CTLA-4 Ig (Abatacept) FOR PREVENTION OF ABNORMAL GLUCOSE TOLERANCE AND DIABETES IN RELATIVES AT-RISK FOR TYPE 1 DIABETES MELLITUS

(Protocol TN-18)

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PREFACE

The TrialNet Type 1 Diabetes Protocol TN-18, CTLA-4 Ig (abatacept) for Prevention of Abnormal Glucose Tolerance and Diabetes in Relatives At-Risk for Type 1 Diabetes Mellitus, describes the background, design, and organization of the study. The protocol will be maintained by the TrialNet Coordinating Center (TNCC) over the course of the study through new releases of the entire protocol, or issuance of updates either in the form of revisions of complete chapters or pages thereof, or in the form of supplemental protocol memoranda.

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1. INTRODUCTION

1.1. Study Overview

Title	CTLA-4 Ig (abatacept) for prevention of abnormal glucose tolerance (AGT) and diabetes in relatives at-risk for Type 1 diabetes mellitus (T1DM)
IND Sponsor	Type 1 Diabetes Trial Network (TrialNet)
Study Supported by	National Institute of Diabetes, Digestive and Kidney Diseases
Conducted By	Type 1 Diabetes Trial Network (TrialNet)
Protocol Chair	Dr. William E. Russell, M.D.
Accrual Objective	206
Study Design	The study is a 2-arm, double blinded, multicenter, 1:1 randomized, placebo controlled clinical trial. All subjects will receive close monitoring for development of AGT or T1DM
Treatment Description	Subjects will receive abatacept or placebo and close monitoring for development of AGT or T1DM.
Objective	To assess the safety, efficacy, and mode of action of abatacept to prevent AGT and T1DM.
Primary Outcome	The primary objective is to determine whether intervention with abatacept will prevent or delay the development of AGT in at-risk autoantibody positive non-diabetic relatives of patients with T1DM.
Secondary Outcome	Secondary outcomes include: the effect of abatacept on the incidence of T1DM; analyses of C-peptide and other measures from the OGTT; safety and tolerability; and mechanistic outcomes.
Major Inclusion Criteria	Autoantibody positive relatives of T1DM proband with normal glucose tolerance who are currently ≥ age 6 and previously enrolled in TrialNet Natural History/Pathway to Prevention Study.

1.2. Statement of Purpose

This protocol describes the background, design, and organization of study of the CTLA-4 Ig (abatacept) for prevention of abnormal glucose tolerance and diabetes in relatives at risk for type 1 diabetes. The protocol was written by William E. Russell MD, Chair of the TrialNet Abatacept in Prevention Protocol Committee, the TrialNet Chairman's Office at the University of Miami and the Benaroya Research Institute, and the TrialNet Coordinating Center (TNCC). Significant changes that occur to this protocol during the course of the trial require the formal approval of the TrialNet Steering Committee. The study protocol, along with the required informed consent forms, will be approved by each participating institution's Institutional Review Board (IRB) or Ethics Committee/Research Ethics Board (EC/REB).

2. BACKGROUND AND SIGNIFICANCE

2.1. Type 1 Diabetes (T1DM)

2.1.1. Definition and Metabolic Characteristics of Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is an immune-mediated disease in which insulin-producing beta cells are completely or near completely destroyed, resulting in life-long dependence on exogenous insulin. It is a chronic and potentially disabling disease that represents a major public health and clinical concern. The number of patients being diagnosed with type 1 diabetes is increasing each year and is approaching an epidemic level in some countries that track this information (1,2).

Compared to individuals with the more common form of diabetes, type 2 diabetes, (where individuals retain some endogenous insulin production which is inadequate to maintain normal glucose and lipid metabolism), the metabolic impairment in T1DM is much more severe and the loss of insulin production more complete. Continuous exogenous insulin therapy is needed to prevent ketoacidosis and other catabolic effects of insulin deficiency and to promote anabolism and to maintain life. Most likely as a consequence of the absolute deficiency of insulin, glucose counterregulation (the hormonal response to insulin-induced hypoglycemia) is impaired, and therefore, hypoglycemia is a frequent complication of the disease. The occurrence of hypoglycemia limits the ability to achieve near normal glucose control. The Diabetes Control and Complications study (DCCT) showed that the long term complications could be reduced with near normal control of glucose levels but at the cost of an increased frequency of severe hypoglycemia (3). While there have been significant improvements in insulin analogs and insulin delivery systems, such as continuous subcutaneous insulin infusions with insulin pumps, normal glucose control, particularly in children, is rarely achieved. Therefore, individuals with type 1 diabetes remain at risk for chronic secondary end-organ complications including visual impairment and blindness, renal failure, vascular disease and limb amputation, peripheral neuropathy, and stroke. They are also at high risk for acute complications such as severe hypoglycemia, recurrent ketoacidosis, and others. Moreover, at the time of diagnosis, many individuals, and children in particular, suffer significant morbidity frequently requiring ICU admission. As described below, virtually all the individuals identified for enrollment into this prevention trial will develop diabetes. Clearly, prevention of the onset of the disease itself would represent a significant advancement.

2.1.2. Natural History of Type 1 Diabetes Mellitus (T1DM)

Much is known about the natural history of the type 1 diabetes disease process (4). Although all people are susceptible, relatives of individuals with T1DM are at much greater risk for development of the disease. In the general population, approximately 0.3 % of individuals will develop T1DM. In contrast, those with a relative with T1DM have a 5% incidence of disease – a 15 fold increase (5). Further risk stratification among family members depends upon genetic, immune and metabolic data (6).

Beta cell destruction generally begins in genetically susceptible individuals years before clinical onset of disease(7). The autoimmune process that causes beta cell destruction is clinically silent and can only be identified by the detection of autoantibodies in the blood such as Islet Cell Antibodies (ICA), anti-glutamic acid decarboxylase (GAD)65ab, anti-ICA512ab/anti-IA2ab, anti-insulin autoantibodies (mIAA) (5), and the recently described antibodies to a zinc transporter (8). Continued immune mediated

beta cell destruction involving both B- and T-cells occurs until physiologic insulin demand cannot be met by the remaining beta cells, resulting in hyperglycemia and clinical diagnosis of T1DM (9, 10).

Based on data from the Diabetes Prevention Trial, Type 1 Diabetes (DPT-1), the TrialNet Natural History/Pathway to Prevention Study, and others, the risk for developing diabetes in relatives without the disease can be defined by the presence of autoantibodies and the degree of metabolic impairment (11-13). The DPT-1 study was one of the first large-scale prevention trials of T1DM. The aim of this trial, which tested >100,000 relatives of individuals with T1DM, was to study whether either low dose parenteral insulin or oral insulin administration would prevent the development of T1DM. The results of the DPT-1 showed that neither parenteral nor oral insulin prevented the development of T1DM, (although a secondary analysis of the data suggested some effect of oral insulin in delaying the onset of diabetes in a subgroup of subjects defined by high anti-insulin antibodies and normal glucose tolerance)(13). Like the DPT-1, the ongoing TrialNet Natural History/Pathway to Prevention Study has tested more than 105,000 relatives for the presence of diabetes associated autoantibodies as of June 1st, 2012.

Approximately 5% of relatives tested are found to have at least one autoantibody. Further testing enables risk assessment of this population. Relatives with at least two autoantibodies and normal glucose tolerance have at least a 42% risk for development of T1DM over 6 years. This was demonstrated in DPT-1 as well as ENDIT (European Nicotinamide Diabetes Intervention Trial), a large European trial enrolling antibody positive relatives (14). This risk has been confirmed in the ongoing TrialNet Natural History/Pathway to Prevention Study (Figure 1). Moreover, while the limited numbers of relatives followed for more than 10 years prevent precision around a 10 year risk estimate, it is noteworthy that available data from those in DPT-1 or TrialNet Natural History/Pathway to Prevention Study suggests no leveling off of this risk over time. Thus our current understanding is that essentially all relatives confirmed to have two or more antibodies will eventually develop clinical T1DM.

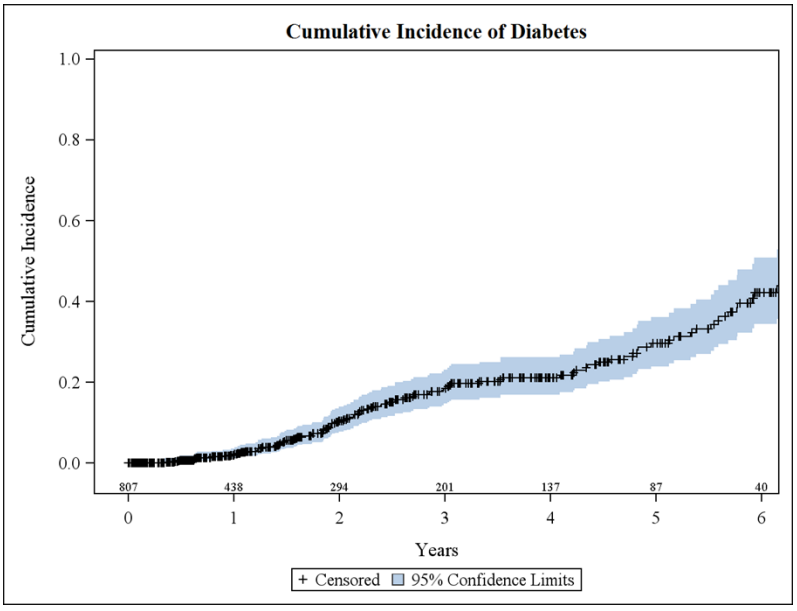

Figure 1: Cumulative incidence of type 1 diabetes in TN01 Natural History Pathway to Prevention Study participants with ≥ 2 autoantibodies positive and normal glucose tolerance on first OGTT Test.

Prior to this clinical diagnosis, antibody positive relatives progress from normal glucose tolerance to impaired or indeterminate glucose tolerance (defined as any glucose level after ingestion of oral glucose of ≥ 200 mg/dL and/or a glucose level 2 hours after ingestion of oral glucose of 140-199 mg/dL and/or

fasting glucose between 110 – 125 mg/dL during a standard oral glucose tolerance test). Subjects in the TN01 Natural History/Pathway to Prevention Study with multiple autoantibody positivity and normal glucose tolerance at baseline were found to have a 38% two-year risk of progression to confirmed abnormal glucose tolerance (Figure 2). Once such abnormal glucose tolerance is present, there is a very high risk of clinical diagnosis; 68% over 4 years (Figure 3). The risk is particularly high for individuals under the age of 18. The extremely high risk of this group has now been demonstrated in three independent studies: DPT-1, ENDIT and the ongoing TrialNet Natural History/Pathway to Prevention Study.

