule for open-label extension period and defined timepoints and study procedures for this period. The existing schedule was indicated for double-blind period. Abbreviations used in the table were mentioned in the footnote. | To accommodate the open-label extension period of the study. |
| Synopsis;<br>2.1. Objectives, Endpoints, and Hypothesis;<br>9.2.2.4. Exploratory Efficacy Endpoints – Open-Label Extension Period;<br>9.2.3.1. Safety Endpoints – Open-Label Extension Period;<br>11.3.1. Exploratory Efficacy Analyses – Open-Label Extension Period;<br>11.9. Safety Endpoints and Analyses | The endpoints for open-label extension period were defined. | |
| 6.2. Dose Administration | A reference to Section 9.1.5 in addition to the existing Section 9.1.3 was mentioned for the procedure where subjects were to be monitored for at least 30 minutes following dosing. | |
| Synopsis;<br>3.1. Overview of Study Design;<br>4.1.2. Additional Inclusion Criteria for Responders<br>9.1.1. Overview;<br>9.2.1.1. Efficacy Evaluation | The requirement and timing of mixed-meal tolerance test (MMTT) was differentiated for the double-blind and open-label extension periods. | To check for any changes in C-peptide AUC and to clarify the timing of 4-hour MMTT for the double-blind and open-label extension periods. |
| Synopsis;<br>3.1. Overview of Study Design;<br>4.1.2. Additional Inclusion Criteria for Responders;<br>9.1.1. Overview;<br>9.2.1.1. Efficacy Evaluation | The requirements for C-responders lacking IDAA1c score were mentioned. | To accommodate the C-responders without IDAA1c score. |

| Section number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis;<br>3.1. Overview of Study Design | The study design was amended to indicate that responders would have an option to restart active therapy while non-responders would continue to follow the originally planned study design. The definition and criteria for responders were defined. | The data monitoring committee (DMC) for the study recommended that responders should have an option to receive active therapy. |
| Synopsis;<br>3.2.1. Blinding, Control, Study Periods, Treatment Groups | The criteria for unblinding subjects after database lock of double-blind period was specified. Requirement of full renewed informed consent was mentioned. Additionally, the conditions under which the subjects can continue off-therapy follow-up period were stated. | Following an amendment in the study design, the blinding/unblinding requirements and a renewed informed consent process for the off-therapy follow-up period required an update. |
| Synopsis;<br>3.2.1. Blinding, Control, Study Periods, Treatment Groups;<br>16.2.3. Informed Consent and Assent Form | Specified that signing of new ICF/assent forms will be required if subject meets the responder's criteria and enters the open-label extension period. | To clarify the requirement of informed consent and assent forms for open-label extension period. |
| 1. Introduction | The author reference 'Lind M, 2014' was removed since the reference number was cited. | To maintain consistency in citation of reference numbers instead of author names. |
| 3.1. Overview of Study Design | The following text was modified as: Following **initial study** screening, subjects must be randomized within 28 days. | To indicate that the screening period mentioned within text belonged to double-blind period. |
| 3.1. Overview of Study Design | The number of planned data base locks were modified for the study from 2 to 3 and the timing of the third data base lock was defined. | Following an amendment in the study design, the data base lock due to inclusion of the open-label extension period was defined. |
| 4.1.1. Inclusion Criteria Applicable to All Subjects Criterion 6;<br>4.4. Prohibitions and Restrictions Criteria 3, 4, and 6;<br>8.3. Prohibited Medications. | The criteria were updated to include open-label extension period. | To indicate that the criteria were applicable for open-label extension period as well. |
| Synopsis;<br>4.1.2. Additional Inclusion Criteria for Responders | Additional inclusion criteria for "responders" who were to receive active drug in the open-label extension period was defined. | To identify patients eligible to continue receiving therapy in the open label extension period. |
| 4.2.1. Exclusion Criteria applicable to All Subjects Criteria 22 and 23 (General Restrictions) | The criteria were modified to indicate that they were not applicable for the CNTO148DML2001 trial. | To exclude CNTO148DML2001 trial from the exclusion criteria. |
| 4.2.2 Additional Exclusion Criteria for Responders | Additional exclusion criteria for "responders" was defined. | Individuals who do not meet response criteria will not be eligible for open-label extension period. |
| 4.3. Exceptions to Inclusion and Exclusion Criteria for Open-Label Extension Period | The exceptions to the initial inclusion and exclusion criteria for the subjects from open-label extension period were stated. | To include subjects who may be older than 21 years, may have become auto-antibody negative, and negative Epstein-Barr Virus (EBV) polymerase chain reaction (PCR) results. |
| 4.4. Prohibitions and Restrictions Criteria 5 and 7 | Modified the term 'through Week 104' to 'throughout the study' | To accommodate the open-label extension period of the study. |

| Section number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5. Treatment Allocation and Blinding | Modified the following text: The Study Responsible Physician will remain blinded throughout the ~~study~~ **double-blind period** to subject level treatment assignment and dosing regimen. | To follow the amended study design and indicate that blinding is specific to double-blind period. |
| 5. Treatment Allocation and Blinding | • Revised the following text to exclude the term 'final': Site investigators and personnel, and the subjects/caregivers will remain blinded until after the ~~final~~ Week 104 DBL (DBL 2) has occurred.<br>• Added the following text: An exception to this rule will be made for those subjects who are meeting the responder criteria at Week 52 of the double-blind period. These will be unblinded to determine eligibility for re-starting active treatment during the open-label extension period. | To clarify that Week 104 DBL is not the final DBL and specify the condition for unblinding. |
| 6.1. Dosage | The responders will not undergo an induction regimen but will start with the maintenance dose was specified. The reason for this was also specified. | To clarify that no induction regimen will be used to avoid risk for immunogenicity or hypersensitivity reactions. |
| 7.1.1.1. Dosing Recording;<br>9.1.1. Overview;<br>9.1.2.1. Screening Period;<br>9.6.1. Safety Evaluations;<br>9.8. Data to be Collected by Subjects | Use of paper diary for open-label extension period was specified. | To clarify usage of paper diaries instead of eDiaries for the open-label extension period. |
| 8.1. Required Medications | A reference to Section 9.8 was provided to indicate paper diary usage for open-label extension period. | |
| Synopsis;<br>2. Objectives, Endpoints, and Hypothesis | Added objective and endpoint for open-label extension period and clarified that the existing objectives and endpoints belonged to double-blind period. | To accommodate the open-label extension period and differentiate and provide clarity between the double-blind and open-label extension periods. |
| 3.1. Overview of Study Design | • Added schematic overview of the open-label extension period.<br>• Renamed Figure 1 title from 'Schematic Overview of the Study' to 'Schematic Overview of the **Double-Blind Period**'. | |
| 6.1. Dosage;<br>Table 1 | Study agent dosage and timings of dosage calculation for open-label extension period were mentioned. | |
| 6.2. Dose Administration | Responsibility and timings of study agent administration for responders in the open-label extension period was added. | |
| 7.1.1.1. Dosing Recording – Open-Label Extension Period | A separate section to define the dose recording for open-label extension period was added. | |
| 7.1.2.1. Dosing Windows - Open-Label Extension Period | A separate section to define the dosing windows for open-label extension period was added. | |
| 8.1. Required Medications; | The timing of recording insulin use for | |

| Section number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 9.8. Data to be Collected by Subjects | open-label extension period was added. | |
| 9.1.1. Overview;<br>16.1. Study-Specific Design Considerations | Blood volume collection for open-label extension period was added. | |
| 9.1.2.1. Screening Period – Open-Label Extension Period;<br>9.1.4. Optional Screening – Open-Label Extension Period | A separate section to define the screening period for the open-label extension period was added. | |
| 9.2.1.1. Efficacy Evaluations – Open-Label Extension Period;<br>9.3.5.Clinical Pharmacology – Open-Label Extension Period;<br>9.4.1. Biomarkers – Open-Label Extension Period.;<br>9.5.1. Pharmacogenomic (DNA) Evaluations – Open-Label Extension Period;<br>9.6.1. Safety Evaluations – Open-Label Extension Period | Separate sections for efficacy, clinical pharmacology, biomarkers, pharmacogenomic, and safety evaluations that pertain to open-label extension period were added. | |
| 9.1.5. Open-Label Extension Period | The different periods, ie, active treatment, and post-treatment visit for the open-label extension period were described. The study agent self-administration and study procedures at different timepoints were also described. | |
| 9.1.6. All Study Visits – Early Detection of Active Tuberculosis | A reference to Section 9.1.2.1 was added to indicate the procedure to be followed if the QuantiFERON-TB Gold test is indeterminate. | |
| 10.1. Completion | The study completion criteria for open-label extension period was specified and the text was modified as: A subject will be considered to have completed the study if he or she has completed assessments at Week 104 of the ~~study~~ **off-therapy follow-up period or Week 60 of the open-label extension period of the study.** | |
| 10.2. Discontinuation of Study Treatment/Withdrawal from the Study | A reference to Section 9.1.2.1 was added under the TB screening criteria for subject to deem ineligible. | |
| 11. Statistical Methods | The definition on baseline measurement for the open-label extension period was added and the existing definition was indicated for the double-blind period. | |
| 11.3.1. Exploratory Efficacy Analyses – Open-Label Extension Period | The exploratory efficacy analyses for open-label extension period were added. | |
| 8. Prestudy and Concomitant Therapy | The recording of prestudy therapies in the CRF was indicated for double-blind period. | To clarify that the prestudy therapies belonged to double-blind period. |
| 9.8. Data to be Collected by Subjects | The criteria for transmitting BG readings from the glucometers was added for the double-blind period. | To specify the condition when the BG readings from glucometer be transmitted. |

| Section number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Synopsis;<br>9.2.1.1. Efficacy Evaluations – Open-Label Extension Period;<br>9.8. Data to be Collected by Subjects | The acceptable glucose monitoring techniques and recording and frequency of BG values for open-label extension period were defined. | To provide acceptable glucose monitoring techniques for open-label extension period. |
| 9.9. Injection Site Reaction Monitoring | Modified the following text: A physician must be immediately available at the site during the first 3 dose administrations of study agent **for the double-blind period and open label treatment period.** | To clearly define the availability of physician at the site during study agent dose administrations. |
| 10.2. Discontinuation of Study Treatment/Withdrawal from the Study | Added the following text: Subjects who permanently discontinue active treatment during the open-label extension period will have their end-of-study visit followed by the post-treatment visit 10 weeks later. | To define that an end-of-study visit will be performed for the subjects who discontinue active treatment during open-label extension period. |
| 10.2. Discontinuation of Study Treatment/Withdrawal from the Study | The withdrawal criteria for responders was specified. | Withdrawal criteria are based on deterioration of C-peptide AUC and/or remission score, similar to eligibility criteria |
| Synopsis;<br>11. Statistical Methods | Specified that hypotheses testing for open-label extension phase will not be performed and data generated will be summarized descriptively. | Provided for data analyses of open-label extension portion. |
| 11.10. Statistical Methods | Added the following text: The DMC serves the IAC function. | To clarify that the DMC is also the IAC for the study. |
| 11.4. Pharmacokinetic Analyses;<br>11.5. Immunogenicity Analyses (Antibodies to Golimumab);<br>11.6. Biomarker Analyses;<br>11.7. Pharmacokinetic/Pharmacodynamic Analyses;<br>11.9. Safety Endpoints and Analyses | A statement to indicate that the analyses performed for double-blind period were applicable for the open-label extension period was mentioned. | To specify the analyses for the open-label extension period. |
| 11.8. Pharmacogenomic analyses | Added the pharmacogenomic analyses for the open-label extension period. | |
| Abbreviations | New abbreviations, ie, C responders, C+R responders, IDAA1c, PCR, OL, and R responders were added. | To accommodate the new terms/abbreviations from the additions/revisions to the protocol. |
| References | Following literature references were added,<br>• Fonolleda M, Murillo M, Vazquez F, Bel J, Vives-Pi M. Remission Phase in Paediatric Type 1 Diabetes: New Understanding and Emerging Biomarkers. Horm Res Paediatr 2017;88:307–315<br>• Max Andersen MLC et al. Partial remission definition: Validation based on the insulin dose-adjusted HbA1c (IDAA1C) in 129 Danish children with new-onset type 1 diabetes. Pediatr Diabetes. 2014;15(7):469–476. | References added to support the updated study design |

| Section number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | • Mortensen H. B., Hougaard P., Swift P., et al. New definition for the partial remission period in children and adolescents with type 1 diabetes. Diabetes Care. 2009;32(8):1384–1390.<br>• Nagl K, Hermann JM, Plamper M, et al. Factors contributing to partial remission in type 1 diabetes: analysis based on the insulin dose-adjusted HbA1c in 3657 children and adolescents from Germany and Austria. Pediatr Diabetes 2017;18:428-434. | |
| Throughout | • Minor formatting, editorial, or spelling changes were made.<br>• The term 'participant' was replaced with 'subject' across the protocol for consistency. | Minor, therefore have not been summarized. |
| | • Added 'OL' before week numbers that pertained to the open-label extension period.<br>• Added 'double-blind' against week numbers or periods that pertained to the double-blind period. | To differentiate between open-label extension and double-blind periods. |

## SYNOPSIS

SIMPONI® to Arrest β-cell Loss in Type 1 Diabetes

SIMPONI® (golimumab) is a fully human monoclonal antibody which binds to human tumor necrosis factor alpha (TNFα) with high affinity and specificity and neutralizes TNFα bioactivity. Golimumab was first approved by the United States Food and Drug Administration (FDA) in 2009 and has been shown to be safe and efficacious in adults with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and ulcerative colitis (UC). Additionally, golimumab has been evaluated in studies conducted under an Investigational New Drug (IND) for the treatment of polyarticular juvenile idiopathic arthritis (pJIA; 2 up to 18 years of age), and pediatric UC (2 up to 18 years of age).

Similar to these above conditions, Type 1 diabetes (T1D) is an autoimmune disorder with severe sequelae, but there are no approved disease modifying therapies for those with T1D. Children and young adults are those that most frequently develop T1D and have the most urgent need for a disease modifying therapy to reduce the associated short- and long-term morbidity and mortality. This study will evaluate whether golimumab administered subcutaneously (SC) in this population with newly diagnosed T1D has the potential to maintain residual β-cell function and improve metabolic control.

### OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

- Double-Blind Period

| Objectives | Endpoints |
|---|---|
| **Primary Objective and Endpoints** | |
| • To determine if golimumab can preserve β-cell function in children and young adults with newly diagnosed T1D. | • The Mixed-meal Tolerance Test (MMTT) - stimulated 4-hour C-peptide area under the concentration-time curve (AUC) at Week 52. |
| **Secondary Objectives and Endpoints: Efficacy** | |
| • To evaluate the impact of golimumab on measures of diabetes control in this subject population.<br>• To evaluate the off-therapy durability of golimumab on measures of diabetes control in this subject population. | • Change from baseline in insulin use in units per kilogram body weight per day over time.<br>• Change from baseline in HbA1c over time.<br>• Hypoglycemic event rates (defined as blood glucose levels (BG) of ≤70, 55, and 35 mg/dL or clinical sequelae in the absence of a BG reading) through Week 52, after Week 52 through Week 104, and the entire study.<br>• MMTT-stimulated 4-hour C-peptide AUC over time. |
| **Secondary Objective and Endpoints: Safety** | |
| • To determine the safety and tolerability of golimumab in children and young adults with T1D. | • Proportion of subjects with treatment-emergent adverse events (AEs) and severe AEs through Week 52 and 104.<br>• Proportion of subjects with severe infections through Week 52 and 104.<br>• Proportion of subjects with study agent injection site reactions through Week 52. |

| Objectives | Endpoints |
|---|---|
| **Secondary Objective and Endpoints: Pharmacokinetics (PK) and Immunogenicity** | |
| • To evaluate the PK and immunogenicity of golimumab in this specific subject population with T1D. | • Summary of serum golimumab concentrations and the PK profile after induction and maintenance dosing.<br>• Incidence and titers of antibodies to golimumab. |
| **Exploratory Objective and Endpoints: Immunologic and Metabolic** | |
| • To evaluate how golimumab impacts immunologic profiles and indicators of β-cell stress, and the correlation with efficacy and safety endpoints in this study. | • Correlation of cellular and serologic immune profiles with clinical metabolic outcomes on-therapy (Weeks 12, 26, 38, and 52) and off-therapy (Weeks 78 and 104).<br>• Relationship of exploratory markers of β-cell stress and survival with clinical metabolic outcomes on-therapy (Weeks 12, 26, 38, and 52) and off-therapy (Weeks 78 and 104). |

- Open-Label Extension Period

| Objective | Endpoint |
|---|---|
| • To evaluate additional one year of safety and exploratory efficacy endpoints in those participants that have shown a particular response in the double-blind period. | • Continue to evaluate safety and exploratory efficacy endpoints as per the Time and Events Schedule (open-label extension period) and no new efficacy hypotheses will be tested compared to the double-blind period. |

**Hypothesis**

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 mixed-meal tolerance test (MMTT)-stimulated 4-hour C-peptide AUC at Week 52.

**OVERVIEW OF STUDY DESIGN**

This is a Phase 2a randomized, double-blind, placebo-controlled, parallel-group, multicenter, study of golimumab in subjects with new-onset T1D.

The duration of study participation will be 108 weeks, including screening and post-randomization. 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.

Responders at Week 52 who are still in the follow-up period and who are determined to be in the active treatment group will have the option to restart active therapy while the non-responders will continue to follow the originally planned study design, ie, the off-therapy follow-up monitoring period.

There will be an open-label extension period of the study for responders. Responders are defined as subjects who have profile at Week 52 which includes:

1. C-peptide and Remission score* responders (C+R responders): either having an increase in C-peptide AUC versus baseline or having a stable C-peptide AUC, not decreasing more than 5% versus baseline and having a remission score ≤9.

   OR

2. C-peptide responders (C responders): either having an increase in C-peptide AUC versus baseline or having a stable C-peptide AUC, not decreasing more than 5% versus baseline but not meeting a remission score of ≤9. Their remission score, however, must be <12.

   OR

3. Remission score responders (R responders): having a remission score ≤9 but not meeting C-peptide response as defined above. However, their C-peptide AUC decline from baseline should be less than or equal to 30% compared to baseline.

*Insulin Dose Adjusted HbA1c: IDAA1c= A1C (percent) + [4 × insulin dose (units per kilogram per 24 h)].

This study will enroll male and female subjects 6 through 21 years of age who have been recently diagnosed with T1D and are able to be randomized within 100 days of diagnosis. A target of approximately 81 subjects will be randomly assigned in a 2:1 ratio to receive golimumab or placebo, administered SC for 52 weeks and monitored for an additional 52 weeks. Subjects will be randomized to receive active therapy (golimumab) or placebo and be stratified based on C-peptide AUC levels of <0.66 pmol/mL or ≥0.66 pmol/mL from a 4-hour MMTT conducted at study screening. The protocol will give the option for study agent administration by the subject or caregiver outside of the study site, ie, self-administration, after proper training.

An independent Data Monitoring Committee will be commissioned to continually assess the safety of study subjects.

Following database lock for the double-blind treatment period (Week 52), subjects who are still in the off-therapy follow-up period (Week 52 to 104 visits), who were on active drug during the double-blind period and who meet the response criteria will be offered the option to participate in the open-label extension period if eligibility criteria are met. Prior to initiating open-label screening assessments, subjects and parents/legal guardians will sign updated informed consent form/assent forms.

Subjects who did not meet the response criteria at Week 52 will continue the off-therapy follow-up period.

Subjects who met the response criteria but either declined to participate in the open-label extension period, or were determined to be on placebo, will continue the off-therapy follow-up period as planned.

**SUBJECT POPULATION**

Male or female subjects 6 through 21 years of age who meet the American Diabetes Association (ADA) standard T1D criteria within 100 days of randomization. Subjects must be positive for at least 1 of the following diabetes-related autoantibodies obtained at study screening:

- Glutamic acid decarboxylase (GAD-65)
- IA-2
- ZnT8
- ICA; or
- Insulin (if obtained within 10 days of the onset of exogenous insulin therapy)

Subjects must be medically stable on the basis of physical examination, medical history, and vital signs performed at screening and have a stimulated C-peptide level ≥0.2 pmol/mL following a 4-hour MMTT obtained at study screening.

The responders for open-label extension period must meet the MMTT criteria at Screening for the open-label extension period. If the most recent MMTT is <3 months ago, a repeat MMTT is not required. Subjects who had their most recent safety laboratory samples drawn within 1 month prior to screening do not need a repeat; eligibility will be assessed based on these most recent laboratory tests. For C-responders who are lacking the necessary information to calculate IDAA1c score, an HbA1c will be performed and 10 days of insulin dose information will be required.

**DOSAGE AND ADMINISTRATION**

All study agent (golimumab or placebo) will be administered subcutaneously using a sponsor-supplied, single-use administration device. This will be either the commercially available prefilled syringe with needle guard (the PFS-Ultrasafe [PFS-U]), designed to deliver a single, fixed dose of 50 mg, or the investigational VarioJect injection device ("VarioJect") which delivers a single, variable dose of 10 to 45 mg in 5 mg increments. Identical devices containing placebo will be used to deliver a volume equivalent to that of active treatment for subjects randomized to the placebo arm.

**EFFICACY EVALUATIONS**

The following efficacy evaluations will be assessed:

- A 4-hour MMTT will be performed to assess C-peptide levels and the C-peptide AUC at screening and Weeks 12, 26, 38, 52, 78, and 104 of the double-blind period. During the open-label extension period, a 4-hour MMTT will be performed at OL screening (unless performed <3 months ago), OL Week 28, and OL Week 52. For C-responders who are lacking the necessary information to calculate IDAA1c score, an HbA1c will be performed and 10 days of insulin dose information will be required. For additional details, see the Time and Events Schedule.
- Blood glucose levels between visits will be obtained by downloading home-glucometer readings. During the open-label extension period, subjects may use either fingersticks or continuous glucose monitoring (CGM) at the discretion of the investigator and/or according to local practice. The subjects will not be required to download BG values from the eDiary.
- Hemoglobin A1c (as % HbA1c) and insulin as U/kg body weight/day. An HbA1c measurement will be done at each study visit and subjects should record the type and amount of insulin they have used during the 7-day period immediately preceding each study visit. During the open-label extension period, subject will record insulin usage on paper diary for 10 days prior to each study visit.
- Hypoglycemic events, defined as a BG level of ≤70 mg/dL or clinical sequelae consistent with hypoglycemia without a BG reading, will be documented throughout the study.
- Records of glucose measurements, insulin use and hypoglycemic events and communication with the subject will be kept in source documentation, on the appropriate case report form, or in the patient diary.

**CLINICAL PHARMACOLOGY EVALUATIONS**

Serum samples will be used to evaluate the pharmacokinetics (PK), the immunogenicity of golimumab (antibodies to golimumab), and pharmacodynamics (PD; free/total TNFα) at the timepoints presented in the Time and Events Schedule.

Serum golimumab concentrations will be summarized for each treatment group over time. If necessary, a population PK analysis will be performed to characterize the PK of golimumab as well as to identify and quantify important covariates of PK using a nonlinear mixed effects modeling approach. If visual trends

are observed, a suitable PK/pharmacodynamic model may be developed to describe the exposure-response relationship.

To assess the immunogenicity of golimumab, detection of antibodies to golimumab will be performed using a validated assay method. Serum samples will be evaluated for antibodies binding to golimumab and the titer of confirmed positive samples and the incidence of antibodies to golimumab will be reported. Other analyses may be performed to more fully characterize the immunogenicity of golimumab in this population.

**BIOMARKER EVALUATIONS**

Serum and cell-based biomarkers will be evaluated for inflammation-associated proteins, changes in immune cell subsets, and will be used to better understand the biology of T1D, to provide a biological assessment of the response of subjects to treatment with golimumab, to analyze differences between responders and nonresponders, and to determine if the markers can be used to classify patients as potential responders prior to treatment.

**PHARMACOGENOMIC (DNA) EVALUATIONS**

A pharmacogenetics blood sample for molecular major histocompatibility complex (MHC) haplotyping will be collected from all subjects at the start of the study. Exploratory pharmacogenomic research may consist of the analysis of one or more genetic markers throughout the genome in relation to golimumab or T1D clinical endpoints. Participation in exploratory pharmacogenetics research is optional. Subjects will need to provide consent/assent to participate in the exploratory phase of the pharmacogenetics research.

Pharmacogenomic assessment of molecular MHC haplotype and insulin DNA methylation will not be performed for the open-label extension period. The open-label extension period will include PBMC sample collection and serum biomarker sample collection.

**SAFETY EVALUATIONS**

Monitoring and evaluation of subjects in this study will focus on study agent, device-related, and disease-related safety issues. Monitoring will include physical examinations, clinical laboratory tests, vital signs, concomitant medications, and adverse events, including injection site reactions.

**STATISTICAL METHODS**

Descriptive statistics (eg, mean, median, standard deviation [SD], minimum, and maximum) will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Graphic data displays may also be used to summarize the data.

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 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. With 81 subjects (54 on golimumab and 27 on placebo) and an alpha of 0.05 (2-sided), there is 90% power to detect the treatment difference through a two-sample t-test.

All efficacy analyses will be performed on the modified intent-to-treat (mITT) population unless otherwise specified. The mITT population includes all randomized subjects who have received at 1 dose of study agent. The primary efficacy endpoint will be analyzed by using a mixed model for repeated measures.

Safety assessments will include the examination of the incidence rates of AEs, vital signs, clinical laboratory parameters, and physical examinations. Safety analyses will be conducted on the safety analysis set, which is defined as all subjects who have received at least 1 dose of study agent.

An interim analysis using the 4-hour C-peptide AUC in response to a MMTT is planned for the study 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.

All the efficacy endpoints defined for the double-blind period will be exploratory for the open-label extension period and will be summarized descriptively; there will be no hypotheses testing during the open-label extension period. Disease progression will be compared between the double-blind period and the extension period in subjects who attended the open-label extension period if deemed reasonable.

