Study Manual

CTLA-4 Ig (Abatacept) (TN-09)

June 2008

Version 1.0

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Document Revision History

Version	***Release Date***	***Study Manual Filename***	***Developer***
1.0	03/12/08	Study Manual	C. Murphy
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CHAPTER 1 STUDY TRIAL GENERAL OVERVIEW

1. Overview

The purpose of the Trial is to assess the safety, efficacy, and mode of action of CTLA-4 Ig (Abatacept) for the treatment of individuals with new onset Type 1 diabetes. This trial is implemented by the Type 1 Diabetes TrialNet at participating clinical sites.

This is a two-arm, multicenter, randomized, double-masked, placebo-controlled comparison of Abatacept versus placebo. The study design involves two arms with 72 participants in the active treatment group and 36 participants in the placebo group. The study will include a total of 108 evaluable participants, ages 6 - 45 with new onset Type 1 diabetes. Study participants enrolled will be those who meet the eligibility criteria and provide written informed consent.

Study Outcomes:

The primary outcome of each participant is the area under the stimulated C-peptide curve over the first 2 hours of a 4-hour mixed meal tolerance test (MMTT) conducted at the two-year visit.

The secondary outcome of this research study will involve the development and examination of surrogate markers for immunologic effects of the treatment on disease-specific and immunological outcomes.

Mechanistic Studies

Throughout the Trial, blood will also be collected for mechanistic studies. These studies will measure (but are not necessarily limited to) samples for RNA, plasma, serum, DNA, measures of B and T cell number and function. These mechanistic samples will be maintained at the NIDDK Repository site.

CHAPTER 2 PARTICIPATING SITES

At least fifteen sites, between Clinical sites and major affiliates will have the responsibility for the screening and enrollment of potential participants during the conduct of the CTLA-4 Ig protocol. Each clinical site and major affiliate will have a Principal Investigator, a full time Trial Coordinator, other investigators, and ancillary personnel as needed. The Principal Investigator will work with the TrialNet Coordinating Center, Protocol Chairman, and NIH Staff assigned to this project to conduct the study in accordance with the Protocol and Study Manuals. The list of the participating sites can be found at the TrialNet website.

CHAPTER 3 INFORMED CONSENT PROCESS

1. Overview

Informed consent obtained at a clinical site should follow all standard procedures. The participant must sign a revised IRB approved I*nformed Consent Form with* each revision of the document.

Each participant will be given a written consent form by qualified study personnel (the Trial Coordinator and/or Investigator or other designee). The personnel will understand the research study, and will complete any necessary courses required by their Institutional Review Board prior to implementing the consent process. The consent process should occur in a quiet setting, and the participant should be given time to review the written consent form and ask questions prior to the initiation of study procedures. This ensures that the participant understands that participation is voluntary and that they may choose to end participation at any time. The consent form will be reviewed with participants and signed **prior** to performing any study-related assessments. It should also be noted in the participant's medical/research chart that the participant consented to participation in the study.

Participants under 18 years of age will be given the opportunity to discuss the study and consent form independently from their parent or guardian, which will allow these participants to ask questions they might not have felt comfortable asking previously. In addition, the parent/guardian of the adolescent participants will be given the opportunity to discuss the study independently from the participant. One or both parents/legal guardians (depending on institutional policies) will be required to sign the Informed Consent Forms. At some sites, the participant will also be required to sign an Assent Form. Care should be taken to explain the study to the participant on a level that is understandable. Specific questions should be addressed to the participant to help ensure that the study is completely understood.

Essential components of the informed consent process include the following:

- understanding that participation in the research study is **voluntary**
- a participant may **choose to end** participation at any time *(participant understanding that they may choose to end participation at any time).*

- consent for screening for the Trial **does not imply commitment to full study participation**.

Study personnel must provide the participant's family with:

- An overview of the full study
- The inclusion and exclusion criteria
- Information on the procedures involved
- A description of the potential visits
- Required time commitments for participating in the study

The participant's signature should be obtained on the Informed Consent Form/Assent Form after a thorough discussion of the study.

Consent for participants 18 years of age or *older*: The participant needs to **sign the last page** of the consent**.** The participant's signature, the current date, and the printed name of the participant are all required. Next, the person obtaining the consent (the person who has explained the study to the participant) must sign the form, provide the current date and print his/her name. Please ensure that the printed areas are completed legibly.

Consent for participants *less* than 18 years of age: The parent of the legal guardian needs to **sign the last page** of the consent**.** Sufficient evidence must be provided to show that the person giving consent for the minor does, in fact, have the legal right to serve as the participant's guardian. The parent/guardian must sign and date the form as well as print his/her name legibly. One or two parental signatures will be required as per the requirements of the local institution. A witness must also sign, date and print his/her name.

**Note: The ages specified in the Study Manual and on the Model Informed Consent Forms may not be the same age limits set by local institutional boards and ethics committees.*

Investigator Statement Section: The Principal Investigator at the clinical site must complete The Investigator Statement section for the Trial.

A copy of the signed Informed Consent and Research Subject Authorization Form (if in the United States) should be provided to the participant. **The original signed documents should remain at**

the clinical site. These original and signed documents should **not** be sent to the TrialNet Coordinating center.

An explanation of the Health Insurance Portability and Accountability Act (HIPAA) should also be included as part of this discussion regardless of whether or not an institution has incorporated the Research Subject Authorization Form (RSAF) into the Informed Consent Forms. It is also a legal requirement that the participant receive a copy of their signed RSAF (if required), regardless of whether or not the authorization is a separate form or is incorporated into the Informed Consent Forms.

1.1 Assent Form

In the event that the participant is between **8 and 17 years of age**, the participant/child may also be required to sign an Assent Form in addition to the parent/legal guardian signing the Informed Consent Form, depending on institutional policies. In this case, the parent/guardian will grant informed permission (consent) for the minor to participate in the study after being presented with all the information about the study. Parents must demonstrate that they fully understand the study and the commitments required by the child. Assent, or the willingness to participate, will also be required from the child following an age appropriate discussion of the study procedures, risks and benefits. A child 8 to 17 years of age is capable of having a limited understanding of the study and is capable of agreeing to participate. A witness must also sign, date and print his/her name on the assent form.

The original signed Assent Form should remain at the site and a copy should be provided to the participant/parent.

1.2 Research Subject Authorization Form (RSAF)

Research Subject Authorization is one aspect of the Health Insurance Portability and Accountability Act of 1996 (HIPAA) for sites in the United States. HIPAA is a federal law in the United States that, among other things, protects the privacy of protected health information (PHI). Under HIPAA regulations, PHI may not be used for research purposes unless the participant gives written authorization in advance. Although it is not the intent of TrialNet to request such Protected Health

Information (PHI) some local IRBs will still require TrialNet Trial participants to give written authorization.

Sites will need to follow their institutional requirements for Research Subject Authorization. The RSAF or similar form only needs to be signed at the beginning of a research study; this process does not need to be repeated (unless required by the institution). Regardless of institutional variations on the procedures for obtaining this authorization, a copy of the signed authorization must be provided to the participant. It is acceptable to incorporate the RSAF into the informed consent forms. The original should be kept at the clinical site with the original signed Informed Consent Form for a participant. These forms should not be sent to the TrialNet Coordinating Center.

2. Informed Consent Process

Before initiating screening activities (data collection, specimen collection, or tests), participants will be given the ***Screening Informed Consent Form***, which provides details about the procedures involved with being screened and allows participants to be screened for the study without committing to full study participation. This consent must be signed at the screening visit. Participants will also be given the ***Intervention Informed Consent Form*** prior to baseline/randomization which will need to be reviewed and signed before participants proceed beyond the screening phase of the study. This consent must be signed at the baseline/randomization visit before any baseline/randomization procedures are completed. All participants must read, and have their site's IRB approved Screening and Intervention Informed Consent Forms explained to them by qualified study personnel (the Trial Coordinator and/or Investigator or other designee).

2.1 Volunteer Understanding Assessment

As part of the informed consent process, the participant will also be required to complete a short, written Volunteer Understanding Assessment that is designed to ensure that the participant understands the study, as well as what is being asked of him/her. The quiz should be given to the participant following a description of the study and after the Screening Informed Consent Form has been signed, but before the Intervention Informed Consent Form has been signed. If the participant

is under the age of 18, the participant's parent/guardian will be required to complete the Volunteer Understanding Assessment independently from the participant. Study personnel will review the completed quiz with the participant (and his/her parent/guardian in the case of an adolescent participant), taking special care to review any questions the participant answered incorrectly and answer any questions about the study. The purpose of the quiz is to enhance informed consent. The key for the Volunteer Understanding Assessment is given in Appendix A.

2.2 Stored Samples

In addition to the standard procedures and tests associated with the study, participants will be asked for permission to store their remaining blood samples including genetic samples for future studies to learn more about factors associated with risk for the development of Type 1 diabetes. The participant must indicate their choice on the Informed Consent Forms and initial in the appropriate area.

Note: Participants are **not** required to provide consent for stored samples in order to participate in the study. Participants also have the right to withdraw their consent to store samples at any time and to have their stored samples destroyed to the extent possible.

2.3 Additional Consent

Additional consent for testing for reportable conditions such as HIV or Hepatitis B or C will be obtained as required by individual institutions. If participants are found to have evidence of HIV or Hepatitis B or C, they will be excluded from the study but referred for appropriate counseling by specialists in these areas according to local regulations.

2.4 Continuing Consent

If there is a revision to the original IRB Approved Informed Consent signed by the participant, he/she must be re-consented with the current IRB Approved Informed Consent.

2.5 Annual Re-Consenting Process

Annual re-consenting of participants occurs to ensure that participants continue to be informed about the study as it progresses. Trial Coordinators should review the consent form with each participant annually to review the purpose of the study, the risks and benefits, and new information that has been learned since the previous consent. Trial Coordinators should reassess the

participant's interest in continuing in the study and address all questions the participant may have. It is recommended that Trial Coordinators note the discussion in the study chart and include the date and discussion points in the notes. Site coordinators must also comply with their institutional IRB regulations.

CHAPTER 4 SITE CERTIFICATION AND REQUIREMENTS

Participating clinical sites must fulfill specific requirements prior to the start of any protocol activity. When a site has met all requirements to start the study, a written notice of **"Site Certification"** will be issued by the TrialNet Coordinating Center. No protocol activities can be undertaken prior to this **"Site Certification"** being received. Once authorized to start protocol screening/enrollment, the site will have a continuing responsibility to update the TrialNet Coordinating Center of any changes, such as personnel changes. Reminders for annual renewals of documents will be sent to the Principal Investigators and Study Coordinators two months in advance of renewal dates.

Documents to be sent to TrialNet Coordinating Center:

The following items are collected and maintained at the TrialNet Coordinating Center (TNCC):

1. IRB approval for study (includes IRB letter of approval for protocol and stamped informed consents (if applicable); additionally, a copy of the IRB approved Research Subject Authorization Form)
2. Annual renewal of IRB approvals
3. Executed Letter of Agreement (LOA) with The George Washington University (GWU)
4. Confidentiality Agreement completed by each Research Staff member
5. Duality of Interest Forms (DU1 and DU7) completed by each Research Staff member
6. Annual update to DU1 by completed DU2 or DU3
7. NIH Education on Human Subjects Protections or equivalent proof of training for each Research Staff member
8. Research staff names, mailing addresses, email addresses, office FAX/telephone numbers
9. Curriculum vitae (signed and dated) for the Investigator and all Sub-Investigators listed on the 1572.
10. Completed and signed Statement of Investigator (Form FDA 1572)
11. Name and location of laboratory utilized for laboratory assays and other facilities conducting tests, including a copy of the laboratory certificate
12. List of normal laboratory values (CBC with Differential)
13. Mailing address and contact information for on-site pharmacy where shipments of study medication will be received

14. Availability of 2 - 8 °C degree refrigerator at on-site pharmacy for storage of Abatacept vials

Site Initiation Activity Checklist:

Research personnel at the site must complete the Site Initiation Activities Checklist (it can be found in the TrialNet Website and Appendix B). This list will serve as documentation that the following items have been completed, among others:

1. IRB Approvals

A copy of IRB approved documents (letter of approval from site IRB, approved informed consent forms, and approved Research Subject Authorization Form) must be received and filed at the TNCC. The IRB documents must reflect the appropriate version number and date of the Protocol. To maintain requirements for continuing participation in TrialNet, the site must provide their annual renewal of IRB approval for the study.

2. Letter of Agreement (LOA)

The Letter of Agreement is a formal document that outlines the responsibilities of all parties for the conduct of the TrialNet studies. The LOA is addressed to the Principal Investigator at the institution and includes appendices of required forms that must be completed by the institution and its research staff that will be involved in TrialNet studies.

The LOA must be executed between The George Washington University (GWU) on behalf of the TNCC and Regional Clinical Centers and Affiliate Sites in order to establish the payment records for reimbursement of study related participant care costs. Only one LOA with GWU is required from the site. The LOA remains in effect throughout the duration of TrialNet.

3. Research Staff Requirements

Each TrialNet Research Staff member at the site is required to sign a TrialNet Confidentiality Agreement, Duality of Interest Form (DU1 and DU7), and complete the NIH Education on Human Subjects Protections or equivalent training. Annually, Research Staff will be requested to provide either a statement of no change (DU3) or conflict (DU2) to their original DU1. The TNCC will send reminders to research staff or Trial Coordinators of impending renewal dates.

The site is expected to contact the TNCC on an ongoing basis of any changes or additions to Research Staff.

4. Clinical Staff Requirements

Certification of staff is required for the Trial. The following table is a guide for the Staff Certification requirements.

Staff Certification Guidance						
	1572 & Updated CV	**CTLA4Ig Dual of interest (DU7)**	**CTLA4Ig Protocol Quiz**	**CTLA4Ig Web Randomi-zation**	**Metabolic Quiz MMTT**	**Shipping Quiz**
Principal Investigator	**X**	**X**	**X**			
Sub/Co-Investigator	**X**	**X**	**X**			
Site Coordinator		**X**	**X**	**X**	**X**	**X**
Trial Coordinator		**X**	**X**	**X**	**X**	**X**
Recruitment Coordinator		**X**	**X**			
Regulatory Coordinator		**X**				
Supporting Research Staff		**X**	**X**	**X**	**X**	**X**
Associated Research Staff					**X**	**X**
Miscellaneous Research Staff						

At least one person (preferably and typically the Study Coordinator) at the site must be certified in these components to satisfy requirements for Site Certification and initiate protocol enrollment activities.

Certification is an important step in ensuring that study procedures are performed consistently across all TrialNet sites. The Trial certification includes the following:

- **Metabolic Tests Quiz -** This quiz applies to all TrialNet studies and only needs to be taken once by all study personnel who will be performing MMTTs on participants.

- **Shipping Procedures Quiz -** This quiz applies to all TrialNet studies and only needs to be taken once by all personnel who will collect specimens and/or prepare samples for shipment to the core laboratories at each site.
- **Protocol Quiz -** This quiz is specific to the Trial. For each new TrialNet study that a site participates in, the relevant staff must complete a separate protocol quiz.
- **Web Randomization System** – All study personnel who will be randomizing participants into the study will be required to randomize a "mock" participant by logging into the system and following the procedures correctly. Refer to Chapter 10 for information on completing a mock randomization.

The Trial or Study Coordinator at each clinical site must be certified in all required components. In addition to the Trial/Study Coordinator, there are two general categories of staff that must be certified:

1) **Research Staff -** work directly with the Trial or Study Coordinator and are involved with the completion of case report forms and research participant files, consenting research participants, communicating with the TNCC, conducting participant visits, randomizing participants, and/or collecting and shipping specimens. These staff must complete <u>all</u> of the certification components listed above.

2) **Other Staff -** nurses and other staff at the GCRC or CRC who will collect specimens and/or prepare samples for shipment to the core laboratories. These staff must complete the Metabolic Tests Quiz and the Shipping Procedures Quiz, but they do not have to complete the protocol quiz or the "mock" randomization.

a. Components of Staff Certification

<u>Written Quizzes (3)</u>

The Metabolic Tests and Shipping Procedures quizzes cover standard study procedures. These include:

- collection of serum for autoantibody measurement
- collection of blood for HbA1c measurement
- collection of blood for HLA typing

- Mixed Meal Tolerance Test (MMTT)

The Protocol Quiz covers key points of the Protocol, such as eligibility criteria and visit procedures, as well as informed consent issues.

Before taking the quizzes, the relevant study documents should be reviewed (see Table 1). Although staff may refer to these documents while taking quizzes, candidates should be familiar with the concepts covered in them.

Table 1. Documents for Review Prior to Certification Quizzes

• Protocol
• Informed Consent/Assent Forms (Screening and Intervention)
• Case Report Forms
• Specimen Transmittal Forms
• Patient Handbook
• Abatacept Investigator Brochure
• Volunteer Understanding Survey

The three quizzes may be taken at the same time or separately. Allow at least 30 minutes to one hour for each quiz. Use of a calculator may be necessary for the 'Metabolic Tests' quiz.