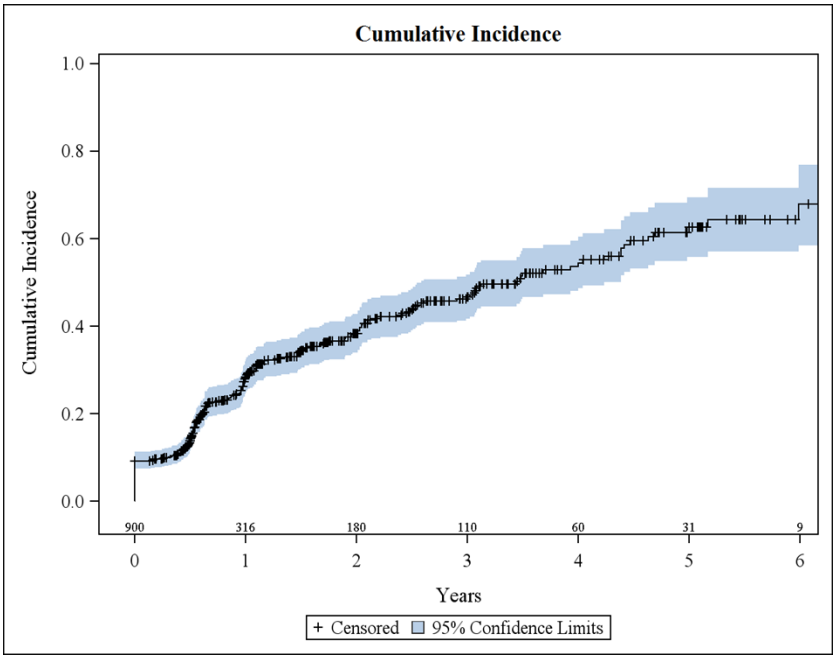

Figure 2: Two year risk of confirmed abnormal glucose tolerance is 38% among individuals with multiple autoantibody positivity and normal glucose tolerance at baseline in the TN01 Natural History/Pathway to Prevention Study.

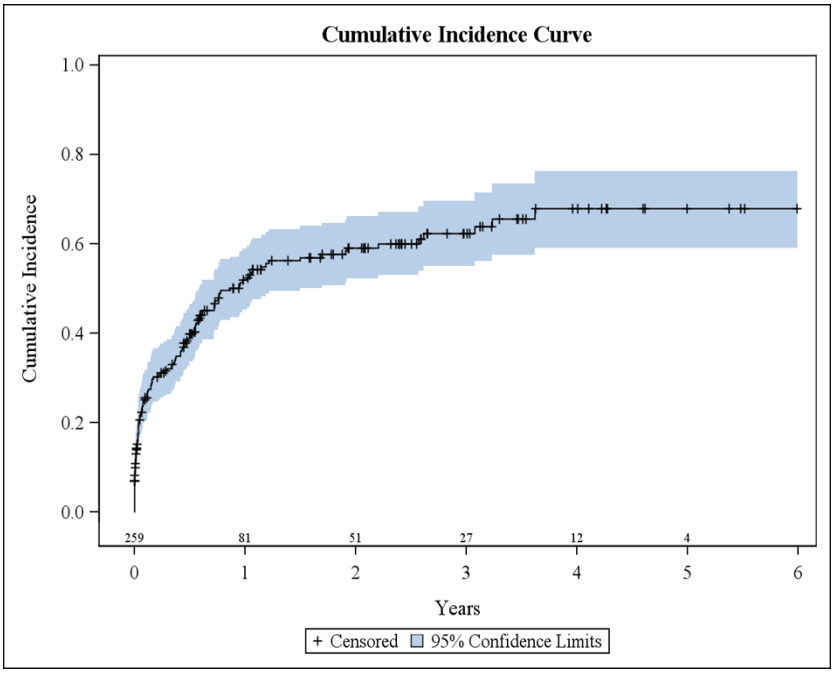

Figure 3: Four year risk of diabetes onset is 68% among individuals with multiple autoantibody positivity and confirmed abnormal glucose tolerance in the TN01 Natural History/Pathway to Prevention Study.

It is important to note that the diagnosis of diabetes is based on a glucose threshold that is associated with risk of secondary end-organ complications of disease rather than the pathologic process that leads to hyperglycemia. Detailed analyses of metabolic function in individuals who do and do not progress to diabetes in the DPT-1 have been published (10,15,16). These studies all describe a progressive predictable loss of beta cell function during the pre-diabetes period leading to abnormal glucose tolerance and clinical disease. In addition, they also suggest that once metabolic impairment has occurred, the risk is extremely high. These combined immunologic and metabolic studies suggest to us that individuals with AGT differ from those in whom the diagnosis of T1DM has been made only in the duration of progression. Intervention at the time of diagnosis of T1DM may be too late for new therapies to alter the course of disease.

The DPT-1 tested whether oral insulin could prevent progression to type 1 diabetes in antibody positive relatives with normal glucose tolerance. That study took approximately ten years to complete and found no overall effect in progression to T1DM. However, a sub-group analysis suggested that oral insulin administration delayed T1DM onset by at least four years in those with high levels of insulin autoantibodies. This promising outcome is now being tested again in the TrialNet Oral Insulin Prevention study. Enrollment in this ongoing trial is limited to individuals with two or more antibodies of which at least one must be insulin autoantibodies (mIAA) and normal glucose tolerance.

In this study, relatives who are confirmed to have two or more antibodies, not including mIAA, and normal glucose tolerance will be eligible for randomization to experimental treatment or placebo groups with the aim to determine whether experimental treatment will prevent or delay the occurrence of abnormal glucose tolerance and type 1 diabetes mellitus. Individuals with normal glucose tolerance are earlier in the disease process; that is, have less beta cell destruction than those with abnormal glucose tolerance or frank diabetes, yet will inevitably progress to clinical disease and essentially complete beta cell loss. Treatment at this early stage in a population who will inevitably progress to

type 1 diabetes provides the greatest opportunity for a clinically important impact on disease prevention. With abnormal glucose tolerance rather than diabetes as the primary endpoint, study participants, regulators, funders, and investigators will be able to determine whether the therapy can alter disease progression.

Therefore, the rationale for this study is that individuals with immunologic markers of T1DM and normal glucose tolerance will inevitably develop clinical T1DM. Prior to development of clinical T1DM they will progress from normal glucose tolerance to abnormal glucose tolerance; and abnormal glucose tolerance results in clinical T1DM within 5 years in almost 80% of subjects. They have a condition that differs from overt diabetes only in the duration of the autoimmune process that results in beta cell destruction. Intervention early in the course of disease may be more effective than intervention in those with abnormal glucose tolerance or clinical T1DM.

2.2. Rationale for use of CTLA-4 Ig

2.2.1. Presumed mechanism of action

Antigen-specific T-cells are thought to play a central role in the pathogenesis of autoimmune diseases. Abatacept binds to CD80/CD86 receptors on antigen presenting cells, thereby inhibiting their binding to the co-stimulatory molecule CD28 on T-cells. By inhibiting full T-cell activation, abatacept also affects the downstream inflammatory cascade.

T lymphocytes are believed to play a major role in orchestrating the immune response that underlies T1DM. T cell activation is thought to involve a “two-signal” model (17). According to this “two-signal” model, “signal 1” is the interaction of the T cell receptor (TCR) with the antigen-MHC complex, meanwhile “signal 2” is the engagement of the co-stimulatory receptors (18,19). Both signals are required for optimal T cell activation; in the absence of signal 2, T cells fail to activate and became anergic. Signal 2 can be stimulatory and inhibitory as well. A large family of co-stimulatory molecules has been described and at the same time T-cell surface receptors providing inhibitory signals have also been reported (20,2). There is an apparent delicate balance between positive and negative regulatory signals, which drives the direction of the specific immune response. The B7-1/2 – CD28/CTLA-4 co-stimulatory pathway has been studied in depth and plays a crucial role in T-cell activation/tolerance. This is, arguably, the most important co-stimulatory pathway for T cell antigen activation.

Both B cell molecules, B7-1 (CD80) and B7-2 (CD86) are ligands for CD28 and CTLA-4 and are expressed on the surface of the antigen presenting cells (APC)(21,22,23). The binding affinity of B7 molecules to CD28 and CTLA-4 on T cells differ substantially and this is important in T cell regulation (24). B7-2 is constitutively expressed on most APCs at a low level and is quickly upregulated; meanwhile B7-1 is only inducibly expressed after activation. CD28 is constitutively expressed on the T cell surface whereas CTLA-4 expression is upregulated 24- 48 hours after T cell activation (25). Engagement of CTLA-4 represents a crucial negative signal, inhibits TCR- and CD28 mediated signal transduction, also inhibits IL-2 production and terminates T cell response by inhibiting cell cycle progression (26,27). CTLA-4 (CD152) is currently viewed as major negative regulator of T cell activation and an important regulator of peripheral tolerance induction.

The effect of CTLA-4 Ig has been studied in various animal models as well as in human trials. It has been used in a series of animal transplantation models, where it showed significant prolongation of transplanted organ survival (28,29,30) and in autoimmune models, where it slowed or prevented the autoimmune process (31,32). It is also effective in animal pancreatic islet transplantation models as well as in prevention in autoimmune models of diabetes (33). Lenschow and coworkers showed that

co-stimulatory blockade with CTLA-4 Ig prevents diabetes in NOD mice model of T1DM, when administered after insulitis developed but before frank diabetes ensues (32,33). Interestingly, in some transplantation models and in some animal models of autoimmunity CTLA-4 Ig effect persisted well beyond any detectable CTLA-4 Ig blood levels, leading to long-term graft survival or long-term suppression of the autoimmunity (29,32).

There is now considerable clinical experience with abatacept (Bristol-Myers Squibb CTLA-4 Ig). As discussed below, abatacept has been extensively tested in subjects with rheumatoid arthritis and is now FDA approved and in clinical use in that patient population. It is also approved for the treatment of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in pediatric patients 6 years of age or older.

CTLA-4 Ig (abatacept) is a novel immunosuppressive agent for type 1 diabetes mellitus. It has shown strong beneficial effect in different animal models of transplantation and organ specific autoimmunity, including diabetes. This agent inhibits/regulates T cell function, but does not deplete T cells in humans. The safety profile reported in human clinical trial appears to be better than any other immunosuppressive agent used to preserve beta cell function in T1DM (34,35,36,37,38). As recently reported, the Type 1 Diabetes TrialNet clinical trial of CTLA-4 Ig (abatacept) in individuals with recently diagnosed T1DM, including children to age 6, demonstrated both an excellent safety profile and efficacy in preserving beta cell function. The combination of good safety profile and strong, therapeutically useful immuno-suppression/-modulation makes this drug particularly suitable for study in clinical trials to prevent T1DM.

3. CLINICAL AND PRE-CLINICAL DATA

There is a large body of data available on the CTLA-4 Ig co-stimulatory blockade in different animal models of transplantation and autoimmunity; key studies in animal models relating to T1DM are described below. Clinical data in patients with type 1 diabetes and other autoimmune diseases is also described. Full information about studies is in the investigator brochure.