## TIME AND EVENTS SCHEDULE

### Double-Blind Period

| Screening Through Off-therapy Follow-up | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Designation** | **Screening** | **Active Treatment[b,c]** | | | | | | | | | | | **Off-therapy Follow-up[d]** | |
| | | | | | | | | | | | | | | |
| **Study Week[a]** | -4 to -1 | 0 | 2 | 4 | 8 | 12 | 18 | 26 | 33 | 38 | 45 | 52 | 78 | 104 (EOSV)[r] |
| **Study Day[a]** (visit window in days) | -28 to -1 | 1 | 15 (±1) | 29 (±1) | 57 (±3) | 85 (±3) | 127 (±3) | 183 (±3) | 232 (±7) | 267 (±3) | 316 (±7) | 365 (±3) | 547 (±10) | 729 (±10) |
| **Study Procedure** | | | | | | | | | | | | | | |
| **Screening/Administrative** | | | | | | | | | | | | | | |
| Informed consent/assent (ICF) | X | | | | | | | | | | | | | |
| Pharmacogenetics consent/assent[e] | X | | | | | | | | | | | | | |
| Inclusion/exclusion criteria evaluation/review | X | X | | | | | | | | | | | | |
| Dispense electronic diary (eDiary) and glucometer and training[f] | X | | | | | | | | | | | | | |
| **Clinical Assessments / Ongoing Review** | | | | | | | | | | | | | | |
| Full Physical examination | X | | | | | | | | | | | | | X |
| Brief physical examination | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height & Body weight measurement | X | X | | | | X | | X | | X | | X | X | X |
| Medical history and demographics | X | | | | | | | | | | | | | |
| Interval history and eDiary review | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Previous/concomitant medication review | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse events | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tuberculosis (TB) exposure review | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| Screening Through Off-therapy Follow-up | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Designation** | **Screening** | **Active Treatment[b,c]** | | | | | | | | | | | **Off-therapy Follow-up[d]** | |
| | | | | | | | | | | | | | | |
| **Study Week[a]** | -4 to -1 | 0 | 2 | 4 | 8 | 12 | 18 | 26 | 33 | 38 | 45 | 52 | 78 | 104 (EOSV)[r] |
| **Study Day[a]** (visit window in days) | -28 to -1 | 1 | 15 (±1) | 29 (±1) | 57 (±3) | 85 (±3) | 127 (±3) | 183 (±3) | 232 (±7) | 267 (±3) | 316 (±7) | 365 (±3) | 547 (±10) | 729 (±10) |
| **Study Procedure** | | | | | | | | | | | | | | |
| **Randomization and Study Agent Administration** | | | | | | | | | | | | | | |
| Randomization | | X | | | | | | | | | | | | |
| Dose determination and modification | | X | | | | X | | X | | X | | | | |
| Required study agent administration at study site[g] | | X | X | X | X | X | X | X | | X | | X | | |
| **Subjects participating in self-administration[b]** | | | | | | | | | | | | | | |
| Injection training by site personnel[b] | | X | X | X | | | | | | | | | | |
| Distribute study agent injection devices | | | | X | X | X | X | X | X[g] | X | X[g] | | | |
| Return study agent injection devices | | | | | X | X | X | X | X | X | X | X | | |
| **Subject Reported Data / eDiary Review** | | | | | | | | | | | | | | |
| Glucometer reading review | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Insulin use report review | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hypoglycemia event review | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Study agent self-administration review[b] | | | | | X | X | X | X | X | X | X | X | | |
| **Clinical Laboratory Assessments** | | | | | | | | | | | | | | |
| 4h - Mixed-meal tolerance test (MMTT)[h] | X | | | | | X | | X | | X | | X | X | X |
| HbA1c | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Type 1 diabetes autoantibodies[i] | X | | | | | | | X | | | | X | X | X |
| QuantiFERON-Gold test | X | | | | | | | | | | | | | |
| Serum pregnancy test[j] | X | | | | | | | | | | | | | |
| Urine pregnancy test[j] | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hematology[k] | X | X | | X | | X | | X | | X | | X | X | X |

| Screening Through Off-therapy Follow-up | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Designation** | **Screening** | **Active Treatment[b,c]** | | | | | | | | | | | **Off-therapy Follow-up[d]** | |
| | | | | | | | | | | | | | | |
| **Study Week[a]** | -4 to -1 | 0 | 2 | 4 | 8 | 12 | 18 | 26 | 33 | 38 | 45 | 52 | 78 | 104 (EOSV)[r] |
| **Study Day[a]** (visit window in days) | -28 to -1 | 1 | 15 (±1) | 29 (±1) | 57 (±3) | 85 (±3) | 127 (±3) | 183 (±3) | 232 (±7) | 267 (±3) | 316 (±7) | 365 (±3) | 547 (±10) | 729 (±10) |
| **Study Procedure** | | | | | | | | | | | | | | |
| Chemistry[k] | X | X | | X | | X | | X | | X | | X | X | X |
| Viral serology[l] | X | | | | | | | | | | | | | |
| Polymerase chain reaction (PCR) Viral load[m] | X | | | | | X | | X | | X | | X | X | X |
| **Clinical Pharmacology** | | | | | | | | | | | | | | |
| Golimumab concentration[n] | | X | X | X | X | X | | X | X | X | X | X | X | X |
| Antibodies to golimumab[n] | | X | | X | | X | | X | | X | | X | X | X |
| Free/total TNFα[n] | | X | X | X | X | X | | X | X | X | X | X | X | X |
| **Biomarkers and Pharmacogenomics[s]** | | | | | | | | | | | | | | |
| Major histocompatibility complex (MHC) haplotype[o] | | X | | | | | | | | | | | | |
| Peripheral blood mononuclear cell (PBMC) sample collection[p] | | X | | | | X | | X | | X | | X | X | X |
| Serum biomarker sample[p] | | X | | | | X | | X | | X | | X | X | X |
| DNA methylation (Optional)[q] | | X | | | | X | | X | | X | | X | X | X |

Abbreviations: eDiary=electronic diary, EOSV=End of Study Visit, ICF=informed consent, IDAA1c=insulin dose-adjusted HbA1c, MHC=major histocompatibility complex, MMTT=mixed-meal tolerance test, PBMC=peripheral blood mononuclear cell, PCR=polymerase chain reaction, TB=tuberculosis, TNFα=tumor necrosis factor alpha

a. The study visit Week and target study visit Day are indicated and calculated based on the day of randomization. Acceptable windows for study visits in days before (-) or after (+) target study visit day are indicated and based on if study agent dosing will be given at that visit and time enrolled in the study.
b. Subjects/caregivers will be given the option for at home "self-administration" for study agent doses after Week 4, since the dosing schedule for subject is q2w through Week 52. Training on self-administration will be provided at Weeks 0, 2, and 4. (See Section 6.2 for details). These subjects will record data regarding self-administration in an eDiary (See Section 7.1.1) or if self-administering at the site, the data will be recorded in the study site's documents, not in the eDiary.
c. Subjects not participating in self-administration will schedule study agent dosing-only visits every 2 weeks through Week 52 (see Section 9.1.3).
d. The 52-week off-therapy follow-up phase of the study begins after the completion of all assessments and administration of study agent for Week 52.

e. All subjects **must** participate in pharmacogenomics evaluation of molecular MHC haplotyping at the start of the study. Subjects do have the **option** to participate in the additional pharmacogenomic (PG) evaluations in this study and to do so subjects/caregivers must sign the PG informed consent/assent form indicating willingness to participate. These optional PG samples will be collected **only** from subjects who sign the PG informed consent/assent.
f. For those who do not meet study criteria or choose not to participate in this study, instructions on how to return the eDiary and glucometer will be given.
g. This does not represent all study agent dosings. Study agent is to be administered every 2 weeks. At Weeks 0, 2, and 4, administration will occur during study visits. At week 8, 12, 18, 26, 38 and 52 study visits where study agent will be administered, either subjects/caregivers or study staff may administer the injection. At the required visits in this table, drawing of pharmacokinetic/immunogenicity (ie, golimumab concentration and antibodies to golimumab) samples must take place **prior** to study agent administration at visits where study agent dosing occurs. Following study agent administration subjects will be observed for 30 minutes for symptoms of injection reactions. At Week 33 and Week 45, pharmacokinetic samples will be drawn and resupply of study agent injection devices will occur; no dosing will occur at these 2 specific study visits.
h. The MMTT will be a 4-hour assessment to be conducted in the morning after an overnight fast. All other blood samples should be drawn prior to the MMTT. When MMTT occurs on study agent dosing days, study agent should be administered after the MMTT.
i. Type 1 diabetes autoantibodies including glutamic acid decarboxylase (GAD-65), insulin, IA-2, ZnT8 and ICA.
j. Females of childbearing potential must have a negative serum pregnancy at screening and a negative urine pregnancy test prior to administration of study agent.
k. Specifics tests are described in Section 9.6. Note: Fasting lipid panel only done at screening, Week 12, 26, 38, 52, 78 and 104. Coagulation panel (PT/PTT/INR) only done at screening.
l. Viral serology panels to include: CMV, EBV, HepB, HepC, HIV.
m. Quantitative PCR testing for CMV and EBV.
n. The same serum samples may be used for the measurement of golimumab concentration, detection of antibodies to golimumab and amounts of free/total TNFα. Drawing of these samples must take place prior to study agent administration at visits where study agent dosing occurs. Priority of analysis depending on sample volume is: PK, ADA, NAB, total TNF, free TNF. Additional serum samples for golimumab concentration and Total/Free TNFα will be collected at Week 33 and Week 45.
o. **Required** pharmacogenomic assessment of molecular MHC haplotype.
p. Anticipated assessments may include T- and B-cell subset analysis by multicolor flow cytometry and serum protein/cytokine profiling.
q. Optional pharmacogenomics assessments anticipated to include insulin DNA methylation.
r. End of Study Visit assessments: May be used in instances where subjects withdraw early from the study, see Section 10.2.
s. All biomarker and pharmacogenomics samples must be collected prior to study agent administration.

.

## Open-Label Extension Period

| Open-Label Extension Period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Designation** | **Screening[q]** | **Active Treatment[b,c]** | | | | | | | | | **Post-Treatment[d]** |
| | | | | | | | | | | | |
| **Study Week[a]** | | OL 0 | OL 2 | OL 4 | OL 12 | OL 20 | OL 28 | OL 36 | OL 44 | OL 52 (EOSV)[n] | OL 60 or 10 weeks post last dose |
| **Study Day[a]** (visit window in days) | -14 to -1 | 1 | 15 (±1) | 29 (±3) | 85 (±3) | 141 (±3) | 197 (±3) | 253 (±3) | 309 (±3) | 365 (±3) | 421 (±7) |
| **Study Procedure** | | | | | | | | | | | |
| **Screening/Administrative** | | | | | | | | | | | |
| Informed consent/assent (ICF) | X[p] | | | | | | | | | | |
| Inclusion/exclusion criteria evaluation/review | X | X | | | | | | | | | |
| Dispense dosing, insulin and hypoglycemia paper diary[e] | X | X | X | X | X | X | X | X | X | | |
| **Clinical Assessments / Ongoing Review** | | | | | | | | | | | |
| Full Physical examination | X | | | | | | | | | X | X |
| Brief physical examination | | X | X | X | X | X | X | X | X | | |
| Vital signs | X | X | X | X | X | X | X | X | X | X | X |
| Height & Body weight measurement | | X | | | X | | X | | X | | X |
| Interval history and paper diary review | | X | X | X | X | X | X | X | X | X | |
| Previous/concomitant medication review | X | X | X | X | X | X | X | X | X | X | X |
| IDAA1c | X | X | X | X | X | X | X | X | X | X | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X |
| Tuberculosis (TB) exposure review | X | X | X | X | X | X | X | X | X | X | X |
| **Randomization and Study Agent Administration** | | | | | | | | | | | |
| Dose determination and modification | | X | | | X | | X | | X | | |
| Required study agent administration at study site[f] | | X | X | X | X | X | X | X | X | | |
| **Subjects participating in self-administration[b]** | | | | | | | | | | | |
| Injection training by site personnel[b] | | X | | | | | | | | | |

| **Open-Label Extension Period** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Study Designation** | **Screening[q]** | **Active Treatment[b,c]** | | | | | | | | | **Post-Treatment[d]** |
| | | | | | | | | | | | |
| **Study Week[a]** | | OL 0 | OL 2 | OL 4 | OL 12 | OL 20 | OL 28 | OL 36 | OL 44 | OL 52 (EOSV)[n] | OL 60 or 10 weeks post last dose |
| **Study Day[a]** (visit window in days) | -14 to -1 | 1 | 15 (±1) | 29 (±3) | 85 (±3) | 141 (±3) | 197 (±3) | 253 (±3) | 309 (±3) | 365 (±3) | 421 (±7) |
| **Study Procedure** | | | | | | | | | | | |
| Distribute study agent injection devices | | | | X | X | X | X | X | X | | |
| Return study agent injection devices | | | | | X | X | X | X | X | X | |
| **Subject Reported Data / Paper Review** | | | | | | | | | | | |
| Insulin use report review | X | X | X | X | X | X | X | X | X | X | |
| Hypoglycemia event review | | X | X | X | X | X | X | X | X | X | X |
| Study agent self-administration review[b] | | | | X | X | X | X | X | X | X | |
| **Clinical Laboratory Assessments** | | | | | | | | | | | |
| 4h - Mixed-meal tolerance test (MMTT)[g] | X | | | | | | X | | | X | |
| HbA1c | X | X | X | X | X | X | X | X | X | X | X |
| QuantiFERON-Gold test | X | | | | | | | | | | |
| Serum pregnancy test[h] | X | | | | | | | | | | |
| Urine pregnancy test[h] | | X | X | X | X | X | X | X | X | X | X |
| Hematology[i] | X | X | | X | | X | | X | | X | X |
| Chemistry[i] | X | X | | X | | X | | X | | X | X |
| Viral serology[j] | X | | | | | | | | | | |
| Polymerase chain reaction (PCR) Viral load[k] | X | | | | X | | | X | | X | |
| **Clinical Pharmacology** | | | | | | | | | | | |
| Golimumab concentration[l] | | X | | X | X | | X | | | X | |
| Antibodies to golimumab[l] | | X | | X | X | | X | | | X | X |
| Free/total TNFα[l] | | X | | X | X | | X | | | X | X |
| **Biomarkers and Pharmacogenomics[o]** | | | | | | | | | | | |
| Peripheral blood mononuclear cell (PBMC) sample collection[m] | X | | | | | | | | | X | |
| Serum biomarker sample[m] | | X | | | | | | | | X | |

Abbreviations: EOSV=End of Study Visit, ICF=informed consent, IDAA1c=insulin dose-adjusted HbA1c, MHC=major histocompatibility complex, MMTT=mixed-meal tolerance test, OL=open-label, PBMC=peripheral blood mononuclear cell, PCR=polymerase chain reaction, TB=tuberculosis, TNFα=tumor necrosis factor alpha

a. The study visit Week and target study visit Day are indicated and calculated based on the day of first dose. Acceptable windows for study visits in days before (-) or after (+) target study visit day are indicated and based on if study agent dosing will be given at that visit and time enrolled in the study.
b. Subjects/caregivers will be given the option for at home "self-administration" for study agent doses after OL Week 4, since the dosing schedule for subject is q2w through OL Week 50. Training on self-administration will be provided at OL Week 0 (See Section 6.2 for details). These subjects will record data regarding self-administration in the paper diary (See Section 7.1.1.1) or if self-administering at the site, the data will be recorded in the study site's documents, not in the paper diary.
c. Subjects not participating in self-administration will schedule study agent dosing-only visits every 2 weeks through OL Week 50 (see Section ~~9.1.3~~9.1.5).
d. The post-treatment visit will be conducted for all subjects at OL Week 60 or 10 weeks after the last dose of study agent to collect SAEs and AEs of interest since the last visit unless the subject has died, has been lost to follow-up, or has withdrawn consent.
e. For those who do not meet study criteria or choose not to participate in this study, instructions on how to return the paper diary will be given.
f. This does not represent all study agent dosings. At OL Weeks 0, 2, and 4, administration will occur during study visits. At OL Weeks 12, 20, 28, 36, 44, and 50 study visits where study agent will be administered, either subjects/caregivers or study staff may administer the injection. At the required visits in this table, drawing of pharmacokinetic/immunogenicity (ie, golimumab concentration and antibodies to golimumab) samples must take place **prior** to study agent administration at visits where study agent dosing occurs. Following study agent administration subjects will be observed for 30 minutes for symptoms of injection reactions. The last dose of study agent is to be administered at Week 50. See Section 6.1 and Section 9.1.5.3.
g. The MMTT will be a 4-hour assessment to be conducted in the morning after an overnight fast. All other blood samples should be drawn prior to the MMTT. When MMTT occurs on study agent dosing days, study agent should be administered after the MMTT.
h. Females of childbearing potential must have a negative serum pregnancy at screening and a negative urine pregnancy test prior to administration of study agent.
i. Specifics tests are described in Section 9.6.1. Note: Lipids will not be measured during the open-label extension period. Coagulation panel (PT/PTT/INR) only done at screening.
j. Viral serology panels to include: CMV, EBV, HepB, HepC, HIV.
k. Quantitative PCR testing for CMV and EBV. For the open-label extension period, subjects may begin open-label study agent while EBV PCR results are pending and if he/she meets all other inclusion/exclusion criteria. If EBV PCR results come back positive, subject must immediately stop treatment and be withdrawn from the study.
l. The same serum samples may be used for the measurement of golimumab concentration, detection of antibodies to golimumab and amounts of free/total TNFα. Drawing of these samples must take place prior to study agent administration at visits where study agent dosing occurs. Priority of analysis depending on sample volume is: PK, ADA, NAB, total TNF, free TNF.
m. Anticipated assessments may include T- and B-cell subset analysis by multicolor flow cytometry and serum protein/cytokine profiling.
n. End of Study Visit assessments: May be used in instances where subjects withdraw early from the study, see Section 10.2. Subjects who permanently discontinue active treatment during the open-label extension period will have their end-of-study visit followed by the post-treatment visit 10 weeks later.
o. All biomarker and pharmacogenomics samples must be collected prior to study agent administration.
p. The retreatment screening visit should occur within 4 weeks of site notification of responders.
q. The optional screening visit should take place no later than 21 days after the subject has been offered the opportunity to enter open-label extension period and in any event must occur within 14 days prior to Week 104.

## 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 |
| C responders | C-peptide responders |
| 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) |
| C+R responders | C-peptide and remission score responders |
| DBL | data base lock |
| 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 |
| HPV | human papillomavirus |
| IAC | Interim Analysis Committee |
| IDAA1c | insulin dose-adjusted HbA1c |
| 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 |
| OL | open-label |
| PBMC | peripheral blood mononuclear cell |
| PCR | polymerase chain reaction |
| 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 |
| R responders | remission score responders |
| 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

SIMPONI® (golimumab) is a fully human monoclonal antibody which binds to human tumor necrosis factor alpha (TNFα) with high affinity and specificity and neutralizes TNFα bioactivity. Golimumab was first approved by the United States Food and Drug Administration (FDA) in 2009 and has been shown to be safe and efficacious in adults with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and ulcerative colitis (UC). Additionally, golimumab has been evaluated in studies conducted under an Investigational New Drug (IND) for the treatment of polyarticular juvenile idiopathic arthritis (pJIA; 2 up to 18 years of age), and pediatric UC (2 up to 18 years of age).

Similar to these above conditions, Type 1 diabetes (T1D) is an autoimmune disorder with severe sequelae, but there are no approved disease modifying therapies for those with T1D. Children and young adults are those that most frequently develop T1D and have the most urgent need for a disease modifying therapy to reduce associated short- and long-term morbidity and mortality. This study will evaluate whether golimumab administered subcutaneously (SC) in this population with newly diagnosed T1D has the potential to maintain residual β-cell function and improve metabolic control.

For the most comprehensive nonclinical and clinical information regarding golimumab, refer to the latest version of the Investigator's Brochure and Addenda for golimumab.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

### Type 1 Diabetes

Type 1 diabetes (T1D) is an autoimmune disease that results in the progressive destruction of pancreatic β cells leading to an absolute insulin deficiency and life-long daily exogenous insulin therapy.[14,17] There is no cure nor approved disease modifying therapy for T1D. Every day, those with T1D are impacted by this disease as they require insulin injections for survival which must be calculated based on regular blood glucose (BG) checks, diet and exercise. Those with T1D are at high risk of acute sequelae from hypo- and hyper-glycemic and in the longer-term severe renal, cardiac, and vascular disease.[6,17,72] Those who develop T1D early in life are at increased risk for significant neurocognitive disorder including behavioral issues, lower intellectual performance and motor dysfunction, and associated structural changes in the brain.[4,7,44,49] Recent data indicate that even adhering to the most current recommendations and using the most advanced approaches for glycemic control, mortality for those with T1D is 2-fold greater than age-matched controls.[45] Even though outwardly those with T1D may appear healthy, they are at high risk for a number of severe short- and long-term life-impacting and threatening sequelae including sudden death.[15,64] Most sequelae accumulate over time and do not appear to be “preventable” even with the most exacting attempts of exogenous glycemic control, and thus those who would most benefit from a disease modifying therapy are those who develop disease earlier in life.[27,41,43,75]

In the United States, approximately 3 million people have this disease.[17,71] It most often presents in children and adolescence and is one of the 3 most prevalent severe chronic diseases of childhood, along with asthma and cancer.[46,71] The annual incidence is highest in children and young adults with ~20 to 25 cases/100,000/year in those younger than 20 years old and there is approximately 30,000 total new cases of T1D annually in North America.[34,71] Due to its short- and long-term complications, T1D is both a daily and life-long burden for individuals and their families and also represents significant socioeconomic and societal-medical ramifications, which are only going to rise as the worldwide incidence of T1D increases approximately 3% to 5% annually.[34,71]

Type 1 diabetes (T1D) is the result of immune destruction of the insulin producing β-cells located in the islets of Langerhans in the pancreas and eventual absolute insulin deficiency. It is believed that those with a certain genetic susceptibility encounter an environmental trigger that breaks self-tolerance to β-cells, and an autoimmune response to β-cells is initiated.[21] Over time, which may be years in some cases, a critical mass of β-cells is destroyed and normal glycemic control cannot be supported. Individuals present with clinical signs and symptoms, including polydipsia, polyphagia, polyuria, and often with severe metabolic disturbances, including life-threatening diabetic ketoacidosis (DKA). Despite there being some residual β-cells at the time of clinical diagnosis of T1D, the vast majority of these, if not all, will be eventually destroyed.[6,72]

Upon diagnosis, those with T1D require daily exogenous insulin for the rest of their lives. Even with the best glycemic control with newer forms of exogenous insulin and enhanced BG monitoring, there continues to be significant disease and treatment-associated morbidity and mortality, both in the short- and long-term. Current data support that maintaining at least a minimal amount of endogenous insulin production can substantially reduce or delay a number of these complications.[19,41,43] There is an urgent need to develop therapeutics that can prevent or slow the rate of β-cell loss to improve outcomes with T1D, which would provide benefit to those with T1D and would be a critical step forward on the path to reverse or prevent this disease.

**Trials of Other Immunomodulators in T1D**

Over the past decades, a number of clinical studies have evaluated immune and non-immune based strategies to try to prevent ongoing destruction of β-cells that are present at the time of diagnosis in order to reverse insulin need or at least maintain clinically relevant amounts of endogenous β-cell function. Of these, it is studies which used immune modulators that have shown the most promise. Small scale trials in the late 1980s and early 1990s using non-specific immune suppressants (ie, cyclophosphamide and azathioprine) were able to subdue the autoimmune progression of T1D and in some cases reverse insulin needs.[9,10,16] However, these were not considered viable therapies due to their significant immune- and non-immune toxicities.

Since the advent of more targeted, safer, and better tolerated immune modulators (ie, biologics), a number of Phase 2a new-onset T1D clinical studies have been conducted. Some of these have been unsuccessful (interleukin [IL] 1β antagonism, thymoglobulin, anti-IL2 receptor/mycophenolate mofetil) while some have shown some ability to slow disease progression (abatacept, rituximab, anti-cluster of differentiation-3 variants, and

alefacept).[25,26,31,52,55,57,60,61] However due to a variety of reasons, none have been successfully developed into an approved disease modifying therapy for T1D.

**Role of TNFα in the Pathogenesis of T1D**

Decades of fundamental research on the autoimmune pathogenesis of T1D have demonstrated that it results from a complex interplay of innate and adaptive immune injury to β-cells involving T cells, B cells, antigen-presenting cells, and pro-inflammatory cytokines.[8,30,73] In addition, recent data indicate that the increases in β-cell damage from metabolic and pro-inflammatory stressors may play an important role in the initiation and propagation of the autoimmune response.[5,6,73]

TNFα is a pro-inflammatory cytokine that has important roles in the immunopathogenesis of a number of human autoimmune diseases and current evidence indicates it plays an integral role in T1D. As detailed below, it has both 1) activating effects on the T1D autoimmune response and 2) important direct pro-diabetogenic metabolic effects.

TNFα appears to promote diabetes autoimmunity by enhancing the recruitment of inflammatory cells to the islets, activating cells and enhancing autoantigen presentation.[40,58,73] TNFα activates vascular endothelium, upregulating major histocompatibility complex (MHC) I and adhesion molecules.[4] In murine models of T1D, some of the first cells to infiltrate islets are dendritic cells.[58,73] Dendritic cells and other antigen-presenting cells, which are critical for β-cell antigen presentation to T cells, are activated by TNFα by up regulation of MHC I and II and costimulatory molecules.[38,58] TNFα also directly increases MHC I, and synergizes with interferon gamma to upregulate MHC II, on β-cells, both of which appear to increase their susceptibility to T-cell killing.[5] Rodent models of autoimmune diabetes show that antagonizing TNFα can delay, prevent or reverse disease whereas TNFα production in the pancreas can accelerate disease.[13,39,58]

There are important non-immune effects of TNFα that make blocking it attractive in T1D. TNFα has direct cytostatic effects and impairs insulin production and secretion, and it has cytocidal activity, killing β-cells directly.[20,37,47,58] TNFα also impairs insulin signaling and increases peripheral insulin resistance, which in experimental models can be reversed by blocking TNFα.[38,58] Patients with new-onset T1D have elevated serum TNFα levels compared with those with long-standing disease or healthy controls.[13] There are case reports of patients with T1D, who were started on TNFα blockers for other autoimmune diseases, in whom insulin requirements dropped due to an apparent increase in insulin sensitivity.[3,11,74,76] Therefore, TNFα also has potent metabolic effects that may contribute to T1D by increasing β-cell stress and death.

Likely the most convincing data of the role of TNFα in T1D pathogenesis in children and young adults comes from a randomized, controlled, pilot clinical trial of etanercept in newly diagnosed T1D conducted at the University of Buffalo.[48] Eligibility included subjects aged 3 to 18 years of age with recently diagnosed T1D. Subjects received etanercept 0.4 mg/kg (maximum 25 mg) or placebo dosed SC twice weekly for 24 weeks. The study enrolled 18 subjects (range 7 to

18 years of age, mean ~12.5 years), 10 into the etanercept arm and 8 into the placebo arm. Over the treatment period, etanercept-treated subjects showed a 39% increase in C-peptide production (as a measure of endogenous β-cell function) from baseline assessed by C-peptide area under the concentration-time curve (AUC) from a 2-hour mixed-meal tolerance test (MMTT). In contrast, the placebo group had a 20% decrease in C-peptide production. In addition, subjects in the active arm had improved glycemic control (lower Hemoglobin A1c's [HbA1c's]) versus those in the placebo group, and a decrease of 18% in daily insulin requirements (units/kg/day) from baseline where the placebo subjects had a 23% increase in requirements. There were no unexpected severe AEs in either group. Even though there has not been further evaluation of these very impressive findings, they are some of the most promising to date on identifying an approach to modify T1D disease course. Specifically, these findings support further evaluation of this approach in the target population and provide critical "prospect of benefit" for TNFα-blockade in children and young adults with newly diagnosed T1D.

**Differences in Natural History and Pathogenesis of Pediatric versus Adult T1D**

Type 1 diabetes usually develops in childhood and adolescence, however it can present late in adulthood in the 5th and 6th decades of life, although much less frequently.[51,71] In addition to being more prone to some short- and long-term complications, there are differences in the clinical course and response to immune therapies between children/young adults and older adults. This supports the well-accepted observations that children suffer from severe diabetes symptoms, including polydipsia, polyuria, and weight loss, days or weeks before initial diagnosis. Often diagnosis is accompanied by DKA and shock which requires hospitalization for treatment and monitoring for cerebral edema and herniation.[6,14,21,23,33,56,62,75] Children and young adults with new-onset T1D usually have an immediate need for exogenous insulin.

This sharply contrasts with the experience of adults (mid-20s and above) who often have months or years of non-specific symptoms or present asymptomatically from routine glycemic screening and can often be managed for prolonged periods of time (months or years) with diet or oral hypoglycemic agents before a demonstrable insulin need. More definitive studies have shown a different rate of decline of β-cells according to age.[14,21] Data from the Diabetes Trial Net group has demonstrated that "age is the most important factor impacting the rate of decline of C-peptide post diagnosis" and with significantly more rapid rate of decline in those 21 years old and younger versus those 22 years and older with new-onset disease.[27,75]

These differences in disease pathophysiology between younger and older individuals with T1D are supported by the data from a number of recent new-onset T1D studies that have demonstrated differences in how younger and older individuals respond to immune interventions. Studies of abatacept, rituximab, alefacept, and teplizumab all appear to have a preferential effect on children and young adults; whereas thymoglobulin appeared to preferentially spare β-cells in those older than 21, but not in those younger.[25,31,55,57,61,75]

Children and young adults are those at highest risk of developing disease and suffer most substantially from short- and long-term morbidity and mortality and have the most to benefit from a disease modifying therapy. The existing data suggest an age "cut-off" of approximately

21 years old as one that distinguishes many of the properties of T1D in younger and older adults and supports the older age threshold of this study. Clearly, there not only appears to be important clinical pathophysiologic differences in T1D in younger and older individuals, but efficacy data of immune interventions from one age group may not be extrapolated to the other. Doing so may result in making misinformed and inaccurate decisions for further development. It is the sponsor's view that the prospect of benefit for TNFα-blockade in children with newly diagnosed T1D has been demonstrated, and conversely because of the aforementioned differences in T1D disease in younger and older individuals, the study of older adults (ie, >21 years of age) would not be supported. As such, the direct study of children and young adults with T1D is required to develop a disease modifying therapy for those are most afflicted with this disease and will benefit the most from such therapies.[6,14,75]

## 1.1. Background

### TNFα-blockers In Human Autoimmune Diseases

The family of TNFα-blockers that golimumab belongs to has some of the most extensive clinical experience and success of biologic immune modulators used in in a variety of adult and pediatric autoimmune diseases. This family, that also includes infliximab, etanercept, certolizumab pegol, and adalimumab, cumulatively has years of demonstrated safety and efficacy for conditions that include adult RA, psoriasis (PsO), PsA, UC, Crohn's disease (CD), AS, and pediatric (pJIA), CD, and UC. Specifically, golimumab is currently approved in adults 18 years and above with RA, PsA, AS and UC.[22,32,59,68]

The adverse effect profile of these TNFα blockers is well known. Treatment with TNFα-blockers, is associated with increased rates of serious infections including tuberculosis, bacterial sepsis, invasive fungal, and other opportunistic infections sometimes leading to hospitalization or death, lymphoma and other malignancies, and new or exacerbation of congestive heart failure, although with very low frequencies.[22,32,59,68]

Based upon their overall positive benefit:risk profile, TNFα-blockers have been studied and approved in the United States and elsewhere for a number of other pediatric autoimmune conditions that arguably have similar morbidity and mortality and impact on life as T1D. Specifically, etanercept has been FDA-approved in children 2 years old and above with pJIA since 1999. Infliximab was approved in children 6 years old and above with CD and UC in 2009 and 2011, respectively. Adalimumab was FDA-approved for pJIA in those 2 years old and above in 2008 and CD in those 6 years old and above in 2014. As detailed in the next section, golimumab has recently been studied in over 200 children in pediatric indications. Polyarticular juvenile idiopathic arthritis includes experience in children age 2 years and above and is currently under review for registration in Europe (Eu), and pediatric UC includes experience in children 6 to 17 years of age.