Completed quizzes are sent to The Coordinating Center for scoring. The Coordinating Center notifies the candidate of any incorrect responses. If there are incorrect items, the Protocol Research Associate/Assistant will discuss and review these items with the individual to ensure that he/she understands the material. In some cases, retesting may be necessary.

5. Notification of Staff Certification

The Coordinating Center tracks all completed certification components at each site. The Coordinating Center will notify individuals of their successful certification and authorize sites to start protocol enrollment. A Site Initiation Activities Checklist is given in Appendix B.

CHAPTER 5 SCREENING VISIT

1. Overview

New onset Type 1 diabetes participants will be identified and referred to participating TrialNet sites. The family will be asked if they would be interested in participating in a research project. Those indicating interest are referred to one of the Investigators or Study Coordinators for a description of the study. TrialNet research personnel authorized to present the study to families have attended an approved IRB course and are registered by the IRB.

Before any study specific procedures a copy of the Informed Consent, the Volunteer Understanding Assessment and the Participant Handbook will be given to the participant. Please refer to Chapter 3 for a complete description of the Informed Consent Process for the study.

After a participant signs the Screening Informed Consent Form, the participant will receive a TrialNet Screening Identification Number, and the Screening Form (CTL01) and Screening Medical History Form (CTL02) will be completed. Blood will be taken to examine whether a participant is eligible for the Trial. Labs, the mixed meal tolerance tests (MMTT), and other screening procedures will also be conducted. For a complete overview of the study, refer to the Schedule of Assessments on Appendix C.

2. Eligibility Criteria

The inclusion and exclusion criteria should be strictly adhered to as described in the study protocol. Participants **must** meet all eligibility criteria prior to randomization, undergoing any baseline study procedures, or completing any study forms, other than the Screening Form (CTL01).

3. Inclusion/Exclusion Criteria

3.1 Inclusion Criteria

The participant MUST:

- ***Be 6 to 45 years of age at the time of randomization***, this indicates that at the time of randomization the participant has passed his/her 6th birthday, but has not passed his/her 46th birthday.
- ***Be within 3-months (100 days) of diagnosis of Type 1 diabetes*** based on ADA criteria ***at the time of randomization.***

The current ADA criteria for diagnosing diabetes include the following:

1. Fasting (no caloric intake for at least 8 hours) plasma glucose is ≥ 126 mg/dl (7.0 mmol/L)

Or

2. Diabetes symptoms (i.e. polyuria, polydipsia, polyphagia, and/or weight loss) exist and casual (any time of day without regard to time since last meal) plasma glucose is ≥ 200 mg/dl (11.1 mmol/L)

Or

3. 2-hour plasma glucose is ≥ 200 mg/dl (11.1 mmol/L) during a 75 gram oral glucose tolerance test (OGTT)

Or

4. Unequivocal hyperglycemia with acute metabolic decompensation (e.g. ketoacidosis)

The first three criteria in any combination on two separate days are diagnostic. If criterion (4) is met, an OGTT is not recommended.

The date of diagnosis will be defined as follows:

- If the participant was symptomatic at diagnosis, the date of diagnosis will be the date of the **first** OGTT
- If the participant did not have symptoms at diagnosis, the date of diagnosis will be the date of the **second** (or confirmatory) OGTT

- ***Have at least one detectable diabetes-related autoantibodies.*** If the participant has been taking insulin therapy for longer than 7 days, the presence of insulin autoantibodies alone is **not** sufficient. In this case the participant must also have evidence of detectable anti-GAD, anti-ICA512/IA-2, or islet cell autoantibodies. The reason for inclusion of these enrollment criteria is to avoid inclusion of participants with "type 1B diabetes mellitus", which may not involve the immunologic criteria measured by the assays that will be utilized. These antibodies will be measured by TrialNet Core Laboratories. See Section 3.5 for autoantibody retesting procedures, if initial tests are negative.

- ***Have stimulated C-peptide levels ≥ 0.2 pmol/ml*** measured during a mixed meal tolerance test (MMTT) conducted at least 3 weeks (**21 days**) from diagnosis of diabetes and within one month (**37 days**) of randomization.
- ***If female with reproductive potential, be willing to avoid pregnancy and have a negative pregnancy test.*** A urine pregnancy test will be conducted at Screening, Baseline, Days 14, 28, 56, 84, 112, 140, 168, 196, 224, 252, 280, 308, 336, 364, 392, 420, 448, 476, 504, 532, 560, 588, 616, 644, and 672. Acceptable forms of birth control include, but are not limited to:
    - Abstinence
    - Barrier methods (condom, diaphragm, cervical cap, sponge, or spermicide)
    - Contraceptives (oral or implant)
    - Surgical methods (sterilization or intrauterine devices)
- ***Be at least three months from last live immunization received and be willing to forgo live vaccines for 3 months following last dose of abartacept/placebo.*** Although no data are available regarding the effects of vaccination in patients receiving abatacept therapy, vaccination with live vaccines is not recommended. The possibility exists for abatacept to affect host defenses against infections since the cellular immune response may be altered. Therefore concurrent use of live vaccines within 3 months of abatacept therapy may result in reduced efficacy of vaccine. All other vaccines are allowed. Tetanus and killed flu vaccine will be administered to subjects as part of the study.
- ***Be willing to comply with intensive diabetes management.*** For all participants, regardless of age, the goal of this management will be to maintain an HbA1c value of 7.0% or lower without significant hypoglycemia.
- ***Weigh at least 20 kg (44lb) at study entry.*** This is to ensure that the participant is of sufficient body weight to allow for the blood volumes drawn for the study assessments.

3.2 Exclusion Criteria

The participant MUST NOT:

- ***Be immunodeficient or have clinically significant chronic lymphopenia.***
- ***Have an active infection or positive purified protein derivative of tuberculin (PPD) test result.*** The PPD test is administered at the initial screening visit. A positive PPD

indicates that the participant has been infected with Tuberculosis, and should be referred for appropriate counseling and treatment.

- ***Be currently pregnant or lactating, or anticipate getting pregnant.*** If the participant has any plans to become pregnant, or to attempt to become pregnant, during the course of the study she should be excluded from participation.
- ***On-going use of medications known to influence glucose tolerance.***
- ***Require use of other immunosuppressive agents.*** Such as chronic use of steroids, regardless of the type or route of administration (inhaled, topical, systemic, oral, etc.). Chronic use of steroids is defined as more than one-week of continuous use over the course of one-month. Acute use of steroids should not be considered grounds for exclusion, as long as the participant is not continuing to take the steroid medication at the time of screening.
- ***Have serologic evidence of current or past HIV, Hepatitis B, or Hepatitis C infection.*** Participants are screened for Human Immunodeficiency Virus (HIV), Hepatitis B virus, and Hepatitis C virus at the initial screening visit to determine if they are currently infected with these viruses. Note that if the participant is infected with HIV or Hepatitis, this information **must** be reported to the appropriate department of health.
- ***Have any complicating medical issues that interfere with study conduct or cause increased risk to include pre-existing cardiac disease, COPD, neurological, or blood count abnormalities (such as lymphopenia, leukopenia, or thrombocytopenia).*** If the screening CBC indicates an abnormal lymphocyte count, white blood cell count, or platelet count, repeating the CBC and taking a good history are recommended. The PI should then decide if the counts are appropriate for participation and consult with the Protocol Chair and Medical Monitor as needed.
- ***Have a history of malignancies.***
- ***Be currently using non-insulin pharmaceuticals that affect glycemic control, such as metformin.*** If a participant is willing to stop therapy with these agents then they will be eligible for study participation following a two week (14 day) washout period.
- ***Be currently participating in another type 1 diabetes treatment study.***

The TrialNet Coordinating Center will be responsible for initially reviewing and adjudicating any instances where eligibility is unclear. If following this initial review eligibility is still unclear, the TrialNet Eligibility and Events Committee will review and adjudicate the

situation. See Appendix H for a copy of the form that needs to be completed and submitted to the TNCC for this review to take place.

3.3 Intensive Diabetes Management

During the study, all participants will receive intensive management of their diabetes. The goal of treatment will be to keep the hemoglobin A1c level (HbA1c) as close to normal as possible without frequent occurrence of hypoglycemia. A goal would be an HbA1c of 7.0%.

The primary responsibility for diabetes management will be with the treating or referring physician, but additional support of the research team including a Certified Diabetes Educator (CDE) will be made available.

Participants will be expected to take a sufficient number of daily insulin injections or use insulin pump therapy to meet this goal, without causing severe hypoglycemic reactions. In general, glucose levels must be checked at least four times per day and records of the glucose levels should be communicated to the CDE every two weeks. After the CDE has reviewed these records, the CDE may contact the participant and the treating physician about adjustments in the insulin regimen, referral to a Registered Dietician, or other approaches that the CDE feels would improve the glucose control. Records of glucose logs and communication with the participant and treating physician will be kept as source documentation.

The general goal of glucose control is to target pre-prandial glucose levels of 90-130 mg/dl (5-7.2 mmol/L) (plasma), post-prandial levels of <180 mg/dl (<10 mmol/L), and bedtime levels of 110-150mg/dl (6.1-8.3 mmol/L). Participants who fail to achieve an HbA1c level according to the guidelines above will not be excluded from the study, but additional measures will be instituted to correct the glycemic control. The intent is not to eliminate a participant who is trying their best to achieve these aims.

In addition to Medical Monitor and DSMB oversight, regular monitoring of HbA1c levels will be done by the TrialNet Clinical Monitoring Group. Members of this group will work with clinical sites to review diabetes care for individual participants not attaining the study goal.

Any episodes of severe hypoglycemia (i.e. unconsciousness, seizure, or needing assistance of another individual to correct the hypoglycemia due to an altered state of consciousness) will prompt a review of the cause of the episode and adjustment of insulin dosing/diet/exercise as deemed appropriate by the treating physician. All episodes of severe hypoglycemia that require hospitalization and/or emergency care will be reviewed by the TrialNet Medical Monitor and reported to the Data Safety Monitoring Board (DSMB). If adhering to these goals of treatment results in any episodes of severe hypoglycemia, the goals of treatment may be relaxed to avoid a recurrent event. This will be decided on a case-by-case basis with recommendations of the DSMB and/or other monitoring committees as appropriate (Safety Monitoring Committee, Clinic Monitoring Committee).

3. 4 Reading the PPD Test

The results of the PPD test need to be read within 48-72 hours of administering the test. The test must be read by a trained nurse or physician (either at the study site or at a site more convenient for the participant). The results of the test should be recorded in the participant's source documents. It may be helpful to call the participant as a reminder to have the test read in a timely manner and to call the site with the results. The Test Reading Guidelines and a Sample Participant Letter are given in Appendix D.

3.1.1. BCG Immunization

Tuberculin skin testing (TST) is required for all participants prior to enrollment in protocol. Previous Bacille Calmette-Guérin (BCG) immunization is not a contraindication to TST (Red Book 2006 Report of the Committee on Infectious Diseases, pg. 683).

Generally, interpretation of TST results in BCG recipients is the same as for people who have not received BCG vaccine. The size of the TST reaction attributable to BCG immunization depends on many factors, including age at BCG immunization, quality and strain of BCG vaccine used, number of doses of BCG received, nutritional and immunologic status of the vaccine recipient and frequency of TST administration.

Evidence that increases the probability that a positive TST result is attributable to latent tuberculosis infection includes known contact with a person with contagious tuberculosis, a family history of tuberculosis disease, a long interval (>5 years) since neonatal immunization and a TST reaction >=15 mm.

Procedure

1) Place TST
    - 5 tuberculin units of purified protein derivative intradermally per local guidelines
    - Creation of a visible wheal 6-10 mm in diameter is crucial to accurate testing
2) Query participants regarding history of BCG vaccine. If there is a history of BCG vaccine, document the number of vaccinations and dates as available.

Interpretation of a Negative TST

Screening participants with a negative TST (<10 mm of induration) regardless of BCG vaccine history are eligible for participation.

Interpretation of a Positive TST

Screening participants with a positive TST defined by the area of induration >=10 mm, regardless of a previous history of BCG vaccine, are excluded from participation. Participants should be referred to primary care physician or infectious disease specialist for appropriate evaluation and management.

3.5 Repeating the BAA

If the initial screening antibody sample indicates that the participant is negative for all antibodies (or positive for mIAA only), the participant is eligible for repeat testing. The following procedure must be followed:

1. Contact participant and schedule re-draw. The scheduling of the re-draw, and time required for results to be reported, **must** fit within the eligibility windows for the study

(randomization must occur no more than 100-days from date of diagnosis and no more than 37 days from screening MMTT).

2. Complete a **new** specimen transmittal form (CTL99AA) and select "Screening" as the visit. Record the **new** draw date for question A1.
3. Apply appropriate barcode labels (BAA) to specimen transmittal form and vials containing the sample. **Note:** These barcode labels must be from a different block of labels than the labels that were included on the sample drawn previously!
4. Results from the new sample will be available within approximately 2 weeks from the date the sample was received by the laboratory. The results will be available on the TrialNet website in the eligibility report. **Note:** The eligibility report always displays the most recent results received.
5. Review results to determine eligibility. If the new results indicate that the participant is positive for any of the other three antibodies (GAD65, ICA512, ICA), in addition to mIAA, than this eligibility criterion has been met. If the new results indicate that the participant is still positive for mIAA only, than the participant has not met this eligibility criterion and is not eligible for a repeat sample.

3.6 Mixed Meal Tolerance Test

The mixed meal tolerance test (MMTT) will be conducted at least 3 weeks (**21 days**) from diagnosis of diabetes and within one month (**37 days**) of randomization. This test is meant to assess the potential participant's insulin production capability. In order for the results to be meaningful, it is important for the participant to follow certain dietary and lifestyle guidelines in the days preceding the test. A high carbohydrate diet must be followed for the three days leading up to the test. The participant is required to fast starting the night before the test, and is instructed to consume only water for at least ten hours preceding the test. More detailed information on the mixed meal tolerance test can be found in Appendix E. This appendix includes detailed information on the procedure. This section also includes a detailed "Sample Menu" with recommended items to maintain the required high carbohydrate diet prior to the test.

The test takes approximately four hours to complete, and must be scheduled in the morning (i.e. must be started before 10 AM). It is important to carefully review the eligibility criteria with the participant before starting the test, *since if certain criteria have* been violated the test

will need to be rescheduled for another date. For participants that live a great distance from the clinic, special arrangements to have the MMTT done the same day as the initial Screening Visit would be attempted if a second trip to the clinic would not be possible.

3.7 Assignment of the TrialNet Screening Number

Participants who are screened for enrollment will receive a TrialNet Screening Identification Number after they sign the Screening Informed Consent Form at the beginning of the screening visit. Participants who are randomized into the study will receive an additional identification number known as the Randomization Number.

The Screening ID consists of five digits. The first four digits will be a sequential number, and the last number will be a check digit. The Coordinating Center will supply each participating clinical site with a Screening Number Log containing a range of numbers to be used for participants at that clinical site. For example, one site might be assigned the range from 0001 to 0300, while another is assigned 4001 to 4300. Each site will maintain a Screening Number Log to keep track of which Screening Numbers have been assigned to which participants. A blank Screening Number Log is given in Appendix F.

TRIAL SCREENING VISIT(S) SUMMARY

NOTE: The participant **NEEDS TO BE FASTING** for this visit. Refer to the Physician Orders for this visit to follow the correct order for drawing the blood samples and administering the MMTT.

1. Forms

A. Forms to be completed prior to the initiation of study procedures:

- TrialNet Screening Informed Consent
- Volunteer Understanding Assessment
- TrialNet Screening Assent *(if applicable)*
- Research Subject Authorization Form *(if applicable)*
- Local HIV Screening Consent *(if applicable)*

B. Case Report Forms:

- Screening Form (CTL01)
- Screening Medical History Form (CTL02)
- Family History Form (CTL04) *(optional)*
- Pre-randomization Exit Form (CTL01E) – *To record participant's ineligibility or withdrawal from the study at any time BEFORE RANDOMIZATION*

C. Specimen Transmittal Forms:

- CBC Results (CTL99CB)
- Chemistries (CTL99CH)
- HIV/Hep B/Hep C Screening (CTL99HV)
- Autoantibodies (CTL99AA)
- 4-hour MMTT (CTL99M4)
- EBV/CMV Serology (CTL99VS)
- EBV PCR (CTL99PC)

2. Barcode Labels

- 4 Chemistries (CHEM)
- 4 HIV/Hep B/Hep C (SERO)
- 4 Autoantibodies (BAA)
- 25 4-hour MMTT (MMT4)
- 4 EBV/CMV Serology (VIRST)
- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 2.6 ml SSG clotting activator tube
- 1 x 2 ml EDTA lavender top tube

- 1 x 2ml EDTA tube
- 1 x 4 ml plain red top tube
- 1 x 4 ml plain red top tube
- 11 x 1.2 ml EDTA tube
- 11 x 1.2 gray top tubes
- 1 x 2 ml EDTA tube
- 1 x 4ml plain red top tube

B. Specimen Shipment

- 24 x 1.8 ml cryovial
- 1 x 2 ml amber vial
- 1 x 4 ml cryovial
- Collection tube

4. Activities to be completed

- Urine pregnancy test
- Physical Examination/history
- 4-hour MMTT
- PPD test

5. Labs to be drawn

- CBC with diff **ANALYSIS AT LOCAL LAB**
- Chemistries
- HIV/Hep B/Hep C
- 4-hour MMTT (glucose and C-peptide)
- Serum for Autoantibodies
- EBV PCR
- EVB/CMV Serology

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit

7. Mechanistic Specimens

- **REFER TO ASSIGNED SCHEDULE OF ASSESSMENTS AND VISIT CHECKLIST**

CHAPTER 6 BASELINE VISIT

1. Overview

At the baseline study visit, the lab results from the screening visit, the results from the MMTT, and the information from the screening and baseline data collection forms will be reviewed to assess whether a participant is eligible to be randomized and enrolled in the study. The Principal Investigator should review all results and data for the participant's eligibility prior to randomizing the participant. Participants who do not meet all of the inclusion criteria or have one of the exclusion criteria will be referred back to the attending diabetologist for standard education, treatment, and care. Participants not eligible for the Trial may also be given the opportunity to participate in another TrialNet study, if one is available.

