Effects of Canakinumab On The Progression of Type 1 Diabetes In New Onset Subjects

(Protocol TN-14)

Version: October 19, 2011

IND # 105,965

Sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Child Health and Human Development (NICHD), the National Center for Research Resources (NCRR), the Juvenile Diabetes Research Foundation International (JDRF), and the American Diabetes Association (ADA)

PREFACE

The Type 1 Diabetes TrialNet Protocol TN-14, Effects of Canakinumab On The Progression of Type 1 Diabetes In New Onset Subjects describes the background, design, and organization of the study. The protocol will be maintained by the TrialNet Coordinating Center over the course of the study through new releases of the protocol, or issuance of updates either in the form of revisions of complete chapters or pages thereof, or in the form of supplemental protocol memoranda.

TABLE OF CONTENTS

1. INTRODUCTION

1.1. Study Overview

Title	Effects of Canakinumab On The Progression of Type 1 Diabetes In New Onset Subjects
IND Sponsor	Type 1 Diabetes Trial Network (TrialNet)
Conducted By	Type 1 Diabetes Trial Network (TrialNet)
Protocol Chair	Antoinette Moran, MD
Accrual Objective	66 subjects over 2 years
Study Design	The study is a two-group, multicenter, randomized, double-masked, placebo-controlled Phase II clinical trial. All groups will receive standard intensive diabetes treatment with insulin and dietary management. 66 subjects will be randomly assigned to receive either monthly subcutaneous injections of 2.0 mg/kg canakinumab or placebo for 12 months.
Treatment Description	Canakinumab is a fully human anti-interleukin-1β (anti-IL-1β) monoclonal antibody (IgG-1κ class). Canakinumab is designed to bind to human IL-1β and to functionally neutralize the bioactivity of this pro-inflammatory cytokine. Participants randomly assigned to canakinumab treatment or placebo will receive a total of 12 injections over one year
Study Duration	All subjects will be followed for 1 year of treatment plus 1-3 years of additional follow-up until study end. Enrollment is expected to occur over two years.
Objective	To assess the safety, efficacy, and mode of action of canakinumab injections for the treatment of individuals with new onset type 1 diabetes.
Primary Outcome	The primary statistical hypothesis to be assessed in this study is whether the mean C-peptide response to MMTT at one year for subjects in the canakinumab treatment group will differ significantly from the mean value for placebo treated subjects.
Secondary Goals	The study will also examine the effect of the proposed treatments on surrogate markers for immunologic effects, namely disease-specific metabolic and immunologic outcomes
Major Inclusion Criteria	Type 1 diabetes diagnosed within the past 3 months. Age 6-45 years. At least one diabetes associated autoantibody.

2. BACKGROUND AND SIGNIFICANCE

2.1. Rationale for intervention trials to preserve beta cell function in subjects with Type 1 diabetes

The onset of human Type 1 diabetes mellitus is the clinical manifestation of the β-cell failure caused by T cell mediated autoimmune destruction. This results in a lifelong dependence on daily insulin injections and exposure to both the acute and late complications of Type 1 diabetes mellitus (T1DM). T1DM is a particular burden to children and their families, representing one of the most common chronic childhood diseases. While onset of T1DM can occur into adulthood, there is a bimodal peak age of onset, between ages 4-7 and ages 14-16 years. The worldwide incidence of T1DM is increasing, with the greatest increase in children under the age of 5 years. Despite the significant progress that has been made in its treatment, diabetes mellitus represents a severe burden on the individual and on society as well. Any intervention that can stop or delay the complete loss of functional residual β-cell mass is significant as it may provide protection against hypoglycemia and provide improved metabolic control resulting in a delay in the micro and macro-vascular complications of diabetes.

Exogenous delivery of insulin is standard care with the aim to obtain near-normalized blood glucose levels. However, despite insulin replacement treatment, T1DM patients suffer from macro- and microvascular diseases (nephropathy, peripheral neuropathy, retinopathy, and cardiovascular disease) resulting in a decrease of life-expectancy.[1] Stringent blood glucose control has been shown to reduce the risk of developing these late diabetic complications.[2] [3] However, stringent blood glucose control is often restricted by the occurrence of life threatening hypoglycemia. Despite enhanced knowledge of the natural history of T1DM, to date there is no intervention that consistently and safely prevents continued beta cell destruction.

T1DM is an immune-mediated disease in which insulin-producing beta cells are completely destroyed, resulting in life-long dependence on exogenous insulin. While this process of beta cell destruction begins well before clinical onset and continues even after development of hyperglycemia and diagnosis, at the time of diagnosis, most subjects retain a significant amount of beta cell function as measured by C-peptide responses to a mixed meal tolerance test. However, this beta cell function deteriorates after diagnosis with the presumed eventuality of absent function over time. As shown in the Diabetes Control and Complications Trial, the persistence of residual beta cell function has been associated with important clinical outcomes, specifically reduction in severe hypoglycemia and complications. In this study, the rate of retinopathy and severe hypoglycemia were reduced by greater than 50% in those with sustained C-peptide when compared with those with undetectable C-peptide.[4] Additionally, there is growing evidence that residual beta cell function shortly after the diagnosis of diabetes may be much greater than previously thought.[5] Preservation of C-peptide is therefore a clinically important goal.[6] [7] An intervention that can enable continued endogenous insulin production would significantly improve the day-to-day management for subjects with diabetes and therefore reduce long-term complications.

2.2. Rationale for use of Canakinumab

2.2.1. Inflammation in Type 1 diabetes

Inflammation has increasingly been recognized as an important contributor to β-cell dysfunction and apoptosis, with recent emphasis on the role of local, hyperglycemia-induced production of IL-1β by pancreatic β-cells, which contributes to worsening β-cell function, and to diabetes disease progression.[8] Studies have shown that hyperglycemia induces production and release of IL-1β by pancreatic β-cells.[9] This was further corroborated by evidence of IL-1β mRNA and protein expression in β-cells in pancreatic sections from diabetic patients but not in those from non-diabetic controls.[10] Endogenously produced IL-1β plays a dual role in mediating pancreatic β-cell glucotoxicity by: 1) reducing β-cell secretory capacity, and 2) inducing β-cell apoptosis by activating the death- receptor Fas.[11]

Inhibition of the IL-1β pathway in the setting of T1DM is therefore expected to have a therapeutic benefit: stabilization of β-cell function may lead to a delay in decline of C-peptide levels which may lead to less hypoglycemia and micro and macrovascular complications.

Thus, the therapeutic rationale for the use of Canakinumab is based on the inhibition IL-1β to result in 1) delay/arrest of β-cell apoptosis, and 2) sustained restoration of β-cell function. Modulation of β-cell function by targeting the inflammatory cytokine IL-1β represents a novel approach, addressing a newly recognized contributor to the pathophysiology of T1DM progression, which could potentially result in a disease-modifying therapy.

2.2.2. Canakinumab

Canakinumab (ACZ885) is a fully human anti-interleukin-1β (anti-IL-1β) monoclonal antibody (IgG-1 class) is designed to bind to human IL-1β and to functionally neutralize the bioactivity of this pro-inflammatory cytokine. It is being developed for the treatment of IL-1β−driven inflammatory diseases.

Canakinumab has the following pharmacological properties:

- Recognizes natural human IL-1β with high affinity
- Blocks binding of human IL-1β to both IL-1 receptors via steric hindrance of the receptor interaction.
- Is selective for human IL-1β. There is no cross-reactivity with human IL-1α or human IL-1Receptor antagonist (IL-1Ra).
- Neutralizes human IL-1β activity in vitro (using an IL-1β-dependent IL-6 release assay in human dermal fibroblasts).

2.3. Preclinical data

Canakinumab was examined in vivo in marmosets and in vitro in human tissue cross reactivity studies. There was no evidence of immunotoxicity, such as infection, hypersensitivity, or anti-canakinumab antibody formation. A subcutaneous early fetal development study in marmosets showed no evidence of maternal toxicity and no adverse effects on the fetus.