Use of golimumab and other TNFα-blockers for both adults and children includes routine evaluation of safety. Subjects in this study will be extensively evaluated as occurs with the routine use of TNFα-blockers including golimumab in adults and children, (and detailed above), subjects in this study will be thoroughly assessed for and excluded from participation if they

have risk factors for serious infections (including but not limited to tuberculosis [TB]), immunosuppression, malignancy and cardiac disorders, to limit the chance of untoward and adverse effects in this study.

**Clinical Studies of Golimumab in Children**

A significant portion of the target population in this study is individuals who are less than 18 years of age. Although it is not currently approved for use in pediatric subjects, golimumab has already been evaluated in studies enrolling over 200 children 2 through 17 years of age with other autoimmune disorders that have been conducted in the US, EU and other regions globally. Specifically, SC golimumab was evaluated in children with pJIA (CNTO148JIA3001), and a clinical development program with SC golimumab in pediatric UC is currently ongoing (CNTO148UCO1001). Thus far, golimumab has been well tolerated in both studies in pediatric subjects of 2 to <18 years of age. In general, the safety profile of golimumab in the pJIA and pediatric UC studies including the type and frequency of the adverse reactions seen is consistent with the known safety profile for the adult populations studied and consistent with other TNFα inhibitors. No new safety signals have been observed.

## 1.2. Rationale for the Study

This study will evaluate whether subcutaneously administered golimumab can maintain residual β-cell function and improve metabolic control in children and young adults with newly diagnosed T1D.

# 2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

## 2.1. Objectives and Endpoints

- Double-Blind Period

| Objectives | Endpoints |
|---|---|
| **Primary Objective and Endpoints** | |
| • To determine if golimumab can preserve β-cell function in children and young adults with newly diagnosed T1D. | • The Mixed-meal Tolerance Test (MMTT) - stimulated 4-hour C-peptide area under the concentration-time curve (AUC) at Week 52. |
| **Secondary Objectives and Endpoints: Efficacy** | |
| • To evaluate the impact of golimumab on measures of diabetes control in this subject population.<br>• To evaluate the off-therapy durability of golimumab on measures of diabetes control in this subject population. | • Change from baseline in insulin use in units per kilogram body weight per day over time.<br>• Change from baseline in HbA1c over time.<br>• Hypoglycemic event rates (defined as BG of ≤70, 55, and 35 mg/dL or clinical sequelae in the absence of a BG reading) through Week 52, after Week 52 through Week 104, and the entire study.<br>• MMTT-stimulated 4-hour C-peptide AUC over time. |

| Objectives | Endpoints |
|---|---|
| **Secondary Objective and Endpoints: Safety** | |
| • To determine the safety and tolerability of golimumab in children and young adults with T1D. | • Proportion of participants with treatment-emergent AEs and severe AEs through Weeks 52 and 104.<br>• Proportion of participants with severe infections through Weeks 52 and 104.<br>• Proportion of participants with study agent injection site reactions through Week 52. |
| **Secondary Objective and Endpoints: Pharmacokinetics (PK) and Immunogenicity** | |
| • To evaluate the PK and immunogenicity of golimumab in this specific subject population with T1D. | • Summary of serum golimumab concentrations and the PK profile after induction and maintenance dosing.<br>• Incidence and titers of antibodies to golimumab. |
| **Exploratory Objective and Endpoints: Immunologic and Metabolic** | |
| • To evaluate how golimumab impacts immunologic profiles and indicators of β-cell stress, and the correlation with efficacy and safety endpoints in this study. | • Correlation of cellular and serologic immune profiles with clinical metabolic outcomes on-therapy (Weeks 12, 26, 38, and 52) and off-therapy (Weeks 78 and 104)<br>• Relationship of exploratory markers of β-cell stress and survival with clinical metabolic outcomes on-therapy (Weeks 12, 26, 38, and 52) and off-therapy (Weeks 78 and 104). |

- Open-Label Extension Period

| Objective | Endpoint |
|---|---|
| • To evaluate additional one year of safety and exploratory efficacy endpoints in those participants that have shown a particular response in the double-blind period. | • Continue to evaluate safety and exploratory efficacy endpoints as per the Time and Events Schedule (open-label extension period) and no new efficacy hypotheses will be tested compared to the double-blind period. |

## 2.2. Hypothesis

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.

# 3. STUDY DESIGN AND RATIONALE

## 3.1. Overview of Study Design

This is a Phase 2a randomized, double-blind, placebo-controlled, parallel-group, multicenter, study of golimumab in subjects with new-onset T1D.

The duration of study participation will be 108 weeks, including screening and post-randomization. Following initial study screening, subjects must be randomized within 28 days. Following randomization there will be a double-blind 52-week treatment period with study agent followed by a 52-week off-therapy follow-up period.

Responders as defined below will be provided the option to participate in the 52-week open-label (OL) extension period.

The period to enroll all 81 subjects is expected to last approximately 12 to 18 months.

Schematic overviews of the double-blind study design and open-label extension period are provided in Figure 1 and Figure 2, respectively.

**Figure 1: Schematic Overview of the Double-Blind Period**

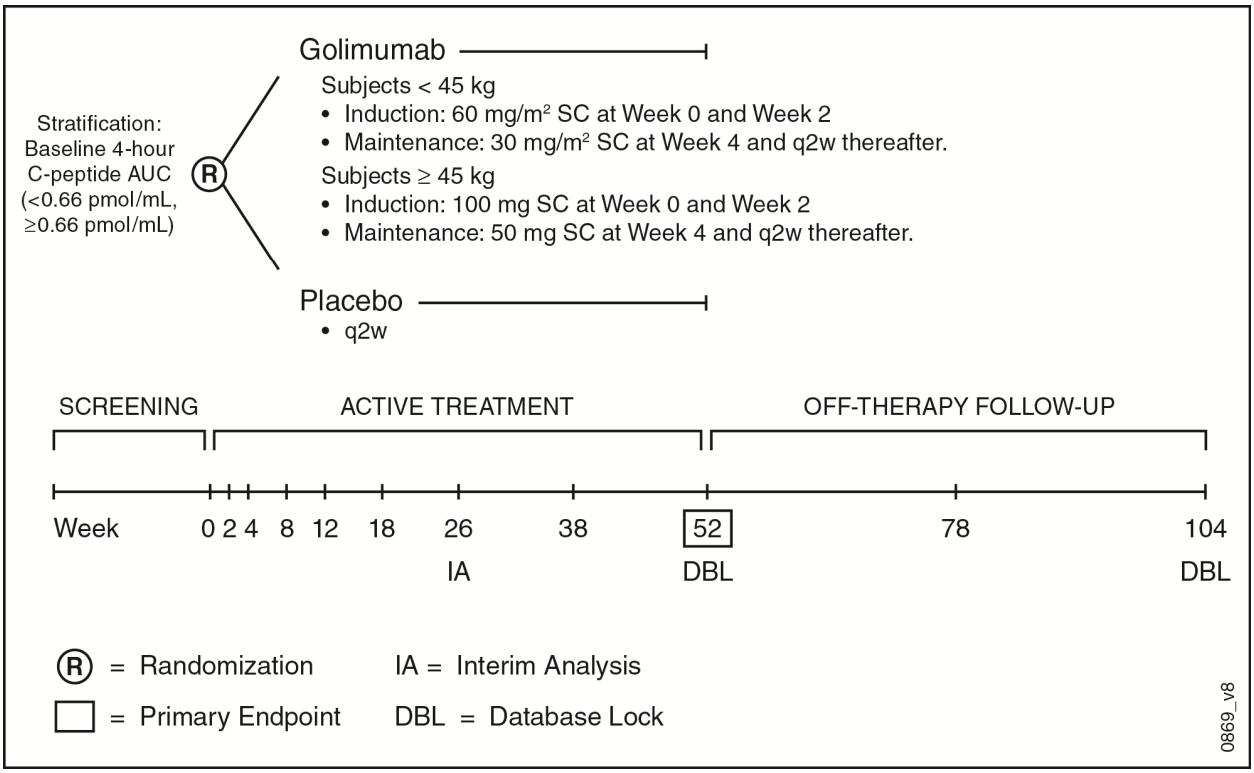
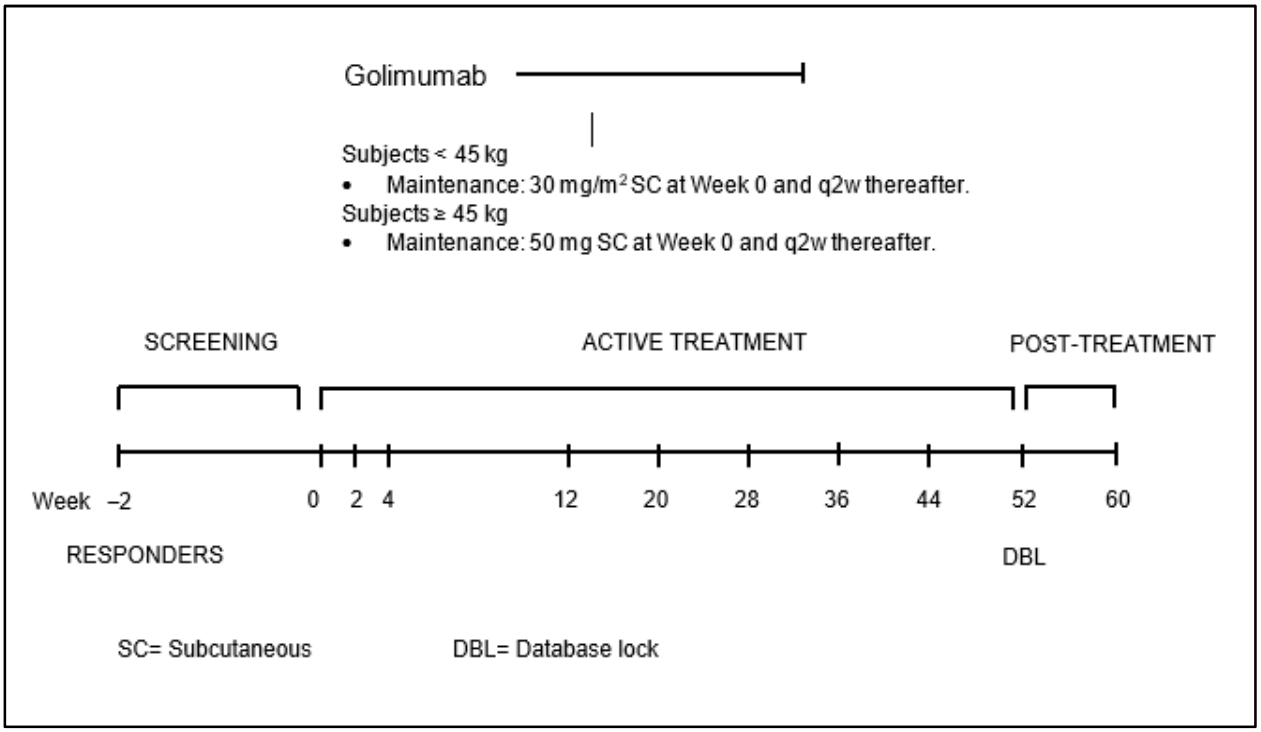


**Figure 2: Overview of the Open-Label Extension Period**




This study will enroll male and female subjects 6 through 21 years old who have been recently diagnosed with T1D. As described above (in Section 1) recent data indicate that the immunopathogenesis, disease progression and even response to immune therapies is different in younger population with T1D versus older adults. There is recent recognition by medical groups, diabetes experts and health authorities that it is important to conduct studies in children with T1D directly to best determine efficacy in T1D, as long as there is a known and acceptable safety profile.[28,29,75] Additionally, the critical "prospect of benefit" of therapeutic TNFα-blockade in these younger individuals with new-onset T1D exists based on the aforementioned pilot trial described above conducted in children and adolescents.[48] The choice of the upper age cut-off of 21 years is based on studies noted above showing a differentiating break in disease progression and response to therapy at this age.[25,27,61,75] Age 6 has been an accepted lower age threshold for enrollment in immunotherapeutic new-onset T1D studies, including those of abatacept and canakinumab.[52,55] In addition there is a substantial amount of efficacy and safety experience of golimumab and other TNFα-blockers in children with other autoimmune diseases, and most of this is in those at and above 6 years old. This study will not enroll adults over 21 years old due to the difference noted above, including that there is not currently a "prospect of benefit" of anti-TNFα therapy in this older population. Most importantly as the goal for the sponsor is to develop a therapy for those who will most benefit from it, if older adults were to have a poorer response to therapy than younger individuals due to some of the reasons discussed above, this may result in diluting or missing important findings necessary to support further development in children, adolescents and young adults with T1D who are clearly those who have the most to gain from a disease modifying therapy.

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.[19,25,42,61]

A target of approximately 81 subjects will be randomly assigned in a 2:1 ratio to receive golimumab or placebo, administered SC for 52 weeks and monitored for an additional 52 weeks. Subjects will be randomized to receive active therapy (golimumab) or placebo 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.

All randomized subjects will receive a total of 27 doses of study agent, either active treatment or matched placebo, administered SC every 2 weeks (q2w). Study subjects weighing <45 kg who are randomized to active treatment will receive an induction dose of golimumab 60 mg/m$^2$ SC at Weeks 0 and 2 followed by a maintenance dose of 30 mg/m$^2$ SC at Week 4 and q2w through Week 52. Study subjects weighing ≥45 kg who are randomized to the golimumab treatment group will receive an induction dose of golimumab 100 mg SC at Weeks 0 and 2 followed by a maintenance dose of golimumab 50 mg SC at Week 4 and q2w through Week 52. Subjects randomized to the placebo treatment group will receive a SC placebo injection q2w through Week 52 to match the active arm (Figure 1). The protocol will give the option for study agent administration by subject or caregiver outside of the study site, ie, self-administration, after proper training (see Section 6).

Following randomization and the 52-week treatment period, there will be a 52-week off-therapy follow-up period focused on determining the off-therapy durability of the effect of golimumab. Thus, the participation for each subject is 104 weeks.

There will be a number of study visits that will include extensive metabolic assessments including a 4-hour MMTT. These assessments will occur at screening, during the double-blind treatment period (Weeks 12, 26, 38, and 52), and the off-therapy monitoring period (Weeks 78 and 104). The primary endpoint analysis will be derived from data obtained at the double-blind Week 52 visit (double-blind period). During the open-label extension period, a 4-hour MMTT will be performed during OL screening (unless performed <3 months ago), OL Week 28, and OL Week 52. For C-responders who are lacking the necessary information to calculate IDAA1c score, an HbA1c will be performed and 10 days of insulin dose information will be required. Data from these and other visits will contribute to other key efficacy and safety endpoints and provide pharmacokinetic and exploratory assessments.

Three data base locks (DBLs) are planned for the study. The first DBL will occur after all subjects complete their Week 52 assessments (double-blind period), the second DBL will occur after the last subject completes the off-therapy follow-up period (Week 104), and the third DBL will occur after the last subject completes the open-label extension period.

An interim analysis based on 4-hour C-peptide AUC in response to an MMTT is planned for the study 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.

During the study, all subjects will receive intensive management of their diabetes with exogenous insulin according to the current recommendations of the American Diabetes Association (ADA). Subjects and, when applicable, their caregivers must agree to follow the current ADA recommendations of tight glycemic control with specific HbA1c targets. These current recommendations are intended to achieve glucose levels that appear to decrease some of the short- and long-term sequelae of T1D. This study will include adhering to the ADA's recommended glycemic control guidelines with an HbA1c target of <7.5% in children 17 years old and younger and <7% in those 18 years old and above.[67] Approaches to achieve these HbA1c goals will be the responsibility of the subject, their caregivers and their health care providers.

Responders at Week 52 who are still in the follow-up period and who are determined to be in the active treatment group will have the option to restart active therapy while the non-responders will continue to follow the originally planned study design, ie, the off-therapy follow-up monitoring period.

There will be an open-label extension period of the study for responders. Responders are defined as subjects who have profile at Week 52 which includes:

1. C-peptide and Remission score* responders (C+R responders): either having an increase in C-peptide AUC versus baseline or having a stable C-peptide AUC, ie, not decreasing more than 5% versus baseline and having a remission score ≤9.

   OR

2. C-peptide responders (C responders): either having an increase in C-peptide AUC versus baseline or having a stable C-peptide AUC, not decreasing more than 5% versus baseline but not meeting a remission score of ≤9. Their remission score, however, must be <12.

   OR

3. Remission score responders (R responders): having a remission score ≤9 but not meeting C-peptide response as defined above. However, their C-peptide AUC decline from baseline should be less than or equal to 30% compared to baseline.

*Insulin Dose Adjusted HbA1c (IDAA1c) = A1C (percent) + [4 × insulin dose (units per kilogram per 24 h)].[24,50,53,54]

An independent Data Monitoring Committee will be commissioned to continually assess the safety of study subjects. Refer to Section 11.11, Data Monitoring Committee, for details.

## 3.2. Study Design Rationale

### 3.2.1. Blinding, Control, Study Periods, Treatment Groups

Blinding and a placebo control will be used in this study since there is no established comparator therapy to prevent β-cell loss in T1D and to reduce potential bias during data collection and evaluation of clinical, safety, and exploratory endpoints.

There will be a 28-day screening period to allow for all assessments required for randomization to be conducted. The primary endpoint will occur at Week 52 (double-blind period). Due to the natural history of β-cell loss following diagnosis, documenting a statistically significant and meaningful effect of a β-cell sparing agent in a study of a reasonable size is best accomplished at Week 52 and allows for important comparisons with other recent immune intervention studies in T1D which have used a 52-week primary endpoint.[25,26,31,52,55,57,61] Golimumab and other TNFα-blockers are usually prescribed as continual "chronic" therapies for their autoimmune indications; therefore, the 52-week treatment duration is consistent with these experiences and will allow the best opportunity for evaluating efficacy of golimumab and ensure robust and meaningful safety evaluations.[22,32,59,68] Following the primary endpoint analysis at Week 52 (double-blind period), an off-therapy follow-up period for 52 weeks will allow for continued assessment of safety and understanding of the durability of effect after discontinuation of therapy. This will provide data to assist in developing dosing strategies of golimumab for T1D in future studies.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics and disease severity) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Per inclusion criteria, all randomized subjects will have a C-peptide level of ≥0.2 pmol/mL from a 4-hour MMTT at screening. Stratification will be employed based on subjects baseline MMTT-stimulated C-peptide AUC level as previous interventional studies in new-onset T1D suggest the response to immune therapies in new-onset T1D studies may be influenced, at least in part, by subject's baseline endogenous β-cell function.[31,55] To achieve balanced populations in the 2 treatment groups, eligible subjects will be randomized based on 2:1 ratio to receive active study agent or placebo within each stratum (<0.66 pmol/mL or ≥0.66 pmol/mL). This stratification threshold of 0.66 pmol/mL was chosen based on simulations and calculations derived from existing data that this level is expected to be close to the median of the baseline MMTT-stimulated 4-hour C-peptide AUC of the study population.[27,60]

Following database lock for the double-blind treatment period (Week 52), subjects who are still in the off-therapy follow-up period (Week 52 to 104 visits), who were on active drug during the double-blind period and who meet the response criteria will be offered the option to participate in the open-label extension period if eligibility criteria are met. Prior to initiating open-label screening assessments, subjects and parents/legal guardians will sign updated informed consent form (ICF)/assent forms.

Subjects who did not meet the response criteria at Week 52 will continue the off-therapy follow-up period.

Subjects who met the response criteria but either declined to participate in the open-label extension period, or were determined to be on placebo, will continue the off-therapy follow-up period as planned.

### 3.2.2. Dose Rationale

This study uses a dosing regimen designed specifically for T1D. It is accepted that different diseases may require unique dosing approaches of the same therapeutic to be most efficacious. In the case of the class of TNFα-blockers, there are a variety of dosing regimens that are disease-specific such as a higher dose regimen of SC golimumab for the treatment of UC as compared to that for rheumatic diseases.

The choice of dose and regimen for this study is based upon 3 factors: 1) disease-specific considerations of T1D, 2) modeling based upon the reported efficacy of TNFα inhibition of etanercept in a pilot study in children with T1D, and 3) the sponsor's safety and pharmacokinetic (PK) the experience with golimumab in adults, adolescents and children.[48] Although, the dose regimen of SC golimumab chosen for the present T1D study has not been studied before, the sponsor's use of golimumab in adult and pediatric subjects with other indications indicate that the overall exposures in this study population are overlapping with previous experience and thus the existing safety profile of golimumab is applicable to this study.

**1. T1D Disease-Specific Considerations**

In T1D, the destruction of β-cells is rapid at the time of diagnosis and is considered irreversible.[6,69,73] For aggressive immune-mediated diseases, higher and/or more frequent induction doses of anti-inflammatory therapies followed by lower regular maintenance doses are often used to gain rapid control of rampant disease activity, and then keep it under control. For most autoimmune indications, including pediatric and adult UC and CD, psoriasis, and in some cases RA, TNFα–blockers are administered using an induction regimen followed by maintenance treatment dosing regimen.[14,22,32,59,68] To preserve residual β-cells in newly diagnosed T1D, rapid neutralization of the inflammatory, anti-β-cell response is likely to be key for an effective therapy. Golimumab steady-state concentrations are only achieved after at least 3 months with routine dosing, and with such a regimen continued β-cell destruction may likely occur. It was determined that 2 SC induction doses spaced by 2 weeks would more rapidly achieve a steady-state level and giving the best opportunity to protect residual β-cells. The induction doses will be followed by a lower maintenance dosing in order to maintain steady-state concentrations and continue to prevent further β-cell loss.

## 2. Model-Based Prediction of TNFα Suppression in T1D Subjects

To date golimumab has been studied in 2 pediatric populations; pJIA and pediatric UC. In the study of golimumab in children 2 to 18 years old with pJIA who were being treated with concomitant methotrexate (MTX) the dose was 30 mg/m$^2$ SC every 4 weeks (q4w). In the study of golimumab in children 6 to 18 years old with pediatric UC that dose was 90 mg/m$^2$ SC at Week 0 and 45 mg/m$^2$ SC at Week 2, and 45 mg/m$^2$ SC q4w for children <45 kg and 200 mg SC at Week 0 and 100 mg SC at Week 2, and 100 mg SC q4w in children ≥45 kg. The approved dose of golimumab in adults (those 18 years old and above) with RA, PsA, and AS is 50 mg SC q4w and for UC is 200 mg SC at Week 0, followed by 100 mg SC at Week 2 and then 100 mg SC q4w.

A mechanistic PK/target engagement (TE) model incorporated PK exposure from a previously established population PK model-based on the pJIA population was paired with a target-mediated drug disposition model to assess the interaction between drug and target and to simulate the suppression of TNFα after TNFα–blocker administration. The PK/TE model was developed based on the assumption that the etanercept dosing regimen tested in T1D results in sufficient TNFα neutralization given the positive results observed in the pilot trial in children with new-onset T1D.[48] The golimumab dosing regimen was designed to approximate the extent of TNFα suppression obtained using the etanercept dosing regimen in this study and accounting for the differences in PK and TNFα binding affinity between golimumab and etanercept. Concomitant use of MTX, which is standard of care in pJIA, reduces golimumab clearance in subjects with this disease, likely due to suppression of anti-drug antibodies.[77] Subjects with T1D do not receive MTX, therefore, a 56% faster clearance of golimumab in subjects with T1D than pJIA subjects was assumed for predicting the PK profile in the T1D population.

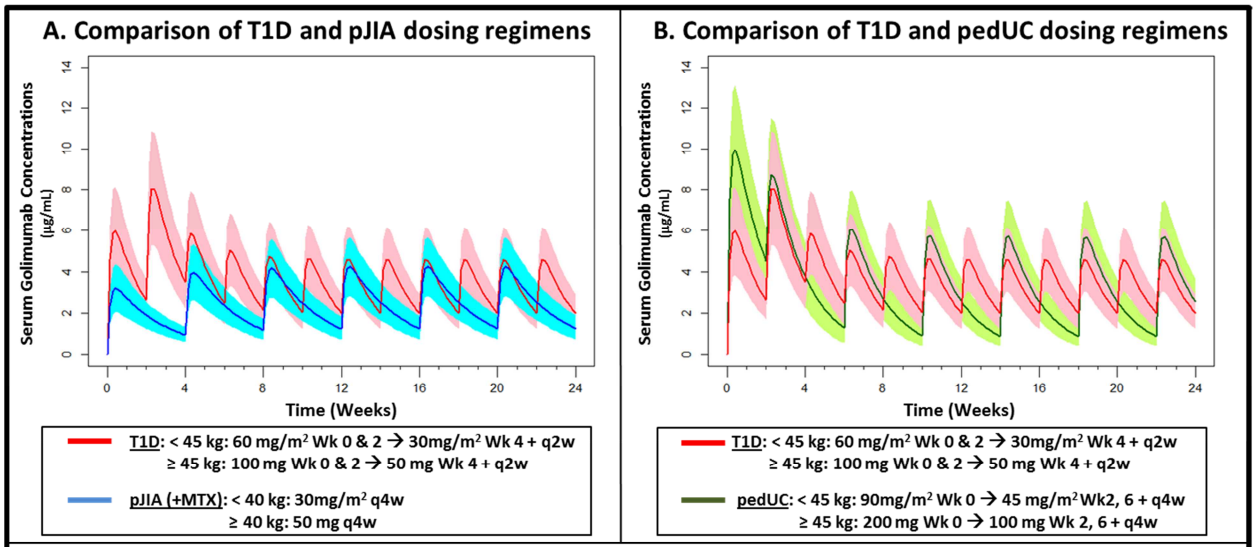
The PK/TE model suggested that an induction dosing regimen of 60 mg/m$^2$ SC (to a maximum of 100 mg) at Week 0 and Week 2 followed by a maintenance dosing regimen of 30 mg/m$^2$ SC (to a maximum of 50 mg) q2w or 60 mg/m$^2$ SC (to a maximum of 100 mg) q4w results in suppression of TNFα to a level approximating that of etanercept. This target would not be achieved with a 30 mg/m$^2$ SC q4w dose. The 30 mg/m$^2$ q2w and 60 mg/m$^2$ q4w maintenance dosing regimens would have the same overall exposure (AUC) and similar TNFα suppression; however, the 60 mg/m$^2$ q4w regimen would have higher peak/trough concentration fluctuations and thus more fluctuation on suppression of TNFα. It is known that TNFα has direct cytostatic and cytocidal effects on β-cells.[2,58] Thus the TNFα elevations that would be expected to occur during the troughs with the higher, but less frequent dosing, may result in more damage to residual β-cells. As the overall exposure to golimumab with these dosing regimens may be considered equivalent, the 30 mg/m$^2$ SC (to a maximum of 50 mg) q2w dosing regimens was preferred due to less peak/trough fluctuation.