2. Initial Study Drug Administration

Once the participant is randomized, he/she will receive an IV infusion of either abatacept or placebo. The participant **does not** need to be fasting prior to this infusion. ***The initial treatment will be given at the end of the Baseline visit, which should take place within 100 days from the day of diagnosis and within 37 days of the screening MMTT.*** Following randomization, the local pharmacy at the TrialNet clinical site should be contacted and given the participant's Randomization Number. The local pharmacy will then prepare the IV infusion to be administered to the participant. The preparation of this IV infusion will be the same regardless of the whether the participant is receiving abatacept or placebo. Refer to Pharmacy Manual for study drug administration.

TRIAL BASELINE VISIT SUMMARY (INFUSION 1)

1. Forms

A. Forms to be completed prior to the initiation of study procedures:

- Volunteer Understanding Assessment *(if not completed at Screening Visit)* **PRIOR TO SIGNING INTERVENTION INFORMED CONSENT**
- TrialNet Intervention Informed Consent
- TrialNet Intervention Assent *(if applicable)*
- Research Subject Authorization Form (RSAF) *(if applicable)*

B. Case Report Forms:

- Family History Form (CTL04)
- Eligibility Form (CTL05)
- Randomization Form (CTL06)
- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications (CTL10)
- Visit Form (CTL12)
- Adverse Event (CTL13) *(if applicable)*

C. Specimen Transmittal Forms:

- CBC with differentials (CTL99CB)
- Chemistry (CTL99CH)
- HbA1c (CTL99HB)
- EBV/CMV PCR (CTL99PC) (only drawn for individuals who are seronegative)
- Other Serology (CTL99SR)

2. Barcode Labels

- 4 Chemistries (CHEM)
- 4 EBV/CMV PCR (VIRVL)
- 4 HbA1c (HbA1c)
- 4 Other Serology (SRLG)

3. Supplies

A. Blood Collection

- 2 x 2 ml EDTA tubes
- 1 x 2 ml EDTA
- 1 x 1.2 ml EDTA tubes
- 1 x 4 ml plain red top tubes
- 1 x 3 ml plain red top tubes

B. Specimen Shipment

- Collection tube for EBV PCR and HbA1c
- 1 x 1.8 ml cryovials
- 1 x 2 ml amber vial

4. <u>Activities to be completed</u>

- Medical history taken **PRIOR TO RANDOMIZATION**
- Physical examination taken **PRIOR TO RANDOMIZATION**
- Urine pregnancy test **PRIOR TO RANDOMIZATION**
- Randomization number obtained from web randomization system *(If eligible)*
- First infusion of abatacept or placebo

5. <u>Labs to be drawn</u>

- CBC with diff **ANALYSIS AT LOCAL LAB**
- Chemistries
- EBV/CMV PCR
- HbA1c
- Other Serology

6. <u>Mechanistic Specimens</u>

- **REFER TO ASSIGNED SCHEDULE OF ASSESSMENTS AND VISIT CHECKLIST**

7. Make sure source documents have been completed for the visit.

CHAPTER 7 STUDY FOLLOW-UP VISITS

Overview

After the Baseline visit, participants will return 14 days (+/- 3 days) and 28 days (+/- 3 days) after the initial infusion. Then the participants will return every 28 days (+/- 7 days) for two years. It is anticipated that a participant would have approximately 27 outpatient visits after the baseline visit over the two year study period.

At each clinic visit, participants will see their diabetologists, CDE, etc. to review blood sugar control and hypoglycemic episodes. Each clinical site will have a Diabetes Educator to assist participants in their diabetes care. In addition to diabetes care, they will review issues related to development of potential side effects of immunosuppression (infections). Routine clinical laboratory tests will be performed (such as CBC with differential, chemistries, C-peptide, HbA1c, EBV viral load, etc.). Autoantibody analysis will be performed at TrialNet central laboratories for all study centers. C-peptide measurements will also be examined by a TrialNet central laboratory.

Laboratory specimens collected at the local clinical sites will be forwarded to appropriate laboratories for analysis. These specimens will be labeled by a study assigned specimen number, the date of collection, and three letters of the participant's choice.

Ideally, all blood draws would be done at the study site. However, if it is inconvenient for a participant to have the blood drawn at the study site, the blood draw may be done at the participant's primary care physician's office or commercial laboratory. The study site will provide instructions to the physician or laboratory for how to process and ship the specimen.

If allowable by blood drawing guidelines and with the participant's permission, samples will also be collected and stored at the NIDDK Repository for later testing. Blood for DNA, T-cells and RNA testing will be stored. These samples will be available for use by investigators within or outside of TrialNet for research related to the development and treatment of type 1 diabetes or related diseases. The utilization of these samples will be subject to NIDDK policies and procedures.

At every visit, the sexual activity of female participants of reproductive age will be re-assessed. If a participant who was previously sexually inactive becomes sexually active, she will be counseled about the need to use a reliable form of birth control. Female participants will also be required to undergo urine pregnancy tests at all visits.

TRIAL DAY 14 (VISIT 1) (INFUSION 2) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- CBC Results (CTL99CB)
- EBV PCR (CTL99PC) – Only for individuals who are seronegative

2. Supplies

A. Blood Collection

- 2 x 2 ml EDTA tube
- 1 x 2ml EDTA tube

3. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

4. Labs to be drawn

- CBC with diff **ANALYSIS AT LOCAL LAB**
- EBV PCR - Only for individuals who are seronegative

5. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit

6. Make sure source documents have been completed for the visit.

TRIAL DAY 28 (VISIT 2) (INFUSION 3) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- Chemistries (CTL99CB)
- EBV PCR (CTL99PC) – Only for individuals who are seronegative

2. Barcode Labels

- 4 EBV PCR (VIRVL)
- 4 Chemistries (CHEM)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes
- 1 x 4 ml plain red top tube

B. Specimen Shipment

- Collection tube for EBV PCR
- 1 x 2 ml amber vial

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

5. Labs to be drawn

- Chemistries
- EBV PCR

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 56 (VISIT 3) (INFUSION 4) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- CBC Results (CTL99CB)
- EBV PCR (CTL99PC) - only drawn for individuals who are seronegative
- HLA (CTL99HL)
- PK Analysis (CTL99PK)

2. Supplies

A. Blood Collection

- 2 x 2 ml EDTA tube
- 1 x 2ml EDTA tube
- 1 X 6ml lavender top tube
- 1 x 5 ml SST

3. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

4. Labs to be drawn

- CBC with diff **ANALYSIS AT LOCAL LAB**
- PK Analysis
- EBV PCR
- HLA

5. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit

6. Make sure source documents have been completed for the visit.

TRIAL DAY 84 (VISIT 4) (INFUSION 5) SUMMARY

SUBJECT NEEDS TO BE FASTING FOR THIS VISIT

Refer to the Physician Orders for this visit to follow the correct order for drawing the blood samples, and administering the MMTT and study drug.

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- CBC Results (CTL99CB)
- Autoantibodies (CLT99AA)
- HbA1c (CTL99HB)
- 2-hr MMTT (CTL99M2)
- PK Analysis (CTL99PK)
- EBV PCR (CTL99PC) - only drawn for individuals who are seronegative

2. Barcode Labels

- 4 Autoantibodies (BAA)
- 4 HbA1c (HbA1c)
- 4 Chemistries (CHEM)
- 17 2-hour MMTT (MMT2)
- 4 EBV PCR (VIRVL)
- 5 PK Analysis (PK)

3. Supplies

A. Blood Collection

- 1 x 2ml EDTA tube
- 2 x 2 ml EDTA tubes
- 8 x 1.2 ml EDTA tubes
- 1 x 2.6 ml SSG clotting activator tube
- 7 x 1.2 ml gray top tubes
- 2 x 5 ml SST

B. Specimen Shipment

- 15 x 1.8 ml cryovials
- Collection tube for EBV PCR
- Collection tube for HbA1c
- 4 x polypropylene tubes

4. **Activities to be completed**

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo
- PK Analysis
- 2-hour Mixed Meal Tolerance Test (MMTT)

5. **Labs to be drawn**

- CBC with differential *(analysis at a local lab)*
- Autoantibodies
- HbA1c
- 2-hr MMTT
- PK Analysis (pre-dose)
- PK Analysis (post-dose)
- EBV PCR - only drawn for individuals who are seronegative

6. **Mechanistic Specimens**

- **REFER TO ASSIGNED SCHEDULE OF ASSESSMENTS AND VISIT CHECKLIST**

7. **Preparation for next visit**

- Remind participant to bring blood glucose and insulin records to next visit.

8. Make sure source documents have been completed for the visit.

TRIAL DAY 112 (VISIT 5) (INFUSION 6) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- Chemistries (CTL99CB)
- PK Analysis (CTL99PK)
- EBV PCR (CTL99PC) – Only for individuals who are seronegative

2. Barcode Labels

- 4 Chemistries (CHEM)
- 5 PK Analysis (PK)
- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 4 ml plain red top tube
- 2 x 5 ml SST
- 1 x 2 ml EDTA tubes

B. Specimen Shipment

- 1 x 2 ml amber vial
- 4 x polypropylene tubes
- Collection tube for EBV PCR

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo
- PK Analysis

5. **Labs to be drawn**

- Chemistries
- PK Analysis (pre-dose)
- PK Analysis (post-dose)
- EBV PCR - only drawn for individuals who are seronegative

6. **Preparation for next visit**

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 140 (VISIT 6) (INFUSION 7) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- EBV PCR (CTL99PC) – Only for individuals who are seronegative

2. Barcode Labels

- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes

B. Specimen Shipment

- Collection tube for EBV PCR

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

5. Labs to be drawn

- EBV PCR - only drawn for individuals who are seronegative

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 168 (VISIT 7) (INFUSION 8) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- CBC Results (CTL99CB)
- EBV PCR (CTL99PC) - only drawn for individuals who are seronegative

2. Barcode Labels

- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 2 x 2ml EDTA tube
- 1 x 2ml EDTA tube

B. Specimen Shipment

- Collection tube for EBV PCR

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

5. Labs to be drawn

- CBC with differential
- EBV PCR - only drawn for individuals who are seronegative

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 196 (VISIT 8) (INFUSION 9) SUMMARY

SUBJECT NEEDS TO BE FASTING FOR THIS VISIT

Refer to the Physician Orders for this visit to follow the correct order for drawing the blood samples, and administering the MMTT and study drug.

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- Chemistries (CTL99CH)
- Autoantibodies (CLT09AA)
- HbA1c (CTL99HB)
- 2-hr MMTT (CTL99M2)
- PK Analysis (CTL99PK)
- EBV PCR (CTL99PC) - only drawn for individuals who are seronegative
- Other serology (CTL99SR)

2. Barcode Labels

- 4 Autoantibodies (BAA)
- 4 HbA1c (HbA1c)
- 4 Chemistries (CHEM)
- 17 2-hour MMTT (MMT2)
- 4 EBV PCR (VIRVL)
- 5 PK Analyisis (PK)
- 4 Other serology (SRLG)

3. Supplies

A. Blood Collection

- 1 x 4ml plain red top tube
- 1 x 2 ml EDTA tubes
- 8 x 1.2 ml EDTA tubes
- 1 x 2.6 ml SSG clotting activator tube
- 7 x 1.2 ml gray top tubes
- 1 x 5 ml SST
- 1 x 3 ml red top tube

B. Specimen Shipment

- 1 x 2ml amber vial
- 16 x 1.8 ml cryovials
- Collection tube for EBV PCR
- Collection tube for HbA1c
- 2 x polypropylene tubes

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo
- PK Analysis
- 2-hour Mixed Meal Tolerance Test (MMTT)

5. Labs to be drawn

- Chemistries
- Autoantibodies
- HbA1c
- 2-hr MMTT
- PK Analysis
- EBV PCR - only drawn for individuals who are seronegative
- Other serology

6. Mechanistic Specimens

- **REFER TO ASSIGNED SCHEDULE OF ASSESSMENTS AND VISIT CHECKLIST**

7. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

8. Make sure source documents have been completed for the visit.

TRIAL DAY 224 (VISIT 9) (INFUSION 10) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- EBV PCR (CTL99PC) – Only for individuals who are seronegative

2. Barcode Labels

- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes

B. Specimen Shipment

- Collection tube for EBV PCR

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

5. Labs to be drawn

- EBV PCR - only drawn for individuals who are seronegative

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 252 (VISIT 10) (INFUSION 11) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- EBV PCR (CTL99PC) – Only for individuals who are seronegative

2. Barcode Labels

- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes

B. Specimen Shipment

- Collection tube for EBV PCR

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

5. Labs to be drawn

- EBV PCR - only drawn for individuals who are seronegative

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 280 (VISIT 11) (INFUSION 12) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- CBC with differential (CTL99CB)
- Autoantibodies (CLT09AA)
- HbA1c (CTL99HB)
- PK Analysis (CTL99PK)
- EBV PCR (CTL99PC) - only drawn for individuals who are seronegative
- Other serology (CTL99SR)

2. Barcode Labels

- 4 Autoantibodies (BAA)
- 4 HbA1c (HbA1c)
- 4 EBV/CMV PCR (VIRVL)
- 5 PK Analysis (PK)
- 4 Other serology (SRLG)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes
- 1 x 2.6 ml SSG clotting activator tube
- 2 x 1.2 ml EDTA tubes
- 1 x 5 ml SST
- 1 x 3 ml plain red top tube

B. Specimen Shipment

- 2 x 1.8 ml cryovials
- Collection tube for HbA1c
- Collection tube for EBV PCR
- 2 x polypropylene tubes

4. **Activities to be completed**

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo
- PK Analysis

5. **Labs to be drawn**

- CBC with differentials (analysis at a local lab)
- Autoantibodies
- HbA1c
- PK Analysis
- EBV PCR - only drawn for individuals who are seronegative
- Other serology

6. **Mechanistic Specimens**

- **REFER TO ASSIGNED SCHEDULE OF ASSESSMENTS AND VISIT CHECKLIST**

7. **Preparation for next visit**

- Remind participant to bring blood glucose and insulin records to next visit.

8. Make sure source documents have been completed for the visit.

TRIAL DAY 308 (VISIT 12) (INFUSION 13) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- Chemistries (CTL99CH)
- EBV PCR (CTL99PC) - only drawn for individuals who are seronegative

2. Barcode Labels

- 4 Chemistries (CHEM)
- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 4 ml plain red top tube
- 1 x 2 ml EDTA tubes

B. Specimen Shipment

- 1 x 2 ml amber vials
- Collection tube for EBV PCR

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

5. Labs to be drawn

- Chemistries
- EBV PCR - only drawn for individuals who are seronegative

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 336 (VISIT 13) (INFUSION 14) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- EBV PCR (CTL99PC) – Only for individuals who are seronegative

2. Barcode Labels

- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes

B. Specimen Shipment

- Collection tube for EBV PCR

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

5. Labs to be drawn

- EBV PCR - only drawn for individuals who are seronegative

6. **Preparation for next visit**

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 364 (VISIT 14) (INFUSION 15) SUMMARY

SUBJECT NEEDS TO BE FASTING FOR THIS VISIT

Refer to the Physician Orders for this visit to follow the correct order for drawing the blood samples, and administering the MMTT and study drug.