2.4. Clinical data

Twenty (20) clinical studies with canakinumab have been initiated and by December 10th, 2008, a total of 985 subjects (about 700 on canakinumab treatment, including 43 children aged ≥ 4 years) had been enrolled. The safety, tolerability and efficacy data of canakinumab are available from 517 male or female subjects. This includes data from 64 healthy subjects, 21 patients with mild asthma, 19 patients with psoriasis, 20 patients with age related macular degeneration, 292 patients with Rheumatoid Arthritis (RA), 23 patients with Systemic Juvenile Idiopathic Arthritis (SJIA), including 22 pediatric patients, and 78 patients with Muckle Wells Syndrome (MWS), including 15 children. [MWS is a rare autosomal dominant disease that causes sensorineural deafness, recurrent hives, episodic fever, chills and painful joints, and can lead to amyloidosis. It is caused by a defect in the CIAS1 gene that creates the protein cryopyrin and is thus termed a cryopyrin-associated periodic syndrome (CAPS)]. The doses administered i.v. ranged from 0.3 mg/kg to 10 mg/kg or a fixed dose of 600 mg, and from 0.5 mg/kg to 9 mg/kg s.c. or fixed doses of 150 and 300 mg s.c. The frequency of dosing ranged from a single dose to weekly to bi-monthly repeated administration.

The mean duration of exposure to canakinumab in CAPS patients is 323 days with four subjects exposed to canakinumab for more than 2 1/2 years. Of the 494 patients receiving canakinumab, 36 discontinued treatment. One patient with asthma treated with 10 mg/kg canakinumab i.v., withdrew consent after experiencing moderate headache, nausea and mild dizziness after the first dose. One psoriasis patient discontinued treatment after 3 doses of 150 mg/week canakinumab s.c. for gastroenteritis. In CAPS studies, 10 patients discontinued canakinumab treatment; 2 withdrew due to AEs (infection; worsening of MS like lesion, which was a pre-existing condition before the study start).

2.5. Efficacy

Canakinumab has demonstrated efficacy in a variety of studied indications. In **RA** patients there is evidence of a statistically significant treatment benefit of canakinumab (150 mg s.c every 4 weeks) based on American College of Rheumatology (ACR)20 and ACR50 scores versus placebo. Other clinical measures were also significantly better with canakinumab treatment including the swollen joint count, patient and physician assessment of disease activity, and hsCRP measurements. In **CAPS** patients, canakinumab treatment (150mg s.c or 2 mg/kg) produces a rapid and complete resolution of signs and symptoms in almost all patients, starting within 1 day of treatment initiation with an immediate and sustained normalization of serological and hematological parameters of inflammation. In **SJIA** patients, 59% of all children were classified responders and achieved at least an adapted pediatric ACR50 at Day 15 and 18% achieved inactive disease at Day 15. Patients treated with canakinumab and responding to canakinumab showed a rapid decline in CRP, and ESR from values that were highly elevated at screening to values that were at or close to normal at day 15 post dose. In mild **asthmatic** patients there is evidence of a small treatment effect of canakinumab (10 mg/kg) on the magnitude of the late asthmatic response to an allergen challenge. There was no evidence of an effect of canakinumab on Psoriasis Area and Severity Index (PASI) score.

2.6 Safety

There have been 36 canakinumab treated subjects who have discontinued treatment due to adverse events, lack of efficacy, or other reasons. There have been 102 SAEs reported with 525 events including two deaths (cardiac and respiratory failure associated with pre-existing conditions and not related to study drug). There were 75 SAE events suspected to be related to canakinumab treatment of which infections (14 events) and gastrointestinal disorders (13 events) were the most common. Other SAEs suspected to be related to study drug included vertigo reported in one adult and one child with MWS. The child underwent a complete neurological examination, including brain magnetic resonance imaging (MRI), ENT examination and blood pressure tests that were all normal. As of March 08, transient vertigo, dizziness, or syncope has been reported in other individuals who have received canakinumab; more frequently in individuals with MWS than in individuals with autoimmunity. Other serious and unexpected events that were suspected as being related to canakinumab included single subjects with appendicitis, chest pain, viral hepatitis with reticulocytopenia and sarcodosis.

Regarding safety among adults with autoimmune disease, mild infections were common in the absence of leucopenia and lymphopenia. Fifty-three adult RA subjects were in a dose escalation trial. Sixty-nine percent of AEs were mild, 29% moderate, and 2% severe (worsening of RA, and two infections). There were 246 adult RA patients in a 12 week randomized Phase 2 study. In that study, AEs were similar between treatment and placebo groups.

In children with SJIA, almost half of children had mild and transient injection reactions (one judged as moderate); none discontinued study treatment due to AEs. The most frequently reported AEs were infections (gastroenteritis, rhinitis, pharyngitis, tonsillitis, URI). Other AEs include urticaria, vertigo, rash, fever, cough, headache, vomiting, and diarrhea. Each of these AE's was reported in 2-6 subjects out of 23. There were 13 SAE's reported in 10 children, two of which were severe (worsening of colitis and anemia). The relationship to therapy of all of these events is unclear since there was pre-existing colitis in one subject and the enrolled SJIA population had severe disease, mostly steroid dependent.

In an ongoing study, 90 subjects with T2DM on a stable dose of metformin each received a single 10 mg/kg intravenous dose of canakinumab. To date, canakinumab was safe and well tolerated in this population with no patients suffering an acute and unexpected hypo– or hyperglycemia following complete neutralization of endogenous IL-1β.

2.7 Dose rationale

Subjects will receive monthly subcutaneous injections of 2 mg/kg of canakinumab. While much higher doses have been shown to be safe and well tolerated, either intravenously (0.3 mg/kg to 10 mg/kg) or subcutaneously (0.5 mg/kg to 9 mg/kg or fixed dose of 150 or 300 mg), the maximal dose for this study was selected based on the clinical response obtained from other inflammatory diseases where this dose appears to be as efficacious as higher doses. At this dose, canakinumab results in rapid normalization of clinical signs and symptoms in those

diseases, including normalization of acute phase serum inflammatory protein markers, WBC counts, and platelets counts.

Pharmacokinetic parameters for canakinumab are typical of an IgG1-type antibody with a long half-life (ranging from 22.9 to 25.7 days) and low clearance (apparent serum clearance following s.c. administration ranging from 0.160 to 0.174 l/day). No clinically significant changes in canakinumab pharmacokinetic profile were observed due to differences in either age (after correction for body weight) or gender. In pediatric CAPS patients, peak concentrations of canakinumab occurred between 2 to 7 days following s.c. administration of either 150 mg or 2 mg/kg s.c. canakinumab and pharmacokinetic parameters were comparable with those seen in adults.

3. STUDY DESIGN

3.1. Overview

It is hypothesized that multiple injections of canakinumab will preserve endogenous insulin production in type 1 diabetes patients diagnosed within 3 months prior to the first injection.