## 3. Comparison of Golimumab Dose Regimens Between the T1D Population with Other Disease Populations of Adults and Children

Population PK simulations were performed comparing the proposed T1D dosing regimen with dosing regimens that have previously been studied in the pediatric populations (pJIA and pediatric UC, Figure 3 Panels A and B, respectively). The simulations to develop this dosing

strategy used demographics for subjects age 6 through 21 years based upon the U.S. Centers for Disease Control and Prevention growth charts.[18] For a child, golimumab 30 mg/m$^2$ (50 mg/1.67 m$^2$) would be approximately equivalent to a 50 mg dose for an adult subject weighing 60 kg (with a body surface area [BSA] of 1.67 m$^2$). Thus the 30 mg/m$^2$ dose is expected to be similar to the 50 mg dose in adults and the 60 mg/m$^2$ dose to be similar to the 100 mg dose in adults. In adults, golimumab 50 mg q4w was the minimum effective dosing regimen for the treatment of RA, PsA, or AS. Due to the absence of concomitant MTX in T1D subjects, it is expected that a 30 mg/m$^2$ q4w dosing regimen that is the pediatric equivalent to the adult 50 mg q4w dose may not result in sufficient systemic exposure for suppressing TNFα in T1D subjects, therefore a higher dose or more frequent dosing interval should be studied. For the simulation, a 40 kg weight cut-off was included (Figure 3 Panel A: <40 kg: 30 mg/m$^2$ q4w; ≥40 kg: 50 mg q4w). For the pediatric UC simulations, a 45 kg weight cut-off was implemented as previously studied, such that subjects <45 kg would receive 60 mg/m$^2$ at Weeks 0 and 2 followed by 30 mg/m$^2$ q2w and subjects ≥45 kg would receive 100 mg at Week 0 and 2 followed by 50 mg q2w. Based on the PK simulations, the proposed T1D dosing regimens (<45 kg and ≥45 kg) are expected to result in drug exposure (AUC) between that observed for the pJIA with MTX and pediatric UC populations without MTX (Figure 3, Panel A and B), although the 30 mg/m$^2$ q2w maintenance dosing interval will produce slightly higher trough concentrations.

**Figure 3: Overlap of simulated golimumab exposure for dosing regimens in current T1D study compared to those in pJIA and pediatric UC studies.**




**Detail:** Shown are simulations including median golimumab concentrations and 95% prediction intervals (95%PI) through Week 24 for dosing regimens in the current T1D study and dosing regimens previously evaluated for pJIA and pedUC in pediatric subjects. The T1D dosing regimen and resulting serum concentrations (median (red line) and 95%PI (pink area)) is displayed in Panels A and B. pJIA dosing regimen and resultant concentrations (median (light blue line) and 95%PI (aqua area)) which incorporate effect of concurrent MTX therapy (standard of care in pJIA) is shown in Panel A. pedUC dosing regimen and resultant concentrations (median (dark green line) and 95%PI (green area)) is shown in Panel B. *This data indicate that golimumab exposure in this study is expected to overlap with previous studies involving children, supporting that the existing safety profile of golimumab is applicable to this study.* See text for details. (MTX = methotrexate; pJIA = polyarticular juvenile idiopathic arthritis; pedUC = pediatric ulcerative colitis)

The safety and efficacy of golimumab has been extensively characterized in adult subjects with RA, PsA, AS, and UC. In a Phase 2 study in subjects with RA, 4 different dosing regimens were

evaluated (50 mg q2w or q4w and 100 mg q2w or q4w) of which all doses tested were generally well tolerated and effective in maintaining clinical response without dose-related safety events through Week 52.[35] In pJIA, a 30 mg/m$^2$ q4w dosing regimen was studied up to a maximum of 50 mg (the approved adult RA dose). In pediatric UC, a 45 kg weight cut-off was implemented such that subjects below 45 kg received BSA-adjusted doses and subjects at or above 45 kg received doses according to adult UC dosing regimens (details discussed above). To date, the dosing regimens studied in pediatric patients were well tolerated. Overall no new adverse drug reactions were identified. Further, the frequency, type, and severities of the events observed were similar to those observed in the adult rheumatology and inflammatory bowel disease studies. Since the dosing regimen for golimumab proposed for this study in T1D subjects is expected to result in drug exposures that overlap with those observed in previous pediatric studies with golimumab, it is appropriate to also expect that a similar safety profile will be demonstrated in the T1D population planned for enrollment in this trial as that seen in pediatric studies in pJIA and UC.

Considering the above-mentioned disease-specific issues of T1D, pharmacologic comparisons of golimumab and etanercept and specific experience with golimumab, an induction dosing regimen of 60 mg/m$^2$ SC (to a maximum of 100 mg) at Weeks 0 and 2, followed by a maintenance dosing regimen with 30 mg/m$^2$ SC (to a maximum of 50 mg) q2w was selected as the recommended dosing regimen in this study. In addition, a weight cut-off (45 kg), which has been implemented in the clinical pediatric UC study of golimumab, will also be studied such that subjects at or over the 45 kg weight cut-off will receive golimumab using the already approved adult PFS-U presentations.

## 4. SUBJECT POPULATION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following subsections. These criteria are consistent with those for recent interventional studies in newly diagnosed T1D, the targeted subject age range in this study, and recent studies of golimumab for other indications. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed. Deviations from the inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, and subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Individuals who meet entry criteria but are not able to be randomized within the allotted time (ie, 28 days from screening) may still participate in the study so long as they repeat study screening and again meet eligibility criteria. Subjects may only be rescreened once.

If a subject is a screen failure but at some point, in the future is expected to meet the subject eligibility criteria, the subject may be rescreened on 1 occasion only after consultation with the sponsor.

Subjects who are rescreened will be assigned a new subject number, undergo the informed consent/assent process, and then restart a new screening phase.

Retesting of abnormal screening values that lead to exclusion is allowed only once using an unscheduled visit during the screening period to reassess eligibility. This should only be considered if there is no anticipated impact on subject safety.

If a subject's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study agent is given such that they no longer meet all eligibility criteria, they should be excluded from participation in the study.

## 4.1. Inclusion Criteria

### 4.1.1. Inclusion Criteria Applicable to All Subjects

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Male or female 6 through 21 years of age who are diagnosed with T1D within 100 days of randomization per the ADA standard T1D criteria.[70]

2. Be positive for at least 1 of the following diabetes-related autoantibodies obtained at study screening:

   - Glutamic acid decarboxylase (GAD-65)
   - IA-2
   - ZnT8
   - ICA; or
   - Insulin (if obtained within 10 days of the onset of exogenous insulin therapy)

3. Have a peak stimulated C-peptide level ≥0.2 pmol/mL following a 4-hour MMTT obtained at study screening.

4. Be medically stable on the basis of physical examination, medical history, and vital signs performed at screening. If there are abnormalities, they must be consistent with the underlying illness in the study population.

5. Females of childbearing potential must have a negative serum (β-human chorionic gonadotropin [β-hCG]) test at screening and a negative urine pregnancy test at the Week 0 visit.

6. Criterion modified per Amendment 3 – open-label extension period

   6.1. Females must be either:

   - Not of childbearing potential: premenarchal; permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy); or otherwise be incapable of pregnancy,

   OR

- Of childbearing potential, and if sexually active, practicing through Week 104 and open-label extension period of the study be practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for subjects participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that subject); true abstinence (when this is in line with the preferred and usual lifestyle of the subject.
- Females of childbearing potential must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction through Week 104 and open-label extension period.

Note: If the childbearing potential changes after start of the study (eg, female who is not heterosexually active becomes active, premenarchal female experiences menarche) she must begin a highly effective method contraception of birth control, as described throughout the inclusion criteria.

- Agrees to remain on a highly effective method of birth control throughout the study.

7. During the treatment period of the study (from randomization through Week 52) and for a minimum of 1 spermatogenesis cycle (defined as 90 days after receiving the last dose of study agent), all males must:

   - Agree to be sexually abstinent or (2) if sexually active with a non-pregnant female of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository) and if sexually active with a female who is pregnant must use a condom.
   - Agree not to donate sperm.

8. Subjects (or their legally acceptable representatives) are willing and able to adhere to requirements, prohibitions, and restrictions specified in this protocol.

9. Subjects (or their legally acceptable representative) must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study. Assent is also required of children capable of understanding the nature of the study (typically 7 years of age and older) as described in Section 16.2.3, Informed Consent and Assent Form.

10. Subjects (or their legally acceptable representative) must sign a separate informed consent form if he or she agrees to provide an optional DNA sample for research. Refusal to give consent/assent for the optional DNA research sample does not exclude a subject from participation in the study. Assent is also required of children capable of understanding the nature of the study (typically 7 years of age and older) as described in Section 16.2.3, Informed Consent and Assent form.

11. Prior to receiving the study agent, subjects must be up-to-date with and agree to receive routine age-appropriate immunizations according to current Centers for Disease Control and Prevention (CDC) guidelines and agree to comply with the guidelines for immunosuppressed individuals and those with chronic disease (diabetes mellitus). Specific to the human papillomavirus (HPV) vaccine, pneumococcal vaccine and any non-routine vaccines for immunosuppressed individuals or those with chronic diseases, subjects must have received these immunizations or initiated the recommended vaccine series and have a completion plan before the first administration of study agent. Documentation of required immunizations or proof of corresponding immunity (eg, vaccination card, medical record, or demonstration of protective antibody titers) must be provided to the study site.

### 4.1.2. Additional Inclusion Criteria for Responders

Each responder must also satisfy the following criteria to be eligible to restart active treatment:

1. Subjects must meet the MMTT criteria at Screening for the open-label extension period. If the most recent MMTT is <3 months ago, a repeat MMTT is not required. Subjects who had their most recent safety laboratory samples drawn within 1 month prior to screening do not need a repeat; eligibility will be assessed based on these most recent laboratory tests. For C-responders who are lacking the necessary information to calculate IDAA1c score, an HbA1c will be performed and 10 days of insulin dose information will be required.

## 4.2. Exclusion Criteria

### 4.2.1. Exclusion Criteria applicable to All Subjects

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

**Coexisting medical conditions or past medical history:**

1. Has a history of significant renal, vascular, pulmonary, gastrointestinal, neurologic, hematologic, rheumatologic, or psychiatric disease.

2 Has significant cardiovascular disease, including history of myocardial infarction, congestive heart failure, angina, abnormal electrocardiogram or abnormal stress test.

3. Has a disease associated with lymphopenia, malignancy, bone marrow or organ transplantation, lymphoproliferative disorder, immune deficiency syndrome (eg,

severe combined immunodeficiency syndrome, T-cell deficiency syndromes, B-cell deficiency syndromes, or chronic granulomatous disease).

4. Has another autoimmune disease (eg, RA, pJIA, PsA, AS, MS, systemic lupus erythematosus [SLE], celiac disease [clinically symptomatic and antibody positive, ie, tissue transglutaminase IgA]). excluding clinically stable autoimmune thyroiditis whether treated or untreated.

5. Has nervous system disorder including but not limited to Guillain-Barre Syndrome, multiple sclerosis (MS), or progressive multifocal leukoencephalopathy (PML).

6. Has known allergies, intolerance and/or hypersensitivity to human immunoglobulin proteins, golimumab or any of its components or its excipients, or a known allergy or severe sensitivity to latex (refer to the SIMPONI and VarioJect Investigator's Brochures).[35,36]

7. Has any of the following hematologic abnormalities at screening, confirmed by repeat tests at least 1 week apart:

   - White blood count <3,500/μL or >14,000/μL;
   - Platelet count <100,000 /μL; or
   - Hemoglobin <10 g/dL.

8. Has a diagnosis of liver insufficiency or disease or hepatic enzymes equal to or above the values below, which represent alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≥2 times the upper limit of the gender- and age-based upper limit of normal confirmed by a repeat test at least 1 week apart (These values are based on the Central Laboratory normal ranges of AST and ALT values (Attachment 5)

   **Aspartate aminotransferase (AST)**

   *Females*

   - 96 U/L (age 6)
   - 80 U/L (age 7 through 17)
   - 68 U/L (age 18 and above)

   *Males*

   - 118 U/L (age 6)
   - 80 U/L (age 7 through 17)
   - 72 U/L (age 18 and above)

**Alanine aminotransferase (ALT)**

*Females*

- 68 U/L (age 6 and above )

*Males*

- 68 U/L (age 6 through 9)
- 86 U/L (age 10 and above)

**Infections or predispositions to infections**

9. Has active infections, is prone to infections or has chronic, recurrent or opportunistic infectious disease, including but not limited to, chronic renal infection, chronic chest infection (eg, bronchiectasis), sinusitis, recurrent urinary tract infection (eg, recurrent pyelonephritis, chronic cystitis), Pneumocystis carinii, aspergillosis, latent or active granulomatous infection, histoplasmosis, or coccidioidomycosis or an open, draining, or infected non-healing skin wound or ulcer.

10. Has any of the following TB screening criteria:

    - A history of latent or active TB prior to screening.
    - Signs or symptoms suggestive of active TB upon medical history and/or physical examination.
    - Recent close contact with a person with known or suspected active TB.
    - A history of or a positive QuantiFERON®-TB Gold test result at screening (see Attachment 1).

    A subject whose first QuantiFERON-TB Gold test result is indeterminate should have the test repeated. In the event that the second QuantiFERON-TB Gold test result is also indeterminate, the subject should be excluded from the study. Subjects with a negative QuantiFERON-TB Gold test result are eligible to continue with pre-randomization procedures.

11. Has a clinically active infection with Epstein-Barr virus (EBV) or an EBV viral load ≥10,000 copies per mL of plasma obtained at study screening.

12. Has a clinically active infection with cytomegalovirus (CMV) or a CMV viral load ≥10,000 copies per mL of plasma obtained at study screening.

13. Is infected with human immunodeficiency virus (HIV), hepatitis B (HBV) or hepatitis C (HCV) or at screening tests positive for HIV, HBV (See Attachment 4 for guidance for HBV test interpretation), or HCV.

**Concomitant or previous medical therapies received:**

14. Current or prior (within 30 days of screening) treatment that is known to cause a significant, ongoing change in the course of T1D or immunologic status, including high-dose inhaled, extensive topical, or systemic glucocorticoids.

15. Current or prior (within 30 days of screening) use of anti-hyperglycemic agents, including but not limited to metformin, sulfonylureas, glinides, thiazolidinediones, exenatide, liraglutide, DPP-IV inhibitors or amylin.

16. Current or prior (within 30 days of screening) use of any medication known to influence glucose tolerance including but not limited to atypical antipsychotics, diphenylhydantoin, thiazide, or other potassium-depleting diuretics, β-adrenergic blockers, or niacin.

17. Has ever received a systemic immunosuppression medicine or immune modulatory biologic therapy, including but not limited to T- or B-cell depleting therapy.

18. Has received or is expected to receive any live viral or live bacterial vaccinations from 90 days before first study agent administration, during the treatment period, and up to 120 days after the last study agent administration.

19. Has had a Bacille Calmette-Guérin (BCG) vaccination within 12 months of screening or is planned to receive BCG vaccination during the treatment period, and up to 12 months following last study agent administration.

**Reproductive**

20. If female, is pregnant, lactating, or breastfeeding, or planning to become pregnant while enrolled in this study.

21. If male, plans to father a child while enrolled in this study.

**General Restrictions**

22. Criterion modified per Amendment 3 – open-label extension period

    22.1. Has participated in any interventional clinical study within the 6 months prior to enrollment or is currently enrolled in an investigational study (apart from CNTO148DML2001 trial).

23. Criterion modified per Amendment 3 – open-label extension period

    23.1. Has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 90 days before the planned first dose of study agent or is currently enrolled in an investigational study (apart from

CNTO148DML2001 trial).

24. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

**NOTE:** Investigators should ensure that all study enrollment criteria have been met at screening and, at randomization. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before randomization and the first dose of study agent is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 9.1.2, Screening Period, describes options for retesting. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

### 4.2.2. Additional Exclusion Criteria for Responders

1. Subjects having reported clinically significant AEs or serious adverse event (SAEs) deemed to be related to the study agent during the double-blind period (e.g. severe infections or hypersensitivity reactions), precluding renewed exposure to golimumab.

2 Subjects who discontinued study agent administration prior to Week 52 or who have completed the Week 104 visit of the double-blind period or discontinued early from the study.

3 Subjects and/or caregivers who are unwilling or unable to administer study agent.

## 4.3. Exceptions to Inclusion and Exclusion Criteria for Open-Label Extension Period

The responders must continue to meet the initial inclusion and exclusion criteria to be eligible for the open-label extension period with following exceptions:

1. Autoantibody status will not be assessed (refer to criteria 2 under Section 4.1.1).
2. Subjects older than 21 years of age are eligible (refer to criteria 1 under Section 4.1.1).
3. For the open-label extension period, subjects may begin open-label study agent while EBV polymerase chain reaction (PCR) results are pending and if he/she meets all other inclusion/exclusion criteria. If EBV PCR results come back positive, subject must immediately stop treatment and be withdrawn from the study.

## 4.4. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 8 for details regarding prohibited and restricted therapy during the study.

2. Agree to follow the contraceptive requirements as noted in the inclusion criteria.

3. Criterion modified per Amendment 3 – open-label extension period

   3.1. Will not receive a live virus or live bacterial vaccination 90 days before first study agent administration, during the 52-week treatment period and the open-label extension period of the study and up to 120 days after the last study agent administration.

4. Criterion modified per Amendment 3 – open-label extension period

   4.1. Will not receive a BCG vaccination within 12 months of screening, during the 52-week treatment period and the open-label extension period of the study and up to 12 months following last study agent administration.

5. Criterion modified per Amendment 3

   5.1. If sexually active and of childbearing potential, females will remain on a highly effective method of birth control and must not donate eggs (ova, oocytes) for the purposes of assisted reproduction throughout the study, or if she withdraws early from the study within 6 months of the last study agent administration.

6. Criterion modified per Amendment 3 – open-label extension period

   6.1. If sexually active with a female of childbearing potential and has not had a vasectomy, males must use a double barrier method of birth control during the study. Males must not donate sperm and must agree not to plan a pregnancy or father a child during the 52-week treatment period and the open-label extension period of the trial and for 90 days after the last study agent administration, or if he withdraws early from the study within 90 days of the last study agent administration.

7. Criterion modified per Amendment 3

   7.1. Must not receive investigational drugs, systemic immunosuppressants (including, but not limited to cyclophosphamide) or other biologics throughout the study.

## 5. TREATMENT ALLOCATION AND BLINDING

### Treatment Allocation

#### *Procedures for Randomization and Stratification*

Central randomization will be implemented in this study. Subjects 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 subjects' 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.

**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 investigative sites will not be provided with randomization codes. The codes will be maintained within the 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 (ie, study agent serum concentrations, anti-golimumab antibodies, and treatment allocation) 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 DBL 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 will 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 and reason for the unblinding must be documented by the IWRS, in the appropriate section of the CRF, 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.

Subjects who have had their treatment assignment unblinded for a SAE will not continue to receive study agent but should continue to return for scheduled evaluations.

Summary level unblinded data will be made available to the sponsor at the Week 52 DBL (DBL 1). Subject level data will be unblinded to selected members of the sponsor’s data management, programming, pharmacology, clinical and biostatistics teams for analysis and reporting, while the subjects are still being followed in the study. Identification of sponsor personnel who will have access to the unblinded subject level data will be documented prior to unblinding. The Study Responsible Physician will remain blinded throughout the double-blind

period to subject level treatment assignment and dosing regimen. Site investigators and personnel, and the subjects/caregivers will remain blinded until after the Week 104 DBL (DBL 2) has occurred. An exception to this rule will be made for those subjects who are meeting the responder criteria at Week 52 of the double-blind period. These will be unblinded to determine eligibility for re-starting active treatment during the open-label extension period.

Subject level data will be unblinded to Data Monitoring Committee (DMC) and Interim Analysis Committee (IAC). Please refer to Section 11.10 and Section 11.11 for details.

# 6. DOSAGE AND ADMINISTRATION

## 6.1. Dosage

All study agent (golimumab or placebo) will be administered SC using a sponsor-supplied, single-use administration device. This will be either the commercially available prefilled syringe with a needle guard (the PFS-Ultrasafe [PFS-U]), designed to deliver a single, fixed dose of 50 mg, or the investigational VarioJect injection device ("VarioJect)" which delivers a single, variable dose of 10 to 45 mg in 5 mg increments. Identical devices containing placebo will be used to deliver a volume equivalent to that of active treatment for subjects randomized to the placebo arm.

Body surface area will be calculated at Week 0 for the induction and maintenance dose of golimumab (and will be adjusted as needed) based on weight cut-off according to Table 1. Detailed charts using height and weight for induction and maintenance doses according to weight cut-off are presented in Attachment 2-A and 2-B, respectively. Body surface area will be calculated using the Mosteller equation: BSA ($m^2$) = ([height (cm) x weight (kg)]/3600)$^{1/2}$. The dosage form (PFS-U or VarioJect) and volumes required for administration are presented in Attachment 2-C. For certain induction doses, 2 injections may be required for administration of 1 induction dose.

**Table 1: Golimumab SC Dosing Regimens by Body Weight Cut-Off For Subjects Who Are Randomized to the Golimumab Treatment Group**

| Body weight* | Week 0 and 2 | Week 4 through Week 52 (Double-Blind) Period | Week 0 through Week 50 (Open-Label Extension) Period |
|---|---|---|---|
| <45 kg | 60 mg/$m^2$ | 30 mg/$m^2$ q2w | 30 mg/$m^2$ q2w |
| ≥45 kg | 100 mg | 50 mg q2w | 50 mg q2w |
| Number of injections/dose | 1 or 2** | 1** | 1** |

*Body weight to be evaluated approximately every 3 months with dose adjustment if necessary (below and see Time and Events Table).
**Refer to Attachment 2

During the 52-week dosing period, subjects may experience changes in their weight and/or height necessitating a change in the dose of the study agent. There will be 4 opportunities to calculate the study agent dose during the 52-week dosing period. Study agent dose for the first 12 weeks will be based on height and weight obtained at the Week 0 visit. At the Week 12 visit, height and weight will be obtained and the dose for the next 14 weeks (until the Week 26 visit)

will be calculated. Similarly, at the Week 26 and 38 visits, the dose for the subsequent 12 and 14-week intervals, respectively, will be calculated (see Time and Events Schedule).

The same procedure will be applied for the responders during the open-label extension period. Study agent dose will be calculated at the OL Week 0, 12, 28, 44, and 50 visits. The last dose of study agent is to be administered at Week 50. Detailed charts using height and weight for open-label extension period according to weight cut-off is presented in Attachment 2-B.

Responders being restarted on active drug will not undergo an induction regimen but will immediately be started on the maintenance dose. A new induction dose may entail an increased risk for immunogenicity and/or hypersensitivity reactions and there is no clear rationale for reaching steady state as quickly as possible given the longer delay after diagnosis of T1D.

Details on dose preparation and administration can be found in the Study Site Investigational Product and Procedures Manual (SIPPM).

For the most comprehensive information regarding the VarioJect, refer to the current version of the VarioJect IB.

## 6.2. Dose Administration

Study agent dosing will be administered using the PFS-U or VarioJect. It will be injected subcutaneously by trained study-site staff and for some dosings, subjects/caregivers will be given the option of "self-administration" after appropriate training (described below). For purposes of this study, the term “self-administration” is defined as study agent administered either by subject or caregiver and can occur at home and/or at study sites. In cases where subjects/caregivers do not want or are unable to participate in self-administration of study agent, subjects will receive all doses of study agent at study sites.

For responders in the open-label extension period, study agent administration will be performed by site personnel at all site visits. In-between visit doses will be administered either by the subject or by the caregiver. In cases where subjects/caregivers do not want or are unable to participate in self-administration of study agent, subjects will receive all doses of study agent at study sites.

Study staff and those subjects/caregivers who will participate in self-administration will receive training on study agent administration at the investigative site under the supervision of a trained health care professional, which must be documented. This will include education regarding instructions for use (IFU), proper handling and storage of devices, guidance on study agent injection, and proper handing and accounting for used devices. Required storage conditions and expiration date are indicated on the label.

Injection sites include the front of thighs (which is recommended), the lower abdomen (avoiding the 2-inch area around the navel), or the back of the upper arms. Different sites should be used for consecutive injections. Sites that are tender for any reason should be avoided. Study agent and insulin injections should be given at different anatomic sites.

Study agent dosing should be held during the course of a febrile episode and other conditions as detailed Section 10.2. If the febrile episode is mild and transient and the subject does not meet any criteria in Section 10.2, that dose may still be administered as long as it is in the current dosing window (See Section 7.1) otherwise dosing should resume with the next planned dose. Refer to Section 10.2 for dose holding and dosing resumption for other conditions. If subjects/caregivers have a question about the subject status and their ability to be dosed, they are to consult with the study-site investigational team. If subjects/caregivers have a question about the subject status and their ability to be dosed, they are to consult with the study-site investigational team.

Administration of the first 3 doses will occur during study visits (Week 0, 2, and 4). For subjects/caregivers who will be participating in self-administration, training will take place at these visits. It is possible that the device required for induction doses differs from the device required for maintenance doses. Training should be provided on the device intended for maintenance dosing. Prior to allowing at home self-administration, at least 1 successful injection by the subject/caregiver using the device to be used for at home self-administration, must be witnessed by study staff. At the Week 8, 12, 18, 26, 38, and 52 study visits of the double-blind period and Week 12, 20, 28, 36, 44, and 50 study visits of the open-label extension period where study agent will be administered, either subjects/caregivers or study staff may administer the injection.

Following dosing, subjects are to be monitored for at least 30 minutes as detailed in Section 9.1.3 and Section 9.1.5. All data regarding study agent administration including date, time, and anatomic location of injection, study agent dosing device and if there are AEs, reactions or device complications will be recorded. During self-administration, subjects/caregivers are to contact the study-site team in the event of problems or complication including but not limited to signs of immediate or delayed local or systemic reaction (Section 9.9).

At any time, if subjects/caregivers are uncertain about how to administer the study agent or has questions regarding self-administration, the sponsor recommends a review of the IFU with the study staff along with practice injections with a training device if necessary. If at any time during one of the 3 opportunities for dose adjustment, there is a change in the device required for dosing, the subject/caregiver must return to the study site for training and the subject/caregiver using the device must be witnessed by study staff self-administering a successful injection prior to performing at home self-administration.

For subjects/caregivers unwilling or unable to self-administer the study agent outside of the study site, subsequent doses will be administered at the study site by qualified personnel on the appropriate dosing schedule per the Time and Events Schedule. During the dosing period these subjects/caregivers can be trained for self-administration of subsequent dosing per the above guidelines.

# 7. TREATMENT COMPLIANCE

## 7.1. STUDY AGENT DOSING COMPLIANCE: RECORDING AND WINDOWS

### 7.1.1. Dosing Recording

Details on the specifics of the study agent including study agent dosing device type, date, time, anatomic location of injection, and person administering the dose, will be documented in the CRF or recorded in the electronic diary (eDiary). Study-site personnel will record this information for study agent administrations conducted at the study visits (see Time and Events schedule). For subjects/caregivers participating in self-administration, this data will be entered into an eDiary unless self-administration is done on-site where this information will be recorded in the study site's documents, not in the eDiary. All information related to self-administration will be reviewed and verified with subjects/caregivers at subsequent study visits.

Subjects are to receive dosing with study agent every 2 weeks following randomization through Week 52, for a total of 27 doses (Table 2). The "target dosing day" for the study will be at 14-day intervals and calculated based on the day of randomization. The target dosing day schedule will not be readjusted due to missed or off schedule dosing.

The investigator or designated study-site personnel will maintain a log of all study agent dispensed and returned both from and to the study site and the sponsor and, in cases of subject self-administration, to and from the study site and subject/caregiver. Drug supplies for each subject will be inventoried and accounted for throughout the study.

Study sites are expected to keep in close contact with subjects/caregivers and encourage dosing and study visit compliance, whether or not they are participating in self-administration. This may occur proactively via telephone or electronic communication, sending automated dosing reminders, and through monitoring eDiaries which will be obtaining regular (ie, daily) subject data entry updates.

#### 7.1.1.1. Dosing Recording – Open-Label Extension Period

Details on the specifics of the study agent including study agent dosing device type, date, time, anatomic location of injection, and person administering the dose, will be documented in the CRF or recorded in the or paper diary. Study-site personnel will record this information for study agent administrations conducted at the study visits (see Time and Events schedule). For subjects/caregivers participating in self-administration, this data will be entered into the paper diary unless self-administration is done on-site where this information will be recorded in the study site's documents, not in the paper diary. All information related to self-administration will be reviewed and verified with subjects/caregivers at subsequent study visits.