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- CBC with differential (CTL99CB)
- Chemistries (CTL99CH)
- Autoantibodies (CLT09AA)
- HbA1c (CTL99HB)
- 2-hr MMTT (CTL99M2)
- PK Analysis (CTL99PK)
- EBV PCR (CTL99PC) - only drawn for individuals who are seronegative
- Other serology (CTL99SR)

2. Barcode Labels

- 4 Chemistries (CHEM)
- 4 Autoantibodies (BAA)
- 4 HbA1c (HbA1c)
- 17 2-hour MMTT (MMT2)
- 5 PK Analyisis (PK)
- 4 EBV PCR (VIRVL)
- 4 Other serology (SRLG)

3. Supplies

A. Blood Collection

- 1 x 2ml EDTA tube
- 2 x 2 ml EDTA tubes
- 1 x 4 ml plain red top tube
- 1 x 2.6 ml SSG clotting activator tube
- 8 x 1.2 ml EDTA tubes
- 7 x 1.2 ml gray top tubes
- 1 x 5 ml SST
- 1 x 3 ml plain red top tube

B. Specimen Shipment

- 1 x 2 ml amber vial
- 16 x 1.8 ml cryovials
- Collection tube for EBV PCR
- Collection tube for HbA1c
- 2 x polypropylene tubes

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo
- PK Analysis
- 2-hour Mixed Meal Tolerance Test (MMTT)

5. Labs to be drawn

- CBC with differential
- Chemistries
- Autoantibodies
- HbA1c
- 2-hr MMTT
- PK Analysis
- EBV PCR - only drawn for individuals who are seronegative
- Other serology

6. Mechanistic Specimens

REFER TO ASSIGNED SCHEDULE OF ASSESSMENTS AND VISIT CHECKLIST

7. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

8. Make sure source documents have been completed for the visit.

TRIAL DAY 392 (VISIT 15) (INFUSION 16) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- EBV PCR (CTL99PC) – Only for individuals who are seronegative

2. Barcode Labels

- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes

B. Specimen Shipment

- Collection tube for EBV PCR

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

5. Labs to be drawn

- EBV PCR - only drawn for individuals who are seronegative

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 420 (VISIT 16) (INFUSION 17) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- EBV PCR (CTL99PC) – Only for individuals who are seronegative

2. Barcode Labels

- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes

B. Specimen Shipment

- Collection tube for EBV PCR

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

5. Labs to be drawn

- EBV PCR - only drawn for individuals who are seronegative

6. **Preparation for next visit**

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 448 (VISIT 17) (INFUSION 18) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- CBC with differential (CTL99CB)
- Chemistries (CTL99CH)
- Autoantibodies (CLT09AA)
- HbA1c (CTL99HB)
- PK Analysis (CTL99PK)
- EBV PCR (CTL99PC) - only drawn for individuals who are seronegative

2. Barcode Labels

- 4 Chemistries (CHEM)
- 4 Autoantibodies (BAA)
- 4 HbA1c (HbA1c)
- 5 PK Analyisis (PK)
- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 2ml EDTA tube
- 2 x 2 ml EDTA tubes
- 1 x 4 ml plain red top tube
- 1 x 2.6 ml SSG clotting activator tube
- 1 x 1.2 ml EDTA tubes
- 1 x 5 ml SST

B. Specimen Shipment

- 1 x 2 ml amber vial
- 1 x 1.8 ml cryovials
- Collection tube for EBV PCR
- Collection tube for HbA1c
- 2 x polypropylene tubes

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo
- PK Analysis

5. Labs to be drawn

- CBC with differential
- Chemistries
- Autoantibodies
- HbA1c
- PK Analysis
- EBV PCR - only drawn for individuals who are seronegative

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 476 (VISIT 18) (INFUSION 19) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- EBV PCR (CTL99PC) – Only for individuals who are seronegative

2. Barcode Labels

- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes

B. Specimen Shipment

- Collection tube for EBV PCR

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

5. Labs to be drawn

- EBV PCR - only drawn for individuals who are seronegative

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 504 (VISIT 19) (INFUSION 20) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- EBV PCR (CTL99PC) – Only for individuals who are seronegative

2. Barcode Labels

- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes

B. Specimen Shipment

- Collection tube for EBV PCR

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

5. Labs to be drawn

- EBV PCR - only drawn for individuals who are seronegative

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

6. Make sure source documents have been completed for the visit.

TRIAL DAY 532 (VISIT 20) (INFUSION 21) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- EBV PCR (CTL99PC) – Only for individuals who are seronegative

2. Barcode Labels

- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes

B. Specimen Shipment

- Collection tube for EBV PCR

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

5. Labs to be drawn

- EBV PCR - only drawn for individuals who are seronegative

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 560 (VISIT 21) (INFUSION 22) SUMMARY

SUBJECT NEEDS TO BE FASTING FOR THIS VISIT

Refer to the Physician Orders for this visit to follow the correct order for drawing the blood samples, and administering the MMTT and study drug.

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- CBC with differential (CTL99CB)
- Chemistries (CTL99CH)
- Autoantibodies (CLT09AA)
- HbA1c (CTL99HB)
- 2-hr MMTT (CTL99M2)
- EBV PCR (CTL99PC) - only drawn for individuals who are seronegative
- Other serology (CTL99SR)

2. Barcode Labels

- 4 Chemistries (CHEM)
- 4 Autoantibodies (BAA)
- 4 HbA1c (HbA1c)
- 17 2-hour MMTT (MMT2)
- 4 EBV PCR (VIRVL)
- 4 Other serology (SRLG)

3. Supplies

A. Blood Collection

- 1 x 2ml EDTA tube
- 2 x 2 ml EDTA tubes
- 1 x 4 ml plain red top tube
- 1 x 2.6 ml SSG clotting activator tube
- 8 x 1.2 ml EDTA tubes
- 7 x 1.2 ml gray top tubes
- 1 x 3 ml plain red top tube

B. Specimen Shipment

- 1 x 2 ml amber vial
- 16 x 1.8 ml cryovials
- Collection tube for EBV PCR
- Collection tube for HbA1c

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo
- 2-hour Mixed Meal Tolerance Test (MMTT)

5. Labs to be drawn

- CBC with differential
- Chemistries
- Autoantibodies
- HbA1c
- 2-hr MMTT
- EBV PCR - only drawn for individuals who are seronegative
- Other serology

6. Mechanistic Specimens

REFER TO ASSIGNED SCHEDULE OF ASSESSMENTS AND VISIT CHECKLIST

7. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

8. Make sure source documents have been completed for the visit.

TRIAL DAY 588 (VISIT 22) (INFUSION 23) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- EBV PCR (CTL99PC) – Only for individuals who are seronegative

2. Barcode Labels

- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes

B. Specimen Shipment

- Collection tube for EBV PCR

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

5. Labs to be drawn

- EBV PCR - only drawn for individuals who are seronegative

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 616 (VISIT 23) (INFUSION 24) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- EBV PCR (CTL99PC) – Only for individuals who are seronegative

2. Barcode Labels

- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes

B. Specimen Shipment

- Collection tube for EBV PCR

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

5. Labs to be drawn

- EBV PCR - only drawn for individuals who are seronegative

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 644 (VISIT 24) (INFUSION 25) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- CBC with differential (CTL99CB)
- Chemistries (CTL99CH)
- Autoantibodies (CLT09AA)
- HbA1c (CTL99HB)
- PK Analysis (CTL99PK)
- EBV PCR (CTL99PC) - only drawn for individuals who are seronegative

2. Barcode Labels

- 4 Chemistries (CHEM)
- 4 Autoantibodies (BAA)
- 4 HbA1c (HbA1c)
- 5 PK Analyisis (PK)
- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 2ml EDTA tube
- 2 x 2 ml EDTA tubes
- 1 x 4 ml plain red top tube
- 1 x 2.6 ml SSG clotting activator tube
- 1 x 1.2 ml EDTA tubes
- 1 x 5 ml SST

B. Specimen Shipment

- 1 x 2 ml amber vial
- 1 x 1.8 ml cryovials
- Collection tube for EBV PCR
- Collection tube for HbA1c
- 2 x polypropylene tubes

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo
- PK Analysis

5. Labs to be drawn

- CBC with differential
- Chemistries
- Autoantibodies
- HbA1c
- PK Analysis
- EBV PCR - only drawn for individuals who are seronegative

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 672 (VISIT 25) (INFUSION 26) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- EBV PCR (CTL99PC) – Only for individuals who are seronegative

2. Barcode Labels

- 4 EBV PCR (VIRVL)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes

B. Specimen Shipment

- Collection tube for EBV PCR

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Study drug administration - abatacept or placebo

5. Labs to be drawn

- EBV PCR - only drawn for individuals who are seronegative

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL DAY 700 (VISIT 26) (INFUSION 27) SUMMARY

1. Forms

A. Case Report Forms:

- Study Drug Administration Form (CTL07)
- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Tetanus Administration Form (CTL17)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- Tetanus/Flu serology (CTL99TF)

2. Barcode Labels

- 4 Flu/Tetanus (FLUT)

3. Supplies

A. Blood Collection

- 1 x 3 ml red top tube

B. Specimen Shipment

- 1 x 1.8 ml cryovial

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- Tetanus administration

5. Labs to be drawn

- Pre-immunization tetanus sample

6. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

7. Make sure source documents have been completed for the visit.

TRIAL MONTH 24 (VISIT 27) SUMMARY

SUBJECT NEEDS TO BE FASTING FOR THIS VISIT

1. Forms

A. Case Report Forms:

- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- CBC with differential (CTL99CB)
- Chemistries (CTL99CH)
- Autoantibodies (CLT09AA)
- HbA1c (CTL99HB)
- 4-hr MMTT (CTL99M4)
- PK Analysis (CTL99PK)
- Tetanus/Viral Flu (CTL99TF)
- Other serology (CTL99SR)

2. Barcode Labels

- 4 Chemistries (CHEM)
- 4 Autoantibodies (BAA)
- 4 HbA1c (HbA1c)
- 25 4-hour MMTT (MMT4)
- 5 PK Analysis (PK)
- 4 Flu/Tetanus (FLUT)
- 4 Other serology (SRLG)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes
- 1 x 4 ml plain red top tube
- 1 x 2.6 ml SSG clotting activator tube
- 12 x 1.2 ml EDTA tubes
- 11 x 1.2 ml gray top tubes
- 1 x 5 ml SST
- 2 x 3 ml red top tube

B. Specimen Shipment

- 1 x 2 ml amber vial
- 25 x 1.8 ml cryovials
- Collection tube for HbA1c

- 2 x polypropylene tubes

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- 4-hour Mixed Meal Tolerance Test (MMTT)
- PK Analysis
- Post-immunization tetanus serology

5. Labs to be drawn

- CBC with differential
- Chemistries
- Serum for Autoantibodies
- HbA1c
- 4-hr MMTT (Glucose and c-peptide)
- PK Analysis
- Other serology
- Post-immunization tetanus serology

6. Mechanistic Specimens

REFER TO ASSIGNED SCHEDULE OF ASSESSMENTS AND VISIT CHECKLIST

7. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

8. Make sure source documents have been completed for the visit.

CHAPTER 8 FOLLOW-UP AFTER 27 MONTHS

Participants will be asked to undergo additional follow-up post-treatment for up to two years with a visit every 6 months. Subjects with undetectable levels of C-peptide on the 30-month visit will not undergo any further MMTTs assessments of C-peptide levels at subsequent visits.

TRIAL MONTH 30 (VISIT 28) SUMMARY

SUBJECT NEEDS TO BE FASTING FOR THIS VISIT

Refer to the Physician Orders for this visit to follow the correct order for drawing the blood samples, and administering the MMTT.

1. Forms

A. Case Report Forms:

- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- CBC with differential (CTL99CB)
- Chemistries (CTL99CH)
- Autoantibodies (CLT09AA)
- HbA1c (CTL99HB)
- 2-hr MMTT (CTL99M2)
- Other serology (CTL99SR)

2. Barcode Labels

- 4 Chemistries (CHEM)
- 4 Autoantibodies (BAA)
- 4 HbA1c (HbA1c)
- 17 2-hour MMTT (MMT2)
- 4 Other serology (SRLG)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes
- 1 x 4 ml plain red top tube
- 1 x 2.6 ml SSG clotting activator tube

- 8 x 1.2 ml EDTA tubes
- 7 x 1.2 ml gray top tubes
- 1 x 3 ml red top tube

B. Specimen Shipment

- 1 x 2 ml amber vial
- 16 x 1.8 ml cryovials
- Collection tube for HbA1c

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- 2-hour Mixed Meal Tolerance Test (MMTT)

5. Labs to be drawn

- CBC with differential
- Chemistries
- Autoantibodies
- HbA1c
- 2-hr MMTT
- Other serology

6. Mechanistic Specimens

REFER TO ASSIGNED SCHEDULE OF ASSESSMENTS AND VISIT CHECKLIST

7. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

8. Make sure source documents have been completed for the visit.

TRIAL MONTH 36 (VISIT 29) SUMMARY

SUBJECT NEEDS TO BE FASTING FOR THIS VISIT

Refer to the Physician Orders for this visit to follow the correct order for drawing the blood samples, and administering the MMTT.

1. Forms

A. Case Report Forms:

- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- CBC with differential (CTL99CB)
- Chemistries (CTL99CH)
- Autoantibodies (CLT09AA)
- HbA1c (CTL99HB)
- 2-hr MMTT (CTL99M2)
- Other serology (CTL99SR)

2. Barcode Labels

- 4 Chemistries (CHEM)
- 4 Autoantibodies (BAA)
- 4 HbA1c (HbA1c)
- 17 2-hour MMTT (MMT2)
- 4 Other serology (SRLG)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes
- 1 x 4 ml plain red top tube
- 1 x 2.6 ml SSG clotting activator tube
- 8 x 1.2 ml EDTA tubes
- 7 x 1.2 ml gray top tubes
- 1 x 3 ml red top tube

B. Specimen Shipment

- 1 x 2 ml amber vial
- 16 x 1.8 ml cryovials
- Collection tube for HbA1c

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- 2-hour Mixed Meal Tolerance Test (MMTT)

5. Labs to be drawn

- CBC with differential
- Chemistries
- Autoantibodies
- HbA1c
- 2-hr MMTT
- Other serology

6. Mechanistic Specimens

REFER TO ASSIGNED SCHEDULE OF ASSESSMENTS AND VISIT CHECKLIST

7. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

8. Make sure source documents have been completed for the visit.

TRIAL MONTH 42 (VISIT 30) SUMMARY

SUBJECT NEEDS TO BE FASTING FOR THIS VISIT

Refer to the Physician Orders for this visit to follow the correct order for drawing the blood samples, and administering the MMTT.

1. Forms

A. Case Report Forms:

- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- CBC with differential (CTL99CB)
- Chemistries (CTL99CH)
- Autoantibodies (CLT09AA)
- HbA1c (CTL99HB)
- 2-hr MMTT (CTL99M2)
- Other serology (CTL99SR)

2. Barcode Labels

- 4 Chemistries (CHEM)
- 4 Autoantibodies (BAA)
- 4 HbA1c (HbA1c)
- 17 2-hour MMTT (MMT2)
- 4 Other serology (SRLG)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes
- 1 x 4 ml plain red top tube
- 1 x 2.6 ml SSG clotting activator tube
- 8 x 1.2 ml EDTA tubes
- 7 x 1.2 ml gray top tubes
- 1 x 3 ml red top tube

B. Specimen Shipment

- 1 x 2 ml amber vial
- 16 x 1.8 ml cryovials
- Collection tube for HbA1c

4. Activities to be completed

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- 2-hour Mixed Meal Tolerance Test (MMTT)

5. Labs to be drawn

- CBC with differential
- Chemistries
- Autoantibodies
- HbA1c
- 2-hr MMTT
- Other serology

6. Mechanistic Specimens

REFER TO ASSIGNED SCHEDULE OF ASSESSMENTS AND VISIT CHECKLIST

7. Preparation for next visit

- Remind participant to bring blood glucose and insulin records to next visit.

8. Make sure source documents have been completed for the visit.

TRIAL MONTH 48 (VISIT 31) SUMMARY

SUBJECT NEEDS TO BE FASTING FOR THIS VISIT

Refer to the Physician Orders for this visit to follow the correct order for drawing the blood samples, and administering the MMTT.

1. Forms

A. Case Report Forms:

- Diabetes Management Form (CTL09)
- Concomitant Medications Form (CTL10)
- Visit Form (CTL12)
- Adverse Events Report Form (CTL13) **IF NECESSARY**

B. Specimen Transmittal Forms:

- CBC with differential (CTL99CB)
- Chemistries (CTL99CH)
- Autoantibodies (CLT09AA)
- HbA1c (CTL99HB)
- 2-hr MMTT (CTL99M2)
- Other serology (CTL99SR)

2. Barcode Labels

- 4 Chemistries (CHEM)
- 4 Autoantibodies (BAA)
- 4 HbA1c (HbA1c)
- 17 2-hour MMTT (MMT2)
- 4 Other serology (SRLG)

3. Supplies

A. Blood Collection

- 1 x 2 ml EDTA tubes
- 1 x 4 ml plain red top tube
- 1 x 2.6 ml SSG clotting activator tube
- 8 x 1.2 ml EDTA tubes
- 7 x 1.2 ml gray top tubes
- 1 x 3 ml red top tube

B. Specimen Shipment

- 1 x 2 ml amber vial
- 16 x 1.8 ml cryovials
- Collection tube for HbA1c

4. **Activities to be completed**

- Physical examination/History
- Adverse events assessed
- Urine pregnancy test
- 2-hour Mixed Meal Tolerance Test (MMTT)

5. **Labs to be drawn**

- CBC with differential
- Chemistries
- Autoantibodies
- HbA1c
- 2-hr MMTT
- Other serology

6. **Mechanistic Specimens**

REFER TO ASSIGNED SCHEDULE OF ASSESSMENTS AND VISIT CHECKLIST

7. **Preparation for next visit**

- Remind participant to bring blood glucose and insulin records to next visit.