Summary of Inclusion and Exclusion Criteria

3.1.1. Inclusion Criteria

Potential participants must **meet all** of the following inclusion criteria:

1. Be between the ages of 6 and 45 years
2. Be within 3-months (100 days) of diagnosis of type 1 diabetes based on American Diabetes Association (ADA) criteria
3. Must have at least one diabetes–related autoantibody present
4. Must have stimulated C-peptide levels $\geq$ 0.2 pmol/ml measured during a mixed meal tolerance test (MMTT) conducted at least 21 days from diagnosis of diabetes and within one month (37 days) of randomization
5. If participant is female with reproductive potential, she must be willing to avoid pregnancy and have a negative pregnancy test during the 12 months of treatment and for an additional 3 months.
6. At least one month from last live immunization received
7. Willing to forgo live vaccinations during the 12 months of treatment and for an additional 3 months.
8. Must be willing to comply with intensive diabetes management
9. Must weigh at least 20 kg at study entry

3.1.2. Exclusion Criteria

Potential participants must **not** meet any of the following exclusion criteria:

1. Are immunodeficient or have clinically significant chronic lymphopenia
2. Have an active infection or
3. Have a positive PPD test result
4. Be currently pregnant or lactating, or anticipate getting pregnant
5. Ongoing use of medications known to influence glucose tolerance
6. Require use of other immunosuppressive agents
7. Have serologic evidence of current or past HIV, Hepatitis B, or Hepatitis C infection
8. Have any complicating medical issues or abnormal clinical laboratory results that interfere with study conduct or cause increased risk to include pre-existing cardiac disease, COPD, neurological, or blood count abnormalities (such as lymphopenia, leucopenia, or thrombocytopenia)
9. Have a history of malignancies
10. Be currently using non-insulin pharmaceuticals that affect glycemic control
11. Be currently participating in another type 1 diabetes treatment study

3.2. Informed Consent

The process of assuring that individuals (and parent/guardian if less than 18 years of age) are making an informed decision about participating in this study includes both verbal and written communication. Written material will include a Patient Handbook and written consent forms. The consent form will be reviewed with participants (and their guardian in the case of participants under 18 years of age) and the participant will be given time to review the written consent form and ask questions. An assent form has also been developed for participants less than 18 years of age (unless local IRB requirements differ in procedure). As part of the informed consent process, the participant and/or parent or guardian (if the participant is less than 18 years of age) will also be required to complete a short, written Volunteer Understanding Assessment that is designed to ensure that the subject understands the study, as well as what is being asked of him/her. The participant will be given a copy of their signed consent/assent forms.

3.3. Description of Treatment Groups

This protocol will enroll a total of 66 participants who will be randomly assigned to the following two groups:

- 44 participants will be assigned to receive 12 injections with 2.0 mg/kg to a maximum 300 mg of canakinumab
- 22 participants will be assigned to receive 12 injections of placebo.

3.4. Treatment Assignment and Double Masking

After participants sign the consent form they will be randomized to one of the two arms. The randomization method will be stratified by TrialNet study site. The participants will not be informed regarding the intervention assignment until the end of the study. The investigator and clinic personnel will also be masked as to study assignment. Laboratories performing assays for this protocol will be masked as to the identity of biological material to be studied.

3.5. Study Assessments

During the course of the study, participants will frequently undergo assessments of their insulin production, immunologic status, overall health and well-being and diabetes care (see schedule of assessments in Appendix A). Information about the subject's experience as a research participant will also be collected. The participants' insulin production will be measured by a series of mixed meal glucose tolerance tests (MMTT) conducted regularly during the study. The

participants' diabetes control will be evaluated by measuring glycosylated hemoglobin (HbA1c) every three months and clinical records including insulin types, doses, and timing and SBGM records.

During the course of the study, samples will be drawn for storage in the National Institute for Diabetes and Digestive and Kidney Disease (NIDDK) Repository and at TrialNet Sites for future analysis.

3.6. Quality Assurance

During the study, duplicate collections of blood samples for assays will be obtained in a small sample of subjects for the purpose of quality surveillance of the performance of the central laboratories.

3.7. Post-treatment Follow-up

All subjects will be followed for at least 24 months to allow for assessment of both the primary and secondary endpoints with respect to stimulated C-peptide at both 1 and 2 years. Depending upon when they enter the study, subjects may then undergo follow-up for an additional two years with a visit every 6 months until study end. Study procedures at these visits will include many of the same assessments as during the previous visits (See Schedule of Assessments). Subjects with undetectable levels of C-peptide on the 30-month visit will not undergo any further MMTTs for assessment of C-peptide levels at subsequent visits.

4. PATIENT MANAGEMENT

4.1. Screening

After informed consent, subjects will undergo assessments to determine if they meet eligibility criteria. Documentation of the subjects understanding of the risks and benefits of the study will be collected through the Volunteer Understanding Assessment.

4.2. Randomization

Eligible study participants will be randomized by the TrialNet Coordinating Center at the baseline visit, and will be assigned a study randomization number corresponding to the treatment group assignment. The subject will receive the initial injection of canakinumab or placebo at the baseline visit.

4.3. Intensive Diabetes Management

During the study period, all participants will receive “intensive” management of their diabetes. The goal of the treatment will be to keep the HbA1c levels within the currently recommended American Diabetes Association age-specific target range in the absence of significant or severe hypoglycemia or diabetic ketoacidosis. The primary responsibility for diabetes management will be the treating or referring diabetes care provider, but the research study team will provide close additional support through regular interaction. Subjects will not be permitted to use non-insulin pharmaceuticals for glycemic control.

Glucose levels should be checked frequently and records of the glucose levels communicated regularly to the study team. Records of communication with the participant will provide source documentation of this interaction.

The Clinic Monitoring Group (or designated TrialNet Committee) will be evaluating the HbA1c data and provide additional guidance to the clinical site as needed to bring diabetes control within goals. Any episode of severe hypoglycemia will be promptly reviewed by the Safety Monitoring Committee with recommendations for changes in diabetes management, if any, conveyed to the clinical site in conjunction with the Clinic Monitoring Group.

4.4. Administration of Canakinumab

4.4.1. Dosing

All patients will receive 12 subcutaneous injections of 2.0 mg/kg to maximum of 300 mg canakinumab or placebo. Subsequent doses will be each calendar month. As the first injection is given at baseline (day 0), the last injection will be given on the 11th month into the study.

The dose is administered based on body weight, and the value will be rounded up by excess to the next half kilogram; i.e., 45.6 kg weight will be rounded up to 46 kg. Weight from the previous visit will be used so the pharmacy can prepare the dose ahead of time.

4.4.2. Drug withholding

Dosing will not be done in subjects with a febrile illness within the previous 48 hours or other signs or symptoms of active infection. These subjects will be rescheduled for another day within study dosing window. If the patient remains ill during the study window, that dose will be skipped and the patient will wait until the next scheduled dose.

Any subject who was EBV seronegative at baseline and who develops laboratory evidence of active EBV infection will not receive additional study drug injections until resolution of active infection (see section 6.3)

4.4.3. Study Drug Preparation

Novartis will supply canakinumab Powder for Solution for Injection as a lyophilized cake. This will be reconstituted to a 150 mg/ml (2.0 mg/kg dose) solution.

From a microbiological point of view, the solution for injection should be used immediately. If it is not used within 60 minutes of preparation, it should be kept at 2-8^{o}C as chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C. If the vial must be stored on wet ice, direct contact to the ice must be prevented to avoid uncontrolled local freezing. The vials should be allowed to come to room temperature for 5-10 minutes but not more than 15 minutes before administration.

Additional information in the Pharmacy Manual of Operations.

4.4.4. Study Drug Administration

Canakinumab Solution for injection should be administered subcutaneously. The injection may be split if desired for patient comfort.

Patients should remain at the study site for observation for at least 1 hour following study drug

administration for the first 3 doses. For the subsequent times, patients should remain at the study site for observation for at least 15 minutes after the study drug administration.

.