Subjects are to receive dosing with study agent every 2 weeks based on Week 0 of the open-label extension period, for a total of 27 doses (Table 3). The "target dosing day" for the study will be at 14-day intervals and calculated based on the day of randomization. The target dosing day schedule will not be readjusted due to missed or off schedule dosing.

The investigator or designated study-site personnel will maintain a log of all study agent dispensed and returned both from and to the study site and the sponsor and, in cases of subject self-administration, to and from the study site and subject/caregiver. Drug supplies for each subject will be inventoried and accounted for throughout the study.

Study sites are expected to keep in close contact with subjects/caregivers and encourage dosing and study visit compliance, whether or not they are participating in self-administration. This may occur proactively via telephone or electronic communication, sending automated dosing reminders, and through or paper diaries during the open-label extension period which will be obtaining regular (ie, daily) subject data entry updates.

### 7.1.2. Dosing Windows

**All attempts should be made to dose on the scheduled target dosing day, yet it is recognized that due to schedules and other events this may not be possible.**

**Weeks 2 and 4:** Study agent dosing for Week 2 and 4 is to occur ± 1 day of the target-dosing day.

**Weeks 6 through 52:** For study agent dosed from Weeks 6 through 52, every effort should be made to administer the study agent on the target dosing day or at least should be given ± 3 days of the target day, regardless of whether subjects are participating in self-administration or being dosed at study sites. In situations where subjects cannot dose within this window, the dose can be administered up to 7 days after the targeted dosing day. If the dose cannot be administered within this period, that dose should not be given, and subjects should resume dosing at the next scheduled dosing interval.

**Entire study:** Throughout the study, administration of sequential study agent dosing's must occur no less than 7 days apart.

**Table 2: Study Agent Dosing Window Table**

| Time | Dose Administration Window Around Target Dosing Day* |
|---|---|
| **Required Administration at the Study Site** | |
| Randomization Visit Week 0 | N/A |
| Visits Week 2 and 4 | ± 1 day |
| Visits and Dosing Weeks 6 through 52 | ± 3 days |
| *Calculated based on 14-day intervals from randomization day. Subjects/caregivers will schedule dosing-only visits to comply with dosing schedule. | |

#### 7.1.2.1. Dosing Windows - Open-Label Extension Period

**Week 2:** Study agent dosing for Week 2 is to occur ± 1 day of the target-dosing day.

**Weeks 4 through 50:** For study agent dosed from Weeks 4 through 50, every effort should be made to administer the study agent on the target dosing day or at least should be given ± 3 days of the target day, regardless of whether subjects are participating in self-administration or being dosed at study sites.

**Entire study:** Throughout the study, administration of sequential study agent dosing's must occur no less than 3 days apart.

| **Table 3: Study Agent Dosing Window Table – Open-Label Extension Period** | |
|---|---|
| **Time** | **Dose Administration Window Around Target Dosing Day*** |
| **Required Administration at the Study Site** | |
| Visit Week 2 | ± 1 day |
| Visits and Dosing Weeks 4 through 50 | ± 3 days |
| *Calculated based on Week 0 of open-label extension period. Subjects/caregivers will schedule dosing-only visits to comply with dosing schedule. | |

## 8. PRESTUDY AND CONCOMITANT THERAPY

During the double-blind period, prestudy therapies administered up to 28 days before screening and between screening and randomization must be recorded in the CRF.

Concomitant therapies must be recorded throughout the study beginning at randomization through completion of the study.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements) different from the study agent must be recorded in the CRF. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication.

### 8.1. Required Medications

Insulin preparations as advised by the principal investigator and/or the subject's primary physician or endocrinologist to target current glycemic control recommendations by the ADA specifically with a HbA1c target of <7.5% in children 17 years old and younger and <7% in those 18 years old and above.[67]

All subjects will be expected to take a sufficient number of daily insulin injections to meet the above glycemic targets. In general, the expectation is that all subjects will receive at least 3 injections of insulin daily, including short- and long-acting insulin preparations, or will utilize a continuous subcutaneous insulin infusion/pump. Glucose levels should be checked at least 4 times daily. HbA1c will be recorded regularly as part of the study and subjects may have HbA1c conducted by their physician who is managing their diabetes.

During the double-blind period, subjects will record insulin use for the 7-days preceding each study visit and hypoglycemic events occurring at any time during the study will be captured using an eDiary. Subjects will also be loading daily glucometer readings into their eDiary. This information will be reviewed at each study visit and recorded using CRFs. Please also refer to Section 9.8.

During the open-label extension period, subjects will record insulin use for the 10-days preceding each study visit and hypoglycemic events occurring at any time during the study will be captured using the paper diary.

If subjects are not meeting the above goals, the study team should contact the subject's primary clinical-care team about possible adjustments in the insulin regimen, referral to a registered dietitian, or other approaches that the diabetes management team believes would improve the glucose control if necessary.

## 8.2. Permitted Medications

There are no medications specifically contraindicated for use with golimumab, so subjects may continue to receive medications as needed for existing medical conditions. Please see Section 8.3 for a list of medications that should not be taken in conjunction with the study agent during the study. Specific permitted medications that subjects may need during the study include, but are not limited to:

- Low-dose estrogen oral contraception.
- Acetaminophen and NSAIDs (eg, ibuprofen and naproxen).
- Diphenhydramine (or equivalent antihistamines).
- Non-infectious (ie, recombinant, inactivated or otherwise "non-live") vaccines recommended by the CDC in individuals 6 years old and above (including the HPV vaccine) and those recommended for immunosuppressed individuals or those with chronic diseases (diabetes mellitus). For these immunizations, if required and applicable, subjects should receive recommended one-time vaccinations prior to first study agent administration. If a subject has started a recommended vaccination series, the next administration in the series should be given before first dosing of study agent, if consistent with recommended administration schedule. If needed, the series may be completed during the study according to the recommenced schedule. If a subject has not received the first dose of a required vaccination series, they should receive this before the first study agent administration and continue to receive vaccinations in this series during the study as recommended. Subjects are to receive non-infectious vaccines during the recommended time frame if they meet specific criterion during the study, ie, becoming age-eligible, while participating in the study. Documentation of all vaccines given during screening and post-randomization participation in the study must be provided to the study site.

## 8.3. Prohibited Medications

The concomitant use of the following drugs is not permitted during the study:

- Live vaccines (eg, varicella, measles, mumps, rubella, cold-attenuated intranasal influenza vaccine, and smallpox) in the 90 days before enrollment, during the treatment periods, and for 120 days after completing study treatment. In addition, household contacts should be encouraged not to receive small pox or oral polio vaccine due to the risk of viral shedding.
- BCG vaccination during the study or for 12 months after the last administration of study agent.
- Agents that influence insulin sensitivity or secretion, which include but are not limited to MTX, sulfonylureas, metformin, diphenylhydantoin, thiazide, or other potassium-depleting diuretics, beta-adrenergic blockers, or niacin through Week 104 including the open-label extension period.

- Agents that may result in immunosuppression or immunomodulation through Week 104 and the open-label extension period. This includes initiation of long- or chronic-dosing of high-dose inhaled, extensive topical or systemic glucocorticoids. This also includes biologic immune modulators including but not limited to abatacept and anakinra. Note: A short course of corticosteroids may be used for treatment of a transient condition.

If a subject receives, or if the principal investigator believes that a subject needs a prohibited medication, the case must be immediately discussed with sponsor Study Responsible Physician to determine whether study treatment should continue or be discontinued.

# 9. STUDY EVALUATIONS

## 9.1. Study Procedures

### 9.1.1. Overview

- The Time and Events Schedule summarizes the frequency and timing of efficacy, PK, immunogenicity, Pharmacodynamics, biomarker, pharmacogenomic, and safety assessments applicable to this study.
- During the double-blind period, a 4-hour MMTT will be performed during screening, and at Weeks 12, 26, 38, 52, 78, and 104[12]. During the open-label extension period, a 4-hour MMTT will be performed to establish eligibility criteria unless the previous MMTT was <3 months ago and will also be performed at OL Screening and OL Weeks 28 and 52. For C-responders who are lacking the necessary information to calculate IDAA1c score, an HbA1c will be performed and 10 days of insulin dose information will be required. This test is to be performed in the morning after an overnight fast. Subjects are to follow the dietary and insulin use guidelines as described in Attachment 3 to perform the MMTT.
- Subjects/caregivers will collect data related to diabetes management, hypoglycemic events, and study agent dosing using sponsor-supplied eDiary and glucometer (for the double-blind period) and paper diary (for the open-label extension period).
- PK and Immunogenicity samples must be collected before study agent administration.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.
- Blood collection:
  - The total blood volume to be collected from each subject, including during screening, the 52-week treatment period and 52-week off-therapy follow-up period is approximately 436 mL for subjects <35 kg and 505 mL in subjects ≥35 kg. During the open-label extension period, approximately 210 mL for subjects <35 kg and 234 mL for subjects ≥35 kg will be drawn.
  - It is recognized that the amount of blood that may be drawn for research purposes in adults and children may not exceed certain limits, both at a single visit and over a set amount of time. Guidance for blood drawing in this study is:

**Adult Subjects (18 years of age and older)**

The amount of blood that may be drawn for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any 8-week period.

**Pediatric Subjects (6 Through 17 Years of Age):**

The amount of blood that may be drawn for research purposes shall not exceed more than 5 mL/kg in a single day and shall not exceed more than 9.5 mL/kg over any 8-week period.

In any subject whose clinical condition might be adversely affected by removal of the blood volumes stated above, for example, a subject with significant anemia or compromised cardiac output, investigators should consider further limiting the volume of blood withdrawn for research purposes.

In instances of medical need, it is the responsibility of the site investigator and/or subject's healthcare providers to determine if blood draws in excess of the above limits should occur. Because blood sampling in excess of those mandated by the protocol may be taken in the course of providing patient care during this study, sites must ensure that all instances of blood collection in excess of permitted volumes are recorded and justified in the subject's record.

### 9.1.2. Screening Period

For all subjects participating in this study, the screening visit must occur within 28 days of study agent administration and may occur over more than 1 day. Prior to screening, the investigator (or designee) will explain the study's rationale, procedures, and risks, and ask each potential subject/caregiver to consent/assent to participate. The start of the screening period of the study will be defined as the day written informed consent/assent is obtained. Subjects may participate in optional pharmacogenomic assessments which will require a separate consent/assent.

Subjects will be assigned a unique subject number and evaluation for inclusion/exclusion criteria (Section 4) will be performed, which will include clinical and laboratory evaluations and the 4-hour MMTT.

An eDiary and glucometer will be issued to subjects during screening for training on how subjects/caregivers are to collect data between study visits related to: including insulin use, BG levels, hypoglycemic events, and study agent administration. Subject data collected using eDiaries will be reviewed and verified at subsequent study visits, including the randomization visit (see Time and Events Schedule). In cases where subjects are not enrolled in the study, they will be directed on how to return the devices.

The measurements collected and procedures performed during the screening visit for all subjects are identified in the Time and Events Schedule. In anticipation of successful screening and continued interest in the study, study personnel should discuss the optimal timing for and even tentatively schedule study randomization at the screening visit. This is due to the limited window between screening and randomization and recognizing that all future dosing and study visits for 2 years will be based on that randomization date.

Subjects must undergo testing for TB (see Attachment 1) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active or suspected TB. The subject should be asked about past testing for TB, including responses to tuberculin skin or other TB testing.

Subjects with a negative QuantiFERON-TB Gold test result are eligible to continue with randomization procedures. Subjects with a positive QuantiFERON-TB Gold test result must be excluded from the study.

A subject whose first QuantiFERON-TB Gold test result is indeterminate should have the test repeated. In the event that the second QuantiFERON-TB Gold test result is also indeterminate, the subject should be excluded from the study.

**Retesting**

If subjects screen but do not meet all study participation criteria (See Section 4.1 and Section 4.2.1), they may be eligible for retesting that may lead to randomization. Retesting of laboratory tests will be allowed once and will take place during an unscheduled visit within 28 days of initial screening phase.

**Rescreening**

If subjects are eligible to participate in the study but do not randomize within 28 days of signing the consent/assent form or do not meet specific enrollment criteria that may change to allow enrollment (ie, development of T1D autoantibodies), subjects may be rescreened and be randomized as long as inclusion and exclusion criteria are met and the subject is able to be randomized within 100 days of T1D diagnosis. Rescreening is allowed only once. Subjects who are rescreened will receive a new subject number, repeat the informed consent process, and then restart a new screening phase.

#### 9.1.2.1. Screening Period - Open-Label Extension Period

For the open-label extension period, the optional screening visit should occur within 21 days after the subject has been offered the opportunity to enter open-label extension period and in any event must occur within 14 days prior to Week 104. Prior to screening, the investigator (or designee) will explain the study's rationale, procedures, and risks, and ask each potential subject/caregiver to consent/assent to participate. The start of the screening period of the study will be defined as the day written informed consent/assent is obtained. Rules for MMTT have been described in Attachment 3.

Subjects will be assigned a unique subject number and evaluation for inclusion/exclusion criteria (Section 4) will be performed, which will include clinical and laboratory evaluations and the 4-hour MMTT.

A paper diary will be issued to subjects during screening for training on how subjects/caregivers are to collect data between study visits related to: including insulin use, hypoglycemic events,

and study agent administration. Subject data collected using paper diaries will be reviewed and verified at subsequent study visits (see Time and Events Schedule).

Subjects must undergo testing for TB (see Attachment 1) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active or suspected TB. The subject should be asked about past testing for TB, including responses to tuberculin skin or other TB testing.

Subjects with a negative QuantiFERON-TB Gold test result are eligible to continue with randomization procedures. Subjects with a positive QuantiFERON-TB Gold test result must be excluded from the study.

A subject whose first QuantiFERON-TB Gold test result is indeterminate should have the test repeated. In the event that the second QuantiFERON-TB Gold test result is also indeterminate, the subject should be excluded from the study.

### 9.1.3. Randomization, Treatment Period, and Follow-up Period

#### 9.1.3.1. Active Treatment Period: Weeks 0 To 52

**Randomization: Week 0**

Randomization will occur no later than 28 days after screening is initiated and will be designated as Week 0 and Day 1 of the study. At this visit, inclusion and exclusion criteria, concomitant medications, and laboratory evaluations should be reviewed and documented to determine that a subject remains eligible for participation in the study. All eDiary data collected since screening will be reviewed by clinic staff. Subjects must have at least 5 days of daily insulin use recorded within the 7 days immediately preceding randomization. If not, subjects/caregivers should be instructed to reschedule this visit to have at least 5 days of daily insulin usage recorded prior to the rescheduled randomization visit. Subjects will be randomly assigned as described in Section 3.1 to receive study agent (golimumab or placebo). Subject weight and height will be obtained to determine dose and device.

After the predose PK/immunogenicity sample is drawn, the dose of study agent (golimumab or placebo) will be administered at the study site. Subjects should be monitored for at least 30 minutes following injection and be observed for any adverse reactions, including injection site reactions (See Section 9.9). Subjects/caregivers who want to participate in study agent administration "self-administration" outside of some study visits begin training on using the sponsor-supplied single-use injection devices (See details Section 6.2). Additional training on the eDiary and glucometer will be given as needed.

Future target dosing and study visit days will be calculated based on the day of initial dosing at randomization (Week 0) and will not be redefined later during the study. Therefore, the study staff are encouraged to discuss the study visit days with subjects/caregivers and consider this schedule to determine what might be the anticipated (ie, day of the week) for future dosing and

study visits. Specific study visits and study agent treatment windows and impact on study compliance is detailed in Section 7.

At this visit, subjects/caregivers will be supplied with a calendar with target dosing days and target study visit days that show dosing and visit windows (See Section 7.1.2).

**Study Visits: Weeks 2 and 4**

At these visits, subjects will have medical and eDiary review and other assessments per the Time and Events Schedule. Subjects will receive study agent by study staff and should be monitored for at least 30 minutes following injection and be observed for any adverse reactions, including injection site reaction (Section 9.9). In addition, for those who will be administering the injection outside of study visits ("self-administration"), subjects and/or caregivers should continue and complete administration training, including conducting a successful injection by the subject or caregiver using the device to be used for self-injection. If the training was considered successful and the site staff considers that the subject or caregiver can successfully self-administer, the subject will be sent home with study agent injection devices at Week 4, with instructions for handling and storage of drug and used devices. The visit window for these visits is ±1 day from the target dosing day.

**Study Visits Including Study Agent Dosing: Weeks 8, 12, 18, 26, 38, and 52**

During Weeks 8 through 52, subjects will return to the site for their scheduled visit, have predose PK/immunogenicity sample drawn, have safety and/or efficacy assessments performed, and receive study agent dosing by site staff according to the Time and Events Schedule. All subject required data, including that recorded via eDiary data, will be reviewed. During these visits, subjects/caregivers who are administering injections are to return used devices and receive additional devices and supplies per the Time and Events Schedule since the last visit. At these visits, subjects/caregivers will also receive additional device training as needed. During Weeks 12, 26, and 38, subjects are to have their weight and height reassessed to determine if dosing adjustments need to be made for the next interval as described in Section 6.1, with additional training as needed. The visit windows for these study visits are ± 3 days from the target dosing day.

**Study Visits for PK Sampling and Clinical Review Only: Weeks 33 and 45**

Visits on Weeks 33 and 45 are not dosing visits however in addition to clinical review and assessments, a random PK sample will be drawn. Subjects/caregivers who are participating in administering injections are to return used devices and receive additional injection devices and supplies, if needed, at these visits. The visit windows for these study visits are ± 7 days from the target dosing (visit) day.

#### 9.1.3.2. Study Agent Self-Administration or Dosing-Only Visits: Study Weeks 6, 10, 14, 16, 20, 22, 24, 28, 30, 32, 34, 36, 40, 42, 44, 46, 48, and 50

After Week 4, subjects/caregivers who have met the training requirement, are given the option to self-administer majority of the study agent doses off-site that do not coincide with study visits. As detailed in Section 6.2 and the IFU, subjects/caregivers will receive training on

administration during the first 3 dosing visits, and at study visits preceding off-site administration subjects will receive the appropriate study agent devices for dosing until the next dosing visit as well as supplies and instructions on handling and storage before and after usage. Subjects/caregivers will enter information including date and time of dosing, device used, anatomic site injected, and person administering dose into their eDiary. Subjects/caregivers will be asked to closely monitor the study agent injection site for at least 30 minutes and intermittently thereafter. During self-administration, subjects/caregivers are to contact the study-site team in the event of problems or complication including but not limited to signs of immediate or delayed local or systemic reaction (Section 9.9). These dose administrations should occur ± 3 day of target dosing day as detailed above.

For subjects/caregivers unwilling or unable to administer the injection, subjects/caregivers are to work with the site team to develop a visit schedule to meet the dosing criteria in Section 9.1.3 and per the Time and Events Schedule. These study agent dosing-only visits are to take place ± 3 days of the target dosing day.

#### 9.1.3.3. Off-Therapy Follow-up Period – Weeks 52 to 104

The last dose of study agent is to be administered at the Week 52 study visit. Subjects will remain in the study until Week 104, continue recording data in their eDiary and followed for evaluations of safety, PK/anti-drug antibodies, and durability of response. Subjects will have assessments only at Week 78 and Week 104. All safety and efficacy assessments will be performed at these visits according to the Time and Events Schedule. The visit windows for these 2 visits are ± 10 days of the target visit day.

During the treatment and off-therapy follow-up periods subjects will continue to receive intensive management of their diabetes and maintain tight glycemic control according to the current ADA.[67]

### 9.1.4. Optional Screening - Open-Label Extension

For the open-label extension period, the optional screening visit should take place no later than 21 days after the subject has been offered the opportunity to enter open-label extension period and in any event must occur within 14 days prior to Week 104.

### 9.1.5. Open-Label Extension Period

Subjects meeting the inclusion criteria applicable for responders and who are willing to participate will restart active study treatment in the open-label extension period.

#### 9.1.5.1. Active Treatment Period: OL Weeks 0 To 52

**Restart: OL Week 0**

Restart will occur no later than 14 days after screening is initiated and will be designated as Week 0 and Day 1 of the study. In no event can a subject be restarted if they have completed the Week 104 visit. At this visit, inclusion and exclusion criteria, concomitant medications, and laboratory evaluations should be reviewed and documented to determine that a subject remains

eligible for participation in the study. All paper diary data collected since screening will be reviewed by clinic staff. Subjects should have at least 10 days of daily insulin use immediately preceding restart. Subjects will be restarted to receive golimumab as described in Section 3.1. Subject weight and height will be obtained to determine dose and device.

The dose of study agent (golimumab) will be administered at the study site. Subjects should be monitored for at least 30 minutes following injection and be observed for any adverse reactions, including injection site reactions (See Section 9.9). Subjects/caregivers who want to participate in study agent "self-administration" outside of some study visits begin training on using the sponsor-supplied single-use injection devices (See details Section 6.2). Additional training on the paper diary and glucometer will be given as needed.

Future target dosing and study visit days will be calculated based on the day of initial dosing (Week 0) and will not be redefined later during the study. Therefore, the study staff are encouraged to discuss the study visit days with subjects/caregivers and consider this schedule to determine what might be the anticipated (ie, day of the week) for future dosing and study visits. Specific study visits and study agent treatment windows and impact on study compliance is detailed in Section 7.

At this visit, subjects/caregivers will be supplied with a calendar with target dosing days and target study visit days that show dosing and visit windows (See Section 7.1.2.1).

**Study Visits: OL Weeks 2 and 4**

At these visits, subjects will have medical and paper diary review and other assessments per the Time and Events Schedule. Subjects will receive study agent by study staff and should be monitored for at least 30 minutes following injection and be observed for any adverse reactions, including injection site reaction (Section 9.9). In addition, for those who will be administering the injection outside of study visits ("self-administration"), subjects and/or caregivers should continue and complete administration training, including conducting a successful injection by the subject or caregiver using the device to be used for self-injection. If the training was considered successful and the site staff considers that the subject or caregiver can successfully self-administer, the subject will be sent home with study agent injection devices at OL Week 4, with instructions for handling and storage of drug and used devices. The visit window for OL Week 2 and Week 4 visits is ±1 day and ±3 days, respectively from the target dosing day.

**Study Visits Including Study Agent Dosing: OL Weeks 12, 20, 28, 36, 44, and 52**

During Weeks 12 through 52, subjects will return to the site for their scheduled visit, have predose PK/immunogenicity sample drawn, have safety and/or efficacy assessments performed, and receive study agent dosing by site staff according to the Time and Events Schedule. All subject required data, including that recorded via paper diary data, will be reviewed. During these visits, subjects/caregivers who are administering injections are to return used devices and receive additional devices and supplies per the Time and Events Schedule since the last visit. At these visits, subjects/caregivers will also receive additional device training as needed. During OL Weeks 12, 28, and 44, subjects are to have their weight and height reassessed to determine if

dosing adjustments need to be made for the next interval as described in Section 6.1, with additional training as needed. The visit windows for these study visits are ± 3 days from the target dosing day.

**Study Visits for PK Sampling and Clinical Review Only: OL Weeks 0, 4, 12, 28, and 52**

A PK sample will be drawn at visits in OL Weeks 0, 4, 12, 28, and 52. Subjects/caregivers who are participating in administering injections are to return used devices and receive additional injection devices and supplies, if needed, at these visits. The visit windows for these study visits are ± 3 days from the target dosing (visit) day except for OL Week 0.

#### 9.1.5.2. Study Agent Self-Administration or Dosing-Only Visits: OL Weeks 0, 2, 4, 12, 20, 28, 36, 44, and 50

After OL Week 4, subjects/caregivers who have met the training requirement, are given the option to self-administer majority of the study agent doses off-site that do not coincide with study visits. As detailed in Section 6.2 and the IFU, subjects/caregivers will receive training on administration during the first 3 dosing visits, and at study visits preceding off-site administration subjects will receive the appropriate study agent devices for dosing until the next dosing visit as well as supplies and instructions on handling and storage before and after usage. Subjects/caregivers will enter information including date and time of dosing, device used, anatomic site injected, and person administering dose into their paper diary. Subjects/caregivers will be asked to closely monitor the study agent injection site for at least 30 minutes and intermittently thereafter. During self-administration, subjects/caregivers are to contact the study-site team in the event of problems or complication including but not limited to signs of immediate or delayed local or systemic reaction (Section 9.9). These dose administrations should occur ± 3 day of target dosing day as detailed above.

For subjects/caregivers unwilling or unable to administer the injection, subjects/caregivers are to work with the site team to develop a visit schedule to meet the dosing criteria in Section 9.1.5 and per the Time and Events Schedule. These study agent dosing-only visits are to take place ± 3 days of the target dosing day except for OL Weeks 0 and 2.

#### 9.1.5.3. Post-Treatment Visit

The last dose of study agent is to be administered at the Week 50. A post-treatment visit will be conducted for all subjects at OL Week 60 or 10 weeks after the last dose of study agent to collect SAEs and AEs of interest since the last visit unless the subject has died, has been lost to follow-up, or has withdrawn consent. If a study visit is not possible, follow-up information may be collected via email or other electronic means.

### 9.1.6. All Study Visits - Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits (refer to the Time and Events Schedule). The following series of questions is suggested for use during the evaluation and should be addressed at all study visits:

- "Have you/Has your child had a new cough of >14 days' duration or a change in a chronic cough?"
- "Have you/Has your child had any of the following symptoms:
  - Persistent fever?
  - Unintentional weight loss?
  - Night sweats?"
- "Have you/Has your child had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

If the evaluation raises suspicion that a subject may have TB reactivation or new TB infection, an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised subjects may present as disseminated disease or with extrapulmonary features. Subjects with evidence of active TB should be referred for appropriate treatment.

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a chest radiograph, a repeat QuantiFERON-TB Gold test and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted. Study agent administration should be interrupted during the investigation. If the QuantiFERON-TB Gold test result is indeterminate, the test should be repeated as outlined in Section 9.1.2 and Section 9.1.2.1. Subjects should be encouraged to return for all subsequent scheduled study visits according to the protocol.

## 9.2. Study Endpoints and Evaluations

### 9.2.1. Efficacy Evaluations

The following efficacy evaluations will be assessed:

- A 4-hour MMTT will be performed to assess C-peptide levels and the C-peptide AUC at screening and Weeks 12, 26, 38, 52, 78, and 104. For additional details, see the Time and Events Schedule.
- Blood glucose levels between visits will be obtained by downloading home-glucometer readings.
- Hemoglobin A1c (as % HbA1c) and insulin as U/kg body weight/day. An HbA1c measurement will be done at each study visit and subjects should record the type and amount of insulin they have used during the 7-day period immediately preceding each study visit.
- Hypoglycemic events, defined as a BG level of ≤70 mg/dL or clinical sequelae consistent with hypoglycemia without a BG reading, will be documented throughout the study.

- Records of glucose measurements, insulin use and hypoglycemic events and communication with the subject will be kept in source documentation, on the appropriate CRF, or in the patient diary.

#### 9.2.1.1. Efficacy Evaluations - Open-Label Extension Period

- A 4-hour MMTT will be performed to assess C-peptide levels and the C-peptide AUC at OL screening (unless performed <3 months ago), OL Week 28, and OL Week 52. For C-responders who are lacking the necessary information to calculate IDAA1c score, an HbA1c will be performed and 10 days of insulin dose information will be required. For additional details, see the Time and Events Schedule.
- During the open-label extension period, subjects may use either fingersticks or continuous glucose monitoring (CGM) at the discretion of the investigator and/or according to local practice. The subjects will not be required to download BG values from the eDiary.
- Hemoglobin A1c (as % HbA1c) and insulin as U/kg body weight/day. An HbA1c measurement will be done at each study visit and subjects should record the type and amount of insulin they have used during the 10-day period.
- Hypoglycemic events, defined as a BG level of ≤70 mg/dL or clinical sequelae consistent with hypoglycemia without a BG reading, will be documented throughout the study.
- Records of glucose measurements, insulin use and hypoglycemic events and communication with the subject will be kept in source documentation, on the appropriate CRF, or in the patient diary.

### 9.2.2. Efficacy Endpoints

#### 9.2.2.1. Primary

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

#### 9.2.2.2. Major Secondary

- 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 BG levels of ≤70, 55, and 35 mg/dL or clinical sequelae consistent with severe hypoglycemia in the absence of a BG reading) through Week 52.

