Immune Tolerance Network

National Institute of Allergy and Infectious Diseases

Preserving Beta-Cell Function with Tocilizumab in New-onset Type 1 Diabetes

Protocol ITN058AI

Version V6.0 (June 13, 2018)

Protocol Co-Chair

[redacted]

Protocol Co-Chair

[redacted]

ITN Clinical Trial Physician

[redacted]

NIAID Medical Monitor

[redacted]

ITN Clinical Operations Manager

[redacted]

NIAID Project Manager

[redacted]

ITN Lead Biologist

[redacted]

NIAID Regulatory Officer

[redacted]

Rho Scientist

[redacted]

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This document is confidential. It is provided for review only to investigators, potential investigators, consultants, study staff, and applicable ethics committees or institutional review boards. It is understood that the contents of this document will not be disclosed to others without written authorization from ITN and NIAID unless it is necessary to obtain informed consent from potential study participants.

Protocol Approval

Protocol: ITN058AI	**Protocol Version: V6.0**
	Dated: June 13, 2018
US IND # 117725	**Protocol Co-Chairs:** [redacted]
Title: ***Preserving Beta-Cell Function with Tocilizumab in New-onset Type 1 Diabetes***	

I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of good clinical practice (GCP) as described in the US Code of Federal Regulations (CFR)—45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the International Conference on Harmonization (ICH) document *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance* dated April 1996. Further, I will conduct the study in keeping with local legal and regulatory requirements.

As the principal investigator, I agree to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without written permission of the NIAID.

_____

Principal Investigator **(*Print*)**

_____ _____

Principal Investigator **(*Sign*)** **Date**

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Synopsis

Title	Preserving Beta-Cell Function with Tocilizumab in New-onset Type 1 Diabetes
Short Title	TCZ in New-onset T1D
US IND	117725
Sponsor	US and Global Study Sponsor: Division of Allergy, Immunology, and Transplantation (DAIT), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), USA Local Sponsor in Australia: Pharmaceutical Product Development, Inc. (PPD) for NIAID, NIH
Conducted by	Immune Tolerance Network, an NIH grantee
Protocol Co-Chairs	[redacted]
Accrual Objective	78 eligible pediatric subjects (6-17 years old) and 30-99 eligible adult subjects (18-45 years old) will be enrolled. Only pediatric participants are eligible for randomization after May 15, 2017.
Study Treatment	Tocilizumab or placebo
Study Design	This trial will be conducted in the US and Australia as a multi-center, prospective, double-blind, placebo-controlled, 2:1 randomized, phase 2 clinical trial for individuals with recent-onset T1DM aged 6−45 years, inclusive. All groups will receive standard intensive diabetes management. The subjects will receive IV infusions of either 8.0 mg/kg (body weight ≥30kg) or 10.0 mg/kg (body weight <30kg) tocilizumab or placebo every 4 weeks for 24 weeks. A staggered enrollment plan is being used for this trial. Prior to initiating the study in the pediatric age group (6-17 years old), adults (18-45 years old) were randomized 2:1 to tocilizumab or placebo, respectively. After 30 adult participants completed 12 weeks of treatment, the DSMB and FDA reviewed the available data to weigh potential risks and benefits as well as prospect of benefit before opening the trial to pediatric participants. The result of those reviews was to allow enrollment of children and adolescents 6-17 years old.
Study Duration	Total study duration will be approximately 4-5 years. • The enrollment phase is expected to last up to 42 months. • The study participation phase will be 104 weeks (2 years), which includes a treatment phase of 24 weeks and a follow-up phase of 80 weeks.

Primary Objective

Determine whether tocilizumab will slow the progression of the autoimmune destruction of ß cells and lead to the preservation of C-peptide secretion in T1DM.

Primary Endpoint

MMTT-stimulated mean 2-hour C-peptide AUC at week 52.

Secondary Endpoints

Efficacy:

1. MMTT-stimulated mean 2-hour C-peptide AUC at weeks 12, 24, and 104.
2. MMTT-stimulated mean 2-hour C-peptide AUC assessed longitudinally at weeks 12, 24, 39, 52, 78, and 104.
3. MMTT-stimulated peak and 4-hour C-peptide AUC at weeks 52 and 104 for subjects ≥12 years old.
4. Insulin use (U/kg/day) at weeks 12, 24, 39, 52, 78 and 104; HbA1c levels at weeks 12, 24, 39, 52, 78 and 104.
5. Glycemic control.

Safety:

1. Rate of AEs related to infusion reactions and hypersensitivity.
2. Frequency and severity of all AEs.

Mechanistic:

1. Determine the effect of TCZ on the ratio of Treg and Teff.

Exploratory Endpoints

Mechanistic:

1. Determine effect of TCZ on measures of immune cell number and function such as:
    a. Changes in proportions and phenotype of Treg and Teff.
    b. Changes in sensitivity of Teff to suppression by Treg.
    c. Changes in circulating B cell compartment and activation state of innate immune cells including antigen presenting cells and NK cells.

Metabolic:

1. Explore the relationship between immune responses, metabolic outcomes and clinical variables.
2. Explore the effect of TCZ on insulin sensitivity.

Inclusion Criteria

1. Male or female aged 6-45 years inclusive who meet the American Diabetes Association T1DM criteria.
2. Diagnosis of T1DM within 100 days of enrollment (V0).
3. Positive for at least one diabetes-related autoantibody, including but not limited to:
    a. Glutamate decarboxylase-65 (GAD-65);
    b. Insulin, if obtained within 10 days of the onset of exogenous insulin therapy;
    c. Insulinoma antigen-2 (IA-2); or
    d. Zinc transporter-8 (ZnT8).
4. Peak stimulated C-peptide level ≥ 0.2 pmol/mL following a MMTT conducted at least 21 days from diagnosis and within 37 days of randomization (V0).
5. Signed informed consent (and informed assent of minor, if applicable).

Exclusion Criteria

1. Severe reaction or anaphylaxis to human, humanized or murine monoclonal antibodies.
2. History of malignancy or serious uncontrolled cardiovascular, nervous system, pulmonary, renal, or gastrointestinal disease, or significant dyslipidemia.
3. Any history of recent serious bacterial, viral, fungal, or other opportunistic infections.
4. Have serologic evidence of current or past HIV, Hepatitis B, or Hepatitis C.
5. Positive tuberculin skin test (PPD) or QuantiFERON TB test, history of tuberculosis, or active TB infection.
6. Active infection with EBV as defined by EBV viral load ≥ 10,000 copies per 10^6 PBMCs or ≥ 2,000 copies per mL of whole blood.
7. Active infection with CMV as defined by CMV viral load ≥ 10,000 IU or copies per mL of whole blood or plasma.
8. Diagnosis of liver disease or elevated hepatic enzymes, as defined by ALT, AST, or both > 1.5 x the upper limit of age-determined normal (ULN) or total bilirubin > ULN.
9. Current or prior treatment that is known to cause a significant, ongoing change in the course of T1D or immunologic status.
10. Current or prior (within last 14 days of screening MMTT visit) use of drugs other than insulin to treat hyperglycemia (e.g. metformin, sulfonylureas, glinides, thiazolidinediones, exenatide, liraglutide, DPP-IV inhibitors, or amylin).
11. Current use of any medication known to significantly influence glucose tolerance (e.g., atypical antipsychotics, diphenylhydantoin, niacin).
12. Any of the following hematologic abnormalities, confirmed by repeat tests:
    a. White blood count <3,000/µL or >14,000/µL;
    b. Lymphocyte count <500/µL;
    c. Platelet count <150,000 /µL;
    d. Hemoglobin <8.5 g/dL; or
    e. Neutrophil count <2,000 cells/µL.
13. Females who are pregnant, lactating, or planning on pregnancy during the 2-year study period.
14. History or diagnoses of other autoimmune diseases, with the exception of stable thyroid or celiac disease.
15. History of alcohol, drug or chemical abuse within 1 year prior to screening (V-1).
16. Any medical or psychological condition that in the opinion of the principal investigator would interfere with safe completion of the trial.
17. Prior participation in a clinical trial that could increase risks associated with this clinical trial.
18. Receipt of live vaccine (e.g. varicella, measles, mumps, rubella, cold-attenuated intranasal influenza vaccine, bacillus Calmette-Guérin, and small pox) in the 6 weeks before randomization (V0).
19. High lipid levels (fasting LDL cholesterol ≥160 mg/dL or ≥4.1mmol/L).
20. History of significant allergy (e.g. anaphylaxis) to milk or soy proteins.

Abbreviations

ACR	American College of Rheumatology
ADA	American Diabetes Association
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BRI	Benaroya Research Institute
CBC	Complete blood count
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CMV	Cytomegalovirus
CRF	Case report form
CRP	C-reactive protein
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events (version 4.0, May 28, 2009)
CVD	Cardiovascular disease
DAIT	Division of Allergy, Immunology, and Transplantation
DKA	Diabetic keto acidosis
DMARD	Disease-modifying antirheumatic drug
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr virus
EC	Ethics Committee
FDA	US Food and Drug Administration
FSIVGTT	Frequently-sampled intravenous glucose tolerance test

GAD-65	Glutamate decarboxylase-65
GCP	Good clinical practice
HBsAg	Hepatitis B surface antigen
HbA_{1c}	Glycosylated hemoglobin
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High-density lipoprotein
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
IA-2	Insulinoma antigen-2
IB	Investigator's Brochure
ICA	Islet cell antibody
ICH	International Conference on Harmonization
IgA	Immunoglobulin A
IL-6	Interleukin-6
IND	Investigational new drug
IRB	Institutional review board
ITN	Immune Tolerance Network
LDL	Low-density lipoprotein
LFT	Liver Function Test
LTE	Long term exposure
MedDRA	Medical Dictionary for Regulatory Activities
MMTT	Mixed-meal tolerance test
MTX	Methotrexate
NCI-CTCAE	National Cancer Institute *Common Terminology Criteria for Adverse Events*
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NIAID	National Institute of Allergy and Infectious Diseases

NIH	National Institutes of Health
NOD	Nonobese diabetic
OGTT	Oral glucose tolerance test
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamics
pJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetics
PPD	Purified protein derivative
RA	Rheumatoid arthritis
RMSE	Root Mean Square Error
SACCC	Statistical and Clinical Coordinating Center
SAE	Serious adverse event
sJIA	Systemic juvenile idiopathic arthritis
T1D	Type 1 diabetes
T1DM	Type 1 diabetes mellitus
Teff	T effector cells
TNFα	Tumor necrosis factor alpha
Treg	Regulatory T cells
TB	Tuberculosis
TCZ	Tocilizumab
TGA	Therapeutic Goods Administration
ULN	Upper limit of normal range
VZV	Varicella zoster
WHO	World Health Organization
ZnT8	Zinc transporter-8

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND AND SCIENTIFIC RATIONALE

1.1.1 Type 1 diabetes (T1D)

Type 1 diabetes (T1D) affects about 1 million people in North America, with an incidence of approximately 30,000 new cases per year (~15,000 children and ~15,000 adults—80 people per day—are diagnosed with T1D in the U.S).[1] Standard of care comprises multiple daily shots of exogenous insulin or pump therapy, with multiple daily pricks for glucose checks. Even with optimal therapy, patients can experience life-threatening episodes of hypoglycemia or diabetic ketoacidosis, and are at high risk for long-term complications, including nephropathy, retinopathy, neuropathy, and CVD. The financial impact to US families with children with T1D is tremendous with an average annual medical cost of ~$9,000 per year, compared to about ~$1,500 for those who don't have diabetes.[2] Although new tools to measure glucose and deliver insulin are available and intensive insulin therapy has been the standard of care for those with T1D for several decades, insulin therapy is woefully inadequate to treat this disease. Thus, while the overall rate of complications is decreasing,[3] T1D remains a substantial burden to those living with the disease and their families, and T1D still results in decreased quality of life (QOL), and increased morbidity and mortality. The picture of T1D in the US has been recently described in a series of studies conducted by the T1D Exchange which includes data on more than 25,000 adults and children from almost 70 clinical centers in the US. The vast majority of youth with T1D do not meet the American Diabetes Association (ADA) HbA1c targets. This is particularly true among adolescents, where only 21% of T1D adolescents (ages 13-20) had HbA1c levels <7.5%, as recommended. Less than half of those 6-12 years of age met the target HbA1c level of <8%, and only 64% of those younger than age 6 met the target of 8.5%, which corresponds to significant hyperglycemia.[4] The T1D Exchange also documented that 7% of those with T1D experienced severe hypoglycemia (resulting in seizure or coma) and 8% had diabetic ketoacidosis (DKA) during the previous 12 months.[5] Strikingly, 18.6% of those with T1D >40 years duration experienced severe hypoglycemia during the previous year. Moreover, the poor glycemic control which increases the risk of DKA did not protect against severe hypoglycemia.[6] The intractable problem of hypoglycemia is also highlighted by data illustrating that excellent self-management is associated with reduced DKA as compared to those with poorer control, but the rate of severe hypoglycemia was independent of these behaviors.[7] The T1D Exchange data also found that ~5-10% of more than 6,000 individuals with T1D were classified as having probable major depression; this was associated with more complications, higher HbA1c, more DKA, and more severe hypoglycemia.[8] Thus, there is a clear, unmet need to provide new therapeutic options for those with T1D.