5. STUDY ASSESSMENTS

See Appendix 1 for detailed schedule of assessments

5.1. General Assessments

Study visits for both groups will occur at baseline, monthly through 12 months, and every 6 months through month 24. Subjects with persistent beta cell function at month 30 will be followed for up to two additional years until study end. General assessments include:

• Medical history including lifestyle and participant experience assessment

• Physical exam

• Concomitant medications

• Adverse events

5.2. Laboratory Assessments

The following general laboratory assessments will be performed:

- Chemistry (sodium, potassium, chloride, CO2, glucose, BUN, creatinine)
- Liver function tests (ALT, AST, alkaline phosphatase, total protein, albumin, total and direct bilirubin)
- Hematology (complete blood count with differential and platelets)

At screening, these additional laboratory assessments will be performed

- Purified protein derivative (PPD) test
- Diabetes Autoantibodies
- Antibodies to HIV, hepatitis B (antiHBcAb, HBsAg), hepatitis C (HCV), Cytomegalovirus (CMV IgG), Epstein-Barr Virus (EBV IgG and IgM)

Additional assessments include

- Urine pregnancy test before each injection for all sexually mature women
- PK/Cytokine levels before and 1 hour after the first 3 injections, then before the 4^{th} and 6^{th} injections, and at the 12 and 18 month visit.
- Tests obtained during the course of the study for infectious disease surveillance will include EBV PCR viral load monthly assessments during the first year in subjects seronegative at baseline. If the subject becomes positive, confirmation testing will be done and study medication withheld until absence of signs and symptoms of infection including negative viral load. This will be assessed by follow-up assessments with appropriate clinical tests.

5.3. Mechanistic Outcome Assessments

TrialNet will perform immune and genetic assays to further understand mechanisms that may be underlying the type 1 diabetes disease process and response to therapy. For this purpose, samples for PMBC, DNA, RNA, plasma, and serum will be obtained. HLA testing will be done. Subjects who are 18 months or more from their previous tetanus immunization will receive tetanus immunization at the time of their last treatment visit, i.e. month 11. At the time of or after the third treatment visit, subjects will receive their annual clinically indicated killed flu vaccine at the appropriate time of year. Responses to these immunizations will be determined through analyses of pre-and 4-week post-dose samples.

5.4. Metabolic Outcome Assessments

Metabolic assessments will consist of:

- Glucose records and reports of hypoglycemia
- Insulin dose
- HbA1c
- Mixed meal tolerance test (MMTT):
    - Subjects ≥12 years of age at screening
        - 4 hour MMTT at screening, 12, and 24 months
        - 2 hour MMTT at 1, 3,6, 9, and 18 months
    - Subjects < 12 years of age at screening
        - 2 hour MMTT at screening, 1, 3,6,9,12,18 and 24 months

5.4.1. Additional Metabolic Outcome Assessments

Canakinumab may have acute as well as prolonged beneficial effects on beta cell function. This study is primarily designed to address effects on beta cell function at one year after diagnosis. To obtain additional information about the possible acute effects of therapy, a 2 hour MMTT will be conducted one week after visit 6, a time consistent with peak canakinumab levels. For each individual subject, these data will be compared with their data from MMTT conducted prior to study drug administration at visit 7. Due to the additional visit required to conduct another MMTT, subjects may decline to participate in this aspect of the protocol while remaining in the main study. Those who do participate will receive compensation for their time and effort.

5.5. Visit Windows

The initial treatment should begin within 100 days from the day of diagnosis and within 37 days from the screening MMTT. Subsequent treatment visit target dates are monthly by calendar month (e.g. Feb 7, March 7, April 7). The treatment visits must occur within 7 days on either side of the targeted date. However, consecutive doses must be greater than 21 days apart. Treatment doses outside of the window will not be made up and target dates will not be reset. In this way, no one will receive more than 12 doses over a one-year period. The first post treatment visit (visit 13, month 12) must also occur within 7 days on either side of the targeted date. The window for all subsequent visits is +/- 2 weeks. Visit 6A (the time of the 2 hour MMTT listed above section 5.4.1) is to occur one week from visit 6 with a window +/- 2 days.

5.6. Withdrawal from treatment

The study will be conducted according to the intent-to-treat principle. This means that once randomized into the study, a participant will be expected to undergo all scheduled follow-up assessments and will remain within the assigned treatment group for purposes of statistical analysis regardless of the actual course of treatment administered. Withdrawal from treatment does not automatically entail withdrawal from the study. Withdrawal from the study will only occur if the participant dies or withdraws consent. Subjects who withdraw consent are classified as inactive but may again become active upon re-entry into the study, if they so choose.

Withdrawal from treatment can occur for a number of reasons, some of which are outlined below. A participant may elect to discontinue study injections, may be unable to continue them, or may be withdrawn (temporarily or permanently) at the discretion of the Principal Investigator if s/he determines that it is unsafe to continue or there is a significant change in the risk/benefit. Non-pregnant individuals who are withdrawn from treatment should remain in the study and undergo all scheduled MMTT assessment visits. MMTT visits will not occur while an individual is pregnant.

In addition, if a participant on active treatment has undetectable C-peptide values on a follow-up MMTT, the participant will be brought back into the clinic for a confirmatory MMTT. If this confirmatory MMTT again shows that all of the participant's stimulated C-peptide levels are undetectable, the participant will be switched from active treatment to placebo for the duration of their scheduled treatment period. The rationale is that the potential for benefit from the study treatment has been diminished once a participant's stimulated C-peptide has dropped below this level. The risk/benefit ratio is no longer sufficient to justify the risks associated with the study treatment. In order to maintain the masking of the study outcome, a random subset of placebo treated participants and/or those with a normal MMTT will also be brought back for an additional MMTT after undergoing a regularly scheduled MMTT.

5.6.1. Re-Entry into Study Treatment

In some circumstances, a participant may temporarily discontinue the study injections and/or not return to the study clinic for follow-up visits. If the participant decides to return for study injections and/or follow-up assessments at a later date, he or she will be allowed and encouraged to do so.

6. PARTICIPANT SAFETY

6.1. Expected Side Effects and Adverse Events

6.1.1. Infectious Adverse Events

As with all immunomodulating agents, there is a risk of infectious adverse events. In clinical trials, the most frequent infections reported were upper respiratory such as nasopharyngitis, rhinitis, and bronchitis. Upper respiratory infections occurred in up to 38% of subjects in canakinumab, the highest in CAPS patients. There have been 35 serious infections, 14 suspected to be related to drug. All infections were resolved following antibiotic therapy. To date, no opportunistic or fatal infections have been seen.

6.1.2. Immunizations

Although no data are available regarding the effects of vaccination in patients receiving canakinumab therapy, vaccination with live vaccines is not recommended during the 12 months of treatment and for an additional 3 months of the study. The possibility exists for canakinumab to affect host defenses against infections since the cellular immune response may be altered. All other vaccines are allowed. Tetanus and killed flu vaccine will be administered to subjects as part of the study (see Mechanistic Assessments).

6.1.3. Injection Site reactions

Injection site reactions are common with biological administered subcutaneously and have been observed almost half the time. However, these have largely been mild and well tolerated, not requiring either treatment or cessation of therapy.

6.1.4. Immunogenicity

Canakinumab is a fully human monoclonal antibody of the IgG-1λ class and it has the potential to induce the formation of anti-canakinumab antibodies. To date, none have been detected, likely since it is a fully humanized antibody. The immunogenicity of the drug will be monitored in this study. If antibodies to canakinumab are detected, their neutralizing potential will be evaluated.

6.1.5. Vertigo

Vertigo has been reported in canakinumab trials in both CAPS patients and SJIA patients. To date, the vertigo observed during the trials has been transient, and did not re-occur. Most resolved spontaneously, although some required therapy. The causality remains unknown.

6.2. Pregnancy

Pregnant and lactating women will not be included in the study. Sexually active females must have a negative pregnancy test prior to enrolling in the study and will be required to use birth control during the study. At every study treatment visit the sexual activity of female participants of reproductive age will be re-assessed. If a subject who was previously sexually inactive becomes sexually active, she will be counseled about the need to use a reliable form of birth control. Female subjects will also be required to undergo pregnancy tests before each study injection. Subjects will be requested to avoid pregnancy for 3 months following the last study injection and instructed to use birth control.