#### 9.2.2.3. Other Endpoints

- Change from baseline in MMTT-stimulated 4-hour C-peptide AUC over time.
- Change from baseline in comparative MMTT-stimulated 2-hour C-peptide AUC over time.
- Change from baseline in MMTT-stimulated C-peptide over time.
- Change from baseline in insulin use in units per kilogram body weight per day over time.
- The proportions of subjects with hypoglycemia from baseline to Week 104, from baseline to Week 52 and from Week 52 to Week 104.

- The event rates of hypoglycemia from baseline to Week 104 and from Week 52 through Week 104.
- Change from baseline in HbA1c levels over time.
- 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.

#### 9.2.2.4. Exploratory Efficacy Endpoints – Open-Label Extension Period

All the efficacy endpoints defined for the double-blind period will be exploratory for the open-label extension period and will be summarized descriptively. Disease progression will be compared between the double-blind period and the extension period in subjects who attended the open-label extension period if deemed reasonable.

### 9.2.3. Safety Endpoints

- Proportion of subjects with treatment-emergent AEs and severe AEs through Weeks 52 and 104.
- Proportion of subjects with study agent injection site reactions through Week 52.
- Proportion of subjects with severe infections through Weeks 52 and 104.

#### 9.2.3.1. Safety Endpoints – Open-Label Extension Period

- Proportion of subjects with treatment-emergent AEs and severe AEs through OL Weeks 52 and 60.
- Proportion of subjects with study agent injection site reactions through OL Week 52.
- Proportion of subjects with severe infections through OL Weeks 52 and 60.

### 9.2.4. Exploratory Endpoints

#### 9.2.4.1. Mechanistic

- [redacted]
- [redacted]

#### 9.2.4.2. Metabolic

- [redacted]
- [redacted]

## 9.3. Clinical Pharmacology

### 9.3.1. Evaluations

Serum samples will be used to evaluate the PK, the immunogenicity of golimumab (antibodies to golimumab), and pharmacodynamics (PD; free/total TNFα). Sera collected may additionally be used to evaluate biomarkers for safety or efficacy aspects to address concerns that may arise during or after the study. Subject confidentiality will be maintained. Sera for the measurement of golimumab concentration, antibodies to golimumab, and free/total TNFα will be derived from the same blood draw.

Instructions for the collection, handling, and shipment of these samples are found in the Laboratory Reference Manual provided by the sponsor.

### 9.3.2. Analytical Procedures

**Pharmacokinetics**

Serum samples will be analyzed to determine concentrations of golimumab using a validated, specific, and sensitive method by or under the supervision of the sponsor.

**Immunogenicity**

The detection and characterization of antibodies to golimumab will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of antibodies to golimumab will also be evaluated for golimumab serum concentration to enable interpretation of the antibody data.

**Pharmacodynamics**

Serum samples will be analyzed to determine concentrations of free and total TNFα (sample volume permitting) using a qualified method by or under the supervision of the sponsor.

### 9.3.3. Pharmacokinetic Parameters

Serum golimumab concentrations will be evaluated and summarized over time for the specified visits as indicated in the Time and Events Schedule.

A population PK analysis with data through Week 52 may be performed to characterize the PK of golimumab as well as to identify and quantify important covariates of PK (eg, body weight, sex and immunogenicity) in subjects with T1D, if necessary. Apparent clearance (CL/F) and volume of distribution (Vd/F) will be estimated using a nonlinear mixed effects modeling (NONMEM) approach.

### 9.3.4. Immunogenicity Assessments (Antibodies to Golimumab)

Antibodies to golimumab will be evaluated in serum samples collected from all subjects according to the Time and Events Schedule. Additionally, serum samples should also be collected at the final visit from subjects who are discontinued from treatment or withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to golimumab and the titer of confirmed positive samples will be reported. For subjects positive for antibodies to golimumab, the positive samples will be evaluated for neutralizing antibodies. Other analyses may be performed to more fully characterize the immunogenicity of golimumab in this population.

The incidence of antibodies to golimumab during the study will be determined.

### 9.3.5. Clinical Pharmacology – Open-Label Extension Period

The same procedures explained in Sections 9.3.1, 9.3.2, 9.3.3, and 9.3.4 for evaluations, analytical procedures, pharmacokinetics parameters, and immunogenicity assessments, respectively will be applied for open-label extension period.

## 9.4. Biomarkers

In addition to samples collected for efficacy and safety evaluation, samples will be collected to assist in the understanding of how golimumab may affect general and T1D-specific immune and metabolic responses. Specifically, serum and cell-based biomarkers will be evaluated for inflammation-associated proteins, changes in immune cell subsets, and will be used to better understand the biology of T1D, to provide a biological assessment of the response of subjects to treatment with golimumab, to analyze differences between responders and nonresponders, and to determine if the markers can be used to classify patients as potential responders prior to treatment. It is important to note that these evaluations will be exploratory in nature as there are no validated measures to interrogate these areas. These studies may help to explain inter-individual variability in clinical outcomes or may help to identify population subgroups in this study that respond preferentially to golimumab (see Section 9.2), and thus characteristics of those with T1D who might benefit the most from golimumab therapy in the future.

Immune assessments may include but are not limited to monitoring T-cell profiles (including changes in specific subtypes such as activated, effector, and regulatory T cells) and B cell profiles by flow cytometry.[61] In addition, serum levels of circulating pro- and anti-inflammatory cytokines, non-specific markers of inflammation (ie, C-reactive protein), and changes in T1D autoantibody profiles may be assessed.

Metabolic assessments may include innovative assessments of β-cell stress and death, which are anticipated to include pro-insulin:C-peptide ratios and serum levels of circulating methylated-insulin DNA, (see Section 9.5, Pharmacogenomic [DNA] Evaluations).[1,63,66]

Samples for serum and cellular biomarkers will be collected for all subjects as indicated in the Time and Events Schedule. To assist a number of these assessments, samples will be obtained and banked for later batch analysis.

### 9.4.1. Biomarkers – Open-Label Extension Period

The same procedure as explained in Section 9.4 will be followed for the open-label extension period.

## 9.5. Pharmacogenomic (DNA) Evaluations

In addition to immune and metabolic factors that may be affected by golimumab and give insight to clinical responses, as discussed above it is recognized that genetic variation can be an important contributory factor to inter-individual differences in drug distribution and response and can also serve as a marker for disease susceptibility, prognosis, and response to therapy.

Required Pharmacogenomic (DNA) Assessments: An individual's MHC haplotype gives insight to interactions of distinct types of lymphocytes that may cause T1D and may help to identify those who are at risk of developing T1D.[6,8] Genetic assessments of MHC haplotypes, may help to explain inter-individual variability in clinical outcomes and may help to identify subgroups that respond preferentially to golimumab. Agreeing to participate in this assessment is required for this study.

Optional Exploratory Pharmacogenomic (DNA) Assessments: Pharmacogenomic research may consist of the analysis of one or more genetic markers throughout the genome in relation to golimumab or T1D clinical endpoints. One goal of this study to use genetic markers, such as but not limited to the methylation status of insulin DNA, obtained from serum to assist in the identification of individuals with T1D who may preferentially respond to golimumab and better understand the magnitude and mechanism of this response. DNA samples will be used for research related to golimumab or T1D. They may also be used to develop tests/assays related to golimumab and or other immune modulators and improved understanding of T1D or other immune-mediated diseases. Subjects participating in this portion of the study must sign a separate pharmacogenetics informed consent/assent and opt-in for exploratory pharmacogenetics research. Further, a subject may withdraw such consent/assent at any time without affecting their participation in other aspects of the study, or their future participation in the study.

### 9.5.1. Pharmacogenomic (DNA) Evaluations – Open-Label Extension Period

Pharmacogenomic assessment of molecular MHC haplotype and insulin DNA methylation will not be performed for the open-label extension period. The open-label extension period will include PBMC sample collection and serum biomarker sample collection.

## 9.6. Safety Evaluations

There will be thorough monitoring and evaluation of subjects in this study focusing on study agent, device-related, and disease-related safety issues.

**Study Agent Related:**

Safety evaluation will include regular monitoring for clinically-related AEs, and in addition, monitoring of clinical laboratory changes (ie, hematological and serum chemistry panel), and active monitoring of early detection of active tuberculosis Monitoring of CMV and EBV viral load will be done to detect if there is any study agent effect on primary immune response to these infections that often take place during childhood and adolescence or impact reactivation of these virus in those who have been infected previously.

**Device-related:**

Device-related AEs, for the PFS-U and the VarioJect, will be collected. Device-related issues may include those that lead to a missed dose, overdose, underdose, application-site bruise, injection site pain, accidental exposure to product, or needle-stick injury issue, for example.

**Disease-related: Hypoglycemia**

As indicated elsewhere, subjects, and when applicable their caregivers, must agree to follow the current recommendations of tight glycemic control as defined by the ADA. In order to achieve these goals, this may require enhanced BG monitoring and greater amounts and frequency of insulin administration and may have the unintended side effects of hypoglycemia.

Hypoglycemia may have severe sequelae including loss of consciousness, coma or death. Subjects and their caregivers must work with local PIs and their primary care physicians to determine an approach that is best, and most safely, allows subjects to target their specific HbA1c goal.

Any BG levels ≤70 mg/dL from the glucometer captured in the eDiary will prompt subjects/caregivers document signs and symptoms consistent with hypoglycemia at the time of (possible) hypoglycemic episodes, interventions administered, and levels of assistance required by the subject. In addition, subjects/caregivers are to document any instances of suspected (clinical) hypoglycemia in the eDiary even in the absence of a confirmatory BG reading.

Serious adverse event reports will be provided to the DMC members on an ongoing basis. The DMC will have access to unblinded data and review tabulated safety summaries (if appropriate) and any additional data that the DMC may request during the conduct of the study. No formal statistical hypothesis testing is planned. In addition, during the study, the sponsor's Study Responsible Physician (or designee) will regularly review blinded safety data from the sites and notify the DMC and appropriate sponsor personnel of any issues. The remit of the DMC and the roles and responsibilities of the members will be described in a separate DMC charter.

Details regarding the Independent DMC are provided in Section 11.11.

Any clinically relevant changes in subjects occurring during the entirety of the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the timepoints provided in the Time and Events Schedule:

**Adverse Events**

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

**Clinical Laboratory Tests**

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

**The following tests will be performed by a Central Laboratory:**

- Hematology Panel

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

- **Serum Chemistry Panel**

-sodium
-potassium
-chloride
-bicarbonate
-blood urea nitrogen (BUN)
-creatinine
-glucose
-alkaline phosphatase
-calcium
-phosphate
-albumin
-total protein
-total and direct bilirubin
-aspartate aminotransferase (AST)
-alanine aminotransferase (ALT)

**Additional Laboratory Tests**

-HbA1c
-Type 1 diabetes antibodies (anti-insulin, anti-GAD-65, ICA, anti-ZnT8, anti-IA2)
- C-peptide
-insulin
-pro-insulin
-C-reactive protein
-CD4 T-cell count
-CD8 T-cell count
-HIV antibody - only at screening
-hepatitis B antibody/antigen panel - only at screening
-hepatitis C virus antibody - only at screening
-CMV and EBV DNA PCR
-MHC haplotype – only at Week 0 (randomization)
-Lipids (cholesterol, HDL, LDL, Triglycerides) – Only done at fasting visits: screening, Week 12, 26, 38, 52, 78 and 104.
-Coagulation panel (PT/PTT/INR) - only at screening
-Serum pregnancy testing - only at screening (for females of childbearing potential)

**The following test will be performed at the study site:**

- Urine pregnancy testing (for females of childbearing potential)

During the study, all abnormal laboratory values will require further explanation from the investigator. Clinically significant abnormal laboratory values should be repeated until they return to normal or are otherwise explained by the investigator.

**Clinical Assessments:**

**Vital Signs (oral or tympanic temperature, pulse/heart rate, respiratory rate, blood pressure)**

Blood pressure and pulse/heart rate measurements can be assessed with a completely automated device. Manual techniques will be used if an automated device is not available. Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

**Physical Examination**

Physical examinations (PE; full or brief) sometimes including height and body weight will be conducted at times indicated in the Time and Events Schedule.

A full physical exam includes an evaluation of general appearance, head, eyes, ears, nose, and throat evaluation, neck palpation for thyroid, lymphadenopathy and tenderness, auscultation of the heart, lungs and abdomen, palpation of abdomen, external evaluation of genitalia with Tanner Staging, evaluation of extremities and skin, and gross neurologic evaluation of strength, sensation and balance.

A brief physical examination includes general appearance, head, eyes, and throat evaluation, neck palpation for thyroid, lymphadenopathy and tenderness, auscultation of the heart, lungs and abdomen, palpation of abdomen, evaluation of extremities and skin.

Any clinically relevant finding or change in physical exam occurring during the study must be recorded on the Adverse Event section of the CRF.

Weight will be measured using a calibrated scale at each weight measurement and subjects will be instructed to remove shoes and outdoor apparel and gear.

### 9.6.1. Safety Evaluations – Open-Label Extension Period

There will be thorough monitoring and evaluation of subjects in this study focusing on study agent, device-related, and disease-related safety issues.

**Study Agent Related (Open-Label Extension Period):**

Safety evaluation will include regular monitoring for clinically-related AEs, and in addition, monitoring of clinical laboratory changes (ie, hematological and serum chemistry panel), and active monitoring of early detection of active tuberculosis Monitoring of CMV and EBV viral load will be done to detect if there is any study agent effect on primary immune response to these infections that often take place during childhood and adolescence or impact reactivation of these virus in those who have been infected previously.

**Device-related (Open-Label Extension Period):**

Device-related AEs, for the PFS-U and the VarioJect, will be collected. Device-related issues may include those that lead to a missed dose, overdose, underdose, application-site bruise, injection site pain, accidental exposure to product, or needle-stick injury issue, for example.

**Disease-related: Hypoglycemia (Open-Label Extension Period)**

As indicated elsewhere, subjects, and when applicable their caregivers, must agree to follow the current recommendations of tight glycemic control as defined by the ADA. In order to achieve these goals, this may require enhanced BG monitoring and greater amounts and frequency of insulin administration and may have the unintended side effects of hypoglycemia.

Hypoglycemia may have severe sequelae including loss of consciousness, coma or death. Subjects and their caregivers must work with local PIs and their primary care physicians to determine an approach that is best, and most safely, allows subjects to target their specific HbA1c goal.

Any BG levels ≤70 mg/dL from the glucometer will prompt subjects/caregivers document signs and symptoms consistent with hypoglycemia at the time of (possible) hypoglycemic episodes, interventions administered, and levels of assistance required by the subject. In addition, subjects/caregivers are to document any instances of suspected (clinical) hypoglycemia in the paper diary even in the absence of a confirmatory BG reading.

Serious adverse event reports will be provided to the DMC members on an ongoing basis. The DMC will have access to unblinded data and review tabulated safety summaries (if appropriate) and any additional data that the DMC may request during the conduct of the study. No formal statistical hypothesis testing is planned. In addition, during the study, the sponsor's Study Responsible Physician (or designee) will regularly review blinded safety data from the sites and notify the DMC and appropriate sponsor personnel of any issues. The remit of the DMC and the roles and responsibilities of the members will be described in a separate DMC charter.

Details regarding the Independent DMC are provided in Section 11.11.

Any clinically relevant changes in subjects occurring during the entirety of the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the timepoints provided in the Time and Events Schedule:

**Adverse Events (Open-Label Extension Period)**

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

**Clinical Laboratory Tests (Open-Label Extension Period)**

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

**The following tests will be performed by a Central Laboratory:**

- Hematology Panel

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

- **Serum Chemistry Panel**

  -sodium
  -potassium
  -chloride
  -bicarbonate
  -blood urea nitrogen (BUN)
  -creatinine
  -glucose
  -alkaline phosphatase
  -calcium
  -phosphate
  -albumin
  -total protein
  -total and direct bilirubin
  -aspartate aminotransferase (AST)
  -alanine aminotransferase (ALT)

**Additional Laboratory Tests (Open-Label Extension Period)**

-HbA1c
- C-peptide
-insulin
-pro-insulin
-C-reactive protein
-CD4 T-cell count
-CD8 T-cell count
-HIV antibody - only at screening
-hepatitis B antibody/antigen panel - only at screening
-hepatitis C virus antibody - only at screening
-CMV and EBV DNA PCR
-Lipids (cholesterol, HDL, LDL, Triglycerides) will not be measured during the open-label extension period.
-Coagulation panel (PT/PTT/INR) - only at screening
-Serum pregnancy testing - only at screening (for females of childbearing potential)

**The following test will be performed at the study site:**

- Urine pregnancy testing (for females of childbearing potential)

During the study, all abnormal laboratory values will require further explanation from the investigator. Clinically significant abnormal laboratory values should be repeated until they return to normal or are otherwise explained by the investigator.

**Clinical Assessments (Open-Label Extension Period):**

**Vital Signs (oral or tympanic temperature, pulse/heart rate, respiratory rate, blood pressure)**

Blood pressure and pulse/heart rate measurements can be assessed with a completely automated device. Manual techniques will be used if an automated device is not available. Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

**Physical Examination (Open-Label Extension Period)**

Physical examinations (PE; full or brief) sometimes including height and body weight will be conducted at times indicated in the Time and Events Schedule.

A full physical exam includes an evaluation of general appearance, head, eyes, ears, nose, and throat evaluation, neck palpation for thyroid, lymphadenopathy and tenderness, auscultation of the heart, lungs and abdomen, palpation of abdomen, external evaluation of genitalia with Tanner Staging, evaluation of extremities and skin, and gross neurologic evaluation of strength, sensation and balance.

A brief physical examination includes general appearance, head, eyes, and throat evaluation, neck palpation for thyroid, lymphadenopathy and tenderness, auscultation of the heart, lungs and abdomen, palpation of abdomen, evaluation of extremities and skin.

Any clinically relevant finding or change in physical exam occurring during the study must be recorded on the Adverse Event section of the CRF.

Weight will be measured using a calibrated scale at each weight measurement and subjects will be instructed to remove shoes and outdoor apparel and gear.

## 9.7. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form.

Refer to the Time and Events Schedule for the timing and frequency of all sample collections. For visits with study agent administration, all blood samples for assessing golimumab concentration and antibodies to golimumab must be collected before the administration of the study agent.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

## 9.8. Data to be Collected by Subjects

For this study subjects/caregivers will obtain and record a number of pieces of data to aid in endpoint analysis and compliance. The data will be collected using an eDiary that will be supplied by the sponsor to the subject/caregiver during the screening visit. Training on devices and what data is to be collected will be conducted by study-site staff at that visit, and at subsequent visits as needed. All data recorded in the eDiaries will be reviewed by study staff during study visits. For the open-label extension period, paper diaries instead of eDiaries will be provided.

- **Exogenous insulin** administration**.** Subjects/caregiver are to record the type and amount of insulin they have used during the 7-day period immediately preceding each study visit (see the Time and Events Schedule). This data will be used to calculate exogenous insulin use in units/kg/day. During the open-label extension period, subjects will be required to record 10 days of insulin use prior to each visit.
- Hypoglycemic **events.** Subjects/caregivers are to record information surrounding all BG measure measurement that are ≤70 mg/mL or of suspected hypoglycemia due to clinical symptomatology. Data including BG level, clinical symptoms (including but not limited to change in mental status or loss of consciousness), length of the event, therapies used to treat the event, and if assistance or medical care (including clinic, emergency room or hospitalization) was required for the event.
- **Study agent dosing**. For subjects/caregivers participating in self-administration they are to record study agent administration date, time, and anatomic location of the injection, person administering study agent, and if there are any complications associated with study agent administration.
- Glucometer readings.
  - Screening – Double-blind Week 104: Subjects/caregivers will be given a sponsor-supplied glucometer and supplies to self-monitor BG levels during the study. Subjects/caregivers may not use their own glucometers. Blood glucose readings should take place at least 4 times a day, ie, premeal and at bedtime, as needed and at any time of suspected hypoglycemia. Blood glucose readings from the provided glucometers will be electronically transmitted to the eDiaries provided or when BG levels ≤70 mg/mL during the double-blind period (Weeks 0 to 104).
  - Open-label Weeks 0 to 52: During this phase, subjects may use either fingersticks or continuous glucose monitoring (CGM) at the discretion of the investigator and/or according to local practice. The subjects will not be required to download BG values from the eDiary.

## 9.9. Injection Site Reaction Monitoring

Injection reactions or allergic reactions have been observed with administration of monoclonal antibodies. Mild to serious local and systemic reactions (including anaphylaxis) may occur at any time during the administration of study agent.

Study agent must not be administered to individuals with known or suspected intolerance or hypersensitivity to any biologic medication or known allergies or clinically significant reactions to human proteins, to monoclonal antibodies or antibody fragments, or to any components of golimumab or its excipients.

A physician must be immediately available at the site during the first 3 dose administrations of study agent for the double-blind period and open-label extension period. All subjects receiving study agent must be carefully observed for symptoms of an injection site reaction and a systemic reaction for at least 30 minutes after study agent administration.

**Injection Site Reactions**

An injection site reaction is any unfavorable or unintended sign that occurs at the study agent injection site. If an injection site reaction is observed, the subject should be treated at the investigator's discretion. Any adverse reaction (eg, swelling, induration, redness/erythema, pain/tenderness, warmth, bruising or bleeding) should be recorded on the AE page of the CRF. The type of reaction should also be indicated.

**Delayed Injection Site, Allergic, and Hypersensitivity Reactions**

Reactions following study agent administration may occur 1 to 21 days after study agent injection and presentation can be variable, and can, for example include myalgia and/or arthralgia with fever and/or rash. In some cases, these may be accompanied by other symptoms including pruritus, localized or systemic edema, dysphagia, urticaria, sore throat, and/or headache. Any and all such adverse reactions should be recorded on the AE page of the CRF. The type of reaction should also be indicated.

**Self-Assessment**

In addition to recording the details of the study agent dosing day, time, anatomic site and if there were any complications of the injection, subjects and/or caregivers should be instructed to monitor the injection site for any reactions, including, but not limited to swelling, redness/erythema, pain, tenderness, warmth, bruising, or bleeding. For severe injection site reactions or changes at the injection site hours to days following injection, the subject/caregiver should contact the study site for consultation.

# 10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

## 10.1. Completion

A subject will be considered to have completed the study if he or she has completed assessments at Week 104 of the off-therapy follow-up period or Week 60 of the open-label extension period of the study.

Subjects who prematurely terminate study participation for any reason before completion of the study will not be considered to have completed the study. Subjects are able to initiate the prohibited medicines and activities per the guidance provided in Section 4.3 and Section 8.3.

## 10.2. Discontinuation of Study Treatment/Withdrawal from the Study

**Discontinuation of Study Treatment**

A subject will **not** be automatically withdrawn from the study if they have to temporarily or permanently discontinue treatment before the end of the treatment regimen.

If a subject permanently discontinues study treatment for any reason before the end of the treatment phase (Week 52), they should be encouraged to continue with all scheduled visits to and including the final study visit (Week 104), but without receiving study agent administration. If unwilling or unable to participate in all visits, subjects should be encouraged to participate in as many of the planned study visits as possible for continued assessment, but without receiving study agent administration. If the subject is not able to participate in the next 2 sequential study visits that include an MMTT, they should be encouraged to return for the End of Study visits (per the Time and Events Tables) approximately 10 weeks after their last dose administration.

Similarly, if a subject withdraws following the treatment period (after Week 52) they should be encouraged to participate in the Week 78 and Week 104 visits, as applicable. If the subject is unwilling or unable to complete any of the remaining scheduled study visits, they should be encouraged to return for the End of Study visit (per Time and Events Schedule) approximately 10 weeks after their last dose administration, as applicable.

Following randomization (ie, between Week 0 and Week 104), consecutive MMTTs should not be repeated if the time interval between them is less than 10 weeks. The MMTT can be repeated in less than 10 weeks only for repeat testing during the screening period or for rescreening.

SAEs will be requested to be submitted for subjects who withdraw early from the study for a year after their last study agent dose (Section 12.4.1).

Subjects who permanently discontinue active treatment during the open-label extension period will have their end-of-study visit followed by the post-treatment visit 10 weeks later.

**Study treatment may be temporarily or permanently discontinued due to events described below.**

- Events That Result in Permanent Discontinuation of Study Treatment.
  - The investigator believes that for safety reasons or tolerability reasons it is in the best interest of the subject to discontinue study treatment.
  - The subject becomes pregnant.
  - The subject has a severe infection requiring inpatient hospitalization or repeated doses of parenteral antibiotics.
  - The subject has a severe hypersensitivity reaction, such as anaphylaxis or angioedema, to the study agent.
  - The subject has a clinically significant cardiovascular event.
  - The subject is deemed ineligible according to the following TB screening criteria:

- A diagnosis of active TB is made.
- A subject has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB, and cannot or will not continue to undergo additional evaluation.
- A subject undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON-TB Gold test result and/or an indeterminate QuantiFERON-TB Gold test result on repeat testing (see Section 9.1.2 and Section 9.1.2.1).

– The subject misses 3 consecutive study agent administrations.

– A general lack of compliance with study visits and procedures per study team or sponsor.

– One confirmed episode of ALT and/or AST >3x upper limit of normal (ULN) as defined in Attachment 5. If a subject has an ALT or AST value of >3x ULN, the next dose of study agent administration should be held pending repeat confirmatory testing which is to take place as soon as possible and preferably within 72 hours. If the value is still >3x ULN then the subject is to permanently discontinue study treatment. If the repeat value is <2x ULN then dosing may proceed. If the repeat value is ≥2x ULN) and ≤3x ULN, follow guidelines in the next section.

– The subject meets criteria for permanent study agent discontinuation based on AST/ALT elevations, AEs, or infections in the next subsection below (Events Resulting In Temporary and Potentially Permanent Discontinuation of Study Agent).

- Events Resulting in Temporary and Potentially Permanent Discontinuation of Study Treatment.

  – An ALT and/or AST elevation ≥2 x the upper limit of normal (ULN) and ≤3x ULN (as defined in exclusion criteria in Section 4.2.1 and Attachment 5).

- Repeat AST and ALT as soon as possible but preferably within 72 hours of receipt of the confirmed results. If one or both are ≥2 x the ULN and ≤3x ULN then:
- Suspend administration of study treatment and recheck the subject within 72 hours and at least weekly as needed thereafter.
- If AST and ALT are <2x ULN on repeat testing, resume dosing at the next expected interval.
- If AST and ALT are not <2x ULN by 4 weeks, permanently discontinue study treatment.

Note: Three independent temporary suspensions from study treatment due to transient elevations in ALT and/or AST ≥2x but ≤3x ULN is allowed during the entire treatment period. If a third elevation occurs that requires a dose to be held, permanently discontinue study treatment.

– A Significant Infection.

– *Defined as:*

1. Any severe infection meeting SAE criteria as defined in Section 12, *or*

2. Any infection not meeting SAE criteria but otherwise clinically significant per investigator's judgment, *or*
3. Infection or reactivation of EBV or CMV as defined by clinical signs of infection; or if the EBV viral load is ≥10,000 copies per mL plasma or the CMV viral load is ≥10,000 copies per mL plasma.

- Suspend administration of study treatment and recheck any abnormal laboratory values as soon as possible and preferably within 72 hours.
- Monitor the subject and abnormal labs at least weekly.
- If the AE resolves or reduces to mild or less, dosing may resume at the next expected interval.
- If the AE does not resolve in 4 weeks, permanently discontinue study treatment.
  - A Serious Adverse Event or Study Agent-related Severe Adverse Event.
  - *Defined as:*
    1. Any SAE (as defined in Section 12.1.1) *or*
    2. Any severe AE that is considered related (possibly, probably, or very likely related) to study agent (as defined in Section 12.1.2).
  - With the exception of:

    When clinical and laboratory abnormalities are considered related to T1D disease activity (ie, hypoglycemia and hyperglycemia) and study treatment is not considered a contributing factor, administration may not need to be modified. The site investigator should consult with the sponsor if this is encountered.

- Suspend administration of study treatment and recheck the subject at least weekly; if based on abnormal laboratory values, repeat abnormal laboratory values as soon as possible within 72 hours.
- If the AE resolves or reduces to a moderate AE (Section 12.1.2) or less, dosing may resume at the next expected interval.
- If the AE does not resolve to a moderate AE or less (Section 12.1.2) in 4 weeks, discontinue study treatment permanently.

Note: If there are more than 2 suspensions from study treatment due to a specific SAE or related-SAE as defined above, permanently discontinue study treatment.

**Withdrawal From The Study**

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Withdrawal of consent/assent.
- Death.

- The study investigator or sponsor, for any reason, decides the subject should be withdrawn from the study.