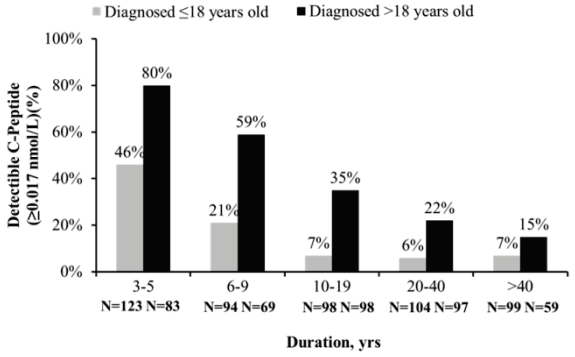
Despite progress toward understanding the genetic, environmental, and immunologic basis for T1D, the prevention and cure of this condition remains elusive. While the

autoimmune pathogenesis of T1D is well established, and clinical trials with immunotherapeutic agents targeting T cells[9], B cells[10], and co-stimulation[11] have demonstrated preservation of insulin secretion, these effects have not been long-lasting.[12] Nevertheless, preservation of even modest amounts of endogenous insulin secretion significantly improves quality of life and reduces long-term complications, thus therapies that can safely alter the course of beta cell destruction would have significant clinical impact.[13,14]

T1D is a particular burden in children.[15] The worldwide incidence of T1D is increasing rapidly in children with the greatest percentage increase in those under age 5. While T1D can occur in all ages, the natural history and burden of disease is different in those diagnosed as children as compared to adults. Disease progression is distinctly slower in adults with a rate of decline of beta cell function that is ~2-fold slower than that in the pediatric population. As illustrated below (

Figure 1), this results in marked differences over time such that considerably more individuals diagnosed as adults as compared with children retain significant levels of C-peptide decades after diagnosis.[16]

Figure 1: C-Peptide Positive Subjects According to T1D Duration and Age at Diagnosis (%)



Several factors have been studied as predictors of the natural history of β-cell response and decline. The most important of these factors is age.[17] Karjalainen et al. reported that T1DM that begins in adulthood (20–55.8 years) is characterized by a longer asymptomatic period before diagnosis and better preservation of residual β-cell function than the type of T1DM observed beginning in childhood (1.3–18.2 years).[18] In fact this observation has been confirmed by others, including Bonfanti et al. who found significantly reduced C-peptide levels in children with T1DM diagnosed at less than 5 years of age compared to those with diagnosis at an older age.[19]

The burden of disease is also different in children as compared with adults. There are significant psychological and financial impacts within families dealing with a life-threatening chronic disease in a child. Moreover, while glycemic variation is a component of T1D in all individuals; recent data suggests a particular impact in a

developing brain with neuroanatomical alterations and diminished cognitive ability.[20] Therefore, safe and effective interventions that can modify the course of T1D in pediatric populations are urgently needed.

1.1.2 Tocilizumab

IL-6 is a systemic cytokine, participating in proinflammatory pathways associated with immunity and autoimmunity. In addition, IL-6 plays an important role in the communication between the innate and adaptive immune systems, mediated through the development and function of regulatory T (Treg) and pathogenic T effector (Teff) cells such as Th17 cells. Data from murine models suggest that IL-6 receptor (IL-6R) blockade may promote both anti-inflammatory and pro-regulatory mechanisms simultaneously. Therefore, IL-6 is considered a "master switch" that regulates Teff vs. Treg responses, and blockade of IL-6 signaling can restore immune tolerance in the setting of autoimmunity. This mechanism is likely responsible for the clinical efficacy of IL-6 receptor blockade in autoimmunity as tocilizumab therapy decreases the frequency of Th17 cells and increases the frequency of Treg cells in patients with rheumatoid arthritis (RA).[21]

Recent studies in murine autoimmunity suggest that Treg function is incapacitated by the local microenvironment, which is full of proinflammatory cytokines, particularly IL-6, which drives Teff lineages and/or inhibits FOXP3 a Treg transcriptional regulator. CD4 T cells co-treated with TGFβ and IL-6 initially express FOXP3, but then Th17 differentiation occurs and FOXP3 expression and Treg function are lost. In multiple mouse models, including autoimmune diabetes, a pivotal role of IL-6 in disease progression, operating through Treg inhibition, has now been validated.[22] In an in vivo study with the non-obese diabetes (NOD) type 1 diabetes mouse model, it has been shown that IL-6 production was increased in isolated islet cells. Mice treated with anti-IL-6 antibodies had a significantly reduced rate of developing diabetes.[23] *Ex vivo* studies with human T cells have shown that Teff from T1D subjects are resistant to suppression by Treg from healthy controls.[24] This resistance of Teff cells to suppression by Tregs has been linked to IL-6. Importantly, in humans, the *IL6R* 358Ala allele, which impairs IL-6 signaling, confers a reduced risk of T1D. The 358Ala allele inhibits IL-6 signaling by reducing the surface expression of membrane-bound IL-6 receptor, thereby providing a compelling rationale for evaluating an anti-IL-6 receptor antibody, such as tocilizumab, in the treatment of new-onset T1D.[25] Other work has demonstrated an increase in Th17 cells in T1D subjects, including islet-antigen specific Th17 cells.[26,27] Mechanistically IL-17 enhances IL-1β, IFN-γ, and TNF-α-induced apoptosis in human islets.[26] Mounting correlative evidence suggest IL-17 producing cells may be pathogenic in the early stages of T1D onset.[28] As noted above, tocilizumab treatment reduced the number of Th17 cells in rheumatoid arthritis subjects.[21] Thus, immune dysregulation is a key component of T1D and restoration of Teff sensitivity to suppression by augmentation of Treg

activity and/or inhibition of Teff is likely to alter the course of disease. IL-6R blockade with tocilizumab has the potential for achieving that goal.

The IV formulation of TCZ is approved in the EU, US, and Japan for RA, sJIA, and pJIA. IV TCZ is also approved in more than 75 other countries for the treatment of RA, in more than 50 additional countries for the treatment of sJIA, and over 30 other countries for the treatment of pJIA. In India and Japan, IV TCZ has additional indications for treatment in Castleman's disease. The SC formulation of TCZ is approved in more than 30 countries (including EU, US, New Zealand, Switzerland, Canada, Japan, South Korea and Taiwan) for the treatment of RA.

Tocilizumab (TCZ) is an anti-IL-6 receptor antibody that is approved in the US and Australia for the treatment of adult rheumatoid arthritis, systemic juvenile idiopathic arthritis (sJIA) in patients 2 years of age and older, and polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older. In the US, tocilizumab is additionally approved for giant cell arteritis, and in Japan, tocilizumab is also approved for Castleman's disease. In addition, preliminary efficacy has been shown in a variety of other autoimmune diseases. In light of the murine data described above and a strong theoretical rationale, a trial of tocilizumab in new-onset T1D is particularly attractive because there is substantial experience in pediatric populations with approval for both sJIA and pJIA. It is well known that T1D is a particular burden in children in whom the disease is more aggressive with a more rapid loss of residual β-cell function.[17] Pediatric T1D therefore represents a major unmet medical need and this is the key population in which the efficacy of novel interventions needs to be demonstrated.

This study will test whether ACTEMRA® (tocilizumab) can preserve remaining beta cells in individuals with recently diagnosed type 1 diabetes. The study is a 2-arm, randomized, double-blind, placebo-controlled, multicenter, phase 2 clinical trial. All groups will receive standard intensive diabetes treatment with insulin and dietary management. Subjects will be randomly assigned (2:1 drug-placebo) to receive either monthly IV infusions of tocilizumab or placebo for 6 months (total of 7 infusions). The effects of the treatment on general and diabetes-specific immune responses and the deterioration of β-cell function that occurs in T1D will be studied to determine the study drug's mechanism of action. Furthermore, how the drug alters T1D-associated immune responses and whether the drug has prolonged clinical efficacy will also be studied.

As of the date of this current protocol version, review of data from the adult cohort has been completed by DSMB and FDA. Enrollment of pediatric participants age 6-17 years old, inclusive, is ongoing.

1.2 PRECLINICAL AND CLINICAL EXPERIENCE

1.2.1 Preclinical Studies

1.2.1.1 Preclinical Safety Data

1.2.1.1.1 Overview

[redacted]

1.2.1.1.2 Toxicity Studies

[redacted]

1.2.1.2 Preclinical Efficacy Data in Other Autoimmune Disease

[redacted]

1.2.2 Clinical Studies

1.2.2.1 Efficacy and Safety Data for Tocilizumab

1.2.2.1.1 Overview

Tocilizumab[redacted]

[redacted]

[redacted]

[redacted]

Efficacy

[redacted]

[redacted] (GI) perforations) increased with increasing duration of treatment.

1.2.2.1.2 Giant Cell Arteritis

[redacted]

1.2.2.1.3 Systemic Juvenile Idiopathic Arthritis

[redacted]

Safety

[redacted]

[redacted]

1.2.2.1.4 Polyarticular Juvenile Idiopathic Arthritis

[redacted]

Efficacy

[redacted]

Safety

[redacted]

[redacted]

1.2.2.1.5 Castleman's Disease

[redacted]

1.2.2.1.6 Other Autoimmune and Inflammatory Diseases

[redacted]

1.2.2.1.7 Clinical Use in Diabetes

IL-6 has been linked to defects in insulin action characteristic of metabolic syndrome and type 2 diabetes, but studies on the metabolic effects of IL-6R blockade are sparse. In a small open-label study of non-diabetic RA patients, tocilizumab therapy resulted in a significant decrease in the HOMA index for insulin resistance and a significant increase in serum adiponectin levels.[43] There have been no clinical studies in diabetes with tocilizumab. However, more than 200 subjects treated with tocilizumab as part of RA trials had concomitant diabetes at baseline. No untoward effect on diabetes control was seen in this group, although no direct measurements of insulin action or secretion were performed. Also of note are the results of a recent Mendelian randomization analysis for a SNP in the IL6R gene (Asp358Ala) that phenotypically recapitulates the effects of tocilizumab, which showed reduced risks for coronary heart disease and type 2 diabetes.[44] Thus, IL-6R-mediated inflammatory pathways may have a causal role in atherosclerosis and, possibly, insulin resistance.

1.2.2.1.8 Pediatric Experience with Tocilizumab

As noted previously, tocilizumab is approved for use in children 2 years of age and older with sJIA and pJIA. Tocilizumab has been studied in two phase 3 clinical trials (WA18221 and WA19977) and a supportive phase 3 study (MRA316JP) performed in Japan with pediatric populations.[41,45-51] The clinical trials included a total of 367 pediatric subjects, 330 of whom received tocilizumab [142 subjects with sJIA and 188 subjects with pJIA]. See Table 1 for pediatric subject age breakdown data below.

Table 1. Pediatric Experience with Tocilizumab (N=330)

Indication	sJIA Systemic Juvenile Idiopathic Arthritis	sJIA Systemic Juvenile Idiopathic Arthritis	pJIA Polyarticular Juvenile Idiopathic Arthritis
Trial	**WA18221 (TENDER) [Ongoing]**	**MRA316JP [Completed]**	**WA19977 (CHERISH) [Ongoing]**
Phase	III (Pivotal)	III (Supportive)	III (Pivotal)
Sponsor	Roche/GEN	Chugai	Roche/GEN
ClinicalTrials.Gov Identifier	NCT00642460	NCT00144599 (open-label lead-in, double-blind phases) NCT00144612 (open-label extension phase)	NCT00988221
Number of Subjects Who Received TCZ	75	67 total = 56 [Phase III] + 11 [Phase II]; Median exposure to TCZ = 3.4 yrs (177 weeks);	Part 1=188 total (open-label) every 4 wks X4 = 16 wks; Part 2=82 [DB, rand. 1:1 TCZ (n=82) or placebo (n=81)] for 24 wks (starting at wk 16);
Age Range that Received TCZ	10 ± 4.6 yrs	2 to 19 yrs	2 to 17 yrs
TCZ Dose	TCZ treated subjects with body wt < 30 kg received 12 mg/kg those with body wt ≥ 30 kg received 8 mg/kg. TCZ was administered, every 2 weeks.	TCZ treated subjects received 8 mg/kg every 2 weeks.	TCZ treated subjects with body wt < 30 kg were randomized (1:1) to receive either 8 mg/kg or 10 mg/kg of TCZ and pts with body wt ≥ 30 kg received 8 mg/kg of TCZ, every 4 weeks.

1.3 SUMMARY OF KNOWN AND POTENTIAL RISKS AND BENEFITS FOR HUMAN PARTICIPANTS

1.3.1 Overview

Like any immunomodulating therapy, the primary risks of tocilizumab relate to infections; however, these are generally well tolerated and the use of this drug is increasing rapidly in the approved autoimmune indications (rheumatoid arthritis, systemic juvenile idiopathic arthritis, and polyarticular juvenile idiopathic arthritis).

The information provided here is summarized from the current F. Hoffman La-Roche LTD Investigator's Brochure for tocilizumab and country-specific Package Insert and is compiled from the clinical studies conducted in patients 2 years of age and older with systemic juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, and rheumatoid arthritis.

1.3.2 Risks

1.3.2.1 Opportunistic Infections and Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including tocilizumab for rheumatoid arthritis.

1.3.2.2 Gastrointestinal Perforations

A total of 30 cases of medically confirmed serious GI perforation (primarily as complications of diverticulitis in RA patients, but also including those related to malignancy) were reported in clinical trials, corresponding to a rate of 0.2 per 100 patient-years. No GI perforations were seen in the two phase 3 studies in juvenile idiopathic arthritis with a pediatric population.

1.3.2.3 Laboratory Abnormalities

Neutrophils

Treatment with tocilizumab in RA was associated with a higher incidence of neutropenia. An observed decrease in neutrophils occurs in about half the subjects in trials, occurred largely within the normal range, and was reversible upon interruption/discontinuation of TCZ. Out of more than 4000 patients, 5% had neutrophil counts < 1000−500/mm^3 and 33 (< 1%) had counts < 500/mm^3. There was no clear relationship between decreases in neutrophils below 1000/mm^3 and the occurrence of serious infections.