3.1. Pre-Clinical Data

In BB rat model of diabetes, the recurrence of autoimmunity was completely prevented by adenovirus-mediated CTLA-4 Ig expression locally in the pancreas (39). Lenschow and colleagues (33) administered human CTLA-4 Ig to female nonobese (NOD) mice and prevented the development of diabetes when treated at the time of the onset of insulitis (2-4 weeks of age) and prior to the onset of disease. In a later paper, however, Lenschow reported use of murine CTLA-4 Ig at the same NOD mouse age as it was used in the original study using the human CTLA-4 Ig (2-4 weeks) and found acceleration of the disease (40). It is difficult to reconcile the seemingly contradictory results of different species of CTLA- 4 Ig's effect (human CTLA-4 Ig protective versus murine CTLA-4 Ig accelerating effect on NOD diabetes); the answer may lie in the opposite effect of B7-1 versus B7-2 on diabetes in NOD mice (33) and may be due to differences in avidity of the murine versus human CTLA-4 Ig to B7-1 versus B7-2. Importantly, CTLA-4 regulates peripheral tolerance induction and promotes Th2 development (41). Moreover, marked prevention of diabetes in the NOD was demonstrated using human CTLA-4 Ig (abatacept) from Bristol-Myers Squibb (the drug we propose to use for this clinical trial) with diabetes occurring in 80% of control mice and 30% of the CTLA-Ig treated animals (Fiorina P et al., unpublished data).

3.2. Clinical Trials

Clinical trials with abatacept have been conducted in individuals with recent onset type 1 diabetes as well as rheumatoid arthritis, psoriasis, multiple sclerosis, Crohn's disease, and polyarticular juvenile idiopathic arthritis (JIA) with more than 60,225 total person-years of exposure.

3.2.1. Type 1 Diabetes Mellitus (T1DM)

Diabetes TrialNet study group conducted a double-masked, randomized clinical trial in 112 individuals with type 1 diabetes. Subjects, ages 6-45 were enrolled within 3 months of clinical diagnosis of T1DM and received abatacept or placebo in a total of 27 infusions over a two year period. As illustrated in Figure 4, those treated with abatacept had significantly more beta cell function at two years, the primary endpoint of the clinical trial. The difference in the rate of fall of bell cell function over time between abatacept and placebo treated subjects was most pronounced within the first six months of treatment (42). Continued treatment through two years and subsequent follow-up off treatment did not further alter the rate of decline. Overall, there was a 9.6 month delay in the rate of fall (Figure 4). The safety profile in this population was excellent, with no differences in adverse event rates between abatacept treated and placebo groups. These data suggest that a 12 month course of treatment in individuals earlier in the disease process is likely to be safe in this population and significantly delay the progression of disease. Subjects were followed for an additional year while off therapy. Those treated with abatacept continued to demonstrate better beta cell function than placebo treated subjects three years after randomization (Skyler et al; unpublished observation TN).

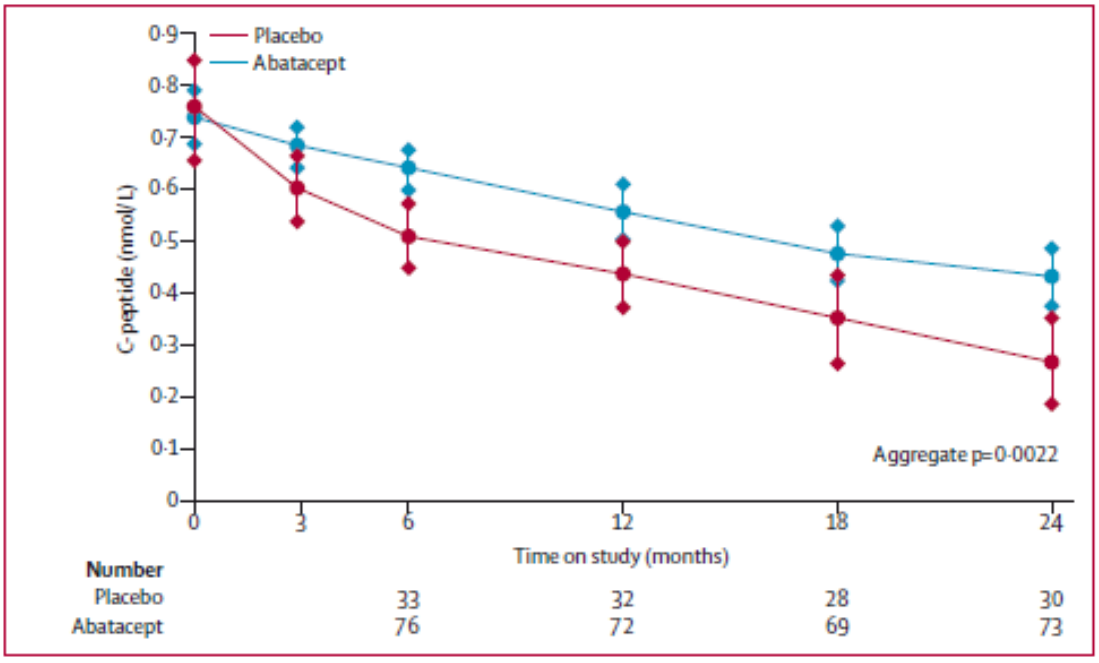

Figure 4: Population mean of stimulated C-peptide 2-h AUC mean over time for each treatment group. The estimates are from the ANCOVA model adjusting for age, sex, baseline value of C-peptide, and treatment assignment. Y-axis is on a log(y+1) scale. Error bars show 95%CIs. AUC=area under the curve.

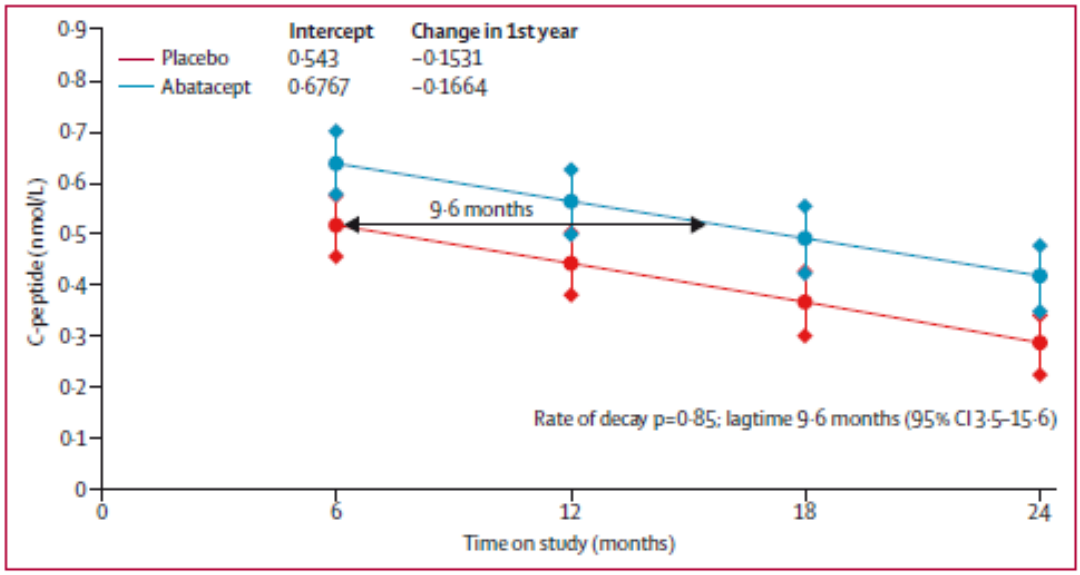

Figure 5: Predicted population mean of stimulated C-peptide 2-h AUC mean over time for each treatment group. Estimates are from the analysis of mixed-effects model adjusting for age, sex, baseline value of C-peptide, and treatment assignment, and including a fixed effect for time as a linear line on the log(y+1) scale. AUC=area under the curve.

3.3. Clinical Experience in Children: Type 1 Diabetes Mellitus (TIDM), Juvenile Idiopathic Arthritis (JIA), Rheumatoid Arthritis (RA), and Other Clinical Experience

3.3.1 Type 1 Diabetes Mellitus (T1DM)

Of the 77 individuals with recently diagnosed T1DM treated with abatacept in the Diabetes TrialNet study discussed above, 61 (79.2%) were children. Thus the overall efficacy and safety data described above largely reflect clinical observations in children (42).

3.3.2 Juvenile Idiopathic Arthritis (JIA)

In a Phase 3, multi-center, multi-national, randomized, withdrawal study to evaluate the safety and efficacy of abatacept in children and adolescents with active polyarticular JIA, 190 children and adolescents, ages 6-16 (mean 12.4 + 3 years), were treated with open-label abatacept at 10 mg/kg IV for 4 months in a lead-in phase (Period A). One hundred twenty-two (122) subjects who responded according to the ACR 30 pediatric definition of improvement were randomized 1:1 into the double-blind withdrawal phase (Period B) either to continue abatacept (60 subjects), or to receive placebo (62 subjects) for 6 months or until the appearance of flare. Half (31/62) of those randomly assigned to continue abatacept completed Period B, while 82% (49/60) of those randomly assigned to placebo completed Period B. Those who did not respond in Period A, those who completed Period B, and those who flared in Period B were offered the option to receive abatacept in Period C, the open-label extension phase of the study. The difference in time to disease flare between the abatacept and placebo groups was statistically significant based on the log-rank test (p = 0.0002). The risk of disease flare among children and adolescent subjects continuing on abatacept was less than one-third that for the placebo subjects withdrawn from the abatacept treatment (hazard ratio = 0.31, 95% CI [0.16, 0.59]). Treatment in children was well tolerated, although 13.2% reported headache, this did not result in

discontinuation of treatment. Nausea, diarrhea, cough, fever, and abdominal pain were also reported. Infections were reported with similar frequencies in abatacept (45%) and placebo (43.5%) treated groups with a slight increase in influenza 8.3% versus 6.5% in abatacept treated subjects. One subject had a varicella infection with normal clinical course. There were no safety issues from the evaluation of the laboratory data (Abatacept: Investigator's Brochure).

3.3.3 Rheumatoid Arthritis (RA)

Results of a series of Phase I-III clinical trials involving 1955 subjects treated with abatacept and 989 placebo treated subjects, have led to FDA approval of the IV formulation of abatacept for treatment of Rheumatoid Arthritis (RA). Abatacept is indicated for reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease Modifying Anti-Rheumatoid Drugs (DMARDs), such as methotrexate or TNF antagonists. Abatacept may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

Adverse events possibly related to treatment were reported in 52.2% of abatacept treated and 46.1% of placebo treated adults, with the most frequent events in abatacept treated subjects being headache (≥10%) and nausea. Treatment was discontinued due to these events in 3.4% of abatacept treated and 2.2% of placebo-treated subjects. Other common (1-10%) adverse effects include upper and lower respiratory tract infection, hypertension and flushing, cough, rash and fatigue.

