ORAL INSULIN FOR PREVENTION OF DIABETES IN RELATIVES AT RISK FOR TYPE 1 DIABETES MELLITUS (Protocol TN-07)

IND #: 76,419

EudraCT #: 2006-006550-96

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

Title	*Oral Insulin For Prevention Of Diabetes In Relatives At Risk For Type 1 Diabetes Mellitus*
IND Sponsor	TrialNet
Development Phase	Phase 3
Study Design	The study is a 2-arm, multicenter, randomized, double-masked, placebo-controlled clinical trial.
Treatment Description	Subjects will receive oral insulin 7.5 mg of recombinant human insulin crystals or placebo in capsules.
First Patient Enrolled	March 02, 2007
Study Completion Date	November 01, 2017
Protocol Chair	Desmond Schatz, M.D.; University of Florida, Gainesville FL.
Sponsor Signatory	Courtney Henderson Phone: 813-396-9183 Email: Courtney.Henderson@epi.usf.edu
Statement of Compliance	This study was 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.
Date of Report	May 01, 2018

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2. Synopsis

Name of Sponsor/Company: TrialNet **Name of Finished Product:** Oral Insulin **Name of Active Ingredient:** Human recombinant insulin	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Title of Study: Oral Insulin For Prevention Of Diabetes In Relatives At Risk For Type 1 Diabetes Mellitus		
Investigators: Professor Polly Bingley, MD, University of Bristol; Jorma Toppari, MD, PhD, University of Turku; Emanuele Bosi, MD, San Raffaele Hospital; Annette Ziegler, MD, Technischen Universitat Munchen.		
Study centre(s): University of Bristol; University of Turku; San Raffaele Hospital; Technischen Universitat Munchen; Skane University Hospital.		
Publication (reference): Effect of Oral Insulin on Prevention of Diabetes in Relatives of Patients With Type 1 Diabetes: A Randomized Clinical Trial. Writing Committee for the Type 1 Diabetes TrialNet Oral Insulin Study Group, Jeffrey P. Krischer, Desmond A. Schatz, Brian Bundy, Jay S. Skyler, Carla J. Greenbaum. *JAMA*. 2017 Nov 21; 318(19): 1891–1902. Published online 2017 Nov 21. doi: 10.1001/jama.2017.17070 PMCID: PMC5798455		
Studied period (years): March 02, 2007- November 01, 2017	**Phase of development:** Phase 3	
Objectives: The primary objective is to determine whether intervention with repeated oral administration of recombinant human insulin will prevent or delay the development of clinical Type 1 Diabetes Mellitus (T1DM) in subjects at risk for T1DM.		
Number of patients (planned and analysed): A fixed target sample size was not specified. Rather, the study was designed as a maximum information trial in which subjects are recruited and followed until the required amount of statistical information is achieved that provides 85% power to detect a 40% risk reduction using a one-sided logrank test at the 0.05 level. A total number of 563 patients were enrolled.		
Diagnosis and main criteria for inclusion: (1) Relatives of T1DM proband with mIAA and at least one other islet autoantibody present (2) Normal OGTT performed within 7 weeks prior to randomization. The primary analysis stratum and secondary analysis strata are defined based on combinations of other autoantibodies present, and presence or absence of first phase insulin response on IVGTT.		
Test product, dose and mode of administration, batch number: All subjects will took one capsule of study medication (7.5 mg of recombinant insulin or placebo) daily by mouth for the duration of the study. Study medication was dispensed at each 6-month visit. Subjects remained on the same dose of insulin/placebo throughout the trial. The batch number varied over time as additional study drug was manufactured.		
Duration of treatment: Subjects remained on study drug throughout their participant in the trial.		
Reference therapy, dose and mode of administration, batch number: N/A		

Name of Sponsor/Company: TrialNet	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Oral Insulin	Volume:	
Name of Active Ingredient: Human recombinant insulin	Page:	

Criteria for evaluation

Efficacy: The primary outcome was time to diabetes in the main study group. Significance was based on a 1-sided threshold of .05, and one-sided 95% CIs are reported.

Safety: Adverse events were assessed and adjudicated, if required, by the TrialNet Medical Monitor. The DSMB conducted regular safety reviews approximately every three to six months (and, as needed) of adverse events by treatment group assignment. Serious adverse events, as well as adverse events leading to study discontinuation, were reviewed by the DSMB as needed.

Statistical methods: The cumulative incidence of diabetes onset over time since randomization within each group was estimated from a modified Kaplan-Meier estimate of the "diabetes-free" survival function. The difference between groups in the cumulative incidence functions, and the associated hazard functions, was tested using the Mantel-logrank test on discrete time to T1D (6 month intervals). The relative risk of diabetes onset between groups was estimated from the discrete Cox Proportional Hazards model. The critical value for the test statistic, p=0.047, and confidence intervals, in the primary analysis is adjusted for a single interim analysis based on Lan and DeMets spending function.