Platelets

Treatment with tocilizumab in RA was associated with a reduction in platelet counts. Transient decreases in platelet counts below 100,000/mm^3 occurred in 1.3% and 1.7% of patients on 4 mg/kg and 8 mg/kg TCZ + DMARD, respectively, compared with 0.5% of patients in the placebo + DMARD group. In the long-term exposure all-exposure population, 52/4002 patients (1.3%) had < 75,000−50,000/mm^3; 18 patients (0.4%) had < 50,000−25,000/mm^3; and 14 patients (0.3%) had platelet counts < 25,000/mm^3. There was no clear relationship between thrombocytopenia and clinical symptoms.

Liver Function Tests

Treatment with tocilizumab in RA was associated with a higher incidence of transaminase elevations. ALT and AST elevations were observed and most were transient and returned towards normal with treatment interruption or treatment discontinuation. Transient elevations in ALT above three times the upper limit of normal (ULN) were observed in 6.5% of patients receiving 8 mg/kg TCZ + DMARD groups, respectively, compared with 1.5% of patients in the placebo + DMARD group. There is no evidence to date of a correlation between liver enzyme changes with TCZ and serious hepatic events; the majority of elevated transaminase reports have shown no clinical sequelae. A total of 99 patients (2.4%) in the long term exposure population were prematurely withdrawn due to transaminase elevations. The percentage of patients with an increase in indirect bilirubin > ULN was higher in patients receiving TCZ than patients in the control group. Based on the long term TCZ exposure data, 0.6% of patients had an indirect bilirubin level > 2 × ULN. However, the change in bilirubin levels when receiving TCZ treatment did not result in negative clinical outcomes.

Lipids

Treatment with tocilizumab in RA was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol. LDL levels increased in the 8 mg/kg treatment groups and responded appropriately to statin therapy. Long-term data from the TCZ phase 3 program over a mean duration of 3.7 years show no evidence that the observed changes in lipid levels in the TCZ-treated patients result in an increase in the rate of reported cardiovascular events. Rates of myocardial infarction and stroke were similar across the TCZ and control treatment groups.

A similar pattern of liver enzyme elevation, low neutrophil count, low platelet count and lipid elevations is noted with tocilizumab treatment in the sJIA population.

1.3.2.4 Immunosuppression

The impact of treatment with tocilizumab on the development of malignancies is not known. Tocilizumab is an immunosuppressant, and treatment with this class of drugs may result in an increased risk of malignancies. In the 6-month double-blind studies in RA, the rate of malignant neoplasms was 1.33 and 1.27 events per 100 patient-years in the TCZ and control groups, respectively.

1.3.2.5 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis and death, have been reported in association with infusion of tocilizumab. Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of RA patients in the 6-month controlled trials, and in 0.2% (8 out of 4009) of patients in the all-exposure rheumatoid arthritis population. Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in

0.9% (1 out of 112 patients) of patients in the sJIA controlled trial. No reports of anaphylaxis or serious hypersensitivity reactions were reported in the pJIA controlled trial (N=188). In the postmarketing setting, a patient with a previous infusion reaction and premedicated with steroids and antihistamines experienced fatal anaphylaxis during subsequent treatment with tocilizumab.

1.3.2.6 Other Potential Risks

Demyelinating Disorders

The impact of treatment with tocilizumab on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in RA clinical studies.

Vaccinations

Live vaccines should not be given concurrently with tocilizumab as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving tocilizumab. Limited data are available on the safety and effectiveness of vaccination in patients receiving tocilizumab, but to date no impairment in seroprotection has been noted.

Viral Reactivation

Though rarely reported within the TCZ program due to exclusion criteria at study entry, reactivation of viral and other serious infections (e.g. EBV, herpes zoster and TB) have been observed with biologic therapies for RA, including TCZ.

Anti-TCZ Antibodies

In the phase 3 RA trials, serum samples of 44/3945 patients (1.1%) tested positive post baseline in the confirmation assay for anti-TCZ antibodies. Five of the 44 anti-TCZ antibody positive patients experience an anaphylactic reaction. The remaining 39 patients did not.

Of 112 pediatric patients treated with tocilizumab in the sJIA trials, 2 (1.8%) developed positive anti-tocilizumab antibodies, of whom one experienced SAEs (urticaria and angioedema) consistent with an anaphylactic reaction which led to withdrawal. Of 19 pediatric patients treated with tocilizumab in the Japanese pJIA trial, one was positive for anti-TCZ antibodies.

Drug Interaction

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g. IL-6) during chronic inflammation. Therefore, it is expected that for molecules that antagonize cytokine activity, such as TCZ, the formation of CYP450 enzymes could be normalized. The clinical implications of this are unknown.

1.3.3 Potential Risks and Benefits of Trial Participation for Children

As noted in section 1.3.2.1.8, tocilizumab has been used in pediatric populations and is approved for treatment of both sJIA and pJIA for children age 2 and older in many countries. For children receiving placebo, the study procedures including blood draws, mixed meal tolerance testing, and IV placebo administration are either minimal risk or slightly greater than minimal risk; these subjects have the possibility of benefit in the close monitoring of their newly diagnosed T1D. For those receiving tocilizumab, the study procedures are greater than minimal risk; however, overall tocilizumab has been well tolerated in both pediatric and adult populations. The rationale for a prospect of benefit in children is motivated by the current approvals for pediatric populations and the specific mode of action affecting autoimmune diseases for which there is ample clinical evidence of efficacy in both adult and pediatric populations. There are currently no approved interventions for new-onset T1DM.

It is important to recognize that the natural history of disease in T1DM is considerably different in children as compared with adults, with adults having a much more indolent disease course. The average reduction in MMTT-stimulated C-peptide AUC mean in adults is ~ 7.5% at 6 months and ~ 15% at 12 months, which is half of the change seen in children. While the mechanisms underlying this difference is unknown, these difference in disease course are likely to be reflected in responses to therapy as well. Like RA and sJIA or pJIA, T1D is a different disease in different aged populations. Thus, either efficacy or lack of efficacy in an adult population is not likely to be informative as to efficacy or lack thereof in a pediatric population. Nonetheless, this study will be initiated in adults to assure no unexpected harms and both safety and efficacy data will be reviewed by the DSMB and FDA before enrollment of 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 FDA 21 CFR 50.52 [Subpart D]. (Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects).

1.3.4 Benefits of Trial Participation

In this study, all participants will receive intensive diabetes management aimed at achieving near-normal metabolic control per the standard ADA guidelines.[45] Although intensive diabetes management is recommended for all patients with T1DM, it is not always available to all subjects in the community. The Diabetes Control and Complications Trial (DCCT) research group documented that improved metabolic control slows the onset of some long-term complications.[13] The means to achieve this improved control in the DCCT has become the idealized standard of care, with

clinical management and education provided by a diabetes specialty team. It should be noted that such care may not necessarily be available to those outside the study, and those who are not seen by a diabetes specialty team may have worse outcomes over time.[52]

Improved metabolic control early in the course of T1DM will have a long-standing effect on lowering the risk for long-term complications for many years to follow; i.e., there appears to be a "metabolic memory" that influences later risk. This effect has been documented in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, the long-term follow-up of the DCCT cohort.[13,14,53-55] Although the conventional group (with less stringent metabolic control) and the intensive group (with near-normal metabolic control) have had comparable HbA_{1c} levels since the end of the formal DCCT study, the intensive group continues to have significantly lower risk for complications 10 years later. An additional benefit that may be realized by all participants is that maintaining near-normal glycemic control through intensive diabetes management may, in and of itself, lead to the preservation of ß-cell function.[56-59] The benefits of endogenous insulin secretion, even if one needs to continue exogenous insulin therapy, have been demonstrated in a number of studies, including the DCCT, where those subjects with residual C-peptide had improved metabolic control, with lower risk for severe hypoglycemia and less likelihood of microvascular complications.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

Determine whether tocilizumab will slow the progression of the autoimmune destruction of ß cells and lead to the preservation of C-peptide secretion in T1DM.

2.2 SECONDARY OBJECTIVES

1. Longitudinal analysis of HbA1c, insulin dose (units/kg) and blood glucose by treatment group.
2. Determine the efficacy and safety of tocilizumab in participants with T1DM.
3. Determine how the ratio of Treg/Teff is altered with tocilizumab treatment

2.3 EXPLORATORY OBJECTIVES

Mechanistic studies:

1. Investigate the mechanism of action for tocilizumab in the maintenance of ß-cell function and determine whether the loss of tolerance associated with this disease is reversed.

Metabolic:

1. Determine whether treatment with tocilizumab improves blood glucose and HbA1c and reduces individual insulin requirements.
2. Explore whether tocilizumab affects insulin sensitivity.

3. STUDY DESIGN

3.1 DESCRIPTION

This trial will be conducted in the US and Australia as a multi-center, prospective, double-blind, placebo-controlled, 2:1 randomized, phase 2 clinical trial for individuals with recent-onset T1DM aged 6−45 years old. 78 eligible pediatric subjects (6-17 years old) and at least 30 eligible adult subjects (18-45 years old) will be enrolled (see Figure 2). All groups will receive standard intensive diabetes management. The subjects will receive IV infusions of either 8.0 mg/kg (body weight ≥30kg) or 10.0 mg/kg (body weight <30kg) tocilizumab or placebo every 4 weeks for 24 weeks.

A staggered enrollment plan is being used for this trial. Prior to initiating the study in the pediatric age group (6-17 years old), adults (18-45 years old) were randomized 2:1 to tocilizumab or placebo, respectively. After 30 adult participants completed 12 weeks of treatment, the DSMB and FDA reviewed the available data to weigh potential risks and benefits as well as prospect of benefit and allowed opening the trial to pediatric participants (children and adolescents 6-17 years old).

The protocol continued to enroll adult participants during and after evaluation of the initial cohort with 55 eligible adult participants enrolled in this clinical trial. Only pediatric participants are eligible for randomization after May 15, 2017.

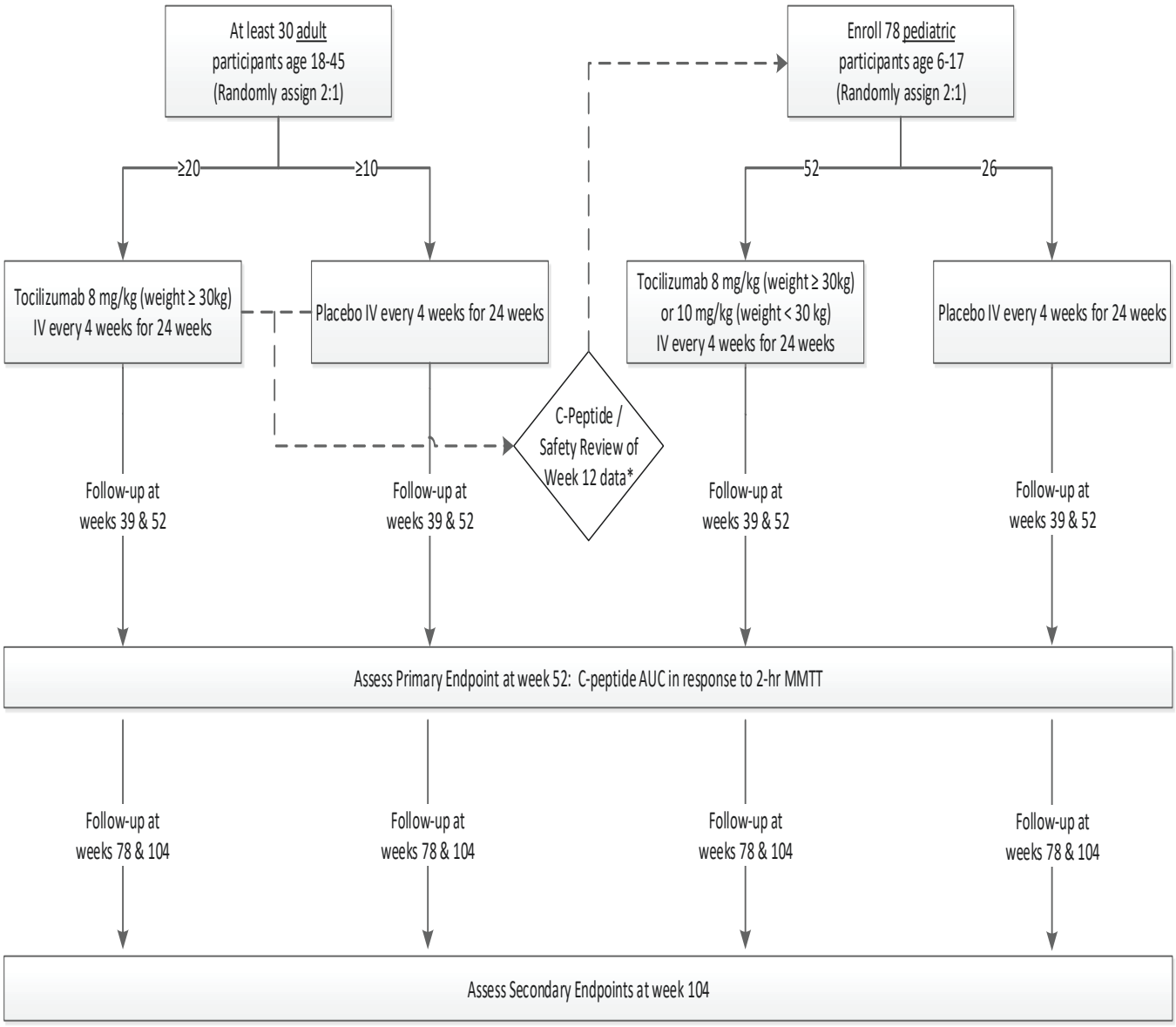


Figure 2: Study Design for Tocilizumab in New-Onset T1DM

**Note: This figure shows the original study design. There were 55 adult participants randomized before opening the study to pediatric participants (6-17 years old).*

3.2 STUDY DURATION

Total study duration will be approximately 4-5 years.