8. Make sure source documents have been completed for the visit.

CHAPTER 9 RANDOMIZATION

1. Overview

The information from the screening and baseline data collection forms will be reviewed to assess whether a participant is eligible to be randomized in the study. Participants who do not meet all of the inclusion criteria or have one of the exclusion criteria will be referred back to their physician for standard education, treatment, and care. Participants not eligible may be offered the opportunity to participate in another TrialNet study, if one is available.

2. Randomization

Eligible participants who have provided written informed consent and have complied with all the Inclusion Criteria and none of the Exclusion Criteria will be randomized to one of the treatment groups. The participant, the clinical investigator and clinical personnel will be masked to the treatment assignment. Laboratories performing assays for this protocol will be masked as to the treatment assignment and the identity of each subject whose biological material is to be studied. The pharmacist and the TNCC will not be masked.

2.1 Randomization Method

Eligible study participants will be randomized at the clinical sites at the baseline visit, and will be assigned a study randomization number, through the TrialNet Web Randomization System. The subject will receive the initial dose of the study drug via infusion of the assigned study treatment (either CTLA-4 Ig or placebo) at the baseline visit. The randomization method will be stratified by TrialNet study site. Participants will be randomized in a 2:1 ratio (active:placebo) to the two arms of the study.

2.2 Randomization Procedure

When it is time to randomize a participant at the Baseline visit, the study personnel will log into the TrialNet website, using their regular username and password. Then, study personnel will need to log in into the randomization system. A password will be issued to each study personnel involved in randomizing the study participants.

The Coordinating Center will generate a randomization schedule for the study sites. The Randomization Number will be a seven-digit code, where each study participant's code is

unique. The Randomization Number will in no way reflect the treatment group to which the participant has been assigned. After a participant is randomized, the study coordinator will contact the site pharmacist to obtain the study medication

3. Web Randomization System

Before logging into the TrialNet Web Randomization System, ensure the following:

- Participant has reviewed and signed the applicable informed consent
- Participant has completed all screening and baseline procedures.
- Participant meets **all** of the inclusion criteria (answered "Yes" to all questions ***in Section B of the Eligibility Form (CTL05))***.
- Participant has **none** of the exclusion criteria (answered "No" to all questions ***in Section C of the Eligibility Form (CTL05))***.
- ***Screening Form (CTL01), Screening Medical History (CTL02), Visit Form – Baseline (CTL12), Concomitant Medications (CTL10), Diabetes Management (CTL09), and Eligibility Form (CTL05) have*** all been completed for the participant.

If all of these criteria have been met, the participant is eligible for randomization and the TrialNet Web Randomization System should be accessed. The system is operable 24-hours per day, 7 days a week. Refer to Chapter 10 for instructions on using the Web Randomization System.

If the web randomization system is down, contact The Coordinating Center immediately for manual randomization number assignment. Please contact either the CTLA-4 Ig Research Assistant or the CTLA-4 Ig Protocol Manager. If the randomization system is down and you cannot reach anybody at the TrialNet Coordinating Center (weekend, late at night), it is important for you to remember that the randomization numbers are sequential. If the last person randomized at the site was XXXX-003, the next randomization number should be XXXX-004, where XXXX is the four digit site number. The Coordinating center must be informed immediately if this happens by phone and by email. All this must be documented in the Source Documents with all the site efforts to contact the Coordinating Center personnel.

CHAPTER 10 TRIALNET WEB RANDOMIZATION SYSTEM

This chapter contains instructions on performing a mock randomization for certification and randomizing a participant into the Study.

Before you login, make sure you have:

- Your personal specific password to access the Randomization system.
- The participant's five-digit Study Specific Screening ID. (four digits plus a check digit for this study)

1. Performing a MOCK Randomization for Certification

1.1 Log In

- Provide the TNCC with your pass-phrase to access the TrialNet Website system. The TNCC will notify you when your pass-phrase has been activated. *Note: the pass-phrase may be any length and consist of letters and/or numbers, include spaces, and is case sensitive.*

- Once you have received your personal randomization system password and your pass-phrase has been activated, log into the TrialNet Website under your username at: https://www2.diabetestrialnet.org.

- Click on Studies/Active Studies/CTLA4-Ig

- Enter your randomization system password and hit submit.

- You will be in the TrialNet Randomization System. If prompted, please select CTLA-4 Ig and click submit.

- Note that throughout the mock randomization, the banner at the top of the page should say "Overview: [Simulated Site]". If not, contact the TNCC.

1. 2 Enter Screening ID

- Note that the mock randomization web pages are identical to the live randomization system, with the exception that you are assigned to the fictitious site number 9999 with corresponding fictitious screening IDs.

- The "Overview" page contains 4 columns of screening IDs for site number 9999.
    - The first column (Not Eligible) contains participants who were entered into the randomization system but who did not meet all of the eligibility requirements, and thus were not randomized.
    - The second column (Eligible, not enrolled) contains participants who have met all of the eligibility requirements but have not been randomized. This should not happen very often.
    - The third column (Enrolled) contains all randomized participants.

- For the purposes of the mock randomization enter a fake ID like 9912-0 into the space provided. *Note: if you choose to enter the screening ID, you must include the "-" (i.e. 9901-5).* Any ID will work, as long as it has 4 digits, plus a check digit (i.e. nnnn-d). For purposes of the mock randomization, do not enter any screening ids between 8000 and 9000.

1. 3 Confirm Eligibility and Randomize

- Answer the following question (s) :
    - Does the subject meet all of the necessary eligibility criteria for the CTLA-4 Ig Study? Click either Yes or No to the question. In case you answer No, a window will pop out for you to enter an explanation and a second question will appear.
    - Was the subject's eligibility reviewed and approved by the TrialNet Eligibility and Events Committee? If the subject's eligibility was reviewed and approved

by the TrialNet Eligibility and Events Committee the answer will be Yes and the participant can be randomized into the study.

- Once you have answered all of the eligibility questions, click on "Randomize" to randomize the participant.

- If the participant is eligible and the "Save" button is clicked, the participant will NOT be randomized and their screening ID will be placed in the second column (Eligible, not enrolled) of the "Overview" page (refer to number 1.2 above). For the purposes of the mock randomization, click on "Randomize", in order to randomize the participant

- This information will be saved and the participant will be assigned a randomization number, which will appear at the top of the page. Once the participant is randomized, their screening ID will be in the third column (Enrolled) of the "Overview" page (refer to number 1.2 above).

At this point you are certified to randomize subjects. You may continue in the mock system for as long as you like. Mock data will periodically be deleted.

1.4 Log Out

- In order to access the live randomization system, log out of the system by clicking on "Log out" at the top of the page, and log back into the system. Note that when you are in the live randomization system, the banner at the top of the page will NOT say "Overview: [Simulated Site]". *Note: if the system automatically prompts you for a password during the mock randomization, you have been logged out of the system. If you log back in, you will be in the live randomization system if you successfully completed the certification process. If you would like to repeat the mock randomization, please contact the TNCC.*

- Note that any page may be printed by clicking on "Print this page" at the top of the page.

2. Randomizing a Participant into the CTLA4-Ig

2. 1 Log In

- Log into the TrialNet Website under your username and password at https://www2.diabetestrialnet.org
- Click on Studies/Active Studies/CTLA4Ig/Randomization
- Enter your randomization system password and hit submit

2.2 Enter Screening ID

- The "Overview" page contains 3 columns of screening IDs for your site. *Note: the valid screening IDs for your site are located on the Screening Number Log provided by the TNCC.*
    i. The first column (Not Eligible) contains participants who were entered into the randomization system but who did not meet all of the eligibility requirements, and thus were not randomized.
    ii. The second column (Eligible, not enrolled) contains participants who have met all of the eligibility requirements but have not been randomized. This should not happen very often.
    iii. The third column (Enrolled) contains all randomized participants.

- To randomize a new participant, either enter the ID into the space provided or click on the screening ID of that participant listed in column two (Eligible, not enrolled) that you previously entered. *Note: to enter the screening ID, you must include the "-" (i.e. 9901-5).*

- To view a previously randomized participant's randomization number, either click on the screening ID of that participant listed in column three (Enrolled) or enter the ID into the space provided.

2. 3 Confirm Eligibility and Randomize

- Answer the following question(s) :
    - Does the subject meet all of the necessary eligibility criteria for the CTLA-4 Ig Study? Click either Yes or No to the question. In case you answer No, a window will pop out for you to enter an explanation and a second question will appear. **Note:** The Eligibility Form (CTL05) provides a review of all of the inclusion and exclusion criteria for the study and should be completed prior to accessing the web randomization system.
    - Was the subject's eligibility reviewed and approved by the TrialNet Eligibility and Events Committee? If the subject's eligibility was reviewed and approved by the TrialNet Eligibility and Events Committee the answer will be Yes and the participant can be randomized into the study.

- Once you have answered the eligibility questions, click the "Randomize" button to randomize the participant. This information will be saved and the participant will be assigned a randomization number, which will appear at the top of the page. This number must be recorded on the study specific form (CTL06). Once the participant is randomized, their screening ID will be in the third column (Enrolled) of the "Overview" page. A link will be provided that allows the participant's visit schedule to be viewed and printed.

- If the participant is eligible and the "Save" button is clicked, the participant will NOT be randomized and their screening ID will be in the second column (Eligible, not enrolled) of the "Overview" page.

2. 4 Log Out

- Log out of the system by clicking on "Log out" at the top of the page when finished.

Note: If there is no activity in the randomization system during 10 minutes, the randomization system will log out the person automatically.

CHAPTER 11 SCHEDULING AND VISIT INFORMATION

1. Scheduling Participant Visits

All visits should be scheduled Monday through Thursday due to inadequate weekend coverage at the laboratories. Visits on Friday, Saturday or Sunday are discouraged, but allowable on a case-by-case basis, for matters of convenience. These restrictions are in place to ensure that any specimens drawn during a visit can be shipped to the laboratory on the same day. Specimens can only be shipped to the laboratory Monday through Thursday, and not on the day preceding a federal US holiday. There are no exceptions. When scheduling a participant's visit, take into consideration holidays surrounding that visit. **No blood samples are to be shipped the day before a holiday**. In the event of an extenuating circumstance, contact the study Research Assistant for the study at TNCC (contact information on the website). International sites should follow their agreed upon schedule.

2. Visit Windows

After the baseline visit, for the next two infusion visits (visit # 1, # 2), the window is +/- 3 days of the target date. The subsequent infusion visits should be within 7 days on either side of the targeted date to be permissible. Study doses outside of the window will not be made up (i.e. if treatment dose 5, scheduled for day 84 cannot be accomplished between days 77 and 91, this dose will not be given and the next dose will be on day 112 +- 7 days). Further, the clock will not be reset (i.e. if treatment dose 5 is given on day 77 (day 84- 7 day window), treatment dose 6 target date remains day 112). In this way, no one will receive more than 27 study doses (infusions) over a two year period. For the two years of post treatment visits, the visit windows are +/- 2 weeks of the target date.

Below are the permissible visit windows by visit for participants enrolled in the study:

Visit	Type	Window
Screening	Screening	MMTT within 7 days of Screening and at least 21 days from date of diagnosis
Baseline	Infusion	Within 100 days of date if diagnosis and 37 days of Screening MMTT
Visit 1	Infusion	+/- 3 days
Visit 2	Infusion	+/- 3 days
Visit 3	Infusion	+/- 7 days
Visit 4	Infusion	+/- 7 days
Visit 5	Infusion	+/- 7 days
Visit 6	Infusion	+/- 7 days
Visit 7	Infusion	+/- 7 days
Visit 8	Infusion	+/- 7 days
Visit 9	Infusion	+/- 7 days
Visit 10	Infusion	+/- 7 days
Visit 11	Infusion	+/- 7 days
Visit 12	Infusion	+/- 7 days
Visit 13	Infusion	+/- 7 days
Visit 14	Infusion	+/- 7 days
Visit 15	Infusion	+/- 7 days
Visit 16	Infusion	+/- 7 days
Visit 17	Infusion	+/- 7 days
Visit 18	Infusion	+/- 7 days
Visit 19	Infusion	+/- 7 days
Visit 20	Infusion	+/- 7 days
Visit 21	Infusion	+/- 7 days
Visit 22	Infusion	+/- 7 days
Visit 23	Infusion	+/- 7 days
Visit 24	Infusion	+/- 7 days
Visit 25	Infusion	+/- 7 days
Visit 26	Infusion	+/- 7 days
Visit 27	Follow up	+/- 7 days
Visit 28	Follow up	+/- 7 days
Visit 29	Follow up	+/- 7 days
Visit 30	Follow up	+/- 7 days
Visit 31	Follow up	+/- 7 days

3. Visit Schedule

- A participant's visit schedule can be accessed by visiting the following webpage https://www2.diabetestrialnet.org/visit.

- Here you will find the participant's schedule of visit dates, the visit target date and the visit window. It can be downloaded in PDF version and printed.

4. Missed Visits

If a participant misses a scheduled visit, every effort should be made to reschedule the visit within the permissible window period surrounding the original visit date. If the visit is rescheduled within this timeframe, no further actions need to be taken, and the visit should go on as planned. If the visit is not rescheduled within this window, every effort should be made to bring the participant into the clinic as soon as possible. Ideally the participant should come in for the visit, even if they are not going to receive the infusion. This will allow for us to check for any adverse events, etc. If the participant comes into the clinic beyond the allowable visit window, the Missed Visit Form should be completed.

Every effort should be made to contact participants who fail to attend their follow-up visits in order to ensure that they are in satisfactory health and to encourage them to continue with future study follow-up visits. This will entail, at a minimum, three telephone contact attempts and two written attempts with return receipt requests. Research staff at each of the sites is responsible for keeping participant contact information up to date at every study visit. Principal investigators may want to contact the noncompliant participants to encourage them to come into the clinic even if they no longer wish to receive infusions.

5. Changing Study Status

5.1 Inactive Status

In the event that a participant is unable or unwilling to continue making future visits then the participant is declared inactive. Every effort should be made to encourage all participants to continue making follow-up visits. If a participant is declared inactive, the Change of Status Form (CTL15) must be completed. If a participant withdraws consent, the Change of Status Form (CTL15) must be completed and the participant is declared inactive.

5. 2 Reactivation into the Study

In some circumstances, a participant may enter inactive status and be unwilling or unable to return to the study clinic for future visits. It is hoped that at a later date this participant may decide to once again resume active participation in the study. If the participant desires to return to the clinic for future follow-up visits, he/she should be allowed and encouraged to do so. The participant should be allowed to return to active participation regardless of the length of the inactivity period, as long as the study is still active. If a participant who is inactive decides to become reactivated, the Change of Status Form (CTL15) must be completed. If a participant withdrew consent and became inactive but later wishes to return to active participation, then the most recent version of the consent must be signed and the Change of Status Form (CTL15) must be completed.

This form is completed for *every* change of status that occurs. Therefore, if a participant becomes inactive and then reactivates at a later date, two separate forms should be completed. Completion of this form allows The Coordinating Center and the clinical site to document and track that a participant is no longer actively participating in the study and, therefore, not to expect any forms or other information. Conversely, if a participant is becoming active again following a period of inactivity, the completion of this form allows The Coordinating Center and the clinical site to document and track that a participant is once again participating in the study and to begin expecting forms and other information from that participant according to the study schedule.

CHAPTER 12 IMMUNIZATIONS

1. Overview

An important aspect of this study is the planned immunizations with killed flu and tetanus vaccines. On the other hand, although no data are available regarding the effects of vaccination in patients receiving abatacept therapy, vaccination with live vaccines is not recommended. The possibility exists for abatacept to affect host defenses against infections since the cellular immune response may be altered. Therefore concurrent use of live vaccines within 3 months of abatacept therapy may result in reduced efficacy of vaccine. All other vaccines are allowed.

2. Tetanus Immunization

The participants in this study will have had a previous series of tetanus shots as part of normal medical care. Subjects who are 18 months or more from their previous tetanus immunization will receive a tetanus immunization at visit 26.

At visit 26, the participants will have a pre-immunization blood draw and then receive a tetanus immunization with follow-up blood draw assessing immune response at visit 27. A Pharmacy Vaccine Request Form is provided on the TrialNet Website.