3.3.4 Other Clinical Experience

Clinical trials have been conducted in psoriasis, psoriatic arthritis, Crohn's disease, SLE, and multiple sclerosis.

Both IV and subcutaneous formulations of abatacept have been studied in clinical trials involving 177 subjects with psoriasis and 170 with psoriatic arthritis. The dose-ranging study in subjects with relapsing-remitting multiple sclerosis (MS) was terminated by BMS when a Data and Safety Monitoring Board (DSMB) review detected an increase in enhancing T1 lesions and MS exacerbations in one of the randomized groups. A descriptive analysis of the primary efficacy endpoint, cumulative new or recurrent T1-enhancing lesions, reported that the 2 mg/kg group (median number of lesions = 8.0) was greater than that in the placebo group (median number of lesions = 5.5), however the 10 mg/kg group (median number of lesions = 1.5) median was less than that in the placebo group. The 10 mg/kg treatment group reported fewer protocol-defined exacerbations (20.6 versus 30.0%), fewer MS related AEs (52.9 versus 65.0%), and a lower mean annualized relapse rate (0.38 versus 0.73) compared with placebo. A similar pattern was observed for other efficacy endpoints (unpublished data). No clinical efficacy was demonstrated for abatacept in Crohn's disease and the safety profile was consistent with studies in RA. Although exploratory endpoints suggested possible biologic activity, a Phase 2 study of abatacept in SLE failed to meet its primary clinical endpoint.

4. STUDY DESIGN

4.1. Overview

This is a double blinded, multicenter, randomized, placebo controlled trial to determine whether treatment of subjects at risk for diabetes with abatacept results in delay or prevention of abnormal glucose tolerance.

4.2. Objectives

4.2.1. Primary Objective

The primary objective of the study is to determine whether treatment of subjects at risk for diabetes with abatacept results in delay or prevention of abnormal glucose tolerance.

4.2.2. Secondary Objectives

- To determine whether treatment with abatacept is superior to placebo with respect to the incidence of T1DM.
- To determine whether treatment with abatacept is superior to placebo with respect to C-peptide responses to oral glucose, as obtained from timed collections during longitudinal tests.
- To compare the safety and tolerability of abatacept to placebo.
- To assess the effects of treatment on mechanistic outcomes.

4.3. Summary of Inclusion/Exclusion Criteria

Participants must meet all entry criteria for the protocol as outlined below.

4.3.1. Inclusion Criteria

Study subjects must be or have:

1. Participant in TrialNet Natural History/Pathway to Prevention Study (TN01) and thus, a relative of a proband with T1DM.

2. Between the ages of 1-45 years at the time of enrollment in TN01 and age ≥ 6 at time of randomization in this trial.

3. Willing to provide Informed Consent or have a parent or legal guardian provide informed consent if the subject is <18 years of age.

4. Normal glucose tolerance by OGTT within 7 weeks (no more than 52 days) of baseline (visit 0). If previous abnormal glucose tolerance, has had two consecutive OGTTs with normal glucose tolerance.
    a. Fasting plasma glucose < 110 mg/dL (6.1 mmol/L), and
    b. 2 hour plasma glucose <140 mg/dL (7.8 mmol/L), and
    c. 30, 60, or 90 minute value on OGTT< 200mg/dL (11.1 mmol/L)

5. At least two diabetes-related autoantibodies confirmed to be present on two occasions, not including mIAA. Confirmation of 2 positive autoantibodies must occur within the six months

prior to randomization, but the confirmation does not have to involve the same 2 autoantibodies.

6. Weight ≥ 16 kg at Baseline Visit.

7. If a female participant with reproductive potential, willing to avoid pregnancy during study drug treatment and up to 14 weeks after study drug administration and undergo pregnancy testing prior to each infusion.

8. At least three months from date of last live immunization.

9. Willing to forgo live vaccines while receiving treatment on study and for three months following last study drug administration.

4.3.2. Exclusion Criteria

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

1. Abnormal Glucose Tolerance or Diabetes (43,44)
    a. Fasting plasma glucose ≥ 110 mg/dL (6.1 mmol/L), or
    b. 2 hour plasma glucose ≥ 140 mg/dL (7.8 mmol/L), or
    c. 30, 60, 90 minute plasma glucose during OGTT ≥ 200 mg/dL (11.1 mmol/L)

2. Insulin autoantibodies (mIAA).

3. Immunodeficient or have clinically significant chronic lymphopenia.

4. Have an active infection at time of randomization.

5. Have a positive PPD test result or history of previously treated TB, or positive interferon-gamma release assay (IGRA) test.

6. Be currently pregnant or lactating, or anticipate getting pregnant within 14 weeks of the last study drug administration.

7. Use of medications known to influence glucose tolerance.

8. Require use of other immunosuppressive agents.

9. Have serologic evidence of current or past HIV, Hepatitis B (positive for Hepatitis B core antibody or surface antigen), or Hepatitis C infection.

10. Have serological evidence of current CMV infection.

11. Have evidence of active EBV infection.

12. Have any complicating medical issues or abnormal clinical laboratory results that interfere with study conduct or cause increased risk. These include pre-existing cardiac disease, COPD, neurological, or blood count abnormalities (such as lymphopenia, leukopenia, or thrombocytopenia).

13. Have a history of malignancies.

14. Have Multiple Sclerosis.

4.4. Enrollment

Potential study subjects will be identified through the ongoing TrialNet Natural History/Pathway to Prevention Study. In this study, first, second and third degree relatives of patients with T1DM are screened for diabetes related autoantibodies. Those individuals who test positive are then further staged with the performance of serial OGTTs. The results of these OGTTs will be used to determine eligibility for this protocol.

The TrialNet Natural History/Pathway to Prevention Study screens participants at multiple clinical sites. The infusion of study drug will occur at designated TrialNet infusion sites, whereas the initial visit and follow-up testing, as described in the Schedule of Assessments, may occur at other TrialNet sites.

4.5. Description of Treatment Groups

The intervention will be conducted only among those who consent to participate. Subjects will be randomized to receive either abatacept or placebo infusions along with close monitoring for abnormal glucose tolerance or diabetes. The infusions will be conducted at approved TrialNet clinical sites with appropriate facilities. All blood and serum samples for the primary and secondary outcome determinations will be sent to the Core Laboratories for analysis. Clinical laboratory studies may be done at the local sites.

Participants will be randomly assigned in a 1:1 ratio (within the two strata defined by age at enrollment: <18 and 18 or older) to the following 2 groups:

- to receive abatacept (intravenous infusion at 0, 2, and 4 weeks following randomization, and then every 28+/-7 days) thereafter for a total of 14 doses. Close monitoring for diabetes development through the duration of study.

- to receive placebo intravenous infusion at 0, 2, and 4 weeks following randomization and then every 28+/- 7 days thereafter for a total of 14 doses. Close monitoring for diabetes development through the duration of study.

4.6. Treatment Assignment

After participants sign the consent form, complete the screening visit(s), and meet all of the inclusion criteria and none of the exclusion criteria, participants will be randomized to receive either abatacept and close monitoring or placebo with close monitoring.

Participants will be randomized in equal allocations to each group. The randomization method will be stratified by TrialNet study site and whether the participant is less than 18 years of age or 18 years and older. This approach ensures that study site will not be a potential confounder. The TNCC will generate the randomization numbers and tables.

4.7. Study Assessments

During the course of the study, participants will frequently undergo assessments of their glucose tolerance status, insulin production, immunologic status, and overall health and well-being (see Schedule of Assessments).

Samples will be drawn for storage in the National Institute for Diabetes and Digestive and Kidney Disease (NIDDK) Repository and at TrialNet Laboratory Sites for future analysis related to T1DM.

4.8. Quality Assurance

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

4.9. Study Timeline

4.9.1. Study Duration

The study has been designed to provide 80% power to detect a 40% risk reduction in the occurrence of abnormal glucose tolerance using a two-sided test at the 0.05 level after six years of study duration. A total of approximately 206 patients will be allocated in a 1:1 ratio to the two groups.

The assumptions underlying the sample size of are 1) 40% two year event rate in the placebo group, 2) 25% two year event rate in the abatacept group, 3) less than a 10% two year dropout rate in both groups, and 4) survival curves which are consistent with an exponential survival distributions.

Under the above assumptions, the target total number of events is equal to 95. If the accrual rate is 50 patients per year, with the above assumptions it is estimated that the enrollment period will last approximately 4 years and a study duration of approximately 6 years will provide a sufficient number of events to detect the assumed treatment difference. Note the accrual period and the study sample are only projections since the actual accrual rate and the loss to follow-up rate are unknown.

Participants who develop AGT will remain on study and be followed according to protocol to assess the secondary objective of time until T1DM development.

4.9.2. Follow-up Studies

Although subjects who develop confirmed abnormal glucose tolerance will have reached the primary study endpoint, while the Abatacept Prevention study is ongoing, these individuals will continue to be followed in the study for monitoring of diabetes development and safety assessments. At the end of the study, individuals without diabetes will be periodically contacted to ascertain whether they develop diabetes and/or continue monitoring in TN01 (Pathway to Prevention) study. If subjects are diagnosed with diabetes they will be offered follow-up in the TrialNet Long Term Investigative Follow-Up in TrialNet (LIFT) Study.

Individuals who develop T1DM may be eligible for interventional studies sponsored by TrialNet or other organizations under separate INDs. In the event that a subject wishes to participate in another investigational study the subject may request and be told of their treatment group assignment for the Abatacept prevention study. Every attempt will be made to minimize potential bias that this may

introduce. The TNCC will make treatment assignment information available to the site investigator of the new study after the subject is determined to be willing to participate and not otherwise excluded from the new study. Other study group members will not be informed of the treatment assignment information. Mitigation of bias issues must be balanced against safety and interests of participants.

5. PATIENT MANAGEMENT

5.1. Screening Visit and Eligibility Assessment

This study will draw participants from the TrialNet Natural History/Pathway to Prevention Study.

The initial testing for autoantibodies, HLA type, and Oral Glucose Tolerance Test (OGTT) will generally be done as part of Natural History/Pathway to Prevention Study. Potential participants in the Abatacept trial will have at least two different diabetes related autoantibodies other than mIAA confirmed to be present on two occasions. The autoantibodies that may be confirmed are anti-GAD65, anti-ICA512/anti-IA2, ZnT8, and/or ICA, but not anti-insulin (MIAA). The confirmation of 2 positive autoantibodies must occur within the six months prior to study drug administration but the confirmation does not have to involve the same 2 autoantibodies.