- The enrollment phase is expected to last up to 42 months.
- The study participation phase will be 104 weeks (2 years), which includes a treatment phase of 24 weeks and a follow-up phase of 80 weeks.

3.3 STUDY ENDPOINTS

3.3.1 Primary Endpoint

The primary endpoint is a MMTT-stimulated mean 2-hour C-peptide AUC at week 52. The mean 2-hour C-peptide AUC, measured in pmol/ml, is computed by dividing the total AUC by 120 minutes.

3.3.2 Secondary Endpoints

Efficacy:

1. MMTT-stimulated mean 2-hour C-peptide AUC at weeks 12, 24, and 104.
2. MMTT-stimulated mean 2-hour C-peptide AUC assessed longitudinally at weeks 12, 24, 39, 52, 78, and 104.
3. MMTT-stimulated peak and 4-hour C-peptide AUC at weeks 52 and 104 for subjects ≥12 years old.
4. Insulin use (U/kg/day) at weeks 12, 24, 39, 52, 78 and 104; HbA_{1c} levels at weeks 12, 24, 39, 52, 78 and 104.
5. Glycemic control.

Safety:

1. Rate of AEs related to infusion reactions and hypersensitivity.
2. Frequency and severity of all AEs.

Mechanistic

1. Determine the effect of TCZ on the ratio of Treg and Teff.

3.3.3 Exploratory Endpoints

Mechanistic:

1. Determine effect of TCZ on measures of immune cell number and function such as:
   a. Changes in proportions and phenotype of Treg and Teff.
   b. Changes in sensitivity of Teff to suppression by Treg.
   c. Changes in circulating B cell compartment and activation state of innate immune cells including antigen presenting cells and NK cells.

Metabolic:

1. Explore the relationship between immune responses, metabolic outcomes and clinical variables.
2. Explore the effect of TCZ on insulin sensitivity.

3.4 RATIONALE FOR SELECTION OF DRUG, ROUTE, DOSE, AND REGIMEN

The dose of 8 mg/kg every 4 weeks via the IV route is the FDA and Australian, Therapeutic Goods Administration (TGA)-approved dose for adults in rheumatoid

arthritis and will be used for adults and children ≥ 30kg in this study. For children <30 kg, TCZ will be dosed at 10 mg/kg. For systemic juvenile idiopathic arthritis (sJIA), the FDA-approved dose is 8 mg/kg every 2 weeks for patients with body weight ≥ 30kg and 12 mg/kg every 2 weeks for patients with body weight < 30 kg. However, in recent clinical trials of polyarticular juvenile idiopathic arthritis (pJIA), other dosing regimens were tested in patients age 2-17. Participants with body mass < 30 kg received 8 mg/kg or 10 mg/kg every 4 weeks. Both pharmacokinetic measurements and clinical outcome in the 8 mg/kg ≥ 30 kg group were more similar to the 10 mg/kg < 30 kg group than the 8 mg/kg <30 kg group. The dosing regimen selected for this trial is consistent with the pJIA dosing regimen because patients with T1DM, similar to those with pJIA likely do not have the systemic inflammation seen in sJIA. The dosing frequency may be altered if an adverse event is encountered as outlined in section 5.2.

In order to preserve blinding of the study, participants receiving placebo will be given an IV infusion of equal volume and appearance to treatment on the same schedule, formulated and prepared by each study site. Placebo will be saline.

3.5 PREMATURE TERMINATION OR SUSPENSION OF THE TRIAL

3.5.1 Ongoing Review

As described in Section 10.1 of the protocol, this clinical trial is conducted through the NIAID NIH-funded Cooperative Agreement awarded to the Benaroya Research Institute at Virginia Mason (Seattle, WA) (BRI) to support the Immune Tolerance Network (ITN), a collaborative network for clinical research. The ITN provides financial support for the conduct of the clinical trial to the clinical sites through subcontracts between the BRI and the clinical sites. The NIAID NIH serves as the US Sponsor of the Investigational New Drug application (IND) for the Protocol and the Global Sponsor in Australia (represented by Pharmaceutical Product Development, Inc. (PPD) as Local Sponsor in Australia) and is responsible for all regulatory filings and safety reporting. In addition, DAIT, NIAID NIH has appointed a medical monitor and convenes a Data and Safety Monitoring Board (DSMB) as described below.

The joint National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and NIAID ACE/ITN/TrialNet DSMB will formally review the safety data at least yearly. The number of participants who discontinue study treatment will also be included in the reports prepared for the DSMB.

In addition, safety data will be reviewed by the DSMB when an event occurs that is of sufficient concern to the DAIT, NIAID medical monitor, ITN physician, or the protocol chair to warrant review, or when an event occurs that contributes to a stopping rule listed in section 3.5.2.

3.5.2 Stopping Rules

3.5.2.1 Study-related Adverse Events

If any of the following events occur, enrollment will be suspended and the DSMB chair will be notified such that a review of safety data will determine if enrollment in the study will be stopped and/or administration of investigational study medication should be halted:

- Any death except those assessed as not related to study treatment on review by the ITN clinical trial physician, and the DAIT, NIAID medical monitor.
- Any demyelinating-related event.
- Any gastrointestinal perforation.
- Evidence of serious opportunistic infection, including tuberculosis, or EBV-associated lymphoproliferative disorder.
- Any grade 4 or higher infusion-related event.
- Any unexpected, treatment-related SAE resulting in permanent treatment discontinuation and not related to glycemic events.
- Three of the first 10 participants or 30% thereafter, in either age cohort, require discontinuation of study medication for the same or similar serious adverse event based on MedDRA preferred term or at the discretion of the DAIT, NIAID medical monitor.
- Five of the first 10 participants, or 50% thereafter, in either age cohort, require discontinuation of study medication for individual stopping rules, as defined in Section 5.3 (excluding pregnancy).

4. ELIGIBILITY

4.1 INCLUSION CRITERIA

Patients must meet *all* of the following criteria to be eligible for this study:

1. Male or female aged 6-45 years inclusive who meet the American Diabetes Association T1DM criteria.
2. Diagnosis of T1DM within 100 days of enrollment (V0).
3. Positive for at least one diabetes-related autoantibody, including but not limited to:
   a) Glutamate decarboxylase (GAD-65);
   b) Insulin, if obtained within 10 days of the onset of exogenous insulin therapy;
   c) IA-2; or
   d) ZnT8.

4. Peak stimulated C-peptide level ≥ 0.2 pmol/mL following a MMTT conducted at least 21 days from diagnosis and within 37 days of randomization (V0).
5. Signed informed consent (and informed assent of minor, if applicable).

4.2 EXCLUSION CRITERIA

Patients who meet any of the following criteria will *not* be eligible for this study:

1. Severe reaction or anaphylaxis to human, humanized or murine monoclonal antibodies.
2. History of malignancy or serious uncontrolled cardiovascular, nervous system, pulmonary, renal, or gastrointestinal disease, or significant dyslipidemia.
3. Any history of recent serious bacterial, viral, fungal, or other opportunistic infections.
4. Have serologic evidence of current or past HIV, Hepatitis B, or Hepatitis C.
5. Positive tuberculin skin test (PPD) or QuantiFERON TB test, history of tuberculosis, or active TB infection.
6. Active infection with EBV as defined by EBV viral load ≥ 10,000 copies per 10^6 PBMCs or ≥ 2,000 copies per mL of whole blood.
7. Active infection with CMV as defined by CMV viral load ≥ 10,000 IU or copies per mL of whole blood or plasma.
8. Diagnosis of liver disease or elevated hepatic enzymes, as defined by ALT, AST, or both > 1.5 x the upper limit of age-determined normal (ULN) or total bilirubin > ULN.
9. Current or prior treatment that is known to cause a significant, ongoing change in the course of T1D or immunologic status.
10. Current or prior (within last 14 days of screening MMTT visit) use of drugs other than insulin to treat hyperglycemia (e.g. metformin, sulfonylureas, glinides, thiazolidinediones, exenatide, liraglutide, DPP-IV inhibitors, or amylin).
11. Current use of any medication known to significantly influence glucose tolerance (e.g., atypical antipsychotics, diphenylhydantoin, niacin).
12. Any of the following hematologic abnormalities, confirmed by repeat tests:
    a. White blood count <3,000/μL or >14,000/μL;
    b. Lymphocyte count <500/μL;
    c. Platelet count <150,000 /μL;
       Hemoglobin <8.5 g/dL; or
    d. Neutrophil count <2,000 cells/μL.
13. Females who are pregnant, lactating, or planning on pregnancy during the 2-year study period.

14. History or diagnoses of other autoimmune diseases with the exception of stable thyroid or celiace disease.
15. History of alcohol, drug or chemical abuse within 1 year prior to screening (V-1).
16. Any medical or psychological condition that in the opinion of the principal investigator would interfere with safe completion of the trial.
17. Prior participation in a clinical trial that could increase risks associated with this clinical trial.
18. Receipt of live vaccine (e.g. varicella, measles, mumps, rubella, cold-attenuated intranasal influenza vaccine, bacillus Calmette-Guérin, and small pox) in the 6 weeks before randomization (V0).
19. High lipid levels (fasting LDL cholesterol ≥160 mg/dL or ≥4.1mmol/L).
20. History of significant allergy (e.g. anaphylaxis) to milk or soy proteins.

4.3 PREMATURE TERMINATION OF A PARTICIPANT FROM THE STUDY

Withdrawal of consent. Participants who withdraw consent for further treatment. These participants will be asked if they would be willing to complete safety and outcome assessments and visits.

Failure to return. Participants who do not return for visits and who do not respond to repeated attempts by the site staff to have them return will be considered *lost to follow-up*.

Investigator judgment. A severe or serious AE occurs, which, based on the medical judgment of the investigator, prevents completion of participation for study treatment.

If study treatment is discontinued, the DAIT, NIAID medical monitor should be notified. If feasible and medically appropriate, subjects will be asked to continue in safety and outcome assessments and visits.

5. STUDY MEDICATIONS

5.1 INVESTIGATIONAL MEDICATION

ACTEMRA® (tocilizumab) is the investigational agent and will be provided to the clinical research sites by the Sponsor. For sites in the US, commercially-labeled licensed product will be obtained by the Sponsor from either the manufacturer (Genentech, Inc. a member of the Roche group, located in South San Francisco, CA) or acquired from commercial sources. For sites in Australia, commercially labeled licensed ACTEMRA® (tocilizumab) will be obtained through each site pharmacy from commercial sources.

Saline from clinical site pharmacies will be used as placebo in this Protocol.

5.1.1 Formulation and Packaging

5.1.2 Reconstitution

5.1.3 Dosage, Preparation, and Administration

For those with weight ≥ 30 kg, tocilizumab will be administered at a dose of 8 mg/kg every four weeks as an IV infusion not to exceed 800 mg. For those with weight < 30 kg, tocilizumab will be administered at a dose of 10 mg/kg. Dosing will be according to the individual's 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 or current visit may be used. If the previous visit was more than three months ago or if there is more than 10% change in body weight from previous dose, then, dosing of study drug will be calculated according to the individual's weight on the day of the visit.

For subjects <30 kg at the start of the trial and if their weight increases above 30 kg and is also greater than 10% from the start of the trial, their current weight will be used to calculate tocilizumab dose based on 8 mg/kg, otherwise the 10 mg/kg will continue to be used.

Tocilizumab should be administered intravenously over approximately 60 minutes. Subjects will be observed in the clinic for 15 minutes after the end of the infusion. Vital signs (blood pressure and pulse) will be recorded within 10 minutes before, 15 minutes during, at the end, and within 15 minutes after completion of each infusion.

5.2 DOSE MODIFICATION AND MANAGEMENT OF ADVERSE EVENTS

5.2.1 Overview

Clinical evaluation including history and directed physical exam, review of adverse events and laboratory values from previous visit will be done prior to each infusion.

5.2.2 Hematologic Abnormalities and Bleeding Events

Decreases in neutrophil and platelet counts have been observed following treatment with TCZ in combination with MTX.

The risk mitigation strategies for neutropenia and thrombocytopenia are summarized in Table 2 and Table 3, respectively.

Table 2. Neutropenia Risk Mitigation

ANC (cells/µL)	Action
> 1,000	Maintain dose.
500 – 1,000	Interrupt tocilizumab dosing and recheck ANC as clinically relevant. When ANC increases to > 1,000, resume tocilizumab at the next expected 4 week interval. The overall course of study treatment will not be extended and missed doses will not be administered. If the adverse event does not resolve in 8 weeks, discontinue study treatment permanently. One suspension due to neutropenia is allowed during the treatment period.
< 500	Discontinue tocilizumab.

ANC = absolute neutrophil count

Table 3. Thrombocytopenia Risk Mitigation

Platelet count (cells/µL)	Action
> 100,000	Maintain dose.
50,000 – 100,000	Interrupt tocilizumab dosing and recheck platelet count as clinically relevant. When platelet count increases to > 100,000, resume tocilizumab at the next expected 4 week interval. The overall course of study treatment will not be extended and missed doses will not be administered. If the adverse event does not resolve in 8 weeks, discontinue study treatment permanently. One suspension due to thrombocytopenia is allowed during the treatment period.
< 50,000	Discontinue tocilizumab.