If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow-up must be documented.

When a subject withdraws before completing the study, the sponsor and the DMC chair is to be notified and the reason for withdrawal is to be documented in the CRF and in the source document. Study agent assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study before the end of study, all attempts should be made to obtain End of Study assessments.

In addition to the above withdrawal criteria, C+R and R responders will be withdrawn if on 2 consecutive occasions 2 months apart, the remission score is >9. The C responders will be discontinued if their remission score is increasing on 2 consecutive occasions by more than 0.5 or if their remission score is 12, whichever comes first.

## 10.3. Withdrawal From the Use of Research Samples

A subject who withdraws from the study will have the following options regarding the optional research samples:

The collected samples will be retained and used in accordance with the subject's original separate informed consent/assent for optional research samples.

The subject may withdraw consent/assent for optional research samples, in which case the samples will be destroyed, and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study-site contact of withdrawal of consent/assent for the optional research samples and to request sample destruction. The sponsor study-site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

**Withdrawal From the Optional Research Samples While Remaining In The Main Study**

The subject may withdraw consent/assent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

**Withdrawal From The Use Of Samples In Future Research**

The subject may withdraw consent/assent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

# 11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

Descriptive statistics (eg, mean, median, standard deviation [SD], minimum, and maximum) will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Graphic data displays may also be used to summarize the data.

Efficacy analyses will be based on the modified intent-to-treat (mITT) population (ie, all randomized subjects who have received at least 1 dose of study agent). Subjects included in the efficacy analyses will be summarized according to their assigned treatment group regardless of whether or not they receive the assigned treatment.

Safety analyses will include all subjects who received at least 1 dose of study treatment.

Pharmacokinetics and immunogenicity analyses for golimumab will include all subjects who receive at least 1 dose of golimumab and have at least 1 post-dose sample collection.

The baseline measurement is defined as the closest measurement taken at or before the time of the Week 0 administration for the double-blind period. The baseline measurement for the open-label extension period is the closest measurement taken at or before the time of the Week 0 administration of the open-label extension period.

No hypotheses testing will be performed for open-label extension period, and data generated will be summarized descriptively.

## 11.1. Subject Information

For all subjects who receive at least 1 dose of study agent, descriptive statistics will be provided. Subject baseline data, demographic, and baseline clinical disease characteristics will be summarized for all mITT subjects.

## 11.2. Sample Size Determination

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[25,26,42,57,60] Based on published data, a common 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. With 81 subjects (54 on golimumab and 27 on placebo) and an alpha of 0.05 (2-sided), there is 90% power to detect the treatment difference through a 2-sample t-test.

## 11.3. Efficacy Analyses

All efficacy analyses will be performed on the mITT population unless otherwise specified. The mITT population 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).

**Primary Endpoints**

The primary endpoint is the MMTT-stimulated 4-hour C-peptide AUC at Week 52. To address the primary objective of the study, the primary endpoint will be analyzed by using a MMRM based on restricted maximum likelihood. The model will be based on a normalizing transformation of log(AUC+1). The analysis will use post-baseline log(AUC+1) data as the response variable 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-patient errors. The treatment comparison at Week 52 in terms of the least square mean difference and the 2-sided 95% confidence interval 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. Additional details will be presented in the SAP.

To assess the robustness of the primary analysis result, some sensitivity analyses will be conducted. Such analyses include but are not limited to the following:

1. Similar repeated measure analysis with some data imputed. If a subject's last observed AUC value prior to Week 52 is 0, then all missing values through Week 52 will be imputed with zero. Repeated measure analysis will be conducted on the partially imputed data.

2. 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 and gender as fixed factors. Different missing data handling strategies such as completers' analysis, and multiple imputation will be explored.

3. Similar ANCOVA model by using different transformation functions.

4. Comparing change from baseline in 4-hour C-peptide AUC directly by using non-parametric method such as rank analysis of covariance or ANCOVA model if the normality assumption holds.

Subgroup analysis of the primary endpoint by selected baseline characteristics will be presented. Details will be outlined in the SAP.

**Secondary Endpoints**

The major secondary endpoints listed below will be analyzed without multiplicity adjustment. Treatment effect in these endpoints will be estimated by the difference between the treatment

groups along with their associated 95% confidence intervals. The hypoglycemia event rate (number of hypoglycemia episodes per patient-year exposure) at Week 52 will be analyzed using a Poisson regression model. Change from baseline in insulin use and change from baseline in HbA1c will be analyzed by using an MMRM model. Additional details will be provided in the SAP.

1. Change from baseline in insulin use in units per kilogram body weight per day at Week 52.
2. Change from baseline in HbA1c at Week 52.
3. Hypoglycemic event rates (defined as BG levels of ≤70, 55, and 35 mg/dL or clinical sequelae consistent with severe hypoglycemia in the absence of a BG reading) through Week 52.

### 11.3.1. Exploratory Efficacy Analyses – Open-Label Extension Period

All the efficacy endpoints defined for the double-blind period will be exploratory for the open-label extension period and will be summarized descriptively. Disease progression will be compared between the double-blind period and the extension period in subjects who attended the open-label extension period if deemed reasonable.

## 11.4. Pharmacokinetic Analyses

Data will be listed for all subjects with available serum concentrations per treatment. All concentrations below the lowest quantifiable concentration (LQC) in a sample or missing data will be labeled as such in the concentration data listings. Concentrations below the LQC in a sample will be treated as 0 in the summary statistics and for the calculation of PK parameters. All subjects and samples excluded from the analysis will be clearly documented in the study report.

For each dose group, descriptive statistics, including arithmetic mean, SD, coefficient of variation, median, minimum, and maximum will be calculated for the golimumab serum concentrations at each sampling time of golimumab.

Serum golimumab concentrations will be summarized over time. In addition, if necessary, a population PK analysis will be performed to characterize the PK of golimumab as well as to identify and quantify important covariates of PK in the T1D population. The apparent total systemic clearance (CL/F) and apparent volume of distribution (V/F) will be estimated using a NONMEM approach and will be presented in a separate technical report.

The same analyses will be performed for the open-label extension period.

## 11.5. Immunogenicity Analyses (Antibodies to Golimumab)

The occurrence and titers of antibodies to golimumab during the study will be summarized over time for all subjects who receive an administration of golimumab and have appropriate samples collected for detection of antibodies to golimumab (ie, subjects with at least 1 sample obtained after their first golimumab administration).

The incidence of neutralizing antibodies (NAbs) to golimumab will be summarized for subjects who are positive for antibodies to golimumab and have samples evaluable for NAbs to golimumab.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

The same analyses will be performed for the open-label extension period.

## 11.6. Biomarker Analyses

Results from exploratory analyses will be presented in a separate biomarker technical report.

The same analyses will be performed for the open-label extension period.

## 11.7. Pharmacokinetic/Pharmacodynamic Analyses

If data permits, the relationships between serum golimumab concentration and efficacy may be analyzed graphically. If a visual trend is observed, a suitable PK/PD model may be developed to describe the exposure-response relationship and will be presented in a separate technical report.

The same analyses will be performed for the open-label extension period.

## 11.8. Pharmacogenomic Analyses

For the double-blind period, results from exploratory and haplotype analyses will be presented in a separate biomarker technical report.

For the open-label extension period, results from the exploratory analyses will be presented in a separate biomarker technical report.

## 11.9. Safety Endpoints and Analyses

Safety assessments will include the examination of the incidence rates of AEs, vital signs, laboratory parameters, and physical examinations. Safety analyses will be conducted on the safety analysis set, which is defined as all subjects who have received at least a 1 dose of study agent.

**Adverse Events**

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are AEs with onset during the treatment period or that are a consequence of a pre-existing condition that has worsened since baseline. All reported treatment-emergent AEs will be included in the analysis. For each AE, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by system organ class and preferred term for treatment group. Treatment-emergent AEs will also be summarized by a maximum severity and relationship to study agent. Separate summaries will be provided for SAEs and AEs leading to study agent discontinuation.

In addition, summary tables will be presented by treatment group for each of the endpoints within each specified period:

Double-Blind Period:

a. Proportion of subjects with treatment-emergent AEs and severe AEs through Weeks 52 and 104.
b. Proportion of subjects with study agent injection site reactions through Week 52.
c. Proportion of subjects with severe infections through Weeks 52 and 104.
d. Open-Label Extension Period:

1. Continue to evaluate safety and exploratory efficacy endpoints as per the Time and Events Schedule (open-label extension period) and no new efficacy hypotheses will be tested compared to the double-blind period.

Listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe or an SAE.

**Clinical Laboratory Tests**

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled timepoint. Frequency tabulations of the changes from baseline will be presented in pre- versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges). Frequency tabulations of the abnormalities will be made. A listing of subjects with any markedly abnormal laboratory results will be provided.

**Vital Signs**

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled timepoint. The percentage of subjects with values beyond clinically important limits will be summarized and a corresponding listing will be provided.

**Physical Examination**

Proportion of subjects with abnormal physical examination findings will be summarized at each scheduled timepoint. Subjects with any post-treatment abnormalities will be listed.

**Open-Label Extension Period**

Clinical laboratory tests, vital signs, and physical examination for the open-label extension period will be assessed as similar to the double-blind period.

## 11.10. Interim Analysis

An interim analysis using the 4-hour C-peptide AUC in response to a MMTT will be planned for the study. The primary goal of this analysis will be to obtain an early examination of the treatment effect to facilitate the planning of future studies. It is anticipated that the interim analysis will take place after at least 60% of subjects complete their Week 26 4-hour, MMTT assessment. All available 4-hour, C-peptide AUC data at interim analysis will be incorporated in this analysis. No formal DBL is planned for this interim analysis.

An IAC will be established to review the interim data and formulate recommendations in accordance with the objectives of the interim analysis. The IAC will consist of at least a clinician and a statistician (neither of whom are involved in the conduct of the study or compound development), one of whom will chair the committee, and other members as required based on the results of the interim analysis. Details will be provided in the IAC charter. The DMC serves the IAC function. The disclosure of unblinded results will be limited to specific sponsor personnel not involved in the study. Interim analyses results will not be disseminated to investigators or individuals associated with the conduct of the study. The interim analyses will not have any statistical impact on the analyses of any other endpoints.

## 11.11. Data Monitoring Committee

An Independent DMC consisting of external experts and internal experts not associated with this study will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study. The committee will meet periodically to review interim data. After the review, the DMC will make recommendations regarding the continuation of the study. The details will be provided in a separate DMC charter.

The DMC will consist of at least one medical expert in the relevant therapeutic area and at least one statistician. The DMC responsibilities, authorities, and procedures will be documented in its charter.

# 12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

## 12.1. Definitions

### 12.1.1. Adverse Event Definitions and Classifications

**Adverse Event**

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal

relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section 12.4.1, All Adverse Events, for time of last AE recording).

**Serious Adverse Event**

An SAE based on ICH and European Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is a suspected transmission of any infectious agent via a medicinal product.
- Is Medically Important.*
- *Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.
- Unlisted (Unexpected) Adverse Event/Reference Safety Information.
- An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For golimumab, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure. For exogenous insulin with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the package insert/summary of product characteristics.
- Adverse Event Attribution Definitions.
- The following provides guidance on how the study team is to assess and categorize the relationship of AEs in relation to study agent:

**Adverse Event Association With The Study Agent**

- **Not Related:** An AE that is not related to the use of the drug.
- **Doubtful:** An AE for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.
- **Possible:** An AE that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.
- **Probable**: An AE that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).
- **Very Likely:** An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

This study will utilize sponsor-supplied study agent dosing devices, the PFS-U and VarioJect as detailed in the SIPPM. The following provides guidance on how the study team is to assess and categorize the relationship of AEs in relation to these devices.

**Adverse Event Association With The Study Device**

- **Not related:** There is another obvious cause of the AE other than the study device.
- **Unlikely:** There is another more likely cause of the AE other than the study device.
- **Possibly:** The AE could be due to the study device.
- **Probably**: The AE is probably attributable to the study device.
- **Definitely:** The AE is most likely or definitely attributable to the study device.

### 12.1.2. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

- **Mild**: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: Sufficient discomfort is present to cause interference with normal activity.
- **Severe**: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

## 12.2. Hypoglycemia Definitions, Recording and Interpretation

This study will use the ADA suggested classification of hypoglycemia to guide the collection of episodes of asymptomatic and/or symptomatic hypoglycemia.[65] A hypoglycemic BG reading will be classified as any confirmed BG reading of ≤70 mg/dL.

In clinical practice, severe hypoglycemia is considered an event requiring assistance of another person for support which may include administration of carbohydrates or glucagon. Individuals with severe hypoglycemia may, experience events such as a seizure, altered/loss of consciousness, or coma. Such events do not need to have a documented BG reading to be classified clinically as a severe hypoglycemic event. This study will collect this "clinical practice" definition of severe hypoglycemia, whether or not the symptoms are associated with an abnormal/low BG reading. Data on all hypoglycemic events as described above will be collected as part of the efficacy analyses.

In terms of AE reporting in this study, the severity of a hypoglycemia AE should be classified as mild, moderate, or severe, or as an SAE according to the definitions in Section 12.1.1, Section 12.1.2, and Section 12.4.1. Because there may be difference in terminology used in clinical practice and AE recording in clinical trials, a hypoglycemic episode that is considered “severe” using clinical definitions may not necessarily be classified as a “severe” (or serious) AE, and conversely an episode the does not meet the common clinical definition of severe hypoglycemia may be classified as a severe AE. Again, it is the investigator’s responsibility to categorize the severity of a hypoglycemic event in terms of AE reporting.

## 12.3. Special Reporting Situations

Safety events of interest on a sponsor study agent that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study agent
- Suspected abuse/misuse of a sponsor study agent
- Accidental or occupational exposure to a sponsor study agent
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study agent, eg, name confusion)
- Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the SAE page of the CRF.

## 12.4. Procedures

### 12.4.1. All Adverse Events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 52 weeks after the last dose of study agent (which is the end of the study), must be reported using the Serious Adverse Event Form. In

addition, SAEs will be requested to be submitted for subjects who withdraw early from the study for a year after their last study agent dose. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments. Anticipated events will be recorded and reported as described in Attachment 6.

All AEs, regardless of seriousness, severity, or presumed relationship to study agent or device, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

All devices associated with device-related AEs will be investigated including the return of the device to the sponsor for inspection.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

For all studies with an outpatient period, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

### 12.4.2. Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study agent or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the CRF).

The cause of death of a subject in a study within 52 weeks of the last dose of study agent, whether or not the event is expected or associated with the study agent, is considered an SAE.

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition (refer to Section 12.1.1, Adverse Event Definitions and Classifications).

### 12.4.3. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the study agent on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

### 12.4.4. Events of Special Interest

Any newly identified malignancy, opportunistic infections, or case of TB occurring after the first administration of study agent(s) in subjects participating in this clinical study must be reported by the investigator according to the procedures in Section 9.1.6. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

## 12.5. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

# 13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, device, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

All VarioJect devices associated with device-related PQCs will be investigated including the return of the device to the sponsor for inspection. PFS-U should be retained for further investigation if requested by the sponsor.

## 13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.4.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

## 13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

# 14. STUDY DRUG INFORMATION

## 14.1. Physical Description of Study Drug(s)

Golimumab will be supplied as a sterile, clear to slightly opalescent, colorless to light yellow liquid for SC injection in single-use prefilled syringes. Each prefilled syringe contains 50 mg (0.5 mL of liquid) of golimumab, histidine, sorbitol and polysorbate 80 at pH 5.5. No preservatives are present. Details regarding the study agent composition are found in the SIPPM.

The placebo will employ the same product presentation without the presence of active drug.

## 14.2. Packaging

Two dosage forms will be used in this study, PFS-U and VarioJect assembled with a PFS. Both dosage forms will be packaged in individual subject kits in tamper resistant packaging.

**Ultrasafe Passive Delivery System With Prefilled Syringe (PFS-U)**

The UltraSafe Passive Delivery System (UltraSafe) is a manually-operated, single-use, disposable needle guard system that is an accessory to a PFS. Each 50 mg-single dose prefilled glass syringe (27-gauge ½ inch needle) contains 50 mg of golimumab per 0.5 mL of solution.

**VarioJect**

A new adjustable dose presentation known as the VarioJect injection device has been developed by the sponsor as a platform device for multiple pediatric indications. This device allows for tiered-fixed dosing in pediatric subjects who are dosed by BSA. The VarioJect is a manual injector capable of delivering doses of 10 mg through 45 mg in 5 mg increments.

For the most comprehensive information regarding the VarioJect, refer to the current version of the VarioJect IB.

## 14.3. Labeling

Study agent labels will contain information to meet the applicable regulatory requirements.

## 14.4. Preparation, Handling, and Storage

All study agents must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C). Study agent must be handled in strict accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions.

Refer to the pharmacy manual/study SIPPM for additional guidance on study agent preparation, handling, and storage.

Subjects or caregivers who are able and who have been appropriately trained in the administration of golimumab may administer golimumab off-site in accordance with Section 6. Study personnel will instruct subjects on how to transport, store and administer medication for off-site use as indicated for this protocol. Details will be provided in the SIPPM.

### 14.5. Drug Accountability

The investigator is responsible for ensuring that all study agent received at the site is inventoried and accounted for throughout the study according to the Time and Events Schedule. In instances where the study agent is administered to the subject, it must be documented on the drug accountability form. All study agent will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study agent containers.

The dispensing of study agent to the subject, and the return of study agent from the subject (if applicable), must be documented on the drug accountability form. Subjects, or their legally acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study agent.

Study agent must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited access area or in a locked cabinet under appropriate environmental conditions. Unused study agent, and study agent returned by the subject, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study agent, or used returned study agent for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study agent supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study agent should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study agent will be supplied only to subjects participating in the study. Returned study agent must not be dispensed again, even to the same subject. Study agent may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study agent from, nor store it at, any site other than the study sites agreed upon with the sponsor.

## 15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following:

- Investigator's Brochures
- SIPPM Laboratory manual
- Sponsor-approved Informed Consent/Assent Form
- Dose assignment system manual

- Investigator site file
- Electronic data capture (eDC) Manual
- IWRS Manual
- Subject eDiaries and manuals
- Subject glucometers and manuals
- Study-specific Patient Participation Cards
- Materials for off-site administration

# 16. ETHICAL ASPECTS

## 16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent/assent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent/assent voluntarily will be enrolled.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or legally acceptable representative(s), as required by local regulations, must give written consent/assent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. For the purposes of this study, all references to subjects who have provided consent/assent (and assent as applicable) refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or legally acceptable representative(s) who have provided consent/assent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

The total blood volume to be collected from each subject, including during screening, the 52-week treatment period and 52-week off-therapy follow-up period is approximately 436 mL for subjects <35 kg and 505 mL in subjects ≥35 kg. During the open-label extension period, approximately 210 mL for subjects <35 kg and 234 mL for subjects ≥35 kg will be drawn.

## 16.2. Regulatory Ethics Compliance

### 16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

### 16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments.
- Sponsor-approved ICF (and any other written materials to be provided to the subjects).
- Investigator's Brochure (or equivalent information) and amendments/addenda.
- Sponsor-approved subject recruiting materials.
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable.
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB).
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects.
- Any other documents that the IEC/IRB requests to fulfill its obligation.

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct).
- Revision(s) to ICF and any other written materials to be provided to subjects.
- If applicable, new or revised subject recruiting materials approved by the sponsor.
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable.
- New edition(s) of the Investigator's Brochure and amendments/addenda.
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually).
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study agent.
- New information that may adversely affect the safety of the subjects or the conduct of the study.
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects.
- Report of deaths of subjects under the investigator's care.
- Notification if a new investigator is responsible for the study at the site.
- Development Safety Update Report and Line Listings, where applicable.
- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

### 16.2.3. Informed Consent and Assent Form

Each subject or a legally acceptable representative must give written consent/assent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) and assent form that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent/assent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort

participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent/assent to participate at any time. They will be informed that choosing not to participate, will not affect the care the subject will receive for the treatment of his or her disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access and denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent/assent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent/assent should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent/assent, a copy of the ICF must be given to the subject.

Subjects will be asked for consent/assent to provide optional samples for research. After informed consent/assent for the study is appropriately obtained, the subject or his or her legally acceptable representative will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent/assent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained.

Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, typically subjects 7 years of age and older, depending on the institutional policies. Written assent should be obtained from subjects who are able to write. A separate assent form written in language the subject can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the subject and to the subject's parent or if applicable to the subject's legally acceptable representative. If subjects meet "responder" definition and are interested in participating in open-label extension phase of study, subjects and parents/legal guardians will have to sign new ICF/assent forms.

### 16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject or his or her legally acceptable representative includes explicit consent/assent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent/assent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

### 16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand golimumab, to understand T1D autoimmunity and/or immune modulation, to understand differential drug responders, and to develop tests/assays related to golimumab. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent/assent for their samples to be stored for research (see Section 10.3, Withdrawal From the Use of Research Samples)

## 17. ADMINISTRATIVE REQUIREMENTS

### 17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate

document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

## 17.2. Regulatory Documentation

### 17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

### 17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study agent to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated Clinical Trial Agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators.
- Documentation of subinvestigator qualifications (eg, curriculum vitae).

- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable.
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

## 17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

## 17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent/assent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; study agent administration information; and date of study completion and reason for early discontinuation of study agent or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.1.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

## 17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All data relating to the study must be recorded in CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

All subjective measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

## 17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a Central Laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study.

The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

## 17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

## 17.8. Monitoring

The sponsor will use a combination of monitoring techniques central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the

sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

## 17.9. Study Completion/Termination

### 17.9.1. Study Completion/End of Study

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

### 17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study agent development

## 17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

## 17.11. Use of Information and Publication

All information, including but not limited to information regarding golimumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic and/or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of golimumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of pharmacogenomic and/or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish

study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

**Registration of Clinical Studies and Disclosure of Results**

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

# 18. PROTOCOL AMENDMENTS HISTORY

| Protocol Version | Issue Date |
|---|---|
| Original Protocol | 26 April 2016 |
| Amendment 1 | 02 Jun 2016 |
| Amendment 2 | 09 May 2017 |

Amendments below are listed beginning with the most recent amendment.

**Amendment 2** (09 May 2017)

**The overall reason for the amendment:** The overall reason for the amendment is to update testing parameters, to address clarifications needed for severe hypoglycemia definition and to correct inconsistencies within the protocol.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** To provide clarity and consistency, the units of laboratory tests for viral load measurements cited in the protocol are being updated to match the units actually used by the Central Laboratory. | |
| 4.2. Exclusion Criteria; criterion 11 and criterion 12, and<br>10.2. Discontinuation of Study Treatment/Withdrawal from the Study | CMV and EBV viral load units updated to match the Covance laboratory units used by the Central Laboratory. Updated to: EBV viral load ≥10,000 copies per mL of plasma and CMV viral load ≥10,000 copies per mL of plasma. |
| **Rationale:** Text describing events resulting in temporary and potentially permanent discontinuation of study agent was updated to provide clarity. | |
| 10.2. Discontinuation of Study Treatment/Withdrawal from the Study; Discontinuation of study treatment; Study treatment may be temporarily or permanently discontinued due to events described below | Text was updated/rearranged. Instructions were updated to clarify that the subject should be rechecked within 72 hours of receipt of confirmed results. Clarification of resumed dosing updated to specify AST and ALT on repeat dosing.<br>Definitions and instructions updated.<br>Section rearranged with minor edits to provide clarity.<br>The following bullet was removed from the protocol:<br>• The overall course of study treatment will not be extended and missed doses will not be administered. |
| 10.2. Discontinuation of Study Treatment/Withdrawal from the Study; Discontinuation of study treatment | Text added to clarify intervals between sequential Mixed-Meal Tolerance Tests (MMTT). |
| **Rationale:** Definitions of terms and examples were updated or added to the protocol to provide clarity. | |
| 12.2. "Severe" Hypoglycemia | Section title updated to "Hypoglycemia Definitions, Recording and Interpretation". Hypoglycemia definitions clarified to assist identification, recording, and interpreting these events. Seaquist ER, Anderson J, Childs B, et al reference added. |
| 4.2. Exclusion Criteria; criterion 4 | Celiac disease was added to the list of examples. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Removal of a full physical exam at Week 0 so that the Tanner Staging at Screening does not need to be repeated at Week 0. | |
| Time And Events Schedule | The full physical exam at Week 0 was changed to a brief physical exam at Week 0. |
| **Rationale:** Analysis of TNFα levels added to the protocol in response to Food and Drug Administration (FDA) Investigational New Drug (IND) request for pharmacokinetic (PK)/pharmacodynamics (PD) modeling | |
| Time And Events Schedule | Free/total TNFα row added under the Clinical Pharmacology section. |
| Time And Events Schedule | Subheading row Pharmacokinetics/Immunogenicity changed to Clinical Pharmacology to encompass all procedures in this subcategory. |
| Time And Events Schedule, footnote n | Footnote updated to include further instructions on timing and bioanalysis of the samples. |
| SYNOPSIS, Pharmacokinetic and Immunogenicity Evaluations and 9.3. Pharmacokinetics and Immunogenicity | The synopsis subsection title updated was updated to Clinical Pharmacology Evaluations.<br>Section title updated to 9.3. Clinical Pharmacology. |
| SYNOPSIS, Pharmacokinetic and Immunogenicity Evaluations and 9.3. Pharmacokinetics and Immunogenicity | The synopsis subsection Clinical Pharmacology and the first paragraph of the protocol body section Pharmacokinetics and Immunogenicity was updated to include Total/Free TNFα. |
| 9.3.2. Analytical Procedures | Pharmacodynamic subsection added to include analysis of serum samples to determine concentrations of free and total TNFα. |
| **Rationale:** Text was updated to match sample names to what is reflected in the laboratory manual and to clarify that optional pharmacogenomics serum collection and optional DNA collections are to be collected prior to dosing. | |
| Time And Events Schedule | Serum sample collection renamed serum biomarker sample. |
| Time And Events Schedule | Optional pharmacogenomics serum collection was renamed DNA Methylation (Optional). |
| 9.5. Pharmacogenomic (DNA) Evaluations | Optional added to the Subsection title: Exploratory Pharmacogenomic (DNA) Assessments. Subsection now called: Optional Exploratory Pharmacogenomic (DNA) Assessments: |
| Time And Events Schedule | New footnote "s" added to state biomarker and pharmacogenomics sample must be collected prior to study agent administration. |
| **Rationale:** Blood volumes were updated to align with the Central Laboratory blood volumes. | |
| 9. Study Evaluations;<br>9.1. Study Procedures;<br>9.1.1. Overview<br>and<br>16.1. Study-Specific Design Considerations | Blood volumes were updated to reflect the Central Laboratory blood volume table. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Additional text was added to provide clarity around rounding rules for body weight. | |
| Attachment 2: Dose And Device Charts For Study CNTO148DML2001 In Subjects With Type 1 Diabetes; Attachment 2-A: Dosing Chart for Induction Doses at Week 0 and Week 2 | Text added to provide additional information around rounding rules for body weight and an example was provided. |
| **Rationale:** Approximately was added to the length of the enrollment period to allow for flexibility. | |
| 3.1. Overview of Study Design | The enrollment period of 12 to 18 months was updated to approximately 12 to 18 months. |
| **Rationale:** Change in description of the packaging of the devices used to match the description in the device packaging. | |
| 14.2. Packaging | The term child resistant was changed to tamper resistant. |
| **Rationale:** Correction of terminology used in the protocol | |
| Attachment 3: Procedures for Performing the Mixed-Meal Tolerance Test | The term Boost High Protein was changed to Boost original.<br>The term central operations manual was changed to Central Laboratory manual. |
| **Rationale:** Text was added in order for local laboratory testing of Quantiferon-TB samples to be allowed in the study. | |
| Attachment 1: Quantiferon-TB Gold Testing | Sentence added to allow for local laboratory to perform the QuantiFERON test in select circumstances approved by the sponsor. |
| **Rationale:** Text describing type of data used for efficacy analyses was updated to provide clarity and the timepoint at Week 52 was removed. | |
| 11.3. Efficacy Analyses; Primary Endpoints | The text was updated to include the fact that the analysis will use post-baseline log(AUC+1) data and the Week 52 timepoint was removed. |
| **Rationale:** Text was updated to provide clarity on 2 MMTT-stimulated C-peptide endpoints. | |
| 9.2.2.3. Other Endpoints | The description of peak was added to the MMTT-simulated C-peptide endpoint. |
| **Rationale**: The timepoints for the distribution of study agent injection devices was corrected in the Time and Events Schedule. | |
| Time And Events Schedule | Distribute study agent injection devices was updated to include Week 33 and Week 45<br>Footnote g was updated with detailed instructions around study agent administration and PK sampling for clarity. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Minor errors were noted | |
| Throughout the protocol | Minor grammatical, formatting, or spelling changes were made. |
| References | VarioJect Injection Pen Investigator's Brochure and Seaquist ER, Anderson J, Childs B, et al references were added to the list of references. |
| 10.2. Discontinuation of Study Treatment/Withdrawal from the Study | Encouraged to participate in the Week 104 and Week 52 visits was changed to encouraged to participate in the Week 52 and Week 104 visits. |

**Amendment 1** (02 June 2016)

**The overall reason for the amendment:** The overall reason for the amendment is to incorporate feedback from health authorities into the protocol.