Those individuals with two confirmed diabetes related autoantibodies (other than mIAA) will then be eligible for additional screening tests and possible enrollment into Abatacept Prevention Trial. A subject must have a normal OGTT either done as part of the Natural History/Pathway to Prevention Study or during Abatacept screening within 7 weeks (52 days) of randomization. If a subject has a previous abnormal glucose tolerance, he/she must have two consecutive OGTTs with normal glucose tolerance in order to be eligible.

Appendix 1 summarizes the flow of subjects from the Natural History/Pathway to Prevention Study into the Abatacept Prevention Trial.

5.2. Abatacept Trial for At-risk Subjects Baseline Visit

Prior to the initial visit, the Abatacept Prevention Trial will be described to the potential participant. The participant/parent/guardian will be asked to sign an informed consent document describing the purpose, risks, and benefits of screening for the trial. A participant's signature indicates that he/she understands the potential risks and benefits of study participation. During these visits, clinical tests will be done to determine eligibility.

Any participant either not eligible or not willing to be randomized into the Abatacept Prevention Trial is eligible for continued follow-up as part of the TrialNet Natural History/Pathway to Prevention Study.

5.3. Randomization and Baseline visits

Prior to randomization, the intervention and follow-up parts of the study will be described to the participant. The participant/parent/guardian will be asked to sign an informed consent document and minors will be asked to sign an age appropriate assent document indicating that he/she understands the study as well as the potential risks and benefits of study participation.

Participants will be randomized to either the treatment arm or the placebo arm. The randomization and the baseline visit may occur up to 24 hours apart and the infusion must occur within 7 weeks of a normal OGTT in order to ensure that participants have normal glucose tolerance at the time of randomization

and study drug administration. Note, subjects who are febrile at the time of baseline visit, may have the visit postponed up to five days outside the 7 week window if needed because of intercurrent illness.

5.4. Close Monitoring

During the study period, all participants will receive close monitoring for development of abnormal glucose tolerance and diabetes. OGTT tests will be performed at six month intervals thereafter. In addition, at three month intervals starting with month 15 in which there is no OGTT scheduled, a random (post-prandial) glucose level will be measured. At each visit, subjects will be asked directed questions about the presence or absence of symptoms associated with diabetes such as blurry vision, unintended weight loss of more than 3 kg, polyuria, and polydypsia. If subjects respond affirmatively to any of these questions or if any of the post-prandial glucose values are greater than 200 mg/dL, further evaluation, including fasting glucose or an OGTT, will be performed. Individuals in both of the study arms will have laboratory and mechanistic studies performed as detailed in the Schedule of Assessments.

5.5. Administration of CTLA-4 Ig (Abatacept)

The CTLA-4 Ig used in these human trials (abatacept) is a soluble fusion protein, which consists of the extracellular domain of the human CTLA-4 (CD152) and a fragment (hinge, CH2 and CH3 domains) of the Fc portion of human IgG1.

A urine pregnancy test will be given to females with reproductive potential. An interim medical history and exam with directed questioning regarding infectious symptoms will be performed before each study infusion is administered.

The study drug (abatacept/ placebo) is administered IV at 10 mg/kg for up to maximum of 1000 mg.

The study drug is administered over 30 minutes and not mixed or diluted with other medications. No routine pre-medication is needed; however medication such as acetaminophen and diphenhydramine may be administered according to investigator discretion as needed.

If mild hypersensitivity or an infusion related event develops, the study infusion should be temporarily interrupted. Subjects may be dosed with acetaminophen and diphenhydramine as needed. The study infusion can continue or be resumed upon improvement of patient symptoms.

Subjects will be monitored for one hour after the end of the infusion.

5.5.1. Dosing and Dose Withholding

The dose was chosen based on demonstrated safety and efficacy in children and adults with type 1 diabetes as well as in other human autoimmune diseases. Dosing will be according to the individual's weight during the previous visit unless the previous visit was more than three months prior. In that case, dosing will be according to the individual's weight on the day of the visit.

Subjects without previous exposure to EBV (EBV IgG and IgM negative during screening) will have EBV viral load determined at each study visit. Those that have evidence of active EBV infection before randomization will not be eligible for the study. Those that have evidence of active EBV infection after randomization will not receive additional study drug until resolution (determined by laboratory assessments and absence of signs and symptoms associated with active disease).

The study drug infusions will also not be given if any subject has had a symptomatic illness with fever, sore throat, or lymphadenopathy during the previous 10 days. The study drug infusions will also be withheld if there are any unresolved grade 3 laboratory abnormalities. Administration of subsequent infusions can occur upon clinical and laboratory resolution.

Subjects with grade 3 hypersensitivity or infusion reactions, those who have developed a serious infection (such as pneumonia, cellulitis or pyelonephritis) and/or those who require pressor support or epinephrine will not be restarted on therapy and will not receive subsequent doses but will continue to be monitored for safety and development of confirmed abnormal glucose tolerance or diabetes per the study schedule of assessments.
Participants who develop AGT will continue to receive a total of 14 doses as described above to address the T1DM study end point.

6. STUDY VISIT ASSESSMENTS

The schedule of evaluations and laboratory studies is presented in Appendix 2, Schedule of Assessments. A summary of assessments for the Protocol is given below.

6.1. General Assessments

General assessments for this Protocol will include:

- Informed consent
- Inclusion/exclusion criteria
- Medical history including lifestyle and participant experience assessment
- Routine or directed Physical examination including height/weight
- Concomitant medications
- Adverse events

6.2. Laboratory Assessments

The following clinical laboratory assessments will be performed during the study as described in the Schedule of Assessments:

- Chemistry (sodium, potassium, chloride, CO2, glucose, BUN, creatinine)
- Liver function tests (ALT, AST, LDH, alkaline phosphatase, total protein, albumin, total and direct bilirubin)
- Hematology (complete blood count with differential and platelets)
- Purified protein derivative (PPD) test or Interferon-Gamma Release Assay Test (IGRA)
- Urine pregnancy test as appropriate
- Antibodies to HIV, hepatitis B (anti-HBcAb, HBsAg), hepatitis C (HCV)
- Cytomegalovirus antibodies (CMV IgG and IgM)
- Epstein-Barr virus antibodies (EBV IgG and IgM, EBNA) and viral load as indicated

6.3. Mechanistic Outcome Assessments

TrialNet will perform immune and genetic assays to further understand mechanisms that may be underlying the type 1 diabetes disease process and response to therapy. For this purpose, samples for PBMC, DNA, RNA, plasma, and serum may be obtained. Islet autoantibodies will be measured at six month intervals in the study. HLA testing may be done either under the auspices of TrialNet Natural History/Pathway to Prevention Study or this protocol.

At any time after the first month of study, subjects will receive their annual clinically indicated killed flu vaccine at the appropriate time of year during the treatment phase of the study. Subjects may receive subsequent killed flu vaccinations later in the study. Responses to these immunizations may be determined through analysis of pre- and 4 week post-dose samples. Samples for thyroid antibodies, virology and other immunization titers may also be collected.

6.4. Metabolic Outcome Assessments

Metabolic assessments will consist of:

1. OGTT
   - The OGTT will be performed every 6 months or more frequently if clinically indicated based on a random glucose level of ≥ 200 mg/dL.
   - The C-peptide and insulin data from the OGTT will be used to measure insulin secretion.
   - The insulin, glucose and C-peptide data from the OGTT may be used to measure insulin sensitivity.

2. HbA1c
   - Measure of glycemic control.

6.5. Laboratory Measures Related to Abatacept Administration

Determination of immunogenicity to abatacept, receptor occupancy, and drug levels may be done to assess pharmacokinetic profiles according to the schedule of assessments (Appendix 2).

6.6. Visit Windows

The baseline visit must occur within 7 weeks after a normal OGTT (with the exception that individuals who are febrile at the time of the scheduled baseline visit, may have up to an additional 5 days). For the next two infusion visits (visit # 1 at 2 weeks, visit # 2 at 4 weeks), the window is +/- 3 days of the target date. The subsequent infusion visits (visits # 3-14, every 28 days thereafter) should be +/- 7 days on either side of the targeted date to be permissible. Study doses outside of the window will not be made up (i.e. if treatment dose # 5, scheduled for day 84 cannot be accomplished between days 77 and 91, this dose will not be given and the next dose will be on day 112 +/- 7 days). Further, the clock will not be reset, i.e. if treatment dose # 5 is given on day 77 (day 84 -7 day window), the target date for treatment dose # 6 remains day 112. In this way, no one will receive more than 14 study doses (infusions) over a one year period. Subsequent semi-annual follow-up visits should be within +/- 3 weeks of the targeted date.

7. ADVERSE EVENT REPORTING AND SAFETY MONITORING

7.1. Adverse Event Definition

7.1.1. Adverse Event

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

Throughout the study, the investigator must record all adverse events on source documents. Events not related to diabetes onset of hyperglycemia which are Grade 2 or greater per the NCI CTCAE (see Section 7.1.5. Grading Event Severity below) must be reported to TNCC. The investigator should treat participants with adverse events appropriately and observe them at suitable intervals until the events resolve or stabilize.

Adverse events may be discovered through:

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

Questioning of the participant should be conducted in an objective manner.

7.1.2. Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the 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 event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction, which means any adverse event caused by a drug. Examples of evidence that suggest a causal relationship (reasonable possibility) between the drug and the adverse event include:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the populations exposed to the drug
- An aggregate analysis of specific 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.

7.1.3. Serious Adverse Event/Reaction

A serious adverse event (SAE) or reaction is defined as “any adverse event occurring at any dose that suggests a significant hazard, contraindication, side effect, or precaution.” An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

1. Death. A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy must be reported whether it is considered to be treatment related or not.
2. A life-threatening adverse event. A life-threatening event is any adverse therapy experience that, in the view of the investigator, places the participant at immediate risk of death from the reaction as it occurred.
3. Inpatient hospitalization or prolongation of existing hospitalization with the exception of hospitalization relating to initial diagnosis of type 1 diabetes.
4. Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. Congenital anomaly or birth defect.
6. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Regardless of the relationship of the adverse event to study drug, the event must be reported as a serious adverse event if it meets any of the above definitions.

7.1.4. Unexpected Adverse Event

An adverse event/reaction is considered unexpected when the nature (specificity) or severity of the event is not consistent with the risks described in the Investigator’s Brochure or the informed consent document. Unexpected refers to an experience that has not been previously observed. This includes events that occur more frequently than expected.

7.1.5. Grading Event Severity and Causality

TrialNet has adopted usage of the National Cancer Institute (NCI) Common Technology Criteria for Adverse Events (CTCAE) and/or study-specific criteria for classification to describe the severity of adverse events with the exception of hypoglycemia and hyperglycemia. Hypoglycemia and hyperglycemia will be reported as adverse events only in the case of requiring the assistance of others due to loss of consciousness or DKA. TrialNet Investigators will also provide an assessment of relationship of AE to study drug as not, unlikely, possibly, probably, or definitely related.