5.2.3 Blood Chemistry Abnormalities

Elevations in ALT and AST have been observed during treatment with the study medications. The recommended dose modification strategies for elevations in ALT and AST are summarized in Table 4.

Table 4. Liver Function Tests Risk Mitigation

ALT/AST	Action
< 3xULN	Maintain dose.
>3xULN to <5xULN	Interrupt tocilizumab dosing and recheck ALT/AST as clinically relevant. When ALT/AST decreases to <3xULN, resume tocilizumab at the next expected 4 week interval. The overall course of study treatment will not be extended and missed doses will not be administered. If the adverse event does not resolve in 8 weeks, discontinue study treatment permanently. One suspension due to elevated ALT/AST is allowed during the treatment period.
> 5xULN	Discontinue tocilizumab.

The recommended dose modification strategies for elevations in bilirubin are summarized in Table 5.

Table 5. Elevated Total Bilirubin Risk Mitigation

Total Bilirubin Lab Values	Action
> 3 mg/dL	For increases in this range, tocilizumab dosing will be stopped permanently. Recheck total bilirubin as clinically relevant.

5.2.4 Infections

Tocilizumab should not be administered in patients with active infection including localized infections, or who report febrile illness within prior 48 hours. These subjects will be rescheduled for another day within the study dosing window. If the patient remains ill during the study window, the dose will be skipped and the subject will wait until the next scheduled dose. Any subject who develops infection or reactivation of EBV or CMV, as defined by clinical signs of infection; or if the EBV viral load is ≥ 10,000 copies per 10^6 PBMCs or ≥ 2,000 copies per mL of whole blood or the CMV viral load is ≥ 10,000 IU or copies per mL whole blood or plasma, will not receive additional study drug until resolution of active infection.

The overall course of study treatment will not be extended and missed doses will not be administered. One suspension due to infection is allowed. If a second suspension due to infection occurs during the treatment period, then discontinue study treatment permanently.

Tocilizumab should be stopped permanently if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with tocilizumab should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored. Patients should be closely monitored for signs and symptoms of tuberculosis.

5.2.5 Elevated Lipids

Tocilizumab will not be administered in subjects with fasting LDL cholesterol ≥160 mg/dL or ≥4.1 mmol/L. Subjects with LDL values between 100 and 160 may be considered for treatment with lipid lowering agents.

5.2.6 Hypersensitivity or Anaphylaxis

An infusion/dose reaction is defined as an adverse event occurring during and within 24 hours after the infusion or subcutaneous injection of tocilizumab. This may include hypersensitivity reactions or anaphylactic reactions.

Signs of a possible hypersensitivity reaction include but are not limited to:

- Fever, chills, pruritus, urticaria, angioedema, and skin rash.
- Cardiopulmonary reactions, including chest pain, dyspnea, hypotension or hypertension.

If a patient has symptoms of anaphylaxis or hypersensitivity, or requires an interruption of the study drug because of symptoms of anaphylaxis or hypersensitivity, administration of TCZ must be discontinued permanently. The patient should be treated according to the standard of care for management of the hypersensitivity reaction.

5.3 DISCONTINUATION OF STUDY MEDICATION IN AN INDIVIDUAL PARTICIPANT

The dosing and administration of investigational medication according to study specification will be discontinued for an individual participant if *any* of the following criteria is met:

- Anaphylaxis or hypersensitivity reaction.
- A confirmed demyelinating event.
- Gastrointestinal perforation.
- Malignancy.
- Adverse events requiring study drug discontinuation as defined in section 5.2.
- The investigator determines that it is in the participant's best interest to discontinue treatment.
- The participant, or participant's legal representative, requests that treatment be halted.
- The participant becomes pregnant.

Further care will be provided according to the judgment and practice of the investigator.

The participant will be asked to remain in the study and participate in follow-up. If study treatment is discontinued, the DAIT, NIAID medical monitor should be notified.

5.4 CONCOMITANT MEDICATIONS

5.4.1 Prohibited Medications

Participants will be instructed not to use the following medications:

- Agents that are known to significantly influence insulin sensitivity or secretion.
- Medications known to affect the laboratory measurement of C-peptide (i.e. Strensiq® (asfotase alfa)).
- Non-insulin pharmaceuticals for glycemic control.
- Live vaccine (varicella, measles, mumps, rubella, cold-attenuated intranasal influenza vaccine, bacillus Calmette-Guérin, and smallpox) 6 weeks before enrollment, during study drug administration, and within 3 months after completing study drug.
- Agents that may result in immunosuppression or immunomodulation, including chronic and persistent use of inhaled, extensive topical or systemic glucocorticoids.

If a participant receives, or if the investigator believes that a participant must receive, a prohibited medication, the case must be immediately discussed with the protocol chair, the DAIT, NIAID medical monitor, and the ITN clinical trial physician.

The use of prohibited medications must be documented on the source document and CRF.

5.5 DRUG ACCOUNTABILITY

Under US code of federal regulations (21CFR 312.62), Australian TGA regulations and ICH E6 Good Clinical Practice guidelines, an investigator is required to maintain adequate records of the disposition of the investigational product, including the date and quantity of drug that was received, the participants to whom drug was dispensed (participant by participant accounting), and an account of any drug accidentally or deliberately destroyed. The investigator will ensure that the investigational product supplies are stored as specified in the protocol and pharmacy manual in a secured area, with access limited to authorized study personnel as described in the clinical study agreement.

Records for receipt, storage, use, and disposition of the study drug will be maintained by the study sites. A drug-dispensing log will be kept current for each participant and will contain the identification of each participant and the date and quantity of drug dispensed. All remaining unused investigational product will be returned to the

Global Study sponsor (DAIT, NIAID, NIH) or sponsor's representative after study termination, or destroyed with the permission of the sponsor in accordance with applicable law and study site procedures. If investigational product is to be destroyed locally, the investigator will provide documentation in accordance with sponsor's specifications.

All records regarding disposition of the investigational product will be available for inspection by the clinical trial monitor.

5.6 ASSESSMENT OF COMPLIANCE WITH STUDY MEDICATION

Tocilizumab will be administered intravenously by trained medical staff; compliance, therefore, will be monitored by the medical staff and documented on the CRF.

6. STUDY PROCEDURES

6.1 INTENSIVE DIABETES MANAGEMENT

During the study period, all participants will receive "intensive" management of their diabetes, and HbA_{1C} will be assessed at every visit to evaluate metabolic control. The goal of treatment will be to maintain the HbA_{1C} levels within the currently recommended ADA age-specific target ranges in the absence of significant or severe hypoglycemia. 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. Glucose levels should be checked frequently and records communicated regularly to the study team.

6.2 VISIT WINDOWS

6.2.1 Scheduled Visits

The initial treatment should begin within 100 days from the day of diagnosis and within 37 days of the screening MMTT. Subsequent treatment visits are every 4 weeks. The treatment visits (V0-V6) must occur within 7 days on either side of the target date. However, consecutive doses must be 21 days apart. Treatment doses will not be administered 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 7 doses over the 6 month period. The window for all subsequent visits is +/- 2 weeks. Appendix 1 presents the schedule of events for this trial.

6.3 RANDOMIZATION, MASKING, AND UNMASKING

6.3.1 Randomization

Participants who sign the informed consent and meet the eligibility criteria will be randomly assigned in a 2:1 ratio to either the experimental or control group. A central automated randomization system will be used for treatment assignment and to create a unique identifier for each new study participant. Adults and children will be

randomized separately. For subjects in the adult cohort, random assignment will be stratified by site. For subjects in the child cohort, random assignment will be stratified by site and baseline mean 2-hour C-peptide AUC (<0.53, 0.53-0.79, >0.79 pmol/ml).

Note that the cutpoints for the baseline mean 2-hour AUC levels are the tertiles observed in a sample that included 104 placebo subjects aged 6 to 17 pooled across 5 TrialNet studies.[10,11,60-62]

6.3.2 Masking to treatment assignment

Masking will be maintained throughout the study for all study participants and study personnel, except the pharmacists.

6.3.3 Unmasking

Unmasking before the study is completed will occur if a participant's well-being is threatened and the investigator believes unmasking is necessary to protect the participant. Unmasking may also occur in the case of pregnancy (participant or partner pregnancy) at the request of the pregnant woman.

Before treatment assignment for an individual participant is unmasked, the investigator should attempt to confer with the DAIT medical monitor. In the event that the DAIT medical monitor was not previously notified of the emergency unmasking, the site investigator will notify the DAIT medical monitor and ITN physician of an unmasking event as soon as possible after the fact.

The emergency unmasking will be recorded and reported to the DSMB. A full account of the event will be recorded, including the date and time of the emergency, the reason for the decision to unmask, and the names of the medical monitor and others who were notified of the emergency. During site visits, the site monitor must verify that the DAIT medical monitor was notified and that a written account was completed. The reasons for unmasking of a participant's treatment will be included in the final study report.

Unmasking will also occur for Safety Reports (SUSARs) that will be reported to the US and Australian Health Authorities, DSMB and IRBs/ECs as specified in the current FDA IND Safety Reporting guidance.

ITN and DAIT, NIAID approval is required for unmasking the treatment of an individual participant or subgroups of participants for unplanned interim analyses to support DSMB reviews and final analysis.

6.4 GENERAL ASSESSMENTS

- Informed consent: Written informed consent will be obtained from the participant before any study assessments or procedures are performed.

- Eligibility criteria: Eligibility for study participation will be assessed during the screening period.
- Medical history: This includes T1DM time of diagnosis and clinically significant diseases or medical procedures.
- Adverse events: Participants will be assessed for AEs.
- Concomitant medications: All concomitant medications and their indications will be recorded.
- Physical examination: This may be a comprehensive or directed exam as noted in the SOE (Appendix 1).
- Vital signs: Weight, temperature, blood pressure, respiration, and pulse will be obtained at all visits. Height will be obtained at initial visits for all subjects and every 6 months for children.

6.5 CLINICAL LABORATORY ASSESSMENTS

Clinical laboratory blood draws are to be performed after vital signs are assessed and prior to study drug infusion during the treatment period. Participants will periodically undergo blood draws for both clinical and immunologic tests. Blood volumes drawn will be based on participant body weight and may be modified to limit the total blood volume drawn at any one visit.

Central laboratory assessments:

- Serum chemistries: Electrolytes (sodium, potassium, chloride, phosphate, total CO_2), blood urea nitrogen (BUN), creatinine, CRP and liver panel (AST, ALT, alkaline phosphate, direct and total bilirubin).
- Hematology: Includes RBC, hematocrit, hemoglobin, platelet count, WBC and differential.
- Lipid panel: Total cholesterol, HDL, LDL, triglycerides.
- Urinalysis: Includes blood (RBCs), glucose, ketones, pH, protein and specific gravity.
- Infectious disease serology: Serology will be performed at screening for HBV, HCV, HIV, EBV, CMV. CMV or EBV serology will be repeated if participants show clinical signs of infection; *or* if the EBV viral load is ≥ 10,000 copies per 10^6 PBMCs or ≥ 2,000 copies per mL of whole blood or the CMV viral load is ≥ 10,000 IU or copies per mL whole blood or plasma.
- Viral load testing: Viral load testing by PCR will be performed for CMV and EBV.
- TB test: Exposure to tuberculosis will be assessed via QuantiFERON TB test (A PPD skin test may be performed locally if the QuantiFERON TB test is not performed at the central lab).

- Serum βHCG: Serum testing will be performed at screening to rule out pregnancy. Serum βHCG will be repeated after screening for participants with a positive urine HCG result at any study visit.

Disease-Specific Assessments:

- C-peptide (as part of MMTT).
- Plasma glucose (as part of MMTT and FSIVGTT).
- Insulin (as part of FSIVGTT).
- HbA1c
- Diabetes-related autoantibodies

Drug-Related Assessments:

- Pharmacokinetics (PK)
- IL-6 and IL-6sR
- Anti-TCZ antibodies

Laboratory assessments evaluated at the site:

- Urine HCG: Urine HCG will be measured before study drug administration during the treatment period for female participants with reproductive capacity to monitor for pregnancy

6.6 PHARMACOKINETIC ASSESSMENTS

All participants will have PK samples taken at the time points listed in Table 6.

Table 6: Pharmacokinetic Samples

Visit #	Time Points	
	Day of Infusion	**7 Days (Post infusion)**
V0 (Week 0)	• before infusion • within 10 minutes after infusion	• 7 (±3) days after infusion
V1 (Week 4)	• before infusion	
V5 (Week 20)	• before infusion • within 10 minutes after infusion	• 7 (±3) days after infusion
V6 (Week 24)	• before infusion	

6.7 METABOLIC ASSESSMENTS

- MMTT: A 2-hour MMTT is to be performed at weeks 12, 24, 39, and 78. A 4-hour MMTT is to be performed at weeks -1 (screening), 52, and 104 for subjects ≥12 years old (for subjects <12 years old, a 2-hour MMTT will be performed instead.
- HbA1c
- Glucose (glucometer readings)
- Continuous glucose monitoring (CGM) to obtain data to evaluate glycemic control; particularly frequency of hypoglycemia. Randomized participants will be invited to use a commercially available FDA or appropriate Health Authorities approved CGM system and its components (Dexcom, Inc., San Diego, CA) for a 14 day period at weeks 0, 12, 24, 52, 78, and 104. Data may also be obtained for the study from the participant's CGM system if used as part of their usual clinical care.
- Insulin use (U/kg body weight/day)
- Major hypoglycemic events
- FSIVGTT (Frequently sampled glucose tolerance test). To obtain additional information about the possible effects of therapy on insulin sensitivity, a FSIVGTT will be offered to subjects age ≥15 at baseline, week 24 and week 52. Due to the additional visits required to conduct these tests, 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.