6.3. Protecting Against or Minimizing Potential Treatment Risks

Subjects will not be enrolled who have other active serious medical problems. Frequent monitoring of patients with history, physical examination, and laboratory studies will allow for early identification of adverse events. All participants will be required to have adequate hemoglobin to allow safe frequent venipuncture. Every attempt will be made to minimize the number of venipunctures.

All study drug injections will take place in a facility that has resuscitation capabilities, and subjects will be closely monitored during and after the injection.

Subjects will be counseled about the potential risk for infections and the need to report any change in health status between or at the time of visits. Directed questioning about concurrent illness will occur before each injection. No injection will occur in those with signs or symptoms indicative of active infection. In addition, those subjects who were EBV serology negative at screening will undergo evaluation of EBV viral load at each visit. If laboratory evidence of active EBV infection is present, subjects will not receive additional study drug injections until resolution of active infection indicated by laboratory evidence and absence of signs and symptoms of disease. In each instance, resumption of injections will occur only after review of the data and consultation with the TrialNet infectious disease consultants.

7. ADVERSE EVENT REPORTING AND SAFETY MONITORING

7.1. Adverse Event Definition

7.1.1. Adverse Event

In this clinical trial, an adverse event is any occurrence or worsening of an undesirable or unintended sign, symptom or disease whether or not associated with the treatment and study procedures.

Throughout the study, the investigator must record all adverse events on source documentation and those that are Grade 2 or greater must be recorded on the appropriate adverse event form as described below. The investigator should treat participants with adverse events appropriately and observe them at suitable intervals until the events resolve or stabilize.

Adverse events may be discovered through:

- observation of the participant;
- questioning the participant;
- unsolicited complaint by the participant.

In questioning the participant the questioning should be conducted in an objective manner.

7.1.2. Serious Adverse Event

A serious adverse event (SAE) or reaction is any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient and/or may require medical or surgical intervention to prevent one of the outcomes listed above.

7.1.3. Unexpected Adverse Event

An adverse event is considered unexpected when the nature (specificity) or severity of the event is not consistent with the risks described in the protocol or informed consent document for a particular protocol required intervention.

7.1.4. Grading Event Severity

TrialNet has adopted usage of the National Cancer Institute (NCI) Common Technology Criteria for Adverse Events (CTCAE) with the exception of hypoglycemia and hyperglycemia for classification to describe the severity of adverse events. For this study, a reportable hypoglycemic event is defined as those resulting in loss of consciousness, seizure, or requiring assistance of others due to altered state of consciousness. A hyperglycemic event is one resulting in diabetic ketoacidosis (DKA).

7.2. Adverse Event Reporting and Monitoring

Study personnel will assess adverse events and the use of concomitant medications throughout the study. All adverse events will be recorded on source documents and those that are ≥ grade 2 will be reported to the TrialNet Coordinating Center as described below. They will be graded as to severity according to common toxicity criteria or study-specific criteria and the investigator will make a determination as to the relation to therapy. Events will be assessed and reported in accordance with the ICH Guideline for Good Clinical Practice and per the guidance of the DHHS Office for Human Research Protections (OHRP). An adverse event report must be completed for all adverse events (AE) of Grade 2 or greater severity regardless of relationship to therapy. For reporting serious adverse events (SAE), the TrialNet MedWatch Form should also be completed and faxed to the TNCC *within 24 hours of when the site was notified of the event.* This will be reviewed by the TrialNet Medical Monitor, the TrialNet Safety Committee, and the DSMB as appropriate. Deaths must be reported immediately. Event outcome and other follow-up information regarding the treatment and resolution of the event will be obtained and reported when available, if not known at the time the event is reported. The follow-up information should contain sufficient detail to allow for a complete medical assessment of the case and an independent determination of possible causality.

Adverse events will be assessed by the TrialNet Medical Monitor. The DSMB will conduct regular safety reviews approximately every three to six months (and, as needed) of adverse events by treatment group assignment. Serious adverse events as well as adverse events leading to study discontinuation will be reviewed by the DSMB.

8. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Analyses of study data will be conducted to address all objectives of the trial and other interrelationships among data elements of interest to the investigators and of relevance to the objectives of the study. Analyses by gender and race/ethnicity, as appropriate, are also planned.

Primary analysis of treatment effect will be conducted under the intention-to-treat principle of eligible subjects whereby outcome data from all eligible subjects will be included regardless of treatment compliance. Note that subjects that are missing their 12 month MMTT assessment will not be included in the primary endpoint analysis.

8.1. Primary Outcome and Analyses

The primary outcome of each participant is the area under the stimulated C-peptide curve (AUC) over the first 2 hours of a mixed meal glucose tolerance test conducted at the one-year visit. The AUC is computed using the trapezoidal rule that is a weighted sum of the C-peptide values over the 120 minutes. The weighted mean C-peptide is simply AUC/120 (pmol/mL). Let Y_{Cp}^{ACZ885} and $Y_{Cp}^{Control}$ represent the C-peptide value for study subjects receiving canakinumab and those receiving placebo, respectively. Likewise, let μ_{Cp}^{ACZ885} and $\mu_{Cp}^{Control}$ represent the mean of Y_{Cp} for these groups, respectively.

The primary statistical hypothesis to be assessed in the study is:

$$\text{H}_0\text{: } \mu_{Cp}^{\text{ACZ885}} = \mu_{Cp}^{Control} \text{ versus H}_a\text{: } \mu_{Cp}^{\text{ACZ885}} > \mu_{Cp}^{Control}$$

The primary analysis will be conducted on the transformed Y_{Cp} using the log function: $\log(Y_{Cp}+1)$. This provides better normal distributional behavior of the random variable. The comparison will be based on a t-test of treatment effect in an ANCOVA model adjusting for gender, baseline age, and baseline $\log(Y_{Cp}+1)$.[12]

8.2. Secondary Outcome and Analyses

Additional analyses of the primary outcome to determine the effect of canakinumab include:

- Mean AUC C-peptide from the stimulated C-peptide curve over 2 hours at 1, 3, 6, 9, 12, 18, and 24 months.

- A log rank test of the difference in the C-peptide failure hazard function between groups (C-peptide failure is defined as the first occurrence at which the 2 hour peak C-peptide < 0.2 pmol/ml during a MMTT)[13]. Also, a proportional hazards model will be used to compare treatment groups while adjusting for baseline level of C-peptide, gender, and baseline age. [14]
- Longitudinal analyses using mixed effects models with a random intercept and slope of the C-peptide values over the treatment period, adjusted for the baseline level of C-peptide, gender, and baseline age. The average intercept and slope will be compared between treatment groups.[15]
- Treatment interactions with the covariates baseline C-peptide, gender and baseline age will be analyzed with a homogeneity test categorizing the continuous variables into 3 approximately equal groups; ladder plots will be constructed.
- Analyses will also be conducted adjusting for HbA1c levels, HLA, other genotype and immune phenotypes, and race/ethnicity, as appropriate.
- If approximately half of the study population elects to have an MMTT approximately one week after the month 5 visit, the change in C-peptide will be determined between this MMTT and month 6 MMTT by treatment group to quantify any short term effect of the drug administration.

Additional secondary objectives include how the canakinumab affects the following:

- Longitudinal analysis of HbA1c, Insulin dose (units/kg) and blood glucose by treatment group using normal variance-covariance structure.[16]
- Adverse events
    - Number and severity
    - The rates of severe adverse events will be computed (total number of events divided by total subject years of follow-up) and the rates compared using a Poisson regression model, allowing for over-dispersion using a quasi-likelihood model as appropriate and adjusted for baseline age, gender, baseline C-peptide and HbA1c.
- Hypoglycemia
    - Number of major hypoglycemic events (defined as loss of consciousness, seizure, or requiring assistance from another person because of altered state of consciousness).
    - Reported hypoglycemic events confirmed with capillary blood glucose measurement less than 70 mg/dl.
    - The rates of severe hypoglycemic will be computed (total number of events divided by total subject years of follow-up) and the rates compared using a Poisson regression model, allowing for over-dispersion using a quasi-likelihood model as appropriate and adjusted for baseline age, gender, baseline C-peptide and HbA1c.
- For individuals with continuous glucose monitoring data available
    - Area under the curve and number of events less than 70 mg/dl on the continuous glucose monitoring record.
    - Hyperglycemia measured as the area under the curve and number of events greater than 180 mg/dl on the CGMS record prior to each study visit.
    - Glycemia and glycemic variability prior to each MMTT visit
    - The daily mean level of glucose, as well as the levels before and after meals will be computed.