7.2. Adverse Event Reporting and Monitoring

Adverse events will be reported to the TrialNet Coordinating Center. The investigator will grade their severity according to common toxicity criteria or study-specific criteria and will make a determination of their relation to therapy. Events will be assessed and reported consistent with the ICH Guideline for Good Clinical Practice, 21 CFR 312.32 for expedited safety reporting, and per the guidance of the DHHS Office for Human Research Protections (OHRP).

The adverse event case report form for the protocol must be completed for all adverse events (AE). For reporting serious adverse events (SAE), the MedWatch Form should also be completed and faxed to the TNCC *within 24 hours of when the site was notified of the event.* This will be reviewed by the TrialNet Medical Monitor, the TrialNet Safety Monitoring Committee, and the DSMB as appropriate. Deaths must be reported immediately. Event outcome and other follow-up information regarding the treatment and resolution of the event will be obtained and reported when available, if not known at the time the event is initially reported. The follow-up information should contain sufficient detail to allow for a complete medical assessment of the case and an independent determination of possible causality.

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

For SAEs that are unexpected and considered possibly or probably drug related, the Medical Monitor will provide information on frequency of similar events, and generate FDA form 3500A reports (MedWatch form) for distribution to FDA, NIDDK, DSMB and site investigators. Expedited safety reports will be submitted to the IND by the TNCC on behalf of NIDDK.

8. PARTICIPANT SAFETY

8.1. Risks, Benefits and Inclusion of Children

The risks of this study are presented below and in the informed consent form and volunteer handbook. This study will examine whether abatacept will delay or prevent the development of abnormal glucose tolerance and diabetes onset in antibody positive relatives, but there is no guarantee that this will occur.

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

The study procedures, while greater than minimal risk, offer the possibility of benefit due to the close monitoring for all participants, including children. Assent of children along with consent of the parent/legal guardian will be obtained prior to any study procedures. This research proposal in children is therefore consistent with the United States Department of Health and Human Services, Protection of Human Subjects, subpart D, section 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects) and with Subpart D. 50. 52 (Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects).

8.2. Protecting Against or Minimizing Potential Treatment Risks

As of the third quarter of 2010, there is an estimated 60,225 total person-years of exposure to abatacept have been documented in the abatacept clinical program with excellent safety profile and tolerability including in children.

In addition, our previous Diabetes TrialNet study administered abatacept in 27 doses over two years in 77 subjects with type 1 diabetes.

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

All infusions will take place in a facility that has resuscitation capabilities.

Participants will be counseled by study personnel and requested to avoid pregnancy for 3 months following drug administration for safety purposes.

8.2.1. Prohibited Medications

Participants will be instructed not to use Prednisone, other immunosuppressive agents, chronic inhaled or nasal corticosteroids, or retinoic acid during this trial in order to prevent possible impact on progression to diabetes. However, as an intention to treat study, no individual will be withdrawn from analysis if this occurs.

Participants who receive abatacept will be instructed not to receive live vaccinations during the dosing period and for 3 months after dosing.

8.3. Expected Side Effects and Adverse Events

A full description of the adverse events experienced by subjects in trials using abatacept is in the Investigator's Brochure. The descriptions below highlight the most common drug related events and potential adverse events.

8.3.1. Infusion and Hypersensitivity Reactions

Between 5-9% of subjects in clinical trials of abatacept reported mild or moderate infusion reactions such as dizziness, hypertension, and headache. No severe infusion reactions have been reported. In the Diabetes TrialNet study involving subjects with type 1 diabetes, infusion related adverse events occurred with low frequency (47 of 2514 infusions; 2%), none were considered to be clinically significant, and the frequency was not different between the abatacept and placebo treated subjects.

Hypersensitivity reactions are rare, with mild urticaria, hypotension and dyspnea occurring in <0.9% of subjects. There have been two episodes of anaphylaxis reported (rate <1:1000). Among 190 patients with juvenile idiopathic arthritis in clinical trials, one case of hypersensitivity reaction was seen. No hypersensitivity reactions were seen among the individuals with type 1 diabetes.

8.3.2. Infectious Adverse Events

As with all immunomodulating agents, there is a risk of infectious adverse events. In placebo controlled clinical trials of adults with rheumatoid arthritis, infections were reported in 54% of abatacept and 48% of placebo treated subjects. Infections occurred in 36% of patients with polyarticular juvenile idiopathic arthritis. The most frequent infections reported were upper respiratory tract infection, and nasopharyngitis which occurred in ≥ 10% of subjects. Other common infections include sinusitis, influenza, and bronchitis. Other infections reported in <5% of subjects in a higher frequency in abatacept treated vs placebo subjects include rhinitis, herpes simplex and pneumonia.

In the Diabetes TrialNet study involving individuals with type 1 diabetes, there was no increase in infection including EBV or in neutropenia.

Serious infections such as cellulitis, bronchitis, acute pyelonephritis, pneumonia and diverticulitis were reported in 3% of treated subjects versus 1.9% of placebo group participants.

8.3.3. Immunizations

Although no data are available regarding the effects of live vaccination in patients receiving abatacept therapy, vaccination with live vaccines is not recommended. The possibility exists for abatacept to affect host defenses against infections since the cellular immune response may be altered. Therefore concurrent use of live vaccines within 3 months of abatacept therapy may result in reduced efficacy of vaccine. Killed flu vaccine will be administered to subjects as part of the study (see Mechanistic Assessments).

8.3.4. Drug Interactions

Higher frequencies of adverse events including serious infections were reported in subjects with rheumatoid arthritis also treated with TNF blockers.

8.3.5. Blood Glucose Testing

The maltose present in abatacept can interfere with the readings of blood glucose monitors that use test strips with glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ). GDH-PQQ based glucose monitoring systems may react with the maltose present in abatacept, resulting in falsely elevated blood glucose readings on the day of infusion. Since individuals in this study do not have diabetes, the effect of abatacept on home glucose monitoring is unlikely to be relevant; however, clinical sites and subjects will be reminded of this effect of the study drug.

8.3.6. Other Reported Adverse Events

More than 10% of subjects reported nausea and headache. Among subjects with chronic obstructive pulmonary disease (COPD), more than 40% had acute exacerbations of COPD. In children, diarrhea, cough and abdominal pain have been reported.

Antibodies directed against the abatacept molecule were assessed by enzyme-linked immunosorbent assays, in rheumatoid arthritis subjects treated for up to two years with abatacept. Thirty-four of 1993 (1.7%) of subjects developed binding antibodies. In subjects assessed for antibodies at least 56 days after discontinuation of abatacept, 9 of 154 (5.8%) subjects developed antibodies. Samples with binding activity to the CTLA-4 region of the molecule were assessed for the presence of neutralizing antibodies. Six of nine evaluable subjects were shown to possess neutralizing antibodies. There was no correlation of antibody development to clinical response or adverse events. However, the number of subjects that developed antibodies was too limited to make a definitive assessment. The clinical relevance of neutralizing antibody formation with Abatacept is not known.

Similarly, antibodies directed against the abatacept molecule were assessed by enzyme-linked immunosorbent assays, in children and adolescents with JIA (age 6-16 years) treated with abatacept in a Phase 3, multi-center, multi-national, randomized, withdrawal study cited earlier. The presence of antibodies was transient and antibody titers were generally low. It did not correlate with any clinical

findings, including an increase in incidence of SAEs, acute infusional AEs, autoimmune disorders, diminution in clinical efficacy, or effect on serum concentrations of abatacept. Immunopositive subjects in the double-blind phase of the study were not at increased risk of experiencing SAEs, acute infusional AEs, or autoimmune disorders when re-initiating abatacept treatment in the open label follow up period.

Doses up to 50 mg/kg have been administered without apparent toxic effect.

There were no significant differences between abatacept and placebo subjects with respect to number of cancers, although more abatacept treated subjects developed lung cancer. Other malignancies including lymphoma have been observed; however the relationship of abatacept to malignancies is unclear.

8.3.7. Pregnancy

Female subjects with reproductive potential will be instructed to avoid pregnancy and use birth control from randomization up to 14 weeks after study drug administration. They will undergo urine pregnancy testing at the start of every study visit. All pregnancies that are identified during the study must be followed to conclusion and the outcome of each must be reported. The investigator should be informed immediately of any pregnancy occurring in a female participant. Monitoring of the participant should continue until the conclusion of the pregnancy. Subjects that are found to be pregnant while on this study shall have treatment withheld, but will still be followed for safety. Treatment may only be resumed when subjects are no longer pregnant or nursing.

9. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

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

All analyses will be conducted under the intention-to-treat principle whereby all outcome data in all randomized subjects will be included in all analyses as appropriate.

9.1. Primary Outcome

The primary outcome is the elapsed time from random treatment assignment to the development of confirmed abnormal glucose tolerance or diabetes among those enrolled in the primary analysis cohort consisting of subjects with islet cell autoimmunity and absence of metabolic abnormalities (normal OGTT). It is expected that abnormal glucose tolerance will be detected prior to diabetes onset by OGTT; however, the presence of diabetes is considered as an endpoint.

Although subjects who develop confirmed abnormal glucose tolerance will have reached the primary study endpoint, these individuals will continue to receive assigned treatment and will be followed in the study for continued monitoring for diabetes development and safety assessments.

The study end point is realized with either confirmed OGTT criteria for abnormal glucose tolerance or diabetes or clinical criteria for diabetes.

OGTT criteria for abnormal glucose tolerance or diabetes:

The presence of an OGTT consistent with abnormal glucose tolerance or diabetes on two sequential dates. A subject with abnormal glucose tolerance or diabetes on an OGTT should undergo a repeat OGTT as soon as possible, but no less than one day apart. Aim to repeat within one month. The time of abnormal glucose tolerance or diabetes will then be taken as the date of the confirmatory abnormal OGTT.
The definition of abnormal glucose tolerance is:

a. Fasting plasma glucose ≥ 110 mg/dL (6.1 mmol/L) and < 126 mg/dL (7 mmol/L), or
b. 2 hour plasma glucose ≥ 140 mg/dL (7.8 mmol/L) and < 200 (11.1 mmol/L), or
c. 30, 60, 90 minute plasma glucose during OGTT ≥ 200 mg/dL (11.1 mmol/L)

Criteria for Diabetes Onset:

Criteria for diabetes onset (T1DM) are, based on glucose testing, or the presence of unequivocal hyperglycemia with acute metabolic decompensation (diabetic ketoacidosis). One of the following criteria must be met on two occasions as soon as possible but no less than one day apart for diabetes to be defined:

1. Symptoms of diabetes plus casual plasma glucose concentration ≥ 200 mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

2. Fasting plasma glucose ≥ 126 mg/dL (7 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.

3. 2 hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L). The test should be performed using a glucose load containing the equivalent of 1.75g/kg body weight to a maximum of 75g anhydrous glucose dissolved in water.