The shot is given intramuscularly. There may be pain and soreness at the site of the injection and possibly a low-grade fever that could develop 24 to 72 hours after the immunization. These could be treated with anti-pyretics and mild analgesics (e.g. acetaminophen and aspirin).

3. Killed flu vaccine immunization

At any time after the first month of the study, subjects will receive their annual clinically indicated killed flu vaccine at the appropriate time of the year. Response to these immunizations will be determined through analysis of pre- and 4 weeks post-dose samples.

October or November is the best time to get vaccinated, but you can still get vaccinated in December and later. Flu season can begin as early as October and last as late as May. The flu season may differ for international sites.

The killed flu vaccine shots are given subcutaneously, in the arm. Different side effects can be associated with the flu shot. Some minor side effects that could occur are

- Soreness, redness, or swelling where the shot was given
- Fever (low grade)
- Aches

If these problems occur, they begin soon after the shot and usually last 1 to 2 days. Almost all people who receive influenza vaccine have no serious problems from it. However, on rare occasions, flu vaccination can cause serious problems, such as severe allergic reactions.

4. Emergency Vaccination

If a subject requires an emergency vaccination of any type, the site staff should be alerted as soon as possible.

For the tetanus, if a subject receives the vaccination outside of the study, the post-vaccination tetanus serology should be drawn at the next study visit that is at least 30 days from the date of the vaccination.

5. List of contraindicated vaccines

The following is a list of contraindicated vaccines in immunosuppressed patients:

- Measles, Mumps, Rubella (MMR)
    - MMR may be given to close household contacts

- Varicella –
    - Close household contacts may receive the vaccine as risk of disease from community-acquired virus greater than that associated with vaccine

- Poliomyelitis –
    - Oral polio only – including vaccination of close household contacts
    - IPV ok for patient and close household contacts

- Yellow Fever

- Typhoid – oral, live attenuated
    - IM polysaccharide vaccine ok

- Smallpox –
    - including vaccination of close household contacts

- Flumist – nasal spray only, including use of close household contacts
    - IM flu vaccine is ok for subjects and close household contacts.)

- BCG – for TB

- Rotavirus

- Zoster vaccine
    - Live attenuated virus vaccine

An updated list of vaccines licensed for use in the United States is provided at the following link to the TrialNet website ("Study Manual of Operations" folder in CTLA-4 Ig documents section):

https://www.diabetestrialnet.org/S_CTLA4IG/Doc.cgi?Folder=3Sb1v3AtXLN4c

CHAPTER 13 REPORTS

This chapter contains descriptions of the reports implemented in the Trial. Examples of these reports are provided in Appendix G.

1. Eligibility Report

The Eligibility Report is a one-page summary of key laboratory results and other participant information related to study eligibility. It is available on the TrialNet Website under the Clinical Site's page and is generated when the Screening Form (CTL01), Screening Medical History Form (CTL02), Specimen Transmittal Forms, and screening lab results have been received by the TNCC.

2. Lab Results

Lab results are available on the TrialNet Website under the Clinical Site's page. The file is a PDF and the results are organized by Screening ID Number and Visit Number. The normal ranges for the lab tests are also included. Contact the Protocol RA with questions.

3. Visit Schedule

- The participant's visit schedule can be accessed at the following link: https://www2.diabetestrialnet.org/visit

- Here you will find the participant's schedule of visit dates, the visit target date and the visit window. It can be downloaded in PDF version and printed.

CHAPTER 14 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

ALL adverse events (Grade 1 and greater), whether observed by the investigator, reported by the participant, or from other means, will be recorded on the Source documents. Adverse Events not related to hypo or hyperglycemia that are grade 2 or higher will be reported on the Adverse Event Report Form (CTL13) and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v.3). Refer to the Safety Monitoring and Adverse Event Reporting Binder distributed in January 2007 for more information.

Other study specific forms are:

- TrialNet MedWatch Form (CTL SA): to be completed in case of a Serious Adverse Event
- the Mortality Event Form (CTL13M): to be completed in case of death
- Pregnancy Confirmation Form (CTL14)
- Pregnancy Outcome Report (CTL14R)

The NCI CTCAE for grading adverse events and the TrialNet Adverse Event Monitoring Plan are both available on the front page of the TrialNet website under the heading Adverse Event Reporting and Monitoring.

CHAPTER 15 PROTOCOL ADHERENCE

This section contains specific information about participant protocol adherence requirements. This includes information on expected adherence to the visit schedule as well as the study medication. The section also includes the details of specific protocol deviations and actions that need to be taken to address these deviations.

1. Major Protocol Deviations

This section provides specific examples of protocol deviations and what actions need to be taken to address these deviations. Every effort should be made to ensure that no protocol deviations occur. If any major deviations do occur, the Major Protocol Deviation Form (CTL21) needs to be completed.

Examples of Major Protocol Deviations

The following list (not meant to be exhaustive) provides examples of other major protocol deviations that would require the completion of the Major Protocol Deviation Form (CTL21):

- Ineligible subject randomized into the study
- Study Medication/Pharmacy error

CHAPTER 16 PROCEDURES TO TRANSFER PARTICIPANTS

This chapter contains instructions for temporarily and permanently transferring participants between sites.

1. Procedures for Temporary Transfer of Participants

The following are procedures for transferring participants from their primary site (originating site) to a secondary site (new site to where participant is being transferred). **Note:** Both sites should be aware of their institutions requirements before proceeding and the secondary site MUST have current IRB approval and full TrialNet certification.

1) The Protocol RA should be notified ***prior*** to initiating any participant transfers.

2) The transferring participant must sign the secondary site's Informed Consent Form before this site may conduct any study-related procedures.

3) The primary site must complete a Participant Transfer Notification Form.

4) The primary site must forward a copy of the participant's study file including copies of all available source documents and completed case report forms to the secondary site.

5) The secondary site must record the primary site's Site Number, and Screening ID Number and Letters assigned to the transferring participant by the primary site, on ALL case report forms and specimen transmittal forms completed for this participant. *Note: The primary site coordinator will receive all data form edits for this participant and will be responsible for coordinating the resolution of edits.*

6) To ensure appropriate reimbursement, the secondary site must indicate on the CTL12 (Visit Form) that the visit is occurring at a site other than the primary site (A.3) and record the secondary Site Number for reimbursement (A.3.a).

7) Both sites must maintain all original documents for visits that take place at their respective site.

8) Both site coordinators must note the transfer in the transferring participant's study file.

9) Copies of all available source documents, case report forms, and specimen transmittal forms completed at the secondary site must be sent to the primary site.

10) If the participant is scheduled to undergo an infusion visit at the secondary site, perform the following:

a) Both site coordinators must inform their pharmacists of the participant transfer.

b) The TNCC will coordinate communication between the primary and secondary site coordinators, and between the pharmacists, to review the transfer process.

c) The primary site pharmacist must fax a copy of the Randomization and Drug Dispensing Form for the transferring participant to the secondary site pharmacist. THIS FORM CONTAINS CONFIDENTIAL INFORMATION AND MUST BE TRANSFERRED BETWEEN PHARMACISTS WITHOUT STUDY PERSONNEL INVOLVEMENT.

2. Procedures for Permanent Transfer of Participants

The following are procedures for transferring participants from their primary site (originating site) to a secondary site (new site to where participant is being transferred). **Note:** Both sites should be aware of their institutions requirements before proceeding and the secondary site MUST have current IRB approval and full certification.

1) The Protocol RA should be notified ***prior*** to initiating any participant transfers.

2) The transferring participant must sign the secondary site's Informed Consent Form before this site may conduct any study-related procedures.

3) The primary site must complete a Permanent Participant Site Transfer Form (CTL20) to ensure appropriate reimbursement and distribution of data form edits and lab results.

4) The primary site must forward a copy of the participant's study file including copies of all available source documents and completed case report forms to the secondary site.

5) Both sites must maintain all original documents for visits that take place at their respective site.

6) Both site coordinators must note the transfer in the transferring participant's study file.

7) If the participant is scheduled to undergo an infusion visit at the secondary site, perform the following:

    a) Both site coordinators must inform their pharmacists of the participant transfer.

    b) The TNCC will coordinate communication between the primary and secondary site coordinators, and between the pharmacists, to review the transfer process.

    c) The primary site pharmacist must fax a copy of the Randomization and Drug Dispensing Form for the transferring participant to the secondary site pharmacist. THIS FORM CONTAINS CONFIDENTIAL INFORMATION AND MUST BE TRANSFERRED BETWEEN PHARMACISTS <u>WITHOUT STUDY PERSONNEL INVOLVEMENT</u>.

CHAPTER 17 BLOOD GLUCOSE MONITORS

1. Blood Glucose Monitors that can be used on CTLA-4Ig Infusion Days

Blood Glucose Monitors that do <u>not</u> use GDH-PQQ strips and can be used on CTLA4-Ig infusion days:

- Lifescan
- One Touch Basic
- **One Touch Ultra 2 (provided by TrialNet to participants in study)**
- One Touch Ultra Smart

Bayer

- Ascensia/ Contour
- Ascensia/ Breeze 2

Abbott

- **Precision Xtra (uses GDH-NAD; meter tests for glucose and ketones)**

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2. Blood Glucose Monitors that should NOT be used on CTLA4-Ig Infusion Days

Blood Glucose Monitors that use GDH-PQQ strips (*should not be used on CTLA4-Ig infusion days*):

Roche

- Accu-Chek Active
- Accu-Chek Advantage
- Accu-Chek Aviva
- Accu-Chek Compact Plus

Abbott

- Free Style
- Free Style Flash
- Free Style Freedom
- FreeStyle Lite

CHAPTER 18 SUPPLIES

Case Report Forms (CRFs), Specimen Transmittal Forms (STFs), Participant Binders (pre-filled with all visit checklists, dividers, and CRFs and STFs, barcode labels, and other study supplies are provided to all study sites by the TrialNet Coordinating Center (TNCC). Supplies obtained directly from The Coordinating Center are requested using the TrialNet Supply Order System and will be processed by TNCC staff. Sites will receive an initial quantity of screening supplies just prior to receiving approval to begin screening. Generally, sites should maintain a 3-month inventory or longer, sufficient for study needs. This is to avoid frequent reordering of supplies.

1. Ordering Clinical Supplies

A central supplies distributor will be responsible for processing orders of clinical supplies for blood collections and shipments. TNCC, through its subcontractor Fisher Bioservices, implemented a web based online order system for all supplies. "Authorized users", those individuals responsible for study supplies at the site, are provided with a login and password for the web order system. Webcast training on use of the web order system is provided by the TNCC.

2. Authorized Users

Only staff at your site that have been authorized to submit orders will be issued a user account (login and password). All Study and Trial Coordinators are authorized users when the site receives site certification from TrialNet. The Study or Trial Coordinator wishing to request additional user accounts for staff at their site should email a request to TNOrders@biostat.bsc.gwu.edu at the TNCC with "Request SOS User" in the subject line. The request should identify the position or role (e.g., research staff) and provide the full name and email address of the new user.

3. TrialNet Supply Order System "SOS" (Web Application)

The website address for the TrialNet Supply Order System SOS is https://www.fisherbio.com/client/bsdweb/trialnet/Login.asp.

The website can also be accessed via a link on the TrialNet website at **TrialNet Studies Area - Order Clinical Supplies Online** https://www.fisherbio.com/client/bsdweb/trialnet/Login.asp..

Technical support for problems on using the web order system is available. A User Manual may also be downloaded from the above website address.

CHAPTER 19 REIMBURSEMENT

This chapter describes reimbursement for protocol-related activities by the TrialNet Coordinating Center. Reimbursement is according to the NIDDK approved reimbursement schedule for the Trial. Reimbursement is provided for:

- Local laboratory services
- Local medical services
- Local pharmacy services
- Other services
- Study costs

Rates vary for Clinical Centers with and without a GCRC, and International Sites. Refer to the TrialNet Fact Sheet of Reimbursement located on the TrialNet website for more information.

1. Reimbursement Schedule

The TrialNet Clinics will be paid for their screening, enrollment, and follow-up of study participants. NIDDK approved reimbursement schedules are posted on the TrialNet website. Payments issued to the Clinical Centers and Major Affiliate Sites are based on complete/accurate forms submitted to the GWU TNCC. All payments will be made in United States dollars. Payments should be generated and mailed within 30 days of the close of the payment period (see Fact Sheet for Reimbursement for details on payment periods). An Invoice Report and a detailed listing of services being reimbursed will be provided to the sites along with the payment.

Reimbursements for all components of a visit are made to the site that completed the visit. All applicable Case Report Forms have a place for recording the Site Number for reimbursement. This number is a unique number to identify the institution where the visit took place.

Appendix A. Volunteer Understanding Quiz Key

CTLA-4 Ig (Abatacept) Study
VOLUNTEER UNDERSTANDING ASSESSMENT
KEY

Screening ID: __ __ __ __ - __ Participant Letters: __ __ __

Volunteer's Understanding Assessment is based on the information that has been presented to you regarding this clinical research study. All of the questions are based on this information. The purpose of this survey is to be sure you know the details of this clinical research study before you agree to be part of it. After you have finished the survey, the research study team will go over the answers with you. The research study team will be sure to discuss any answers that were incorrect, because it is important to us that you understand the study.

Date that survey was completed: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

Put an "X" or a check in the box next to the best answer(s) to each question.
You may take as much time as you want to answer these questions.

1. The reason I am being asked to be in this research study is:
   - ☒ 1 I have recently been diagnosed with type 1 diabetes
   - ☐ 2 I am at high risk for developing type 1 diabetes
   - ☐ 3 I have recently been diagnosed with type 2 diabetes
   - ☐ 4 I do not know why I am being asked to be in this research study

2. The reason for doing this research study is to see:
   - ☐ 1 If giving experimental treatment *before* type 1 diabetes starts will keep a person from getting type 1 diabetes
   - ☒ 2 If giving experimental treatment within 12 weeks *after* type 1 diabetes starts will help my insulin producing cells work longer by keeping them from being destroyed
   - ☐ 3 If testing my blood sugar more frequently will keep my type 1 diabetes under control
   - ☐ 4 I do not know a reason for doing this study

3. If I decide to be in this research study, I will come to a study site for:
   - ☐ 1 One year
   - ☒ 2 Two years during the treatment phase and up to 2 more years for additional follow-up
   - ☐ 3 Three years
   - ☐ 4 I do not know

4. If I decide to be in this research study, I will receive study drug or placebo infusions:
   - ☒ 1 Three times in the first month, then every four weeks (28 days) for 2 years
   - ☐ 2 On the first of every month for 2 years
   - ☐ 3 Three times in the first month, then every four weeks (28 days) for 4 years

5. If I decide to be in this research study, visits will be made to the study site *(check all that apply)*:
   - ☒ 1 For infusion visits for 2 years
   - ☒ 2 At the end of the first 2 years, I will have follow up visits every 6 months for up to two more years
   - ☐ 3 At the end of the first 2 years, I will have follow up visits every 28 days for up to two more years

6. If I agree to be in this research study, I will have to *(check all that apply)*:
   - ☒ 1 Let my study team know about any health problems that occur whether or not I think they are important because I am in the study
   - ☒ 2 Stay in the treatment group I am assigned to until the research study ends
   - ☒ 3 Keep all appointments at the clinic
   - ☐ 4 I do not know

7. My assignment to a treatment group will be random. This means:
   - ☒ 1 I will have a 2 out of 3 chance of getting the medicine and a 1 out of 3 chance of getting the placebo (A placebo is a "pretend" medicine that looks like the real medicine, but is not active)
   - ☐ 2 I can choose which treatment group I want to be in
   - ☐ 3 The doctor decides which treatment group I will be in
   - ☐ 4 I will be put in the treatment group that is best for me to be in
   - ☐ 5 I am not sure of how I will be assigned to a treatment group

8. My participation in this research study is voluntary. This means:
   - ☐ 1 I must stay in this research study until the entire research study ends
   - ☐ 2 I can choose to not be in this research study or to stop being in this research study at any time, but I will not get as good of diabetes care if I do
   - ☒ 3 I can choose to not be in this research study or to stop being in this research study at any time and no one will be mad at me, I will still receive the same diabetes care
   - ☐ 4 I do not know what voluntary means

9. The risks of being in this research study may include *(check all that apply)*:
   - ☒ 1 Developing headaches, dizziness or high blood pressure during the infusion
   - ☒ 2 A higher risk of getting certain infections
   - ☐ 3 Worsening of my blood sugar control
   - ☐ 4 There are no risks to being in this research study

10. The guaranteed benefits of being in this research study include *(check all that apply)*:
    - ☐ 1 I will not need to take insulin anymore
    - ☒ 2 There are no guaranteed benefits to being in this research study
    - ☐ 3 I will not need to check my blood sugar as frequently
    - ☐ 4 I will no longer have diabetes