6.8 MECHANISTIC ASSESSMENTS

Mechanistic samples drawn during the study drug treatment period are collected prior to study drug infusion. See section 7 for detailed discussion of additional mechanistic assays.

7. TOLERANCE ASSAYS

7.1 MECHANISTIC HYPOTHESIS

The primary mechanistic hypotheses are that anti-IL6R therapy in T1D will promote T regulatory cell activity, suppress innate immune responses, and alter B cell activity. Studies will address multiple questions but will be prioritized based on the amount of blood available. Questions to be addressed in current rank order are:

- Anti-IL6R results in increased numbers of the peripheral regulatory T cell population and diminishes numbers of pro-inflammatory T cells, including Th17 cells.

- Anti-IL6R results in altered functional status of both regulatory T cells and pro-inflammatory T cells.
- Anti-IL6R enhances the sensitivity of effector T cells to suppression by Tregs.
- Anti-IL6R alters the proportions of circulating B cell compartment.
- Anti-IL6R alters innate immune responses, including changes in the composition and activation of monocytes, dendritic cells, and NK cells.

7.2 RETENTION OF SAMPLES

Specimens collected in this trial may be used to reevaluate biologic responses as new research tools become available. Samples collected from this study in the United States, will be stored centrally at the ITN sample repository for future analysis. Samples collected in Australia will be stored centrally at the University of Queensland Diamantina Institute, Queensland, and some of these samples may be transferred to the ITN sample repository in the US for archive and future analysis as needed. Residual specimens may be used by investigators for development of new immunologic assays or for cross-trial comparisons. While specimens are described in this protocol in the context of assays to be performed, it should be noted that not necessarily all assays will be performed for all participants at each time point. Decisions to perform assays will be made according to statistical and scientific planning, questions being asked, and current technologies to be utilized. Finally, clinical outcomes will be taken into account to determine the potential value of the assays. For example, if a significant clinical effect fails to occur, the assays performed by the ITN may be minimal. Specimens and data may be used for future research related to diabetes and autoimmune diseases.

7.2.1 Sample Types

Samples will be collected under the auspices of the clinical sites as outlined in the schedule of events (Appendix 1).

7.3 MECHANISTIC ASSAYS

The following assay methodologies may be used to address the mechanistic hypotheses:

- Multi-chromatic flow cytometry on banked PBMCs to monitor the changes in number and phenotype of various immune cell subsets including T cells, B cell subsets and innate cells. Flow cytometry may also be used to assess the functional status of cells in response to *ex vivo* stimuli for example, phosphorylated status of STAT proteins (STAT-3 or STAT5) and intracellular cytokine secretion.
- Multiplex immunoassays may be used to measure changes in circulating markers using serum or plasma collected at multiple time points during therapy.

- Cell-based proliferation assays may be used to examine the changes in resistance to Treg-mediated suppression of Teff cells using viably frozen PBMCs.
- Epigenetic analysis may be performed on DNA extracted from frozen whole blood to assess changes in native Treg, Th17, Th1 and Tfh cell numbers.
- One or more gene expression analysis platforms may be used to evaluate changes in expression of various genes using blood frozen in presence of RNA stabilizing agents.
- Genetic variation and SNP analysis of genes of interest may be performed on DNA isolated from frozen whole blood.
- Other assays as approved by the ITN study management team.

8. ADVERSE EVENTS

8.1 OVERVIEW

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE (adverse event) or SAE (serious adverse event) as described in Section 8.2 in this protocol. All AEs and SAEs will be recorded in the source documents and on the appropriate electronic CRF(s). All data will be reviewed periodically by the DSMB, which may provide recommendations to NIAID about withdrawing any participant and/or terminating the study because of safety concerns.

Adverse events that are classified as serious according to the definition of Health Authorities must be reported promptly and appropriately to the Global Study Sponsor (DAIT, NIAID, NIH), ITN, principal investigators in the trial, IRBs/ECs, and appropriate Health Authorities. This section defines the types of AEs and outlines the procedures for appropriately collecting, grading, recording, and reporting them. Information in this section complies with 21CFR 312; *ICH Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting; and ICH Guideline E-6: Guidelines for Good Clinical Practice;* and applies the standards set forth in the National Cancer Institute's *Common Terminology Criteria for Adverse Events Version 4.03* (published June 14, 2010) with the exception of reporting of hyperglycemia and hypoglycemia as noted below. This document referred to herein as the "NCI-CTCAE manual."

8.2 DEFINITIONS

8.2.1 Disease-specific Adverse Event

For the purposes of this study, *major hypoglycemic events* will be recorded in the eCRF. Major hypoglycemic events are defined as:

- Blood glucose concentration < 40 mg/dL; (Grades 3–5, NCI-CTCAE version 4.03), or

- Hypoglycemic events involving seizure or loss of consciousness (coma), or requiring assistance from another individual in order to recover.

All episodes of hypoglycemia that require hospitalization and/or emergency care will be reported to the DSMB in an expedited manner as described in Section 8.5.3.

8.2.2 Adverse Event

An adverse event (AE) is any occurrence or worsening of an undesirable or unintended sign, symptom, laboratory finding, or disease that occurs during participation in the trial. An AE will be followed until it resolves or until 30 days after a participant terminates from the study, whichever comes first. All AEs will be reported as specified in Section 8.3.1 whether they are or are not related to disease progression or study participation.

8.2.3 Suspected Adverse Reaction and Adverse Reaction

Suspected adverse reaction (SAR) means any adverse event for which there is a reasonable possibility that the study drug caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse reaction. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (21 CFR 312.32(a))/(ICH E2A).

An adverse reaction (AR) means any adverse event caused by a study drug. Adverse reactions are a subset of all suspected adverse reaction for which there is reason to conclude that the drug caused the event.

8.2.4 Serious Adverse Event

An AE or SAR is considered "serious" if, in the view of either the investigator or DAIT, NIAID it results in any of the following outcomes (21 CFR 312.32(a))/(ICH E2A):

- Death: A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported whether it is considered treatment related or not.
- A life-threatening event: An AE or SAR is considered "life-threatening" if, in the view of either the investigator or DAIT, NIAID, its occurrence places the subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

- An event that requires intervention to prevent permanent impairment or damage. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.
- Congenital anomaly or birth defect.

8.2.5 Adverse Events of Special Interest (AESIs)

Adverse Events of Special Interest (AESIs) are identified for ACTEMRA® (tocilizumab) and will be collected and reported as **study-specific AEs or SAEs** in this trial. Investigators should use their clinical judgement to identify events falling in any of the following categories:

- Opportunistic and serious infections (including all opportunistic infections and all non-serious infections as defined by those treated with IV anti-infectives).
- Myocardial infarction/acute coronary syndrome.
- Gastrointestinal perforations and related events, including complications of diverticulitis, appendicitis, generalized purulent peritonitis, lower GI perforation, fistula, and/or abscess.
- Anaphylaxis (and/or related hypersensitivity reactions that require treatment discontinuation).
- Malignancies.
- Hepatic Events, including elevated hepatic transaminase levels (ALT/AST levels > 3× ULN) or total bilirubin > 3 mg/dL.
- Bleeding Events, including any clinical sign of hemorrhage that requires diagnostic studies, hospitalization, and/or treatment.
- Stroke, including ischemic or hemorrhagic stroke, or transient ischemic attack.
- Demyelinating disorders (with signs or symptoms of a demyelinating disorder such as multiple sclerosis or chronic inflammatory demyelinating polyneuropathy).

If an adverse event meets any of the above study-specific categories, regardless of the relationship of the event to study drug or severity, the event must be reported to the Global Study Sponsor (DAIT, NIAID, NIH) as described in Section 8.5.1. For all Adverse Events of Special Interest received by the Global Study Sponsor (serious and non-serious), a guided questionnaire will be used to obtain follow-up information.

8.2.6 Unexpected Adverse Reaction

A SAR is considered "unexpected" when its nature (specificity), or severity, or rate of occurrence is not consistent with applicable product information as described in the safety information provided in the developmental core safety information section of the current F. Hoffman La-Roche LTD Investigator's Brochure and country-specific package inserts for tocilizumab.

8.3 COLLECTING AND RECORDING ADVERSE EVENTS

8.3.1 Methods of Collection

All adverse events (AEs) will be collected and recorded from visit -1 until the time the participant completes the study, or prematurely withdraws from the study. All serious adverse events (SAEs) will be collected from visit -1 until 30 days after the participant completes the study, or 90 days after the participant prematurely withdraws from the study.

Adverse events and serious adverse events may be collected as follows:

- Observing the participant.
- Questioning the participant in an objective manner.
- Receiving an unsolicited complaint from the participant.

An AE that is an asymptomatic abnormal value or result from a clinical or laboratory evaluation (e.g., a radiograph, an ultrasound, or an electrocardiogram) will be documented and maintained in the source records. Asymptomatic adverse events must be recorded on the AE form when they meet the criteria for a Grade 3 or greater AE per CTCAE criteria, with the exception of AESIs (Section 8.2.5) and hyperglycemia and hypoglycemia as defined in Section 8.4.1. The evaluation that produced the value or result should be repeated until that value or result returns to normal or can be explained and the participant's safety is not at risk.

8.3.2 Specific Instructions for Recording Adverse Events

Correct medical terminology/concepts should be used when reporting AEs and SAEs. Avoid colloquialisms and abbreviations.

- **Diagnosis vs. Signs and Symptoms**
  If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

- **Deaths**

  All deaths that occur during the protocol-specified AE reporting period (see Section 5.1.2), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death."

- **Preexisting Medical Conditions**

  A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

- **Hospitalizations for Medical or Surgical Procedures**

  Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

8.3.3 Recording AEs

Throughout the study, the investigator will record all symptomatic AEs on the appropriate eCRF regardless of their severity or relation to study participation and asymptomatic AEs of grade 3 or above. The investigator will treat participants experiencing AEs appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

8.3.4 Recording SAEs

Serious AEs will be recorded on the SAE eCRF and Health Authorities will be notified as outlined in Section 8.5.

8.4 GRADING AND ATTRIBUTION OF ADVERSE EVENTS

8.4.1 Grading of Major Hypoglycemic and Hyperglycemic Events

For this study of participants with type 1 diabetes, the NCI-CTCAE will not be used to grade hypoglycemia and hyperglycemia. Please refer to the grading criteria for major hypoglycemic and hyperglycemic events below. In this study, non-major hypoglycemic and hyperglycemic events will not be reported as AEs.

Major hypoglycemic events will be graded as follows:

- Grade 3 = blood glucose concentration < 40 mg/dL or <2.2 mmol/L; (Grades 3–5, NCI-CTCAE version 4.03), or events resulting in seizures, loss of consciousness, or requiring the assistance of others for the purpose of altered consciousness.
- Grade 4 = events resulting in coma or life-threatening event requiring hospitalization.
- Grade 5 = death.

Major hyperglycemic events will be graded as follows:

- Grade 4 = coma or life-threatening event or event resulting in hospitalization.
- Grade 5 = death.

For this study significant diabetic ketoacidosis (DKA) will be reported together with grade 4 hyperglycemia (as a single adverse event) resulting in hospitalization and life threatening consequences.

8.4.2 Grading for All Other Adverse Events

The study site will grade the severity of AEs experienced by study participants according to the criteria set forth in the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE, v 4.03) manual and provides a common language to describe levels of severity, to analyze and interpret data, and to articulate the clinical significance of all AEs, with the exception of hypoglycemia and hyperglycemia.

Adverse events will be graded on a scale from 1 to 5 according to the following standards in the NCI-CTCAE manual:

- Grade 1 = mild adverse event.
- Grade 2 = moderate adverse event.
- Grade 3 = severe and undesirable adverse event.
- Grade 4 = life-threatening or disabling adverse event.
- Grade 5 = death.

For additional information and a printable version of the NCI-CTCAE manual, go to http://ctep.cancer.gov/reporting/ctc.html.

8.4.3 Attribution

Adverse events will be categorized for their relation to tocilizumab. The principal investigator will make the initial determination of the relation, or attribution, of an AE to study drug and will record the initial determination on the appropriate eCRF and/or SAE reporting form. Infusion reactions occurring within 24 hours of starting study

drug infusion will be considered related to the study drug as defined in Section 5.2.6. The relation of an AE to study drug will be determined using definitions in Table 7. Final determination of attribution for safety reporting will be decided by DAIT, NIAID.

Table 7. Attribution of Adverse Events

Code	Descriptor	Definition
Unrelated Category		
1	Unrelated	The adverse event is clearly not related.
2	Unlikely	The adverse event is unlikely related.
Related Categories*		
3	Possible	The adverse event has a reasonable possibility to be related; there is evidence to suggest a causal relationship.
4	Probable	The adverse event is likely related.
5	Definite	The adverse event is clearly related.
**Infusion reactions defined as fever, chills, pruritus, urticarial, angioedema, skin rash, anaphylaxis, and cardiopulmonary reactions, not limited to chest pain, dyspnea, hypotension or hypertension, occurring within 24 hours of starting study drug infusion will be considered related to the study drug per section 5.2.6*		

8.5 REPORTING SERIOUS ADVERSE EVENTS

8.5.1 Reporting SAEs to the Global Study Sponsor (DAIT, NIAID, NIH)

The following process for reporting a SAE ensures compliance with 21CFR 312 and ICH guidelines. After learning that a participant has experienced a SAE, the investigator or designee will report the SAE via the electronic SAE report form (SAE eCRF) within 24 hours of becoming aware of the event. Initial SAE eCRF should include as much information as possible, but at a minimum must include the following:

- AE term.
- Study drug treatment.
- Relationship to study medications.
- Reason why the event is serious.
- Supplementary CRF pages that are current at the time of SAE reporting: medical history, concomitant medications, demographics, study drug administration, death.