It is preferred that at least one of the two testing occasions involve an OGTT. Cases identified will be confirmed as having diabetes if the glucose values to make these determinations were obtained in a TrialNet laboratory as part of an OGTT. Cases diagnosed with diabetes by symptoms and casual glucose ≥ 200mg/dL or by other criteria than the above will be adjudicated by the TrialNet Endpoint Adjudication Committee.

9.2. Primary Analysis

The primary objective of the study is to assess the effect of abatacept therapy versus placebo on the risk of developing confirmed abnormal glucose tolerance (AGT) as measured from an OGTT.

The cumulative incidence of AGT over time since randomization within each treatment group will be estimated from a Kaplan-Meier estimate of the "AGT-free" survival function. The difference between groups in the cumulative incidence functions, and the associated hazard functions, will be tested at the 0.05 level, two-sided, using the Cox regression including site and age group as covariates (45,46). The estimates of cumulative incidence and the test will adjust for periodic outcome assessment visits to assess diabetes status. The critical value for the test statistic, and confidence intervals in this primary

analysis will be determined by the group-sequential procedure.

Data from the TrialNet Pathway to Prevention Study may be used to determine participant eligibility. Outcomes from other studies may be used in meta-analyses, but not in the evaluation of this study's efficacy.

9.3. Secondary Outcomes and Analyses

A variety of secondary analyses are planned that include the following.

Subgroup analyses will be conducted comparing the effects of abatacept versus placebo on the risk of AGT with a test of the group by subgroup factor interaction in a Cox proportional hazard (PH) Model. Subgroups of the population classified by age (children ≤ 12 years of age, adolescents 13-17 years and adults ≥ 18 years), gender, race/ethnicity, and specific antibody status at baseline. Differences in the treatment effect between subgroups will be tested using a covariate by treatment group effect in a Cox PH model (45). The effects of age will also be assessed as quantitative covariates.

Similar analyses will be conducted using the values of quantitative baseline factors including weight, BMI, and the immunologic and metabolic factors described in Section 6 that include the autoantibody titers, basal C-peptide, stimulated C-peptide (peak and AUC mean), and measures of insulin resistance modeled from the OGTT. The dependence of the treatment effect on the quantitative levels of a covariate will also be assessed by a covariate by treatment group interaction in a PH model.

Additional factors may be defined before unmasking of the study data to the investigators. The analyses will distinguish between factors specified prior to unmasking, and those identified post-hoc during analysis. If the assumption of proportional hazard is not appropriate, the data will be examined to determine the cause of non-proportional hazard, such as the presence of a decaying, diverging, or crossing effect of hazard ratios over time. Based on the cause of the non-proportional hazard, post-hoc analyses such as frailty models, parametric models, or models with interactions and time-dependent covariates may be employed.

Longitudinal analyses will assess the effects of abatacept versus placebo treatment on immunologic and metabolic markers over time up to the onset of AGT. Differences between groups in the mean levels of quantitative factors over time will be assessed using a normal errors linear model for repeated measures. Differences between groups in the prevalence of qualitative factors over time will be assessed using generalized estimating equations for categorical measures. Generalized estimating equations may also be employed for the analysis of quantitative factors if the assumption of multivariate normal random errors is violated.

Immunologic and metabolic markers will be modeled to determine the effects of abatacept versus placebo treatment while adjusting for subject characteristics for each follow-up time point of interest. For continuous endpoints that lend themselves to normal error linear models, ANOVA and ANCOVA models will be employed. Generalized linear modeling will be employed for dichotomous and categorical endpoints by using the most appropriate link functions. Longitudinal analyses maybe employed in order to characterize the relationship among the repeated measures during the treatment period and possibly beyond. Due to the exploratory nature of the longitudinal modeling, treatment effect hypothesis testing will not conducted.

The association of demographic, genetic, immunologic, metabolic, and lifestyle factors, the presence of illness and concomitant meds, among others, both at baseline and over time, with the risk of AGT onset will be assessed in Cox PH Models over time. The effects of changes in longitudinal factors on AGT risk will be assessed using time-dependent covariates for these factors. Analyses will be conducted separately within the abatacept and placebo groups, and differences between groups in covariate effects (group by covariate interactions) will be assessed. Models will then be assessed within the two groups combined, taking account of any group by covariate interactions.

Additionally, as noted in section 4.9.2, subjects will be able to be followed for the occurrence of diabetes. The treatment arms will be compared on the corresponding incidence rates of type 1 diabetes using the logrank statistic. Subgroup analyses analogous to those described for the AGT endpoint will be conducted on the endpoint of type 1 diabetes.

9.4. Study Power and Accrual Target

The study has been designed to provide 80% power to detect a 40% risk reduction in the rate of AGT using a two-sided test at the 0.05 level after six years of study duration.

Study enrollment will stop on approximately July 31, 2019 and follow-up will continue for up to two additional years. A model of observed events (confirmed abnormal glucose tolerance; AGT) in the placebo group now provides a more realistic estimate of the number that will have developed AGT at the conclusion of the follow up period. The model suggests that the total number of events will be between 64 and 70; resulting in detectable hazard ratios of ***0.496 to 0.512***. The hazard ratios and differences in cumulative incidence are based on 80% statistical power when testing at the 0.05 level (2-sided).

The final test of significance up through the six year time point will employ group sequential critical values to protect against inflation in the type I error probability due to interim assessments of the emerging data for review by the DSMB. However, there is only a minimal loss in power with this approach so that the fixed sample size power based on the above information calculation is virtually identical to the group sequential power. Thus, there is no need to adjust for the group sequential critical values in these computations.

Note the original accrual period and the study target sample are only projections since the actual accrual rate and the loss to follow-up rate are unknown. As the study progresses, more accurate projections of the study end date will be computed based on the observed rate of enrollment, the observed number of events, and the observed rate of loss-to-follow-up. This data will be provided to the DSMB and the TrialNet governing body, and if need be, this document will be amended.

9.5. Interim Monitoring Plan

The Lan-DeMets spending function with an O'Brien-Fleming boundary will be used to protect the type I error probability for the primary outcome analyses, and to assess the significance of the interim results that emerge during the trial (49). The DSMB may terminate the trial prematurely if a statistically significant effect is observed and it is considered that all major trial objectives have been met.

The DSMB will also consider early termination due to absence of a treatment effect (i.e. futility) based on computations of conditional power conducted both under the initial study design and under the

current trend of the data (50).

9.6. Withdrawal Criteria – Individual Subjects

An intent–to-treat approach will be used. Subjects will not be replaced. All data acquired prior to termination for the reasons outlined below will be included in the primary analysis unless a participant withdraws consent. Every effort will be made to conduct a final study visit with the participant and participants will be followed clinically until, if applicable, all adverse events resolve.

- Withdrawal of consent
- Withdrawal by the participant
- Withdrawal by the investigator
- Intercurrent illness or event that precludes further visits to the study site or ability to evaluate disease.

10. ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

10.1. Statement of Compliance

This study will be conducted in compliance with the protocol and consistent with current Good Clinical Practices (GCP), adopting the principles of the Declaration of Helsinki, and all applicable regulatory requirements (*ICH E6, 45CFR46, and FDA 21CFR sections 11, 50, 56, 312)*.

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

10.2. Participating Centers

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

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

The investigational sites participating in this study will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from participants participating in this study. When a subject participates in this study at more than one TrialNet site, sharing of this information is required. Sharing of information obtained during this study between TrialNet clinical centers and

affiliates will be done to assure subject understanding and consent, safety, and adherence to protocol. Medical and research records will be maintained at each site in the strictest confidence. However, as a part of the quality assurance and legal responsibilities of an investigation, the investigational site must permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. Unless required by the laws permitting copying of records, only the coded identity associated with documents or other participant data may be copied (obscuring any personally identifying information). Authorized representatives, as noted above, are bound to maintain the strict confidentiality of medical and research information that may be linked to identify individuals. The investigational site will normally be notified in advance of auditing visits.

10.3. Informed Consent

The process of assuring that individuals (and parent/guardian if less than 18 years of age) are making an informed decision about participating in this study includes both verbal and written communication. Written materials include a Volunteer Handbook, Volunteer Understanding Assessment, and written consent forms. There are several consent forms for this study. One is a Screening consent form that describes the procedures, risks, and benefits, and determines eligibility for the study. The second is the Intervention consent form, which describes the procedures, risks, and benefits for the remainder of the study. A third consent form is for use at clinical sites that will be performing the post-treatment visits, but not the treatment visits. The consent forms will be reviewed with participants (and their parent/guardian in the case of participants under 18 years of age) and the participant will be given time to review the written consent form and ask questions. An assent form has also been developed for participants less than 18 years of age (unless local IRB/REB requirements differ in procedure).

As part of the informed consent process, the participant and/or parent or guardian (if the participant is less than 18 years of age) will also be required to complete a short, written Volunteer Understanding Assessment that is designed to ensure that the subject understands the study, as well as what is being asked of him/her. The participant will be given a copy of their consent/assent forms.

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

When a participant turns 18 they are permitted to re-consent remotely should they be unable to return to the study site for an in-person visit. When providing remote consent (via phone or video conference) the POC will review the checklist and long-form informed consent document with the subject/parent or guardian. After the subject/parent or guardian is provided the printed long form informed consent document, the POC will address any questions the subject/parent or guardian may have before the informed consent form is signed and any procedures are performed. The informed consent document may be provided to the subject/parent or guardian using any method that the complete content can be available in print. Signed and completed documentation must be available to the subject/parent or guardian and the study team, by any method that assures that the complete content can be available in print.

Re-assent when a participant reaches age 12 is waived until the participant returns for an in-person visit at the study site.

The informed consent form must be updated or revised whenever there is new, clinically significant information applicable to the safety of the participants, when indicated for a protocol amendment,

and/or whenever any new information becomes available that may affect a subject's participation in the study.

Subjects will be re-consented if they reach the age of 18 years while enrolled in the study.

10.4. Study Subject Confidentiality

The investigational sites participating in this study will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from subjects. Participant identifying clinical and research information will be shared between TrialNet sites to support participants and assure protocol compliance as applicable. As a part of the quality assurance and legal responsibilities of an investigation, the investigational site must permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. Unless required by the laws permitting copying of records, only the coded identity associated with documents or other participant data may be copied (obscuring any personally identifying information). Authorized representatives, as noted above, are bound to maintain the strict confidentiality of medical and research information that may be linked to identify individuals. The investigational site will normally be notified in advance of auditing visits. Study records with the study subject's information for internal use at the clinical sites will be secured at the study site during the study. At the end of the study, all records will continue to be kept in a secure location. There are no plans to destroy the records.

Study subject data, which is for reporting purposes, will be stored at the TrialNet Coordinating Center. Case report forms sent to the Coordinating Center will identify participants by the unique TrialNet Identification Number. The data entry system at the Coordinating Center is a secured, password protected computer system. At the end of the study, all study databases will be archived at the Coordinating Center, and the data collection forms will be electronically scanned and saved in electronic format for long-term storage.