11. If I decide to be in this research study, I will have to pay for *(check all that apply)*:
    - ☐ 1 The procedures and tests that will be required
    - ☐ 2 The study medicines I will be taking
    - ☒ 3 My diabetes treatment supplies (e.g., insulin, needles, insulin pump supplies)
    - ☐ 4 I do not know what I will have to pay for

12. As part of this study, I will receive immunizations for *(check all that apply)*:
- ☒ 1 Tetanus
- ☐ 2 Pneumonia
- ☒ 3 Flu
- ☐ 4 I do not know which immunizations I will receive

13. If I decide to be in this research study, my diabetes management plan will require that I *(check all that apply):*
- ☐ 1 Take insulin injections only every other day and test my blood sugars when I don't feel well
- ☒ 2 Report my insulin use (i.e., number of injections, type of insulin, use of an insulin pump) and blood sugar results to the study site every two weeks
- ☐ 3 Use an insulin pump and test my blood sugars before bedtime only
- ☒ 4 Check and record my blood sugars at least four times a day
- ☐ 5 I do not know how often I will need to take insulin or test my blood sugars

14. If I agree to be in this research study, I will have to fast (not eat or drink) for 10 hours prior to:
- ☐ 1 Every study visit when I am having an infusion
- ☒ 2 Only study visits when I am having a Mixed Meal Tolerance Test
- ☐ 3 Any appointment when my blood will be drawn
- ☐ 4 I will never be asked to fast prior to an appointment

15. If I agree to be in this research study, I can expect the infusion to last
- ☒ 1 30 minutes
- ☐ 2 2 hours
- ☐ 3 1 hour
- ☐ 4 I do not know how long the infusion will last

Female participants with reproductive potential only:

16. *If I agree to be in this research study, I must agree to use effective birth control for the 2 years while I am receiving infusions plus an additional 3 months after my last infusion.*
- ☒ 1 True
- ☐ 2 False

END OF QUIZ

Appendix B. Site Initiation Activities Checklist

February 22, 2008

Site Initiation Activities for CTLA4-Ig Trial

_____
Site Name

The following is an internal checklist for use by clinical sites that covers the basic steps for initiating the CTLA4-Ig Trial. The checklist covers the following general areas:

- Providing TNCC with contact and other information
- Training and Certification
- IRB approval and other compliance documents
- Preparing for implementation

Item	Completed	Date / Initials
Getting Started		
Confirm site interest in participation and timeline for implementation with TNCC	☐	
Provide contact information for investigator(s) and coordinator(s) participating in the study	☐	
Complete Form FDA 1572 and Financial Disclosure Form FDA 3455 (if applicable) for principal investigator and submit to TNCC along with updated CVs for all participating investigators	☐	
Provide TNCC with name of coordinator(s) and email addresses where results alerts should be sent	☐	
Complete EMINENT client contact form which provides TNCC with contact and shipping information for local pharmacy or alternate location that will receive shipments of study medications (Note: The name of a contact at the pharmacy **must** be provided and the person ordering study drug **must** be a licensed medical professional)	☐	
Access to 2°C to 8°C (36°F to 46°F) degree refrigerator in the pharmacy for storage of study medication	☐	
Access to of -20° C freezer for storage of frozen samples.	☐	
Training and Certification		
Review current protocol, study procedures, and other study documents.	☐	
Complete CTLA4-Ig protocol quiz for all staff members and send it to TNCC	☐	
Have a password for web randomization system and complete mock randomization as certification	☐	
Appropriate staff at site: Complete other TrialNet-wide certifications, as needed (shipping and metabolic tests)	☐	
Staff at site: Complete DU7s and send it to TNCC	☐	
Provide name, location and normal ranges to TNCC for local laboratory that will be performing CBC with differentials	☐	

February 22, 2008

Site Initiation Activities for CTLA4-Ig Trial

Item	Completed	Date / Initials
IRB Approval		
Prepare IRB submission and submit local IRB	☐	
Inform TNCC when protocol has been submitted to local IRB and expected date of review	☐	
Respond to any issues raised by local IRB (TNCC and Chairman's Office can assist with this).	☐	
Send approval letter and approved consents that reflect the appropriate version number and date of the Protocol to TNCC for review (Note: TNCC **must** review and approve consents before a site can start the study).	☐	
Preparing for Implementation		
Implementation can begin once protocol activation letter is received from the TNCC.	☐	
Review laboratory supplies at the site and order what site needs to start CTLA4-Ig study using SOS.	☐	
Receive screening study forms, participant CRF binder(s), and barcode labels from TNCC. If paper forms are unavailable, forms may be downloaded from the website for use. (Use order form available on website for all re-orders.)	☐	
Review shipping procedures for TrialNet laboratory samples and forms.	☐	
Review protocol and procedures with lab coordinator to ensure site is prepared for mechanistic sample collections.	☐	
Order study medication from TrialNet Central pharmacy Note: Sites will not received study drug and infusion kits until 1 subject has been screened at the site as evidenced by the screening CRF being received at the TNCC for data entry and eligibility report generated	☐	
Implementation		
TNCC recommends reviewing steps involved with first 1-2 visits and contact the TNCC with any questions.	☐	

_____ _____

Printed Name *Signature*

_____ _____

Printed Name *Signature*

Appendix C. Schedule of Assessments

APPENDIX 1 - Schedule of Assessments

Visit	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28-31
year																1													2	
~day of Trial:	-1[1]	0	14	28	56	84	112	140	168	196	224	252	280	308	336	364	392	420	448	476	504	532	560	588	616	644	672	700	728	[8]
History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Assessments		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with Differential	X	X	X		X	X			X				X			X			X				X			X			X	X
Chemistries	X	X		X			X			X				X		X			X				X			X			X	X
PPD Test	X																													
Viral serology (EBV, CMV, HIV, Hep B and C)	X																													
EBV viral load [3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Urine Pregnancy Test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum for Autoantibodies	X					X				X			X			X			X				X			X			X	X
Study drug Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
PK, receptor occupancy, immunogenicity					X	X[4]	X[4]			X			X			X			X							X			X	
Immunizations;tetanus/ flu/ response[5]																												X		
Hemoglobin A1c		X				X				X			X			X			X				X			X			X	X
MMTT (4-hour)	X																												X	
MMTT (2-hour)						X				X						X							X							X
Serology/viral monitoring[6]		X								X			X			X							X						X	X
Mechanistic Assessments[7]	X	X			X	X				X			X			X							X						X	X

1. **Screening Visit**: Screening MMTT must be at least 3 weeks after diagnosis and within one month (37 days) of randomization.
2. **Physical Exam**: Routine exam at screening and quarterly, directed exam prior to administration of study drug infusion.
3. **EBV viral load**: To be determined in individuals who were previously unexposed (EBV IgG and IgM negative at screening). Those with evidence of active EBV infection will not receive further study drug infusions until resolution of infection.
4. **Study drug level and receptor occupancy and immunogenicity analysis**: Collect pre and post-dose.
5. **Immunizations and response**: At study visit 26, subjects will have a pre-immunization blood draw and then receive a tetanus immunization with follow up blood draw assessing immune response at study visit 27. Subjects will have a pre-immunization blood draw and then receive killed flu vaccine annually during a study visit at least one month from study entry occurring at a clinically appropriate month with follow up blood draw assessing immune response at next visit.
6. **Serology/viral monitoring**: Anti-thyroid antibodies as well as titers to childhood immunizations and illnesses will be measured on these samples as well as tested for viral load if clinically indicated.
7. **Mechanistic Assessments**: Includes samples for RNA, plasma, serum, DNA, measures of B and T cell number and function. The schedule for these assessments may vary as appropriate. At no time will the blood draw volume exceed what is allowable according to the subject's body weight (3ml/kg for subjects <18).
8. **Follow-Up After 24 Months**: Visits will be conducted approximately every 6 months.

1

Updated: November 3, 2005

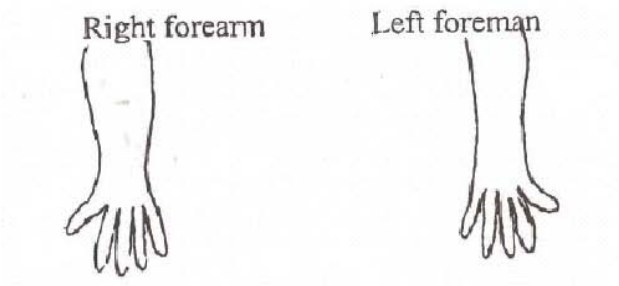
PPD Test Reading Guidelines

Reading the Test: Please measure the TB test site at 48-72 hours post injection.

Given date/time: _____
Read date/time: _____

There will be one site to measure and report. Using the scale provided on the bottom of the page, measure in millimeters and write the results below. If there is no reaction, write that as well. **Note:** The results of the test are based on the size of the induration **only**, not the size or extent of redness. The size or extent of redness **DOES NOT** need to be measured and recorded.

Measure the largest width of induration. You must feel the induration.



Skin Test Type	Induration Width
1.	mm

Subject's name: _____
Name of person reading test: _____
Title: _____ Facility: _____ Date: _____ Time: _____

Please fax to: (_ _ _)-_ _ _ -_ _ _ _
Thank you!

Dear Study Participant,

The results of the tuberculosis (PPD) test need to be read within 48 to 72 hours of administering the test. The results of the test must be read by a trained healthcare professional that has experience in reading these tests.

Please make an appointment to have your result read on one of the following dates:

_____ or _____
(48 hours) *(72 hours)*

Have your local healthcare professional complete the section below.

Fax the completed form to <Name> at <phone>

Dear Healthcare Professional,

_____ received a tuberculosis (PPD) test at our site on the date below. Please measure in millimeters the largest width of redness and the largest width of any lump. Record the results in the box below. If there is no reaction, indicate that as well.

Date Given	Indicate Site Right / Left Forearm	Date Read	Lump Width	Redness Width
			mm	mm

Name and Title of person reading test: _____

Facility: _____ Phone Number: _____

Questions or Concerns Contact us at <phone number>

Appendix E. Mixed Meal Tolerance Test (MMTT) Procedure

Background

The MMTT assesses the participant's insulin production capacity. The CTLA4-Ig Trial includes both 2-hour and 4-hour MMTTs. The 2-hour MMTT will be administered at Day 84 (visit 4), 196 (visit 8), 364 (visit 14), 560 (visit 21), visits 28 to 31, and the 4-hour MMTT will be administered at Screening and day 728 (visit 27).

Clinic Preparation

The following are the steps that need to be taken to adequately prepare the clinic for the upcoming participant visit:

- Retrieve the participant's study materials.
- Make sure you have all appropriate supplies for tests scheduled
- Make sure you have all appropriate specimen transmittal forms pertinent to the scheduled visit. If this is 4-hour MMTT, the appropriate specimen transmittal form is CTL99M4. If this is the 2-Hour MMTT, the appropriate specimen transmittal form is CTL99M2.
- Affix all barcode labels to the appropriate cryovials.
- Prepare for the shipment of laboratory specimens making sure you have all necessary supplies including adequate dry ice.

Supplies Needed

Item	Number Needed
Specimen Tubes	
1.2 ml gray top tube (glucose)	7* or 11†
1.2 ml lavender top EDTA monovette tube (C-peptide)	7* or 11†
Cryovials	
1.8 ml Nunc cryovials (glucose, C-peptide)	14* or 22†
Color Code Caps	
gray (glucose)	7* or 11†
lavender (C-peptide)	7* or 11†
Syringes and Needles	
18-22 gauge intra-catheter or butterfly needle	1
10 ml syringe	2
Solutions	
0.9% Sodium Chloride Inj. U.S.P.	x
BOOST High Protein	x
Paperwork	
Specimen Transmittal Form	x
CTL99M2 or CTL99M4†*	x
Federal Express Pre-Printed Labels:	
Northwest Lipid Research Laboratories	x
Bar Code Labels	x
Indelible marking pen	x
Equipment	
polyfoam shipping box	x
packing tape	x
ziplock bag	x
ice/refrigerator	x

Supplies Needed Continued

Item	Number Needed
dry ice	x
dry ice label (*FedEx*)	x
Biohazard label	x
IV tubing	1 line
3-way stop-cock	2
T-connector extension tubing (optional)	x
Multi-Adapter Luer Lock, IST	2
clock/timer	x
rack (for tubes)	x
sterile strip bandage	x
ice bath (C-peptide)	x
IV poles	1
tourniquet	x
Band-Aids	x
First-aid tape	x
latex gloves	x
heating pads (optional)	2
alcohol wipes	x
2 x 2 sterile gauze pads	x
Medications	
EMLA cream (optional, recommended for children)	x
Snack	x

* Supplies needed for a 2-hour MMTT

† Supplies needed for a 4-hour MMTT

Participant Preparation

The participant should be reminded at the prior visit to the clinic about the upcoming MMTT and should be given guidelines to be followed prior to the test. Within one week of the scheduled visit, a letter should be sent to the participant reminding him/her of the upcoming appointment and repeating the guidelines that need to be followed.

The participant should be reminded:

a. To fast (not to eat) after 10:00pm the night before the test, and should continue fasting up until the start of the test. The participant should not eat or drink anything except for water. This means no coffee, tea, sodas, cigarettes, alcohol, or chewing gum during the fasting period.
b. To refrain from vigorous exercise during the fasting period.
c. To refrain from working during the night preceding the morning of the test.
d. To refrain from taking any over the counter medications during the fasting period.
e. To let the study staff know about any prescription medications the participant must take 3 days before the test to give them the appropriate directions on how to deal with the medication before the test. To discontinue taking any prescription medications that must be taken on a daily basis.
f. To eat a high carbohydrate diet (at least 150 grams) (see below for sample) for 3 days prior to testing.
g. In children, application of EMLA cream is encouraged.
h. Water consumption is encouraged, especially in small children
i. To let the study staff knows if any they have had any illness, surgery or infection during the two weeks before the test. Test will be rescheduled.
j. To let the study staff know if they are pregnant or have any chronic illness such as cancer, nephritic syndrome, active hepatitis or some other life threatening illness.

The **eligibility checklist** should be reviewed prior to starting the test to be sure that the participant has followed the above guidelines.

(To be certain that all above guidelines have been followed, the **eligibility checklist** should be reviewed prior to administrating the test)

150 Gram Carbohydrate Diet

The menu below contains 150 grams of carbohydrate. In order to prepare for your test, please consume a minimum of 150 grams of carbohydrate per day for the 3 days prior to the test. You must be fasting on the morning of the test.

The number of grams of carbohydrates is listed in parentheses for each serving of food. You may substitute any items from the lists below; and you can eat more than this if you wish. Add as many servings of meats or vegetables as desired; the menu below is only an example. Be sure to drink plenty of water in preparation for the test.

Breakfast 4 oz. orange juice (15)
4 oz. milk (whole, low fat, 1%, or non-fat) (6)
3/4 cup dry cereal (15)

Snack 1 medium apple (20)

Lunch Sandwich with 2 slices of bread (30) and any filling
1 banana (20)

Dinner 1 serving of meat, fish or poultry (0)
1 medium size potato (20) with topping
1 serving of vegetables (5)
1/2 cup canned fruit (15)

Snack 2 cups popcorn (10)

---

10 grams	**15 grams**	**20 grams**	***30 grams***
10 grapes	½ cup cooked cereal	1 medium apple	*2 toaster waffles*
1 cup strawberries	6 saltines	1 hamburger bun	*1 cup pasta*
8 oz. tomato juice	4 oz. fruit juice	1 small corn on the cob	*1 small bagel*
1 plum	1 slice angel food	9 animal crackers	*1 cup chicken noodle soup*
1 Fig Newton	½ pita	3 dates	*1 piece plain cake*
4 vanilla wafers	2 tbsp. raisins	½ cup rice	
4 Ritz crackers			

Directions For Use Of Local Anesthetic Cream

For participants who may wish to use a local anesthetic cream, the anesthetic cream and instruction sheet should be sent to the participant or parent in advance so that it can be applied prior to the appointment.

Procedure for Mixed Meal Tolerance Test (MMTT)

The MMTT will be performed at Screening, Day 84 (visit 4), 196 (visit 8), 364 (visit 14), 560 (visit 21), day 728 (visit 27), and visits 28 to 31. The tests done at Screening and day 728 (visit 27) will be 4 hours in length, whereas the tests done at other times will only be 2 hours in length. The test uses a standard oral mixed formula meal (Boost) composed of liquid sucrose, soy protein, casein, and soy oil.

Do not proceed with performing the MMTT if the participant manifests unequivocal elevation of fasting plasma glucose (> 200 mg/dl (>11.1 mmol/L) on the participant's home blood glucose meter). The participant should ideally have a fasting glucose level in the range defined by **70 to 200 mg/dl (3.85 to 11.1 mmol/L)** the morning of the test. Any participants with values outside of this range should have the test rescheduled.

Preparation for MMTT

Because a large number of factors may affect the MMTT, care must be taken to properly prepare participants for the test.