- Measures of diurnal variability in glucose will be measured by the J-value, standard deviation of glucose values, and the mean amplitude of glycemic excursion (MAGE).

8.3. Additional Outcomes and Analyses

Additional outcomes of interest include the effects of the canakinumab treatment with regard to the Mechanistic Studies assessed from blood draws as outlined in the Schedule of Assessments (Appendix 1). These measures include, but are not limited to, exploration of pharmacogenetic signatures that may differentiate response to treatment, and the relationship between hsCRP and IL-1β levels and beta cell function and/or other metabolic measures

Additional analyses will compare the results in this trial to other trials using canakinumab and other TrialNet studies. Data in this trial will be used in conjunction with other TrialNet data for exploratory analysis.

Additional analysis will be conducted evaluating primary, secondary, and other outcomes using the subjects that have received their intended treatment.

8.4. Sample Size and Power Calculations

The primary analysis will compare the difference between the experimental and placebo treatment groups in the levels of $\log(Y_{Cp}+1)$ using an ANCOVA model adjusting for gender, baseline age and $\log(Y_{Cp}+1)$. Estimates of the mean and standard deviation of $\log(Y_{Cp}+1)$ (expressed algebraically as: $\hat{\mu}_{\log(Y_{Cp}+1)}$ and $\hat{\sigma}_{\log(Y_{Cp}+1)}$) in the placebo group were obtained from previous studies.[17] The estimates are $\hat{\mu}_{\log(Y_{Cp}+1)}=0.248$ and $\hat{\sigma}_{\log(Y_{Cp}+1)|X}=0.179$ (i.e., the residual mean squared error from the linear modeling of $\log(Y_{Cp}+1)$ adjusting for gender, baseline age and C-peptide). An approximation of the mean of Y_{Cp} for the placebo group is $\exp(0.248)-1=0.281$ pmol/mL.

Using standard equations for the comparison of two means, a sample size of 40 canakinumab treated and 20 placebo treated subjects with complete data would provide power of 85% to detect a $0.75\sigma_{\log(Y_{Cp}+1)}$ increase over $\mu^{Control}_{\log(Y_{Cp}+1)}$ in the experimental treatment group using the Wald test at the 0.05 level (one-sided).

Assuming that 10% of the subjects will have missing data (one-year MMTT was not done or subject withdrew prior to the one-year assessment), the sample size goal for this study is 66 subjects (44+22). The plan is to follow these subjects for two years from baseline and for up to 2 additional years post-treatment if residual beta-cell function is detected.

The actual final sample size may be slightly greater than the numbers above because of staggered subject entry and the sequential enrollment phases. The study will be closed to new

subjects entering the screening phase when the total number then randomized plus a fraction of those in screening is expected to provide the proper number of eligible subjects. Subjects who had already conducted the initial screening visit at that time will be allowed to complete screening and be randomized if both consenting and eligible.

8.5. Interim Monitoring Plan

Interim analyses will be conducted periodically during the study and will be reviewed by the TrialNet DSMB for assessment of effectiveness and safety. The Lan-DeMets spending function with an O'Brien-Fleming boundary will be used to protect the type I error probability from early and multiple testing and to assess the significance of the interim results that emerge during the trial.[18] The spending function that approximates the O'Brien-Fleming boundaries is:

$$\alpha_1(t^*) = 2 - 2\Phi\left[\frac{Z_{\alpha/2}}{\sqrt{t^*}}\right]$$

where t^* is the information fraction ($0 < t^* \leq 1$), α_1 is the $\alpha\text{-}level$ of the interim (one-sided) test and α is the over-all type I error (i.e., 0.05). The monitoring plan will allow for early termination based on the treatment effect on C-peptide values at 1 year of follow-up using the ANCOVA model described above.

The DSMB will also be informed if there is a serious lack of evidence of a treatment effect (i.e. futility analysis). The boundaries are based on the paper by Lachin.[19] The study should be "stopped" based on the futility of rejecting the null hypothesis at the completion of the trial if: $z_{ACZ885}(t^*) \leq 0$ when $0.5 \leq t^* < 0.8$ or if $z_{ACZ885}(t^*) \leq 0.8$ when $t^* \geq 0.8$. These $t^* = 0.5$ and 0.8 are equivalent to when there are 30 and 48 subjects with one-year C-peptide results, respectively. Lachin showed that a onetime use of either boundary contributes less than 0.003 to the type II error. It is straight forward to show that if conducted at a larger value of t^* the increase to the error probability is even less. Furthermore, a single use of each rule will increase the type II error no more than twice this probability (i.e., 2x0.003). Simulation studies conducted confirmed that a single use of each interim test will increase the type II error by 168/20000 = 0.0084. Additional analysis will assess potential adverse outcomes of treatment and will assess the incidence of all severe adverse events.

An informal analysis of the mean AUC C-peptide at 6 months by treatment group will be conducted when such data is mature. These results will not be disclosed until the last subject completes their 12 month (primary endpoint) evaluation. Such analysis will have no effect on the conduct of this study.

9. ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

9.1. Statement of Compliance

This study will be conducted in compliance with the protocol and generally consistent with current Good Clinical Practices (GCP), adopting the principles of the Declaration of Helsinki, and all applicable regulatory requirements.

Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate Independent Ethics Committee (IEC) or Institutional Review Board (IRB). Any amendments to the protocol or consent materials must also be approved before they are implemented.

9.2. Participating Centers

Participating TrialNet clinical sites must have an appropriate assurance, such as a Federal-wide Assurance (FWA), with the Office for Human Research Protections (OHRP), since they are actively engaged in research and provide informed consent. The protocol and consent forms will be approved by Institutional Review Boards at each of the participating clinical sites. HIPAA regulations will be followed by each participating institution in accordance with each institution's requirements. The participating international sites will obtain approval from their corresponding review boards in accordance with their local procedures and institutional requirements.

The investigator is required to keep accurate records to ensure the conduct of the study is fully documented. The investigator is required to ensure that all case report forms are legibly completed for every participant entered in the trial.

The investigational sites participating in this study will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from participants participating in this study. Medical and research records should be maintained at each site in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, the investigational site must permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. Unless required by the laws permitting copying of records, only the coded identity associated with documents or other participant data may be copied (obscuring any personally identifying information). Authorized representatives as noted above are bound to maintain the

strict confidentiality of medical and research information that may be linked to identify individuals. The investigational site will normally be notified in advance of auditing visits.

9.3. Informed Consent

The consent process will be conducted by qualified study personnel (the Trial or Study Coordinator and/or Investigator or other designee). All participants (or their legally acceptable representative) must read, sign and date a consent form prior to participation in the study, and/or undergoing any study-specific procedures.

The informed consent form must be updated or revised whenever important new safety information is available, when indicated for a protocol amendment, and/or whenever any new information becomes available that may affect a patient's participation in the study.

9.4. Study Subject Confidentiality

Study records with the study subject's information for internal use at the clinical sites will be secured at the study site during the study. At the end of the study, all records will continue to be kept in a secure location. There are no plans to destroy the records.

Study subject data, which is for reporting purposes, will be stored at the TrialNet Coordinating Center. Electronic Case report forms submitted to the Coordinating Center will identify participants by the unique TrialNet Identification Number. The data entry system at the Coordinating Center is a secured, password protected computer system. At the end of the study, all study databases will be archived at the Coordinating Center.