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** An additional inclusion criterion was needed to confirm current or future immunization status. | |
| 4.1. Inclusion Criteria; inclusion criterion 11 | New criterion added to confirm current or future immunization status. |
| **Rationale:** Clarification of the definition and timing for immunizations that can be received was needed in the protocol. | |
| 8.2. Permitted Medications | Details were added around vaccines permitted in the study and their schedule. |
| **Rationale:** The handling of laboratory samples from the Mixed-Meal Tolerance Test (MMTT) needed clarification for storage and shipping instructions in the protocol. | |
| Attachment 3: Procedures for Performing the Mixed-Meal Tolerance Test | Instructions were added for processing, storage, and shipping of laboratory samples from the MMTT. |
| **Rationale:** Recognition that those with clinically stable autoimmune thyroiditis may be able to participate in this study needed to be added to the protocol. | |
| 4.2. Exclusion Criteria; criterion 4 | Criterion updated to provide an exception for subjects with clinically stable autoimmune thyroiditis. |
| **Rationale:** Clarity needed around the number of injections in Table 1. | |
| 6.1. Dosage; Table 1 | Number of injections updated to number of injections/dose in Table 1. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Consistency needed in the protocol in relation to neutralizing antibodies. | |
| 9.3.4. Immunogenicity Assessments (Antibodies to golimumab) | Text added describing evaluation of positive samples for neutralizing antibodies. |
| **Rationale:** The title of the study was decided after issuing of the protocol. | |
| Title page | The study title was added to the cover page of the protocol. |
| **Rationale:** Where to record self-administration done at the study site needed clarification. | |
| TIME AND EVENTS SCHEDULE; Screening through Off-therapy Follow-up; Footnote b | Footnote updated to include instructions for recording self-administration done at the study site. |
| 7.1.1. Dosing Recording | Text added to clarify self-administration done at the study site should not be recorded into an eDiary. |
| **Rationale:** Clarification was needed on subject/caregiver data collection using the sponsor-supplied eDiary and glucometer. | |
| 9.1.1. Overview | Collection of hypoglycemic events was added to list of data that subject/caregivers are to collect using the sponsor-supplied eDiary and glucometer. |
| **Rationale:** Clarification was needed around length of time subject/caregivers need to record data in their eDiary. | |
| 9.1.3.3. Off-Therapy Follow-up Period – Weeks 52 to 104 | Text was added instructing subject/caregivers to record data in their eDiary until Week 104. |
| **Rationale:** Members of the Independent DMC needed to be defined in the protocol. | |
| 11.11. Data Monitoring Committee | Text was added to define associations of individuals who can be members of the Independent DMC for this study. |
| **Rationale:** The IAC may consist of individuals external to the sponsor. | |
| 11.10. Interim Analysis | Removed “internal” in reference to the IAC. |
| **Rationale:** Clarification regarding timing of administration of study agent needed in the dosing charts. | |
| Attachment 2-A; Attachment 2-A | Title of the tables were updated with range of weeks for study agent administration. |

| Applicable Section(s) | Description of Change(s) |
|---|---|
| **Rationale:** Minor errors were noted. | |
| 1. INTRODUCTION; Type 1 Diabetes | Shots changed to injections. |
| 4.2. Exclusion Criteria; criterion 14 | Current of prior corrected to: current or prior. |
| ABBREVIATIONS | Abbreviations for CDC and HPV were added to the list of abbreviations. |

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**Attachment 1: Quantiferon-TB Gold Testing**

# QuantiFERON®-TB Gold Testing

The QuantiFERON-TB Gold test is one of the interferon-γ (IFN-γ) based blood assays for TB screening (Cellestis, 2009). It utilizes the recently identified *M. tuberculosis*-specific antigens ESAT-6 and CFP-10 in the standard format, as well as TB7.7 (p4) in the In-Tube format, to detect in vitro cell-mediated immune responses in infected individuals. The QuantiFERON-TB Gold assay measures the amount of IFN-γ produced by sensitized T-cells when stimulated with the synthetic *M. tuberculosis*-specific antigens. In *M. tuberculosis*-infected persons, sensitized T lymphocytes will secrete IFN-γ in response to stimulation with the *M. tuberculosis*-specific antigens and, thus, the QuantiFERON-TB Gold test should be positive. Because the antigens used in the test are specific to *M. tuberculosis* and not found in BCG, the test is not confounded by BCG vaccination, unlike the tuberculin skin test. However, there is some cross-reactivity with the 3 Mycobacterium species, *M. kansasii*, *M. marinum*, and *M. szulgai*. Thus, a positive test could be the result of infection with one of these 3 species of Mycobacterium, in the absence of *M. tuberculosis* infection.

In a study of the QuantiFERON-TB Gold test (standard format) in subjects with active TB, sensitivity has been shown to be approximately 89% (Mori et al, 2004). Specificity of the test in healthy BCG-vaccinated individuals has been demonstrated to be more than 98%. In contrast, the sensitivity and specificity of the tuberculin skin test was noted to be only about 66% and 35% in a study of Japanese patients with active TB and healthy BCG-vaccinated young adults, respectively. However, sensitivity and specificity of the tuberculin skin test depend on the population being studied, and the tuberculin skin test performs best in healthy young adults who have not been BCG-vaccinated.

Data from a limited number of published studies examining the performance of the QuantiFERON-TB Gold assay in immunosuppressed populations suggest that the sensitivity of the QuantiFERON-TB Gold test is better than the tuberculin skin test even in immunosuppressed patients (Ferrara et al, 2005; Kobashi et al, 2007; Matulis et al, 2008). The ability of IFN-γ-based tests to detect latent infection has been more difficult to study due to the lack of a gold standard diagnostic test; however, several TB outbreak studies have demonstrated that the tests correlated better than the tuberculin skin test with the degree of exposure that contacts had to the index TB case (Brock et al, 2004; Ewer et al, 2003). In addition, TB contact tracing studies have shown that patients who had a positive QuantiFERON-TB Gold test result and were not treated for latent TB infection were much more likely to develop active TB during longitudinal follow-up than those who had a positive tuberculin skin test and a negative QuantiFERON-TB Gold test result (Higuchi et al, 2007; Diel et al, 2008).

Although the performance of the new IFN-γ-based blood tests for active or latent *M. tuberculosis* infection have not been well validated in the immunosuppressed population, experts believe these new tests will be at least as, if not more, sensitive, and definitely more specific, than the tuberculin skin test (Barnes, 2004; personal communication, April, 2008 TB Advisory Board).

**Performing the QuantiFERON-TB Gold In-Tube Test**

The QuantiFERON-TB Gold test In-Tube format will be provided for this study. The In-Tube format contains 1 additional *M. tuberculosis*-specific antigen, TB7.7 (p4), which is thought to increase the specificity of the test.

To perform the test using the In-Tube format, blood is drawn through standard venipuncture into supplied tubes that already contain the *M. tuberculosis*-specific antigens. Approximately 3 tubes will be needed per subject, each requiring 1 mL of blood. One tube contains the *M. tuberculosis*-specific antigens, while the remaining tubes contain positive and negative control reagents. Thorough mixing of the blood with the antigens is necessary prior to incubation. The blood is then incubated for 16 to 24-hours at 37°C, after which tubes are centrifuged for approximately 15 minutes at 2000 to 3000g. Following centrifugation, plasma is harvested from each tube, frozen, and shipped on dry ice to the Central Laboratory. The Central Laboratory will perform an ELISA to quantify the amount of IFN-γ present in the plasma using spectrophotometry and computer software analysis.

The Central Laboratory will analyze and report results for each subject, and sites will be informed of the results. Subjects who have an indeterminate result should have the test repeated.

In select circumstances as approved by the sponsor, a local laboratory may be used to perform the QuantiFERON®-TB Gold test.

**Adherence to Local Guidelines**

Local country guidelines for immunocompromised patients should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

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**Attachment 2: Dose and Device Charts for Study CNTO148DML2001 in Subjects With Type 1 Diabetes**

# DOSE AND DEVICE CHARTS FOR STUDY CNTO148DML2001 IN SUBJECTS WITH TYPE 1 DIABETES

## Attachment 2-A: Dosing Chart for Induction Doses at Week 0 and Week 2

Volume (mL) from VarioJect (shaded white) and/or 50 mg PFS-U (shaded light gray)

- Body weight rounded to the nearest 5 kg and height rounded to the nearest 10 cm using standard rounding rules, round body weight up or down to the nearest 5 kg and height up or down to the nearest 10 cm. (Example: weight of 27.6 kg and height of 114.9 cm round weight up to 30 kg, and height down to 110 cm, resulting in an induction dose volume of 0.55 mL).
- **See device selection table (Attachment 2-C) for additional administration instructions.**

**Induction Dosing Chart - VarioJect or PFS-U Volume to be Dispensed (mL) for Week 0 and Week 2 Only***

| | Weight (kg) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Height (cm)** | **10** | **15** | **20** | **25** | **30** | **35** | **40** | **45** |
| **80** | 0.30 | 0.35 | 0.40 | 0.45 | | | | |
| **90** | 0.30 | 0.35 | 0.40 | 0.45 | 0.50 | 0.55 | | |
| **100** | 0.30 | 0.40 | 0.45 | 0.50 | 0.55 | 0.60 | 0.65 | 1.00 with 2 PFS-U |
| **110** | 0.35 | 0.40 | 0.45 | 0.50 | 0.55 | 0.60 | 0.65 | 1.00 with 2 PFS-U |
| **120** | 0.35 | 0.40 | 0.50 | 0.55 | 0.60 | 0.65 | 0.70 | 1.00 with 2 PFS-U |
| **130** | | 0.45 | 0.50 | 0.55 | 0.60 | 0.65 | 0.70 | 1.00 with 2 PFS-U |
| **140** | | 0.45 | 0.55 | 0.60 | 0.65 | 0.70 | 0.75 | 1.00 with 2 PFS-U |
| **150** | | | 0.55 | 0.60 | 0.65 | 0.70 | 0.75 | 1.00 with 2 PFS-U |
| **160** | | | 0.55 | 0.65 | 0.70 | 0.75 | 0.80 | 1.00 with 2 PFS-U |
| **170** | | | | 0.65 | 0.70 | 0.75 | 0.80 | 1.00 with 2 PFS-U |
| **180** | | | | | 0.75 | 0.80 | 0.85 | 1.00 with 2 PFS-U |

* See Attachment 2-C:Device Selection Chart for device(s) and settings to achieve the total dose indicated above

**Attachment 2-B: Dosing Chart for Maintenance Dosing Regimens at Week 4 through Week 52**

Volume (mL) from VarioJect (shaded white) or 50 mg PFS-U (shaded light gray)

- Body weight rounded to the nearest 5 kg and height rounded to the nearest 10 cm.
- See device selection table (Attachment 2-C) for additional administration instructions.

**Maintenance Dosing Chart - VarioJect (White) or PFS-U (Light Gray) Volume to be Dispensed (mL) for Week 4 Through Week 52***

| | Weight (kg) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Height (cm)** | **10** | **15** | **20** | **25** | **30** | **35** | **40** | **45** |
| **80** | 0.15 | 0.15 | 0.20 | 0.20 | | | | |
| **90** | 0.15 | 0.20 | 0.20 | 0.25 | 0.25 | 0.30 | | |
| **100** | 0.15 | 0.20 | 0.20 | 0.25 | 0.25 | 0.30 | 0.30 | 0.50 with PFS-U |
| **110** | 0.15 | 0.20 | 0.25 | 0.25 | 0.30 | 0.30 | 0.35 | 0.50 with PFS-U |
| **120** | 0.15 | 0.20 | 0.25 | 0.25 | 0.30 | 0.30 | 0.35 | 0.50 with PFS-U |
| **130** | | 0.20 | 0.25 | 0.30 | 0.30 | 0.35 | 0.35 | 0.50 with PFS-U |
| **140** | | 0.25 | 0.25 | 0.30 | 0.30 | 0.35 | 0.35 | 0.50 with PFS-U |
| **150** | | | 0.25 | 0.30 | 0.35 | 0.35 | 0.40 | 0.50 with PFS-U |
| **160** | | | 0.30 | 0.30 | 0.35 | 0.35 | 0.40 | 0.50 with PFS-U |
| **170** | | | | 0.35 | 0.35 | 0.40 | 0.40 | 0.50 with PFS-U |
| **180** | | | | | 0.35 | 0.40 | 0.40 | 0.50 with PFS-U |

* See Attachment 2-C: Device Selection Chart for device and settings to achieve the dose indicated above

**Attachment 2-C: Device Selection Chart**

Volume (mL) from VarioJect or PFS-U

| Device Selection Chart** | | | | |
|---|---|---|---|---|
| Volume (mL) | Induction Dose | | Maintenance Dose | |
| | Number of Devices | Volume | Number of Devices | Volume |
| 0.15 | | | 1 VarioJect | 1 VarioJect: 0.15 mL |
| 0.20 | | | 1 VarioJect | 1 VarioJect: 0.20 mL |
| 0.25 | | | 1 VarioJect | 1 VarioJect: 0.25 mL |
| 0.30 | 1 VarioJect | 1 VarioJect: 0.30 mL | 1 VarioJect | 1 VarioJect: 0.30 mL |
| 0.35 | 1 VarioJect | 1 VarioJect: 0.35 mL | 1 VarioJect | 1 VarioJect: 0.35 mL |
| 0.40 | 1 VarioJect | 1 VarioJect: 0.40 mL | 1 VarioJect | 1 VarioJect: 0.40 mL |
| 0.45 | 1 VarioJect | 1 VarioJect: 0.45 mL | N/A | N/A |
| 0.50 | 2 VarioJects | 1st VarioJect: 0.25 mL; 2nd VarioJect : 0.25 mL | 1 PFS-U 50 mg | PFS-U: whole volume |
| 0.55 | 2 VarioJects | 1st VarioJect: 0.25 mL; 2nd VarioJect : 0.30 mL | | |
| 0.60 | 2 VarioJects | 1st VarioJect: 0.30 mL; 2nd VarioJect : 0.30 mL | | |
| 0.65 | 2 VarioJects | 1st VarioJect: 0.30 mL; 2nd VarioJect: 0.35 mL | | |
| 0.70 | 2 VarioJects | 1st VarioJect: 0.35 mL; 2nd VarioJect: 0.35 mL | | |
| 0.75 | 2 VarioJects | 1st VarioJect: 0.35 mL; 2nd VarioJect: 0.40 mL | | |
| 0.80 | 2 VarioJects | 1st VarioJect: 0.40 mL; 2nd VarioJect: 0.40 mL | | |
| 0.85 | 2 VarioJects | 1st VarioJect: 0.40 mL; 2nd VarioJect: 0.45 mL | | |
| 0.90 | N/A | N/A | | |
| 0.95 | N/A | N/A | | |
| 1.00 | 2 PFS-U 50 mg | 1st PFS-U: whole volume; 2nd PFS-U: whole volume | | |

** Due to a rare chance of excess study agent administration with the 0.10 ml setting on the VarioJect, this dose increment is not to be used.
NA = Not applicable

**Attachment 3: Procedures for Performing the Mixed-Meal Tolerance Test**

NOTE: These procedures for performing the mixed-meal tolerance test instructions are a summary of the how subjects should prepare for the MMTT and how the test should be performed by the study team. Further detail will be provided in the Central Laboratory manual. Minor adjustments of this procedure may occur by the sponsor including, but not limited, to modifications or refinements of sample preparation and processing that will not necessitate a protocol amendment.

**Procedures for Performing the Mixed-Meal Tolerance Test:**

The MMTT is performed in the morning (between 7:00 a.m. and 10:00 a.m.), which means that administration must begin within this time. It is recommended that the tests be scheduled early in the morning (7:00–7:30 am) because BG will be more likely to be within the target range at that time.

The mixed-meal used in this protocol will be the Boost original Nutritional Energy Drink® (Mead-Johnson). If a subject has a known food allergy to one or more components of Boost, an equivalent substitution may be used contingent upon agreement with the study team. The 4-hour MMTT should take 250 minutes to perform.

**Dietary Guidelines and Pretest Instructions:**

Carbohydrates (CHO) should not be restricted from the diet before the test. A general guideline is that preadolescent subjects should consume at least 25 kcal (6.25 g) CHO/kg/day and adolescent and adult subjects should consume at least 15 kcal (3.75 g) CHO/kg/day for 3 days before the test. These are minimum amounts of CHO; most diets will include greater amounts of CHO. There is no need to alter the subject's diet unless he or she has been on a CHO-restricted diet.

In preparation for the visit, each subject should:

- Fast for at least 10 hours (but not more than 16 hours) before the test. Fasting should start the night before the test and should continue up until the start of the test. Subjects should not eat or drink anything except water. This means no coffee, tea, soda, cigarettes, alcohol, or chewing gum during the fasting period.
- Refrain from vigorous exercise during the fasting period.
- Refrain from working the night before the morning of the test.
- Discontinue taking any prescription medications that must be taken daily.

**Glucose and Insulin Before the Test:**

- Short-acting insulin analogues (such as lispro or l-aspart) may be administered up to 2 hours before the test.
- Regular insulin may be administered up to 6 hours before the test.

- Intermediate-acting insulin (such as Neutral Protamine Hagedorn [NPH]) may be administered on the evening before the MMTT, but not on the morning of the test. Subjects managed with intermediate-acting insulin (NPH or Lente) should administer their usual dose on the evening before the MMTT, but not on the morning of the test.
- Long-acting basal (such as glargine) insulin or continuous subcutaneous insulin infusion may be administered before, during and after the test as usual. Subjects on glargine may take their usual injection at the appropriate time, and those on continuous subcutaneous insulin infusion may continue with their usual basal settings.

**Target Glucose Level at the Start of Test:**

The target glucose level at the start of the test is between 70 and 200 mg/dL. Regular insulin or short-acting insulin analogues may be used up to 6 and 2 hours before the test, respectively, to achieve the desired glucose level. The principal investigator and the study subject should discuss the individual situation for insulin administration to attain the goal of meter capillary glucose values within the range of 70–200 mg/dL at the start of the test. For example, as a practical matter, subjects may be instructed to check their BG by meter before coming to the study site 2 hours before the start of the test, so that marked hyperglycemia can be treated with a short-acting insulin analogue. Alternatively, subjects who arrive at the research unit with elevated BG can receive additional short-acting insulin analogues at the time of their arrival, if the test itself does not start until at least 2 hours after insulin administration and occurs before 10 a.m.

If a subject's BG is below the limit (70 mg/dL) prior to performing the MMTT, the subject should be treated according to local practice, and the MMTT should be rescheduled.

**IV Placement During the Test:**

The IV should be in place for the duration of the test and must be flushed after each draw with saline solution or heparin flush.

The subject should remain sitting or resting in bed quietly throughout the test and until the test is completed. However, he or she may engage in quiet, non-strenuous activities, such as reading, playing cards, or watching TV. The subject may walk to the bathroom between blood draws if necessary.

**Testing Instructions:**

*Timepoint −10 minutes*

The first sample should be taken at least 10 minutes after establishing the line(s) and when the subject is calm and relaxed (if possible, depending on age) — this is the "−10 minute" sample.

Draw one 2-mL sample into the purple-top tube. After each vacutainer is collected the tube must be inverted gently at least 8 to 10 times. Chill sample in a bucket of crushed ice or in a refrigerator set at 4˚C for 20 to 30 minutes. At the laboratory, spin the tube in a tabletop

centrifuge (1000–1300 g, ~3000 RPM) for 10 minutes. Tubes must be spun within 30 to 60 minutes from blood draw. Freeze, store, and ship spun samples according to the Central Laboratory manual instructions.

*Timepoint 0 minutes*

The second sample should be taken just before the subject drinks the Boost; this is the "0-minute" sample.

Then the MMTT dose should be given with 6 kcal/kg @ 1 kcal/mL of mixed-meal to a maximum of 360 mL. The subject should consume the MMTT dose in no more than 5 minutes.

*Timepoints 15, 30, 60, 90, 120, 150, 180, 210, and 240 minutes*

Draw one 2-mL sample into the purple-top tube.

Invert all tubes gently 8 to 10 times after collection. If it is not possible to centrifuge the sample immediately post collection, chill sample in a bucket of crushed ice or in a refrigerator set at 4˚C for 20 to 30 minutes. Refrigerate the sample no longer than one hour prior to centrifugation. Freeze, store and ship the spun samples according to the Central Laboratory manual instructions.

Please check and record BG by meter at each timepoint.

At the conclusion of the test, please check BG by glucometer, and administer insulin as per subject's standard insulin plan.

**Tube-Processing Instructions:**

Spin the purple---top tubes, then transfer the plasma into 2 individual vials. Please make sure that each vial is properly identified with a label that indicates the timepoint.

Freeze, store and ship the spun samples according to the Central Laboratory manual instructions.

A clogged line, missed sample, or other deviation from the protocol must be noted on the Comments section of the MMTT specimen transmittal form.

**Sample:**

| Time (minutes) | Sample Collection* |
|---|---|
| –10 | x |
| 0 | x |
| Subjects drinks Boost | |
| 15 | x |
| 30 | x |
| 60 | x |
| 90 | x |
| 120 | x |

| Time (minutes) | Sample Collection* |
|---|---|
| 150 | x |
| 180 | x |
| 210 | x |
| 240 | x |

*assessments to include C-peptide, insulin, glucose, and/or pro-insulin per the Central Laboratory manual

**Attachment 4: Hepatitis B Virus (HBV) Screening**

Hepatitis B Virus (HBV) Screening

Subjects must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Subjects who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) are ***eligible*** for this study.
- Subjects who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) are ***eligible*** for this study.
- Subjects who test **positive only** for **surface antibody** (anti-HBs+) are ***eligible*** for this study.
- Subjects who test **positive** for surface antigen (HBsAg+) are ***NOT eligible*** for this study, regardless of the results of other hepatitis B tests.
- Subjects who test **positive only** for **core antibody** (anti-HBc+) are ***NOT eligible*** for this study.

For subjects who **are not eligible for this study due to HBV test results**, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended.

| **Eligibility Based on Hepatitis B Virus Test Results** | | | |
|---|---|---|---|
| | **Hepatitis B test result** | | |
| **Action** | **Hepatitis B surface antigen (HBsAg)** | **Hepatitis B surface antibody (anti-HBs)** | **Hepatitis B core antibody (anti-HBc total)** |
| | | | |
| **Include** | — | — | — |
| | — | + | + |
| | — | + | — |
| | | | |
| **Exclude** | + | — *or* + | — *or* + |
| | — | — | + |

**Attachment 5: Study Defined AST and ALT Normal Ranges, 2x ULN, and 3x ULN**

## AST and ALT normal ranges, 2x ULN, and 3x ULN*

| Test | Sex | Age Range (Yrs) | Normal Range (U/L) | 2x ULN (U/L) | 3x ULN (U/L) |
|---|---|---|---|---|---|
| | | | | | |
| **AST** | **Female** | Through 6 | 10-48 | 96 | 144 |
| | | 7 through 17 | 10-40 | 80 | 120 |
| | | 18 and above | 9-34 | 68 | 102 |
| | | | | | |
| | **Males** | Through 6 | 10-59 | 118 | 177 |
| | | 7 through 17 | 10-40 | 80 | 120 |
| | | 18 and above | 11-36 | 72 | 108 |
| | | | | | |
| **ALT** | **Female** | 6 and above | 6-34 | 68 | 102 |
| | | | | | |
| | **Male** | 6 through 9 | 6-34 | 68 | 102 |
| | | 10 and above | 6-43 | 86 | 129 |
| * From Covance Laboratories | | | | | |

**Attachment 6: Anticipated Events**

An anticipated event is an AE (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

1. Severe hypoglycemia. This is defined as a BG reading of <70 mg/dL and/or clinical signs and symptoms consistent with hypoglycemia even in the absence of a BG reading.
2. Diabetic Ketoacidosis (DKA). This is a condition of ketosis and metabolic acidosis that can occur in individuals with T1D.

Both severe hypoglycemia and DKA may present along a spectrum of severity. The site principal investigator will be responsible for the AE classification according to the definitions in Section 12.

**Reporting of Anticipated Events**

These events will be captured on the CRF and in the database and will be reported to the sponsor as described in Section 12.4.1, All Adverse Events. Any event that meets SAE criteria will be reported to the sponsor within the appropriate timeline as described in Section 12.4.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to health authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study agent, the sponsor will report these events in an expedited manner.

**Anticipated Event Review Committee (ARC)**

An Anticipated Event Review Committee (ARC) will be established to perform reviews of pre-specified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study agent. As this is a blinded study, an unblinded physician within the sponsor's organization not involved with the study but with subject matter expertise will be available to assist the ARC in the assessment and categorization of AEs if needed.

**Statistical Analysis**

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be described in a separate Anticipated Events Safety Monitoring Plan (ASMP).

## INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

**Coordinating Investigator (where required):**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

**Principal (Site) Investigator:**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

**Sponsor's Responsible Medical Officer:**

Name (typed or printed): Donald Raible, MD

Institution: Janssen Research & Development

Signature: [electronic signature appended at the end of the protocol] Date: _____

(Day Month Year)

Note**:** If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

**Janssen Research & Development ***

**Clinical Protocol**

**COVID-19 Appendix**

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# SIMPONI® to Arrest β-cell Loss in Type 1 Diabetes

# T1GER

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**Protocol CNTO148DML2001; Phase 2a**

**SIMPONI® (golimumab)**

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

**Status:** Approved
**Date:** 24 April 2020
**Prepared by:** Janssen Research & Development, LLC
**EDMS number:** EDMS-RIM-37356, 1.0

**THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL CNTO148DML2001**

**GCP Compliance:** This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

## COVID-19 APPENDIX

## GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study -related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If at any time a participant's safety is considered to be at unacceptable risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the participant and investigator, and with the agreement of the sponsor (see below).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance.

If a participant has tested positive for COVID-19, the investigator should contact the sponsor's medical officer or designee to discuss plans for study intervention and follow-up.

**ADDITIONAL ELEMENTS, WHERE APPLICABLE:**

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of participant care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:
    - remote (e.g. by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and participants for study procedures e.g. those related to safety monitoring / efficacy evaluation / study intervention storage and administration (including training where pertinent)

- procurement of study intervention by participants (or designee) or shipment of study intervention from the study site directly to participants for at home administration (including the potential for self-administration of study intervention)

- laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed

- other procedures, eg, imaging, may be conducted at an appropriate facility

- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

    - other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in CRFs and / or other study systems, as directed by detailed sponsor guidance. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.

- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).

- Exclusion: a potential participant with the following features will be excluded from participating in the study protocol:

    - During the 6 weeks prior to baseline, have had ANY of (a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), OR (b) suspected SARS-CoV-2 infection (clinical features without documented test results), OR (c) close contact with a person with known or suspected SARS-CoV-2 infection

        - Exception: may be included with a documented negative result for a validated SARS-CoV-2 test

        (i) obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, e.g. fever, cough, dyspnea)

        AND

        (ii) with absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit

- NOTES on COVID-related exclusion:

    1. If a participant is excluded due to recent COVID-19-related features, the reason for screen failure should be documented in the case report form under the exclusion criterion of having a condition for which participation would not be in the participant's interest or could confound study assessments.

    2. The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations / guidance from authorities / standards of care.

- Precaution: for those who may carry a higher risk for severe COVID-19 illness (e.g. those aged over 65 years), follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

## INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

**Coordinating Investigator (where required):**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

**Principal (Site) Investigator:**

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

**Sponsor's Responsible Medical Officer:**

Name (typed or printed): Frank Vercruysse MD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____
(Day Month Year)

**Note:** If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.