Dietary guidelines:

- High (at least 150 grams) CHO diet for at least 3 days prior to the test
- Fasting after 10:00pm the night before the test.
- 10 hr abstinence from coffee, tea, sodas, caffeine containing drinks, cigarettes, alcohol, chewing gum , vigorous exercise
- Water consumption is encouraged, especially for young children

Other guidelines:

- No consumption of over the counter medications during the fasting period.
- Inform study staff if taking any prescription medications that you, or your child, must take, 3 days before the test so that appropriate directions can be given on how to deal with this medication before the test.
- Not participate in vigorous exercise during the 10 hours before the test.

If the participant has not consumed sufficient dietary carbohydrate before the test, the insulin secretory response to the mixed meal stimulus may not be as great as it should be (*may not be accurate)* and the test results may be unreliable. Therefore, the participant must consume a high carbohydrate diet, with ≥ 150 grams carbohydrate per day, for a minimum of three full days prior to testing.

- The test should be **rescheduled** if the participant has a blood glucose (measured on his/her home meter) **less than 70 mg/dl (3.85 mmol/L) or greater than 200 mg/dl**. **(11.1 mmol/L)**
- The test must begin between the hours of **7(AM) and 10AM**.
- The participant should remain seated during the performance of the test.
- The test is started in the morning after a night's sleep (*a full night's rest)*. Participants may not work during the night preceding the morning of the test.
- The test should be postponed for at least one week after any intercurrent infectious illness, surgery or other stress.

Insulin Guidelines

- Long-acting insulin can be administered the day before the test is scheduled.
- Corrective insulin (Humalog (H) and NovoLog) can be administered up to two hours before the test.
- Regular (R) insulin can be administered up to six hours before the test.
- Participants on insulin pumps (continuous insulin infusions (CSII)) should continue with the normal basal rate, but a Humalog (H) or NovoLog bolus may be added up to 2 hours prior to the test, and Regular (R) bolus up to 6 hours prior to the test.

Mixed Meal Dose

The test meal (Boost) is given at a dose of 6 ml per kilogram body weight. Maximum dose is 360 ml. Boost is supplied in 8 fluid ounce cans.

Test Procedures

1. The MMTT must begin between 7:00 - 10:00 a.m. for proper interpretation.
2. Obtain the weight of the participant and calculate Boost meal size = 6 ml/kg, up to 360 ml, 1lb = 0.45 kg

   The MMTT test uses a standard oral mixed meal formula (Boost®, Mead Johnson Nutritional Division, Evansville, Indiana) composed of liquid sucrose, soy protein, casein, and soy oil. **The test meal is given at a dose of 6 kcal/kg body weight, at 1 kcal/ml to a maximum of 360 kcal.**
3. The participant should remain sitting or resting in bed quietly throughout the test. The participant can engage in quiet, non-strenuous activities such as reading, playing cards, watching TV and may walk to the bathroom between blood draws if necessary (but should otherwise remain in resting position until the test is completed). It is recommended that participants not be asked to answer questions for the purpose of completing case report forms during the MMTT.
4. Place an I.V. line into an antecubital vein, using an intracatheter/butterfly needle (usually 20 or 22 gauge depending upon the size of the participant). The **intracatheter** may be kept patent between samples with a slow saline drip or heparinized saline solution (as per the guidelines of your institution) in a 20 ml syringe, injecting about 2-3 ml after each blood draw.
5. Before the procedure, fill several 3 ml syringes with luer-lock tips with 1 ml normal saline solution to flush the **adapter** after each blood draw. This is only necessary if the blood sampling is more than 3 minutes apart.
6. Obtain baseline samples:
   - The first sample should be taken at least 10 minutes after establishing the line(s) and when participant is calm and relaxed (if possible, depending on age) - this is the "-10 minute" sample
   - The second sample should be taken just prior to drinking the Boost - this is the "0 minute" sample

7. Meal consumption - Start the clock at the beginning of the drink. The dose of Boost must be completely consumed within **five (5) minutes**.
8. Obtain post-meal blood samples.
9. Samples are taken at 15, 30, 60, 90, and 120 min after time 0' (if this is a 4-hour test, samples should also be taken at 150, 180, 210 and 240 minutes)
    - A timer should be turned on at 0 min
    - The actual start time for each blood draw should be recorded on the MMTT specimen transmittal form

Sampling Protocol

Time (min)	**Glucose Sample Taken 1.2 ml gray top tube**	**C-peptide Sample Taken 1.2 ml lavender top EDTA tube**
-10	X	X
0	X	X
Drink Boost		
15	X	X
30	X	X
60	X	X
90	X	X
120	X	X
150†	X	X
180†	X	X
210†	X	X
240†	X	X

† Samples only taken at these times during a 4-hour MMTT

10. If a clogged line, missed sample, or other deviations from the protocol occur, these must be noted on the "Comments" section of the MMTT specimen transmittal form.
11. Termination of MMTT
    - Test is terminated after the blood sample at 120 minutes for a 2-hour MMTT, or 240 minutes for a 4-hour MMTT. At that time, the indwelling cannula(e) will be withdrawn, pressure applied and a sterile strip bandage applied.
    - Upon completion of the test, the participant should have a snack, for example peanut butter or cheese crackers, coffee, milk or ginger ale.

Procedures for blood preparation, storage and shipping

A. **Glucose**: For each time point, 1.2 ml of blood is drawn in a 1.2 ml gray top tube (-10, 0, 15, 30, 60, 90, 120, *150, 180, 210 and 240* min):
   - Label each 1.8 ml cryovial with the appropriate bar-coded label from an unused MMTT barcode label sheet. Apply the labels vertically and snap on appropriate color codes (**Glucose = Gray**).
   - Immediately invert the tube gently 6 times, avoid jarring or shaking.
   - Place the tube upright in an ice bath or in a refrigerator.
   - Centrifuge within 1 hour of drawing for 10-15 minutes.
   - Transfer serum to an appropriately labeled (check both sample type and time point) 1.8 ml cryovial. Screw top on tightly.
   - Freeze samples at -20° C or ship on dry ice the same day.
   - **Ship samples only on Monday, Tuesday, Wednesday** or **Thursday.**
   - Affix both Biohazard and dry ice label on box indicating shipment of blood specimens on dry ice, according to instructions provided on the Specimen Transmittal Form. Record the FedEx waybill number on the exterior of the box in case the waybill becomes separated from the box.

B. **C-peptide**: For each time point, 1.2 ml of blood is drawn in a 1.2 ml lavender top tube (-10, 0, 15, 30, 60, 90, 120, *150, 180, 210 and 240* min):
   - Label each 1.8 ml cryovial with the appropriate bar-coded label from an unused MMTT barcode label sheet. Apply the labels vertically and snap on appropriate color codes (**C-peptide = Lavender**).
   - Immediately invert the tube gently 6 times, avoid jarring or shaking.
   - Place the tube upright in an ice bath or in a refrigerator.
   - Centrifuge within 1 hour of drawing for 10-15 minutes.
   - Transfer serum to an appropriately labeled (check both sample type and time point) 1.8 ml cryovial. Screw top on tightly.
   - Freeze samples at -20° C or ship on dry ice the same day.
   - **Ship samples only on Monday, Tuesday, Wednesday** or **Thursday.**
   - Affix both Biohazard and dry ice label on box indicating shipment of blood specimens on dry ice, according to instructions provided on the Specimen Transmittal Form.

Note: Each Core lab will return shipping boxes via Federal Express; please affix a return address label on the inside flap of the box.

Documentation

The appropriate specimen transmittal form must accompany all samples sent to the laboratory. Specimen transmittal form **CTL99M2 is** the appropriate form for a 2-hour MMTT. Specimen transmittal form **CTL99M4** is the appropriate form for a 4-hour MMTT. Please do **not** mark in sections labeled for **Laboratory Use Only**.

- The **white copy** of this form should be mailed to the TrialNet Coordinating Center
- The **yellow copy** should be sent to the Core Beta Cell Function Laboratory, along with the specimens
- The **pink copy** should be kept at the clinic.

Shipping Address for MMTT Samples

Address: Specimen Processing
Northwest Lipid Research Laboratories
401 Queen Anne Avenue North
Seattle, WA 98109-4517

Phone: (206) 685-3327

Appendix F. Blank Screening Log

TrialNet Screening Id Number Log for the CTLA-4 Ig Study

Study: CTLA-4 Ig
Site: SAMPLE

SiteNo	Screening Id	Initials	Date Screened (DD/MMM/YYYY)	Comments
9999	11111			

Appendix G. Eligibility Report and Lab Results

CTLA4-IG Subject Eligibility Report 1

Data as of: 18APR08

Site Number: 10
Screening Number: 81364
Letters: ANT

Diagnosis Information			**Eligible**
Date of Diagnosis	*02JAN2008*		
Date subject must be randomized by, if eligible (w/in 100 days)	*11APR2008*		
Date 4-hour MMTT was performed	*06MAR2008*		
Days from diagnosis MMTT was performed	*64*		
Date 4-hour MMTT expires (37 days)	*12APR2008*		
Participant Information			
Age*	*9*		*Y*
Laboratory Results			
Stim.C-peptide: >= 0.2pmol/ml(0.6ng/ml)?	*N/A*	*06MAR2008*	*Y*
Detectable autoantibodies?			*Y*
--Anti-GAD65 AA:	*Positive*	*06MAR2008*	
--Anti-ICA512:	*Positive*	*06MAR2008*	
--MIAA:**	*Positive*	*06MAR2008*	
--Islet Cell Antigen:	*Positive*	.	
Hepatitis B screening	*Negative*	*06MAR2008*	*Y*
Hepatitis C screening	*Negative*	*06MAR2008*	*Y*
HIV screening	*Negative*	*06MAR2008*	*Y*

*Participant must weigh at least 20 kg/(44lb) to be eligible.
**Participant is NOT eligible if MIAA is the ONLY positive antibody and the participant has been on insulin therapy for more than one week.

Lab results by visits for CTLA-4Ig Study
18APR08

Site Number: 10
Screening Number: 81364
Letters: ANT Sex: M
Date of Birth: 05JAN99
VisitNo: Screening

ResultName	Description of Result Name	Sample No	Col Date	Results	Normal range of result
GAD65	Anti-GAD65 AA	28134575	06MAR08	Positive	<=0.032
ICA512	Anti-ICA512(IA-2) AA	28134575	06MAR08	Positive	<=0.049
MIAA	Micro Insulin AA	28134575	06MAR08	Positive	<=0.01
ICA	Islet Cell Antigen	28134575	.	Positive	<10
ALB	Albumin(g/dL)	79520620	06MAR08	4.1	3.4-4.8
ALP	Alkaline phosphatase(U/L)	79520620	06MAR08	240.0	12-17:(M)<390,(F)<187;Adults:(M)40-129,(F)35-104
ALT	Alanine aminotransferase(U/L)	79520620	06MAR08	17.0	M:10-40,F:7-35
AST	Aspartate aminotransferase(U/L)	79520620	06MAR08	37.0	M:15-40,F:13-35
CHL	Chloride(mmol/L)	79520620	06MAR08	103.4	96-108
CREA	Creatinine(mg/dL)	79520620	06MAR08	0.34	M:0.5-1.2,F:0.4-1.1
DBIL	Direct bilirubin(mg/dL)	79520620	06MAR08	0.07	0-0.3
GLOIGG	IgG Globulin(mg/dL)	79520620	06MAR08	814	700-1600
GLOIGM	IgM Globulin(mg/dL)	79520620	06MAR08	76	40-230
GLU	Glucose(mg/dL)	79520620	06MAR08	142	Adult:70-105,Child:60-110
POT	Potassium(mmol/L)	79520620	06MAR08	4.63	3.3-5.1
SOD	Sodium(mmol/L)	79520620	06MAR08	135	133-145
TBIL	Total bilirubin(mg/dL)	79520620	06MAR08	0.22	<=1.0
TPRO	Total proteins(g/L)	79520620	06MAR08	6.4	6.4-8.3
UREA	Urea(mg/dL)	79520620	06MAR08	12.8	2.0-186
ALB	Albumin(g/dL)	79520620	06MAR08	4.1	3.4-4.8
ALP	Alkaline phosphatase(U/L)	79520620	06MAR08	240.0	12-17:(M)<390,(F)<187;Adults:(M)40-129,(F)35-104
ALT	Alanine aminotransferase(U/L)	79520620	06MAR08	17.0	M:10-40,F:7-35
AST	Aspartate aminotransferase(U/L)	79520620	06MAR08	37.0	M:15-40,F:13-35
CHL	Chloride(mmol/L)	79520620	06MAR08	103.4	96-108
CREA	Creatinine(mg/dL)	79520620	06MAR08	0.34	M:0.5-1.2,F:0.4-1.1

Lab results by visits for CTLA-4Ig Study
18APR08

Site Number: 10
Screening Number: 81364
Letters: ANT Sex: M
Date of Birth: 05JAN99
VisitNo: Screening

ResultName	Description of Result Name	Sample No	Col Date	Results	Normal range of result
DBIL	Direct bilirubin(mg/dL)	79520620	06MAR08	0.07	0-0.3
GLOIGG	IgG Globulin(mg/dL)	79520620	06MAR08	814	700-1600
GLOIGM	IgM Globulin(mg/dL)	79520620	06MAR08	76	40-230
GLU	Glucose(mg/dL)	79520620	06MAR08	142	Adult:70-105,Child:60-110
POT	Potassium(mmol/L)	79520620	06MAR08	4.63	3.3-5.1
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TBIL	Total bilirubin(mg/dL)	79520620	06MAR08	0.22	<=1.0
TPRO	Total proteins(g/L)	79520620	06MAR08	6.4	6.4-8.3
UREA	Urea(mg/dL)	79520620	06MAR08	12.8	2.0-186
CMVIGG	CMV IgG	79733811	06MAR08	NEGATIVE	Negative
CMVIGM	CMV IgM	79733811	06MAR08	NEGATIVE	Negative
EBNA	EBV-EBNA	79733811	06MAR08	NEGATIVE	Negative
EBVVCAIGG	EBV-VCA IgG	79733811	06MAR08	NEGATIVE	Negative
EBVVCAIGM	EBV-VCA IgM	79733811	06MAR08	NEGATIVE	Negative
CMVVL	CMV-PCR (DNA copies/mL)	79823308	06MAR08	99	<100
EBVVL	EBV-PCR (DNA copies/mL)	79823308	06MAR08	99	<100
HEPB	Serology test for Hepatitis B	79904832	06MAR08	NEGATIVE	Negative
HEPC	Serology test for Hepatitis C	79904832	06MAR08	NEGATIVE	Negative
HIV	Serology test for HIV	79904832	06MAR08	NEGATIVE	Negative

Appendix H. Eligibility and Deviation Review Form

Type 1 Diabetes TrialNet

ELIGIBILITY AND DEVIATION REVIEW FORM

Form ELIG
10JUN2005
Page 1 of 1

Study: | PIN: __ __-__ __-__ __ __ __-__ | Issue Number: ___ ___ ___

A. GENERAL INFORMATION

1. Date of review request: ___/___/___ (MM/DD/YYYY)
2. Date response needed by: ___/___/___ (MM/DD/YYYY)

B. GENERAL SUBJECT INFORMATION

1. Age (years): ___ ___ ___
2. Sex: ☐ Male ☐ Female
3. Date of diagnosis with type 1 diabetes *(if applicable)*: ___/___/___ (MM/DD/YYYY)
4. Date of screening visit *(if applicable)*: __ __/__ __/__ __ __ __ (MM/DD/YYYY)

C. ELIGIBILITY ISSUE DETAILS

1. Provide a brief description of the eligibility issue/deviation that requires review:

2. Provide a brief justification for the subject's enrollment into the study:

D. RELEVANT INFORMATION FROM STUDY DOCUMENTS

TNCC USE ONLY

1. Eligibility reviewed? Y N
   IF YES,
   a. Date of review: __ __/__ __/__ __ __ __ (MM/DD/YYYY)
   b. Reviewer ☐1 TNCC ☐2 Committee Chair ☐3 Full Committee
   c. Eligibility decision: ☐1 Eligible ☐2 Not Eligible
   If NO,
   a. Reason not reviewed:
2. Comments:

Appendix I. Glucose Log Template

Week of _____-_____

Long acting insulin/Basal Rate:
Short Acting Insulin:
Correction factor:
Insulin/carb ratio:

Fax or e-mail weekly to:

Fax:
Email:

Day of the week / date		BREAKFAST		LUNCH		DINNER		PM Snack		BEDTIME	NIGHT	COMMENTS
		PRE	POST	PRE	POST	PRE	POST	PRE	POST			
MONDAY	TIME											
	BG											
	CARB											
	INSUL											
TUESDAY	TIME											
	BG											
	CARB											
	INSUL											
WED	TIME											
	BG											
	CARB											
	INSUL											
THURS	TIME											
	BG											
	CARB											
	INSUL											
FRIDAY	TIME											
	BG											
	CARB											
	INSUL											
SAT	TIME											
	BG											
	CARB											
	INSUL											
SUNDAY	TIME											
	BG											
	CARB											
	INSUL											