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

10.5. Risks and Benefits

The risks of this study are presented in this protocol, the Investigator's Brochure and informed consent form. There is no guaranteed benefit to subjects for their participation in the study. This study will examine whether intervention with abatacept will delay or prevent the development of abnormal glucose tolerance and diabetes, but there is no guarantee that this will occur. However, all subjects will benefit from close monitoring for the development of diabetes. This close monitoring significantly reduces the morbidity typically associated with clinical onset of disease.

Special consideration regarding risks and benefits for children is described in section 8.1.

10.6. Ethics

The study protocol, along with the required informed consent forms, will be approved by each participating institution's Institutional Review Board (IRB) or Ethics Committee/Research Ethics Board

(EC/REB) at international sites prior to the initiation of any research procedures (at the site). In addition to details described in the sections above (informed consent, confidentiality, and risks and benefits), the investigators have reviewed and considered ethical ramifications in the design and development of this protocol. The investigators have made every effort to minimize and monitor risks and discomforts to participants throughout the course of the study.

11. STUDY ADMINISTRATION

11.1. Organizational Structure

This study is part of Type 1 Diabetes TrialNet, which is funded by the National Institutes of Health. Funding will cover the costs of administration and laboratory tests associated with this study.

11.2. Role of Industry

Bristol-Myers Squibb will provide the abatacept for clinical trial conduct. Under TrialNet's direction, Bristol-Myers Squibb may perform measurements such as PK and anti-Abatacept antibodies as indicated on coded samples. Data and data analysis will be conducted by TrialNet investigators.

11.3. Groups and Committees

11.3.1. Abatacept Prevention Study Chair Committee

The Study Chair and TrialNet Executive Committee will receive periodic reports from the TNCC on the progress of the study. These will include accrual rates and baseline demographic characteristics. Interim data summaries provided to others (except those that could lead to unmasking of study outcome) will first be supplied to the Study Chair for review. Criteria and results of ongoing monitoring of the TrialNet labs in terms of reproducibility will also be provided on a routine basis and reported on during TN18 Abatacept Prevention Study Chair Committee meetings, as scheduled. As appropriate, abstracts and manuscripts dealing with the progress of the trial shall be directed by the TN18 Abatacept Prevention Study Chair Committee.

11.3.2. TrialNet Chairman's Office and TNCC

The TrialNet Chairman's Office and TNCC will work together in providing leadership to the TrialNet study group to include protocol and manual preparation, training for clinical sites, development of statistical design for each study, and analysis of study results. The TNCC will also coordinate interactions among the participating TrialNet Clinical Centers, test laboratories including TrialNet Core Laboratories and other subcontract laboratories, NIDDK, and other sponsoring agencies.

11.3.3. Clinical Sites

Principal Investigators at each participating TrialNet clinical site will oversee all operations at that site. The clinical sites will forward all laboratory and data collection form information to the TNCC for analysis. Direct communication and site visits, as needed, will facilitate evaluation of the trial management.

11.3.4. Endpoint Adjudication Committee

A TrialNet Endpoint Adjudication Committee will review all relevant information for each subject who does not meet the criteria stated in section 9.1 but has been otherwise diagnosed as having developed diabetes or abnormal glucose tolerance. The Committee will determine whether the diagnosis of diabetes or abnormal glucose tolerance in each of these subjects is sufficiently sound so as to include that subject among the cases who have reached the primary outcome in the statistical analysis. The Committee will be masked to treatment assignment as it reviews each case.

11.3.5. Clinical Site Monitoring

In order to conduct this study with established research principles, site visits will be conducted during the study to evaluate study conduct and ensure subject safety. All sites will be monitored by the TNCC and appropriate TrialNet committees for patient enrollment, compliance with protocol procedures, completeness and accuracy of data entry, the occurrence and reporting of adverse events (AEs) and serious adverse events (SAEs), site pharmacy accountability/operations and to confirm the presence of appropriate IRB/REB regulatory approvals/documents.

11.4. Medical Monitor and Data Safety and Monitoring Board (DSMB)

All adverse events will be recorded on the adverse event forms, which will be sent to the local IRBs/REBs, per their reporting requirements, and to the Coordinating Center.

An independent physician will be designated to serve as the medical monitor for this study who will maintain regular contact with the study and the Study Chair. (S)he will review all adverse event reports, masked to treatment assignment, and will file event reports with regulatory authorities as appropriate.

The DSMB will meet approximately every 3 months and as needed to review indicators of safety. In addition, they will meet every 6 months to review the interim effectiveness and potential toxicity of the study treatments based on interim analyses of indicators of effectiveness and safety prepared by the TNCC separately by treatment group. The DSMB will independently evaluate whether there are grounds to modify or discontinue the study.

11.5. Sample and Data Storage

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

Data collected for this study will be sent to the TNCC. De-identified data will be stored at the NIDDK Repository, under the supervision of the NIDDK/NIH, for use by researchers including those outside of TrialNet.

With permission of the subject, when TrialNet is completed, samples will continue to be stored at the NIDDK Repository. Since the stored data will be fully de-identified upon the completion of TrialNet, it

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

11.6. Preservation of the Integrity of the Study

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

11.7. Participant Reimbursement and Compensation

Participants may be compensated for each visit attended in the study. In compliance with ICH Guidance E6, the amount and method of payments to subjects shall be designed to avoid coercion or undue influence on the study subjects. Payments to subjects will be prorated and not wholly contingent on completion of the trial by the subject.

APPENDIX 1: Natural History/Pathway to Prevention to Abatacept in At-Risk Relatives: Study Flow Chart

Natural History/Pathway to Prevention Study Screening

Procedures	Relative of individual with type 1 diabetes Age 1-45 Initial Autoantibody draw
Results to move on to	**Autoantibodies**
Natural History Monitoring	At least one autoantibody confirmed positive, or at least two autoantibodies present

Natural History/Pathway to Prevention Study **Monitoring**

Procedures	Confirmation of autoantibody status, OGTT, HLA
Results to move on to Abatacept Prevention Screening	**Autoantibodies**[1] At least two diabetes related autoantibodies confirmed to be present on two occasions not including mIAA. Confirmation of 2 positive autoantibodies must occur within six months prior to randomization, but the confirmation does not have to involve the same 2 autoantibodies. **OGTT**[2] **OGTT within 52 days of infusion:** Fasting Plasma Glucose <110 mg/dL (6.1 mmol/L) AND 2 hour Plasma Glucose <140 mg/dL (7.8 mmol/L) AND 30, 60 or 90 minute glucose < 200 mg/dL (11.1 mmol/L)

Abatacept Prevention Study Screening

Procedures	Screening consent is reviewed and signed. Laboratory assessments, PPD (or IGRA), History, PE, Volunteer Understanding Assessment, Study Education. OGTT if not performed during Natural History Monitoring Visit
Results to move on to Abatacept Randomization	Meets all study inclusion criteria Does not meet any exclusion criteria[3]

Abatacept Prevention Study **Baseline and Randomization (infusion must occur within 24 hours of randomization)**

Procedures	Intervention consent is reviewed and signed. Confirmation of eligibility, randomization, baseline laboratory assessments, administration of abatacept study drug/placebo.

[1]If autoantibodies are not confirmed positive on the second test a tiebreaker draw will be required.

[2]*If previous abnormal glucose tolerance, has had two consecutive OGTTs with normal glucose tolerance.* Note, individuals are permitted to undergo OGTT testing to determine eligibility for Abatacept during a screening visit if not yet eligible through OGTT testing in Natural History Monitoring Visit

[3]*If subject is not eligible or unwilling to participate in this study, the subject may be followed in TN01 Natural History/Pathway to Prevention Study.*

APPENDIX 2 - Schedule of Assessments

Week of Trial			2	4	8	12	16	20	24	28	32	36	40	44	48	61	74	87	100	113	126
Month of Trial				1	2	3	4	5	6	7	8	9	10	11	12	15	18	21	24	27	30[1]
Visit number	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19[1]
Study drug/placebo administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Chemistries and liver function tests	X								X						X		X		X		
CBC with diff and platelet count	X					X			X			X			X		X		X		
History/Physical exam[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X
Oral Glucose Tolerance[3]	X[3]								X						X		X		X		X
EBV viral load[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
EBV/CMV serology[4]	X																				
HIV, Hep B and C serology	X																				
PPD test or IGRA	X																				
Urine pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X
HbA1c	X					X			X			X			X		X		X		X
Islet Autoantibodies		X							X						X		X		X		X
Mechanistic assessments[5]	X	X				X			X			X			X		X		X		X
Interim Phone Contact and Glycemic status[6]																X		X		X	
Flu Vaccine Administration[7]																					

1= Subjects will be followed every three months until development of diabetes or the end of the trial.

2= Interim medical history and directed/limited physical exam prior to study drug/placebo infusion and after 24 months. Routine exam at screening and months 12, 24. All include adverse event assessment and collection of concomitant medications.

3= If OGTT consistent with Abnormal glucose tolerance or DM, repeat as soon as possible, but no less than one day apart. Aim to repeat within 1 month. Glucose, insulin, and C-peptide are collected at each OGTT. In order to maintain the masking of the study outcome, a random subset of participants with a normal OGTT will also be brought back for an additional OGTT after undergoing a regularly scheduled OGTT.
Individuals may undergo OGTT testing for eligibility during the Abatacept Screening visit.

4= Subjects will be screened for EBV infection with serology (VCA IgG, VCA IgM, and EBNA) with viral load measured in those except subjects who are IgG+, IgM-, EBNA+. Those with positive viral load at screening are not eligible for at least 90 days after viral load becomes undetectable. During the study, EBV seronegative subjects will have viral loads determined at each visit through visit 12. Those with positive viral loads will not receive additional study drug until laboratory and clinical evidence of resolution of EBV infection. EBV assessments will be done after visit 12 as clinically indicated.

5= May include samples for RNA, plasma, serum, DNA, measures of B and T cell number and function to understand the effect of therapy on the immune system and infectious disease. The schedule for these assessments may vary as appropriate. At no time will the blood draw volume exceed what is allowable according to the subject's age and body weight (For subjects <18 years, 5 mL/kg per visit, 9.5 mL/kg in an 8 week period.)

6= All subjects may have interim phone contact with study personnel for formal inquiry about adverse events, presence or absence of blurred vision, polyuria, polydypsia, unintended weight loss. In addition, random glucose samples may be obtained at 3 month intervals beginning at month 15 in which there is no OGTT scheduled. Those with symptoms or glucose ≥ 200 mg/dL will undergo fasting glucose or OGTT evaluation.

7= At any time after the first month of study, subjects will receive their annual clinically indicated killed flu vaccine at the appropriate time of year during the treatment phase of the study. Subjects may receive subsequent killed flu vaccinations later in the study. Responses to these immunizations may be determined through analysis of pre- and 4 week post-dose samples.

12. REFERENCES

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