HLA genotyping is for research purposes only. The HLA genotyping result will not be made available to the participant and his or her physician. DNA will be stored for future use with the permission of the study subject.

Stored samples could be utilized to learn more about causes of Type 1 diabetes, its complications (such as eye, nerve, and kidney damage) and other conditions for which individuals with diabetes are at increased risk, and how to improve treatment. The results of these future analyses will not be made known to the participant.

9.5. Risks, Benefits, and Inclusion of Children

The risks of this study are presented in this protocol and in the informed consent form. This study will examine whether canakinumab will preserve beta cell function, but there is no guarantee that this will occur.

There is the prospect of direct benefit to the individual subjects for their participation in the study. These potential benefits include the recognized benefits of being in a clinical study, including close monitoring and additional resources available to maintain tight glycemic control offered to all subjects, regardless of group assignment. Further, the intervention has the prospect of direct benefit to a given subject and is likely to yield general knowledge about T1DM that is of importance for the understanding and amelioration of T1DM in children.

The study procedures, while possibly slightly greater than minimal risk, offer the possibility of benefit in the close monitoring for all children. Assent of children along with consent of the parents will be obtained prior to any study procedures. This research proposal in children is therefore consistent with United States Department of Health and Human Services, Protection of Human Subjects, subpart D, section 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects) and with Subpart D. 50.52 (Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects).

10. STUDY ADMINISTRATION

10.1. Sponsor

This study is part of Type 1 diabetes TrialNet, which is funded by the National Institutes of Health. As sponsor, NIH and TrialNet are responsible for the study conduct and data analysis

10.2. Relationship with Industry

Novartis will provide canakinumab and placebo free of charge for the study, and will also be providing addition support for the conduct of the study. They may also receive de-identified samples to conduct mechanistic studies solely as directed by TrialNet.

10.3. Groups and Committees

10.3.1. Canakinumab Study Committee

The Canakinumab Study Committee, the TrialNet Clinic Monitoring Group, Laboratory Monitoring Group, Steering Committee and Data and Safety Monitoring Board will receive periodic reports from the TrialNet Coordinating Center on the progress of the study. These will include accrual rates and baseline demographic characteristics.

As appropriate, abstracts and manuscripts dealing with the progress of the Canakinumab Study shall be prepared by the Canakinumab Study Committee under the guidance of the TrialNet Publications and Presentations Committee under the policies established by TrialNet.

10.3.2. TrialNet Chairman's Office and TrialNet Coordinating Center

The TrialNet Chairman's Office and TrialNet Coordinating Center (TNCC) will collaboratively provide leadership to the TrialNet study group to include protocol and manual preparation, training for clinical sites, development of statistical design for each study, analysis of study results and the preparation of publications and presentations. The TNCC will also coordinate interactions among the participating TrialNet Clinical sites, laboratories including TrialNet core laboratories and other subcontract laboratories, NIDDK, and other sponsoring agencies.

10.3.3. Clinical Sites

Each Principal Investigator at the participating TrialNet clinical site will oversee all operations. The clinical sites will forward all laboratory and data collection form information to The TrialNet

Coordinating Center for analysis. Conference calls and site visits, as needed, will facilitate evaluation of the trial management.

10.3.4. Clinical Site Monitoring

In order to conduct this study consistent with established research principles and ICH-GCP guidelines, there may be site visits conducted during the study to evaluate study conduct. All sites will be monitored by the Coordinating Center and appropriate TrialNet committees for patient enrollment, compliance with protocol procedures, completeness and accuracy of data entered on the case report forms (CRFs), and the occurrence and reporting of adverse events (AEs) and serious adverse events (SAEs).

10.3.5. Data and Safety Monitoring Board (DSMB)

The DSMB will meet approximately every 6 months to review efficacy issues and adverse events prepared by the Coordinating Center. All adverse events will be recorded on the adverse event forms, which will be sent to the local IRBs, per their reporting requirements, and to the Coordinating Center. The DSMB will independently evaluate whether the adverse events constitute grounds to discontinue the study.

10.4. Sample and Data Storage

Samples to be stored for research purposes will be located at the NIDDK Repository and at TrialNet Sites. While TrialNet is active, the use of the samples will be restricted to TrialNet researchers unless researchers from outside of TrialNet obtain approval from the TrialNet Steering Committee and the NIDDK to utilize the samples. The samples will be coded with unique study numbers, but TrialNet researchers will be able to identify samples if it is necessary to contact participants for reasons of health or for notification to them about future studies. Approval from the TrialNet Steering Committee and the NIDDK would be required before such linkage could occur. Researchers from outside of TrialNet will not be permitted to identify samples.

Data collected for this study will be sent to the TrialNet Coordinating Center.

After the study is completed, de-identified data will be stored at the NIDDK Repository, under the supervision of the NIDDK/NIH, for use by researchers including those outside of TrialNet.

When TrialNet is completed, samples will continue to be stored at the NIDDK Repository Sites. Since the stored data will be fully de-identified upon the completion of TrialNet, it will no longer be possible to identify samples. Thus, whereas a sample can be destroyed upon a participant's request during the existence of the TrialNet, it can no longer be destroyed once TrialNet is completed. However, there will still be the potential to link data derived from the samples with data that had been derived from TrialNet studies. Once TrialNet is completed, researchers will only obtain access to samples through proposals approved by the NIDDK. The NIDDK will convene an external panel of experts to review requests for access to samples.

10.5. Preservation of the Integrity of the Study

The scientific integrity of the trial dictates that results be reported on a study-wide basis; thus, an individual center will not report the data collected from its center alone. All presentations and publications using TrialNet trial data must protect the main objectives of the trial. Data that could be perceived as threatening the masking will not be presented prior to release of the primary study outcomes. Approval as to the timing of presentations of data and the meetings at which they might be presented will be given by the TrialNet Steering Committee. Study results should be discussed with the news media only upon authorization of the Steering Committee, and never before the results are presented. Any written statements about this study that are shared with national media should be approved by the Steering Committee before release. All publications and presentations must be approved by the TrialNet Publications Committee.

10.6. Participant Reimbursement and Compensation

Participants will be compensated for each visit attended in the study.

11. STUDY TIMELINE

It is anticipated that patient enrollment will occur during the first two years of the trial. Subjects will be followed for at least two years after beginning treatment. Depending on when they enroll, subjects will then undergo additional follow-up after two years for up to an additional two years with a visit every 6 months. Subjects with undetectable levels of C-peptide on the 30 month or any subsequent visits will not undergo any further MMTT for assessment of C-peptide.

12. NEW CLINICAL INFORMATION AND PROCEDURES

Novartis published the Periodic Safety Update Report 4 (PSUR 4) for canakinumab in August 2011. In this publication, it was noted that there appeared to be an increased incidence of neutropenia and thrombocytopenia in subjects from selected populations treated with canakinumab as compared to placebo. Subsequently, Novartis also published the EU Annual Safety Report indicating that neutropenia would be "upgraded to an identified risk in the next risk management plan".

The neutropenia data from PSUR 4 show differences in canakinumab vs placebo treated subjects with rheumatoid arthritis (RA), but not gouty arthritis or CAPS disease. Neutropenia, in this analysis, is defined as an absolute neutrophil count ≤0.9 times the lower limit of normal. The rate of neutropenia by this definition was 0.9% (1/121) in RA subjects receiving placebo, 5.9% (4/69) in RA subjects receiving 150 mg of canakinumab, and 6.8% (16/263) in RA subjects receiving >150 mg of canakinumab.