As additional details become available, the SAE eCRF should be updated and submitted. Every time the SAE eCRF is submitted, it should be electronically signed by the investigator or subinvestigator.

For additional information regarding SAE reporting, contact Rho Product Safety:

Rho Product Safety

[redacted]

8.5.2 Reporting SAEs to Health Authorities

After the SAE has been reported by the principal investigator and assessed by the Global Study Sponsor (DAIT, NIAID, NIH). In the US, the IND sponsor (DAIT, NIAID, NIH) must report an event to the FDA using one of these two options:

- **Standard reporting (report in the IND annual report).** This option applies if the AE is classified as one of the following:
  - Serious, expected, suspected adverse reactions described in Sections 8.2.4 and 8.2.5.
  - Serious and not a suspected adverse reaction described in Section 8.2.3.
- **Expedited reporting is required.** This option applies if the AE is classified as one of the following:
  - Serious and unexpected suspected adverse reactions described in Section 8.2.3, and unexpected per Section 8.2.5.
  - The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study drug and the adverse event, such as:
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, or Stevens-Johnson Syndrome).
    - One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).
  - Aggregate analysis of specific serious adverse events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

- Any findings from clinical or epidemiological studies, analysis of data pooled across multiple studies, published or unpublished scientific papers, or from animal or in vitro testing that would result in a safety-related change in the protocol, informed consent, Investigator's Brochure, or other aspects of the overall conduct of the trial will be reported.

Safety reports must be reported by DAIT, NIAID to the FDA within 15 calendar days; fatal or immediately life-threatening, serious, unexpected, suspected adverse reactions must be reported within 7 calendar days.

Australian Suspected Unexpected Serious Adverse Reactions (SUSARs) should be reported to the TGA by the Study Sponsor following the timelines outlined below:

- Fatal or life-threatening SUSARs: as soon as possible but no later than 7 calendar days after first knowledge, followed by as complete a report as possible within 8 additional calendar days.
- All other serious SUSARs: as soon as possible but no later than 15 calendar days after first knowledge.

All principal investigators must report SAEs to their respective IRBs/ECs as mandated by them.

8.5.3 Reporting SAEs to the DSMB

The Study Global Sponsor (DAIT, NIAID, NIH) will provide the DSMB with data of all SAEs on a regular basis, including quarterly reports of all SAEs. Major hypoglycemic events that require emergency care will also be reported to the DSMB in an expedited fashion regardless of whether they met the criteria for an SAE or not.

8.5.4 Reporting of Adverse Events to IRBs/ECs

All investigators must report adverse events, including expedited reports, in a timely fashion to their respective IRBs/ECs in accordance with applicable regulations and guidelines. All Safety Reports to the FDA or the appropriate Health Authorities shall be distributed by DAIT NIAID or designee to the participating institution for site IRB/EC submission according to local regulation and guidelines.

8.5.5 Reporting AEs to Genentech, Inc.

The DAIT, NIAID will provide Genentech, Inc. with data for AEs of Special Interest (AESIs) and SAEs on an ongoing basis as specified in the protocol-specific safety management plan part B.

Distribution as follows:

1. DAIT SACCC (Rho Federal) will forward a notification including a copy of the eCRF of all SAEs including significant follow-ups, AESIs, and pregnancies to DAIT, NIAID and Genentech Drug Safety (GDS) within 24hrs of becoming aware of the event.

2. DAIT SACCC (Rho Federal) will forward the final version of all SAEs, AESIs and pregnancies to Genentech, Inc. within 15 days of sponsor notification.
3. All IND Safety Reports with an Analysis of Similar Events will be sent to GDS at the time of transmission to the FDA.
4. Any study report submitted to the FDA by the Sponsor should be copied to Genentech, Inc. This includes all IND annual reports and the Clinical Study Report (final study report).
5. Final Reports format:
    a. For expedited reports: MedWatch
    b. For non-expedited related reports: Medical Summary Report
    c. AESIs: Event-Specific Guided Questionnaire
    d. All other non-serious AEs: Line listings
6. DAIT SACCC (Rho Federal) statistician will post cumulative line listings of serious and non-serious AEs and pregnancy reports monthly to Rho Portal. Genentech, Inc. will receive an email notification when the reports are posted or updated and will be able to access the study website to retrieve the listings as needed.

8.5.6 Reporting Pregnancy

The investigator should be informed immediately of any pregnancy in the participant or a partner pregnancy of a male participant occurring from randomization through the end of the follow-up period (two-year study period). All available pregnancy information should be entered into the electronic data capture (EDC) system within 24 hours of becoming aware of the event. The investigator should be available to counsel the participant or refer the participant (or partner) for counseling to discuss the risks of continuing with the pregnancy and the possible effects on the fetus. The pregnant woman will have the option to be informed of treatment assignment should she wish to know. She will be asked to sign a specific informed consent giving her approval for the site to monitor and report the conclusion of the pregnancy. Follow-up information detailing the outcome of the pregnancy should be entered into the EDC system as it becomes available. Any premature termination of the pregnancy would also be reported.

Pregnancy will be recorded as an AE for tracking purposes. Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in Sections 8.3.2 and 8.3.3.

9. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

9.1 ANALYSIS SAMPLES

Modified Intent to Treat (mITT) sample will include all randomized participants who received any dose of study treatment. The efficacy analyses will be based on the mITT sample according to the group to which the participants are assigned.

Per protocol samples will be assessed for week 52 (**PP1**) and week 104 (**PP2**), and will include all participants in the mITT sample with no major protocol deviations that impact efficacy assessments, who have completed at least 5 of the 7 monthly infusions of study drug and who received at least 80% of the expected dose in each infusion, and who have the week 52 and week 104 MMTT assessment for C-peptide, respectively. The reported major deviations will be reviewed during a masked data review after the last subject's primary endpoint visit and the end of the study to determine which participants should be excluded from the per-protocol populations.

Safety sample (SS) will be defined as all participants who received any degree of study treatment. Safety analyses will be based on actual treatment the participants receive.

9.2 ANALYSIS OF ENDPOINTS

Because the natural history of disease in T1DM is considerably different in children as compared with adults, with adults having a much more indolent disease course, the primary analysis of the primary endpoint will be evaluated using the pediatric participants in the mITT sample. Primary analysis of treatment effect will be conducted under the mITT principle of eligible patients, whereby outcome data from all pediatric patients in the mITT sample will be included regardless of treatment compliance or duration of study participation.

All analyses for the primary and secondary endpoints will be completed in the pediatric mITT sample (ages 6 to 17 years) and will also be repeated on the pooled mITT sample (i.e. both adult and pediatric subjects) as secondary analyses.

9.2.1 Primary Endpoint

The primary analysis of the primary endpoint, change in MMTT-stimulated mean 2-hour C-peptide AUC at week 52, will test the null hypothesis of "no treatment group difference" versus the two-sided alternative using pediatric participants from the mITT sample. The hypothesis test and baseline-adjusted treatment group estimates will be derived from an ANCOVA model fit to the change in mean 2-hour C-peptide AUC response at week 52 with fixed effects for treatment group, baseline mean 2-hour C-peptide AUC, and age. Transformations of data will be considered if evidence of significant departures from model assumptions are apparent.

For a participant who misses the entire week 52 MMTT assessment, the missing AUC values will be imputed using the following approach for the primary analysis of the primary endpoint:

- If the subject's last observed AUC value is 0, the missing week 52 AUC will be imputed to zero.
- If the subject's last observed AUC value was at time t and was >0, then the missing AUC at week 52 will be imputed using data from subjects in the same arm and age group who had available AUC values at both time t and week 52. Specifically, a linear regression line will be fit where week 52 AUC values are regressed on AUC values at time t (e.g. week 24). In each arm and age group, a missing week 52 AUC value will be imputed as the value predicted from the linear regression line.

At a minimum, the following sensitivity analyses for the primary endpoint will be performed:

- An analysis analogous to the primary endpoint analysis using only mITT subjects with observed data at week 52 (i.e., without imputing any missing week 52 AUC values).
- An analysis analogous to the primary endpoint analysis using the PP1 subjects.
- An analysis analogous to the primary endpoint analysis in the mITT sample using imputed values for missing week 52 AUC values as described above but using a conservative approach. In the active therapy arm, a missing week 52 AUC value will be imputed as the value predicted from the estimated lower limit of a 90% confidence band about the linear regression line. In the Control group, a missing week 52 AUC value will be imputed as the value predicted from the estimated upper limit of a 90% confidence band about the regression line.

Note that, if research suggesting better methods for handling missing C-peptide AUC data becomes available, changes to the above plan will be pre-specified in the Statistical Analysis Plan prior to data lock and unmasking of treatment assignments for planned end-of-study analyses.

9.2.2 Secondary Endpoints

The null hypothesis proposes that there is no difference in the secondary endpoint (measured either as means or proportions) between study groups. The alternative hypothesis proposes the opposite; that there is a difference in the secondary endpoints between the treatment and control groups. All secondary inferential analyses are considered supportive; p-values will be presented without adjustment for multiple comparisons.

Treatment group differences in change in mean 2-hour C-peptide AUC from baseline at weeks 12, 24, 39, 78, and 104 will be compared using ANCOVA analyses controlling for baseline. Effect modification by baseline mean 2-hour C-peptide AUC and age will be evaluated. In addition, treatment groups will also be compared at weeks 12, 24, 39, and 52 using a random regression approach. A random regression model will be fit to the mean 2-hour C-peptide AUC responses at baseline and weeks 12, 24, 39, and 52 with fixed effects for treatment, time, age, and interactions for treatment*time and age*time. Random within-subject effects for intercept and slopes over time will be included assuming an unstructured covariance matrix. All subjects with at least 1 post-baseline assessment will be included in the random regression model. A separate random regression model will include C-peptide assessments through week 104. For these models, piece-wise slopes will be considered to allow for the potential rise and fall in mean 2-hour C-peptide. Transformations of data will be considered if evidence of significant departures from model assumptions are apparent. Alternative covariance structures will be considered if models fail to converge.

Treatment group differences in the change in mean 4-hour C-peptide AUC from baseline at weeks 52 and 104 will be compared using ANCOVA analyses controlling for baseline. ANCOVA models adjusting for baseline will also be used to analyze the change in peak 4-hour C-peptide at weeks 52 and 104.

In addition, analogous analyses will be used to analyze glucose values, insulin use and HbA_{1c}.

The mechanistic hypothesis for secondary endpoint determination (Section 3.3.2) is that the treatment will promote Treg and/or reduce Teff cell frequency in the periphery. Multi-chromatic flow cytometry will be used to monitor the frequency of Treg and Teff cell populations during the course of study and the ratio of Treg/Teff will be determined to investigate the effect of TCZ on these cell types. A linear mixed model analysis will be used to evaluate Treg/Teff longitudinal differences between control and treatment groups at weeks 12, 24, 39, 52, 78 and 104.

9.2.3 Safety Analysis

Reports summarizing safety data will be prepared at the end of the study and periodically throughout the study for regulatory filings, the DSMB, and for the medical monitor and study management team. Safety reports will be prepared to meet the needs of those groups and individuals responsible for monitoring safety and may include (but are not limited to) masked summaries and listings of SAEs, AEs, changes in vital signs, events requiring drug discontinuations for individual subjects (See Section 5.3), and events listed as study stopping rules (Section 3.5.2.1). AEs and SAEs in the summary displays and listings will be coded using the MedDRA system organ classes and/or preferred terms. Severity will be reported using NCI-CTCAE

grading criteria, with the exception of hypoglycemia and hyperglycemia. Relationship to study drug will be reported as per Section 8.4.2.

The joint NIDDK and NIAID ACE/ITN/TrialNet DSMB will perform ongoing review of C-peptide data to monitor for unexpected declines, as follows:

- For adult subjects, mean 2-hour C-peptide AUC levels within 12 weeks of randomization will be reviewed on an ongoing basis in a masked fashion for all subjects. Once > 30% of randomized subjects are shown to have a mean 2-hour C-peptide AUC at 12 weeks that is ≥ 50% of their baseline mean 2-hour C-peptide AUC, monitoring may be discontinued. However, if 70% or more of the subjects show a > 50% drop in mean 2-hour C-peptide AUC by week 12, then the data will be unmasked by study statisticians, the percent of events in each arm will be computed, and the DSMB will be notified.
- For pediatric subjects, mean 2-hour C-peptide AUC levels within 12 weeks of randomization will be reviewed on an ongoing basis. Once there are at least 10 subjects with week 12 C-peptide data available in the active treatment group, the C-peptide data will be monitored using the following guideline. If 70% or more of the subjects in the active treatment group show a > 50% drop in mean 2-hour C-peptide AUC by week 12, then the DSMB will be notified of the overall C-peptide data from the study by age cohort and treatment assignment.

For the end of study analyses, the proportions of subjects in each treatment arm experiencing safety endpoints of particular interest (see Section 3.3.2) will be compared using the Fisher's Exact statistics.

9.2.4 Medical History

Medical history within the past 12 months—including the existence of current signs and symptoms—will be collected for each body system.

9.2.5 Use of Medications

All medications taken by or administered to study participants beginning 30 days before enrollment and continuing throughout the study will be collected. All medications used will be coded according to the World Health Organization (WHO) drug dictionary. The number and percentage of participants receiving prior and concomitant medications/therapies will be presented overall and by medication class.

9.3 INTERIM ANALYSES AND DATA REVIEW

Per the protocol, an interim report of safety and metabolic data from adult participants was reviewed by the DSMB and FDA. At least 30 adult subjects had week 12 C-peptide data available for the report.

Prior to initiating the study in the pediatric age group (6-17 years old), adults (18-45 years old) were randomized 2:1 to tocilizumab or placebo, respectively. After 30 adult participants completed 12 weeks of treatment, the DSMB and FDA reviewed the available data to weigh potential risks and benefits as well as prospect of benefit before opening the trial to pediatric participants. The result of those reviews was to allow enrollment of children and adolescents 6-17 years old.

Progress of the study will be monitored at least yearly throughout the trial by the DSMB. The DSMB will review interim data on subject accrual, subject disposition, early C-peptide levels (baseline through week 12), safety (see Section 9.2.3), site performance, and data quality. In addition, data will be reviewed by the DSMB when an event occurs that is of sufficient concern to the DAIT, NIAID medical monitor, ITN physician or protocol chairs to warrant review.

- Study-related AEs associated with stopping rules (Section 3.5.2) will be brought immediately to the attention of the DSMB.
- SAEs will be reported to the DSMB per Section 8.5 of the protocol.

9.4 SAMPLE SIZE

The primary analysis of the primary endpoint will be conducted using data from the 78 pediatric participants. This target number was selected with the goal of detecting a clinically meaningful improvement of 39% for tocilizumab over placebo. Power estimates associated with these targets are discussed below (see Table 8). Prior to enrolling pediatric subjects, 55 adult participants were enrolled to support safety, mechanistic, and exploratory analyses.

Control subject estimates used in these calculations are based on data from 104 control pediatric subjects (aged 6 to 17 years) pooled from 5 new-onset T1DM studies.[10,11,60-62] At baseline, the mean (SD) for the mean 2-hour C-peptide equaled 0.70 (0.312) pmol/ml. Control group estimates for average change in the mean 2-hour C-peptide AUC from baseline to Month 12 and the associated root mean square error (RMSE) were derived from analysis of covariance models (ANCOVA) using baseline AUC as a covariate. The average change in the mean 2-hour C-peptide AUC (RMSE) equaled -0.31 (0.221) pmol/ml (i.e. a 44% drop).

Under the assumption that these computed values represent the parameters expected for the control group and using a 2:1 random assignment of tocilizumab versus placebo with a significance level of 5%, a study of 78 eligible pediatric subjects will have at least 80% power to detect a 39% improvement of tocilizumab over controls. That is, assuming a control group drop in mean 2-hour C-peptide AUC of 44% at Month 12 (i.e. 0.70 at baseline, 0.39 at Month 12) and a drop of 22% in the tocilizumab (i.e. 0.70 at baseline, 0.542 at Month 12), then power equals 80%. The design has 89% power to detect a 44% improvement (i.e. groups differ by 0.17 pmol/ml). If the RMSE equals 0.25, which is the upper 90% confidence limit for

RMSE estimated from the control data, then power to detect a 44% improvement drops to 80%.

Table 8. Summary of Power/Sample Size Results for Pediatric Participants

Total N	mean AUC at baseline	Average change in mean AUC at Month 12: placebo	Average change in mean AUC at Month 12: tocilizumab	RMSE	Difference between groups at Month 12 (% improvement of tocilizumab over placebo)	% Power
78	0.70	-0.310 (44% drop)	-0.158 (a 22% drop)	0.22	0.15 (39%)	80%
78	0.70	-0.310	-0.138 (a 20% drop)	0.22	0.17 (44%)	89%
78	0.70	-0.310	-0.138	0.25	0.17 (44%)	80%

Note: % improvement of tocilizumab over placebo is computed as: ($AUC_{12\_tocilizumab} - AUC_{12\_placebo}$) divided by $AUC_{12\_placebo}$.

9.5 PHARMACOKINETIC ANALYSES

All PK analyses will use the actual sampling times. PK parameters C_{max} (µg/mL), t_{max} (h), C_{min} (µg/mL), AUC 0–28 d (µg·h/mL) (following the first and last infusions), and AUC 0-t or AUC 0-∞, will be estimated, as data permit. In addition, terminal phase half-life ($t_{1/2}$,z) and clearance (CL) may also be estimated from the data.

PK data may be used to explore the exposure-response relationship in T1DM patients.

9.6 REPORTING DEVIATIONS FROM THE ORIGINAL STATISTICAL PLAN

The principal features of both the study design and the plan for statistical data analysis are outlined in this protocol and in the statistical analysis plan (SAP). Any change in these features requires either a protocol or an SAP amendment, which is subject to review by the DSMB, the study sponsor(s), and the appropriate Health Authorities. These changes will be described in the final study report as appropriate.

10 STUDY ADMINISTRATION

10.1 SPONSOR

This clinical trial is conducted through the NIAID NIH-funded Cooperative Agreement awarded to the Benaroya Research Institute at Virginia Mason (Seattle, WA) (BRI) to support the Immune Tolerance Network (ITN), a collaborative network for clinical research. The ITN provides financial support for the conduct of the

clinical trial to the clinical sites through subcontracts between the BRI and the clinical sites. The NIAID NIH serves as the US Sponsor of the Investigational New Drug application (IND) for the Protocol and the Global Study Sponsor in Australia (represented by Pharmaceutical Product Development, Inc. (PPD) as Local Sponsor in Australia) and is responsible for all regulatory filings and safety reporting.

10.2 RELATIONSHIP WITH INDUSTRY

Tocilizumab provided by the drug manufacturer (Genentech, Inc. a member of the Roche group, South San Francisco, CA) free of charge will be used in the United States for treatment of adult and pediatric participants, and Genentech, Inc. will also be providing additional financial support for the conduct of the study. They will receive de-identified samples to conduct mechanistic studies solely as directed by ITN or the Global Study Sponsor (DAIT, NIAID, NIH).

11 ACCESS TO SOURCE DATA/DOCUMENTS

The investigational sites participating in this study will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from participants in this clinical trial. 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 sites must permit authorized representatives of the Global Study Sponsor (DAIT, NIAID, NIH); Local Sponsor – (PPD Australia), ITN, Genentech, Inc. (the study drug manufacturer), and the Health Authorities (US FDA, Australian TGA) to examine (and to copy when required by applicable law) clinical 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 (and any personally identifying information must be obscured). Authorized representatives as noted above are bound to maintain the strict confidentiality of medical and research information that may be linked to identified individuals. The investigational sites will normally be notified in advance of auditing visits.

12 QUALITY CONTROL AND QUALITY ASSURANCE

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

The Global Study Sponsor (DAIT, NIAID, NIH) is responsible for regular inspection of the conduct of the trial, for verifying adherence to the protocol, and for confirming the completeness, consistency, and accuracy of all documented data.

The CRFs will be completed online via a web-based electronic data capture (EDC) system that has been validated and is compliant with Part 11 Title 21 of the U.S. Code

of Federal Regulations. Study staff at the site will enter information into the electronic CRFs, and the data will be stored remotely at a central database. Data quality will be ensured through the EDC system's continuous monitoring of data and real-time detection and correction of errors. All elements of data entry (i.e., time, date, verbatim text, and the name of the person performing the data entry) will be recorded in an electronic audit trail to allow all changes in the database to be monitored and maintained in accordance with federal regulations.

13 ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

13.1 STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol, current Good Clinical Practice (GCP) guidelines—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 the sponsor and an institutional review board or appropriate ethics review committee (IRB/EC). Any amendments to the protocol or consent materials must also be approved by the Global Study Sponsor (DAIT, NIAID, NIH) and the sponsor representative (PPD Australia), the IRB/EC and submitted to the appropriate Health Authorities before they are implemented.

13.2 INFORMED CONSENT

The informed consent form is a means of providing information about the trial to a prospective participant and allows for an informed decision about participation in the study. All participants (or their legally acceptable representative) must read, sign, and date a consent form before participating in the study, taking the study drug, and/or undergoing any study-specific procedures.

The informed consent form must be updated or revised whenever important new safety information is available, whenever the protocol is amended, and/or whenever any new information becomes available that may affect participation in the trial.

A copy of the informed consent will be given to a prospective participant for review. The attending health care provider will review the consent and answer questions. The participant will be informed that participation is voluntary and that he/she may withdraw from the study at any time, for any reason. Assent will also be obtained from children with due consideration for age appropriate private conversations between study health care provider and participant.

13.3 PRIVACY AND CONFIDENTIALITY

A participant's privacy and confidentiality will be respected throughout the study. Each participant will be assigned a sequential identification number. This number, rather than the participant's name, will be used to collect, store, and report participant information.

14 PUBLICATION POLICY

The ITN policy on publication of study results will apply to this study. Authorized participants may find details regarding the policy statement on the ITN internet website [redacted] As a jointly sponsored study with Type I Diabetes TrialNet, publications will also comply with TrialNet publications policy and procedures[redacted]

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APPENDIX 1. SCHEDULE OF EVENTS[1]

Phase of Trial	Dosing								Follow Up				Unsch.
Week	**-1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**39**	**52**	**78**	**104**	**U**
Visit	**V-1**	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10[2]**	**U[3]**
GENERAL ASSESSMENTS													
Informed consent	X												
Eligibility criteria	X												
Randomization		X											
Medical history	X												
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive physical examination	X							X[4]		X		X	
Directed physical examination		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]		X		X		X
Additional vital signs (during infusion)		X	X	X	X	X	X	X					
CENTRAL LABORATORY ASSESSMENTS													
Serum Chemistries (includes liver panel and CRP)	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X
Lipid Panel	X		X					X		X	X	X	X
Viral load (PCR)[5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Infectious disease serology[5]	X												
Serum ßHCG[6]	X												
QuantiFERON TB test[7]	X												
LOCAL LABORATORY ASSESSMENTS													
Urine HCG[6]		X	X	X	X	X	X	X	X	X	X	X	X
TB test[7]	X												

[1] With approval of study sponsor (DAIT, NIAID) and after informed consent, study procedures and/or sample collections may be performed at a location convenient for the participant as described in the Manual of Operations (MOP).

[2] Participants who terminate early from the study should complete all procedures listed for this visit (see sections 4.3 and 5.3).

[3] Assessments for unscheduled visits will be at the discretion of the principal investigator.

[4] Physical exam should be conducted prior to study drug administration.

[5] Serology will be repeated after screening for CMV and EBV if participants show clinical signs of infection; *or* if viral load testing shows that the EBV viral load is ≥ 10,000 copies per 10^6 PBMCs or ≥ 2,000 copies per mL of whole blood or the CMV viral load is ≥ 10,000 IU or copies per mL whole blood or plasma.

[6] Female participants with reproductive capacity will be monitored for pregnancy.

[7] Sites may perform a PPD skin test in place of a QuantiFERON TB test.

Phase of Trial	Dosing								Follow Up				Unsch.
Week	**-1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**39**	**52**	**78**	**104**	**U**
Visit	**V-1**	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10[2]**	**U[3]**
DISEASE-SPECIFIC ASSESMENTS													
2-Hour MMTT[8]					X			X	X		X		
4-Hour MMTT[9]	X									X		X	
FSIVGTT[10]		X						X		X			
Diabetes-related autoantibodies	X												
HbA1c	X	X	X	X	X	X	X	X	X	X	X	X	
Glucometer Readings	X	X	X	X	X	X	X	X	X	X	X	X	
CGM Readings[11]		X			X			X		X	X	X	
Insulin use	X	X	X	X	X	X	X	X	X	X	X	X	
Hypoglycemic events	X	X	X	X	X	X	X	X	X	X	X	X	
STUDY DRUG ADMINISTRATION AND DRUG-RELATED ASSESSMENTS													
Study drug infusion		X	X	X	X	X	X	X					
Pharmacokinetics (PK)		X[12]	X[13]				X[12]	X[13]					
IL-6 and IL-6sR	X				X			X	X	X	X	X	
Anti-TCZ antibodies[14]	X												
MECHANISTIC ASSESSMENTS[15]													
Serum	X	X	X	X	X	X	X	X		X	X	X	
Cellular Assays		X	X	X	X	X	X	X		X		X	
Gene Expression		X			X			X		X		X	
DNA		X			X			X		X		X	

[8] A 2-hour MMTT is to be performed at weeks 12, 24, 39, and 78. MMTT should be performed prior to study drug infusion for weeks 12 and 24.

[9] A 4-hour MMTT is to be performed at weeks -1 (screening), 52, and 104 for subjects ≥12 years old (for subjects <12 years old, a 2-hour MMTT will be performed instead).

[10] FSIVGTT will be offered to subjects age ≥15. Week 0 visit may be done on the same day before the first infusion or within 2 weeks prior to week 0. Week 24 and week 52 visits will be done on a separate day than the MMTT visits; the window for these two visits are +/- 2 weeks of target date.

[11] Randomized participants will be invited to use a commercially available FDA approved CGM system and its components for a 14 day period at weeks 0, 12, 24, 52, 78, and 104; the window for the CGM will be ± 3 weeks. Participants may repeat the 14 day period once during these widows if less than 10 days of data is evaluable from initial wearing.

[12] Pharmacokinetics (PK) samples for week 0 and week 20 will be collected before, 10 minutes after, and 7 (±3) days after the infusions (see section 6.6).

[13] Pharmacokinetics (PK) samples for week 4 and week 24 will be collected before the infusions (see section 6.6).

[14] Baseline anti-TCZ antibodies samples will be collected for all participants and will only be analyzed in event of specified adverse event (defined as anaphylaxis, serious hypersensitivity, or study treatment discontinuation due to hypersensitivity, whether serious or non-serious). Additional anti-TCZ antibodies samples will be collected at the time of an adverse event and then again at least 6 or 8 weeks after the last TCZ dose.

[15] 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 per country specific requirements.