In subjects with gouty arthritis, but not in other diseases, there was an increase in thrombocytopenia observed in those treated vs not treated with canakinumab. This was true at higher doses of canakinumab (150 mg and ≥200 mg). Rates of grade 1 thrombocytopenia in gouty arthritis subjects were 12.7% (32/253) in 150 mg group and 12.3% (13/107) in ≥200 mg group, as compared to 5.6% (22/108) in colchicine only group, and 7.7% (6/286) in triamcinolone only group. Of note is that all thrombocytopenia (with one exception) were grade 1 events. There was a single grade 4 event which occurred in one subject in the triamcinolone only group.

Ongoing review of data from this protocol as of October, 2011 demonstrated asymptomatic neutropenia in several subjects. In light of this data, TrialNet has proposed and the DSMB has agreed to institute increased monitoring of subjects in our trial as described below:

1. CBC monthly prior to injection of study drug. CBCs may be drawn within 2 weeks prior to study visit and if acceptable, drug may be given without delay on day of study visit. If the CBC was not obtained prior to, it will be obtained at time of study visit but must be resulted prior to drug administration.
2. If a CBC shows an ANC <1,500/mm3 or a platelet count <75,000/mm3 drug will not be given. Missed doses will not be made up and next tentative dose will be scheduled based on original (study entry) calendar.
3. Repeat CBC to be obtained within 2 weeks if any values constitute a grade 2 or 3 event; within one week if grade 4 event. Additional follow-up as needed clinically.
4. Subsequent administration of study drug to individuals with CBC values Grade ≥ 3 will require approval of medical monitor or designee

APPENDIX 1 - Schedule of Assessments

Visit Number	-1	1	2	3	4	5	6	6A[2]	7	8	9	10	11	12	13	14	15	16-19
Year															1		2	
Month	-1[1]	0	1	2	3	4	5		6	7	8	9	10	11	12	18	24	[10]
History	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Physical exam[3]	X	X			X				X			X			X	X	X	X
AE Assessments		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
CBC with Differential[11]	X								X	X	X	X	X	X	X			
Chemistries	X								X						X			
PPD Test	X																	
Viral serology[4]	X																	
EBV viral load [5]	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
Serum for Diabetes Autoantibodies	X																	
Study drug Administration		X	X	X	X	X	X		X	X	X	X	X	X				
PK, cytokines		X	X	X	X		X								X	X		
Immunizations;[7]														X				
Hemoglobin A1c		X			X				X			X			X	X	X	X
MMTT (4-hour)[8]	X														X		X	
MMTT (2-hour)			X		X			X	X			X				X		X
Mechanistic Assessments[9]	X	X	X	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. **Visit 6A**: 2 hr MMTT in subjects who agree to this additional test (this visit will occur 1 week after visit 6 (month 5)
3. **Physical Exam**: Routine exam at screening, baseline, and quarterly during first year, every six months thereafter; directed exam prior to administration of study drug injection if clinically indicated.
4. **Serology/viral monitoring**: EBV, CMV, HIV, Hep B and C will be done at screening, and subsequently if clinically indicated
5. **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 injections until resolution of infection.
6. **Study drug level and cytokines analysis**: PK levels before and 1 hour after the first 3 injections, then before the 4th and 6th injections, and at the 12 and 18 month visit.
7. **Immunizations and response**: At study visit 12, 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 13. Subjects will have a pre-immunization blood draw and then receive killed flu vaccine during a study visit from visit 3 until visit 12 inclusive. These will occur during a clinically appropriate month with follow up blood draw assessing immune response at next visit.
8. **MMTT (4 –hour):** Subjects < 12 years of age at time of screening will undergo 2 hour MMTT instead of 4 hour MMTT
9. **Mechanistic Assessments**: includes samples for RNA, plasma, serum, DNA, measures of B and T cell number and function to understand the effect of therapy on the immune system and infectious disease. 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 age and body weight (For subjects <18 5ml/kg per visit, 9.5 ml/kg in an 8 week period unless local IRB indicates otherwise).
10. **Follow-Up After 24 Months**: Visits will be conducted approximately every 6 months.
11. CBC with differential may occur within 2 weeks of scheduled injection visit. This may occur at a laboratory facility convenient for the subject. Results to be evaluated before injection of study medication. No injection to be given if platelets <75,000 or ANC <1500. If grade 2 or 3 CBC values, repeat testing within two weeks; if grade 4 CBC values, repeat testing within one week. Additional repeat testing of abnormal values will occur as indicated clinically.

REFERENCES

[1] Ng,WY, Thai,AC, Lui,KF, Cheah,JS: Humoral immune abnormalities in diabetes mellitus. Annals of the Academy of Medicine, Singapore Jul;19:443-6, 1990

[2] DCCT group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 329:977-986, 1993

[3] DCCT group: Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. American Journal of Cardiology 75:894-903, 1995

[4] DCCT group: Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. The Diabetes Control and Complications Trial Research Group. Ann Intern Med 128:517-523, 1998

[5] Steele,C, Hagopian,WA, Gitelman,S, Masharani,U, Cavaghan,M, Rother,KI, Donaldson,D, Harlan,DM, Bluestone,J, Herold,KC: Insulin secretion in type 1 diabetes. Diabetes 53:426-433, 2004

[6] Greenbaum,CJ, Harrison,LC: Guidelines for intervention trials in subjects with newly diagnosed type 1 diabetes. Diabetes 52:1059-1065, 2003

[7] Palmer,JP, Fleming,GA, Greenbaum,CJ, Herold,KC, Jansa,LD, Kolb,H, Lachin,JM, Polonsky,KS, Pozzilli,P, Skyler,JS, Steffes,MW: C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21-22 October 2001. Diabetes 53:250-264, 2004

[8] Donath,MY, Storling,J, Maedler,K, Mandrup-Poulsen,T: Inflammatory mediators and islet beta-cell failure: a link between type 1 and type 2 diabetes. J Mol Med 81:455-470, 2003

[9] Maedler,K, Sergeev,P, Ris,F, Oberholzer,J, Joller-Jemelka,HI, Spinas,GA, Kaiser,N, Halban,PA, Donath,MY: Glucose-induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets. J Clin Invest 110:851-860, 2002

[10] Maedler,K, Sergeev,P, Ris,F, Oberholzer,J, Joller-Jemelka,HI, Spinas,GA, Kaiser,N, Halban,PA, Donath,MY: Glucose-induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets. J Clin Invest 110:851-860, 2002

[11] Maedler,K, Schumann,DM, Sauter,N, Ellingsgaard,H, Bosco,D, Baertschiger,R, Iwakura,Y, Oberholzer,J, Wollheim,CB, Gauthier,BR, Donath,MY: Low concentration of interleukin-1beta induces FLICE-inhibitory protein-mediated beta-cell proliferation in human pancreatic islets. Diabetes 55:2713-2722, 2006

[12] Cochran WG, Snedecor GW: Statistical Methods. Ames, The Iowa State University Press, 1967

[13] Mantel,N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163-170, 1966

[14] Cox DR: Regression model and Life Tables (with discussion). J R Stat Soc 34B:187-220, 1972

[15] Diggle PJ, Liang KY, Zeger S: Analysis of Longitudinal Data. Oxford, Clarendon Press, 1994

[16] Diggle PJ, Liang KY, Zeger S: Analysis of Longitudinal Data. Oxford, Clarendon Press, 1994

[17] Palmer,JP, Fleming,GA, Greenbaum,CJ, Herold,KC, Jansa,LD, Kolb,H, Lachin,JM, Polonsky,KS, Pozzilli,P, Skyler,JS, Steffes,MW: C-peptide is the appropriate outcome measure for type 1 diabetes clinical trials to preserve beta-cell function: report of an ADA workshop, 21-22 October 2001. Diabetes 53:250-264, 2004

[18] Lan,KKG, DeMets,DL: Descrete sequential boundaries for clinical trials. Biometrika 70:659-663, 1983

[19] JM Lachin. Futility interim monitoring with control of type I and II error probabilities using the interim Z-value or confidence limit. Clinical Trials 2009; 6 (6) 565-573.