The effect of treatment with oral insulin versus placebo was tested using the intention-to-treat principle in the primary and secondary analysis strata, each consisting of participants defined using different combinations of autoantibodies and metabolic status using the same analyses as above for the primary analysis. An additional analysis assessed the effect of treatment within all strata combined using a Cox Proportional Hazards model stratified by strata. Significance was based on a 1-sided threshold of .05 and 1-sided 95% confidence intervals.

The study was designed as a maximum information trial, which did not include a fixed sample size. Instead, participants were recruited and followed until the required amount of statistical information was achieved9. At any point in time during the study, the information in the data for a logrank test is provided by I =(DOI•DC)/(DOI+DC), where DOI and DC refer to the number of participants who have developed diabetes in the oral insulin and control groups, respectively. The information required to provide 85% power to detect a 40% risk reduction (identical to the DPT-1 Oral Insulin Trial) with a one-sided logrank test at the 0.05 significance level is I = 27.551. All but 7 participants contributed to the analysis in the primary stratum. No attempt was made to impute missing data and no adjustment has been made for multiple comparisons, excepting the interim monitoring and multivariate analyses. Consequently, all but the primary analysis should be considered exploratory. Except for the post hoc hazard rate comparison with the DPT-1 study, all analyses were prespecified.

Summary - Conclusions

Efficacy Results: In this randomized clinical trial that included 389 participants in the primary analysis who were first- and second-degree relatives of patients with type 1 diabetes, oral insulin compared with placebo did not significantly reduce the risk of diabetes onset over a median of 2.7 years (hazard ratio 0.87).

Safety Results: The most common adverse event was infection (n=254), with 134 and 120 events reported in the oral insulin and placebo groups, respectively, but no significant study-related adverse events occurred.

Conclusion: Among autoantibody positive relatives of patients with T1D, oral insulin at a dose of 7.5 mg per day, compared to placebo, did not delay or prevent the development of T1D over 2.7 years. These findings do not support oral insulin as used in this study for diabetes prevention.

4. List of Abbreviations

IEC = Independent Ethics Committee
IRB = Institutional Review Board
GCP = Good Clinical Practices
TNCC = TrialNet Coordinating Center
NIDDK = National Institute of Diabetes, Digestive and Kidney Diseases
ICH = International Conference on Harmonization
DSMB = Data Safety Monitoring Board
T1DM = Type 1 Diabetes Mellitus
OGTT = Oral Glucose Tolerance Test
mIAA = Microinsulin Autoantibodies
ICA = Islet Cell Autoantibodies
GAD = Glutamic Acid Decarboxylase
ICA512 = Insulinoma-Associated Antigen 2
IVGTT = Intravenous Glucose Tolerance Test
HbA1c = Hemoglobin A1c
FPIR = First Phase Insulin Release
HLA = Human Leukocyte Antigen Alleles

5. Ethics

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

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

5.2 Ethical Conduct of the Study

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

5.3 Patient Information and Consent

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

The consent form was reviewed with participants (and their guardian in the case of participants under 18 years of age) and the participant was given time to review the written consent form and ask questions. An assent form was also developed for participants less than 18 years of age (unless local IRB requirements differed in procedure).

The informed consent form was updated or revised whenever important new safety information is available, when indicated for a protocol amendment, and/or whenever any new information became available that affected a participants' participation in the study.

6. Investigators and Study Administrative Structure

This study is part of Type 1 Diabetes TrialNet, which is funded by the National Institutes of Health, principally the National Institute of Diabetes, Digestive and Kidney Diseases. Funding will cover the costs of administration and laboratory tests associated with this study during the participant's period of follow-up. Eli Lilly and Company will provide oral insulin crystals free of charge.

Oral Insulin Trial Protocol Committee
The Oral Insulin Trial Committee, the TrialNet Clinical Monitoring Group, Laboratory Monitoring Group, Steering Committee and Data and Safety Monitoring Board will receive periodic reports from the TrialNet Coordinating Center on the progress of the study. These will include accrual rates and baseline demographic characteristics. Throughout the study, the Oral Insulin Trial Protocol Committee and the Laboratory Monitoring Group will review various indices of the performance of the TrialNet central laboratories including the reproducibility of results, within assay coefficients of variation, autoantibody rates of positivity and confirmation.

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

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

Clinical Sites
Each Principal Investigator at the participating TrialNet clinical site will oversee all operations. The clinical sites will forward all laboratory and data collection form information to the Coordinating Center for analysis. Conference calls and site visits, as needed, will facilitate evaluation of the trial management.

TrialNet Laboratories
TrialNet core laboratories will be utilized to perform tests and assays for this trial. All laboratory results will be forwarded to the TrialNet Coordinating Center for analysis.

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

events (SAEs).

Data and Safety Monitoring Board (DSMB)
The DSMB met approximately 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 Coordinating Center. The DSMB independently evaluated whether there were grounds to discontinue the study.

7. Introduction

In the Diabetes Prevention Trial–Type 1 (DPT-1) oral insulin trial (1,2), oral insulin compared to placebo did not show a reduction in development of diabetes , but a post-hoc analysis identified an at-risk subgroup with higher insulin autoantibody titers that suggested benefit 2. Consequently, the Type 1 Diabetes TrialNet clinical trials network (the successor group to DPT-1) conducted this new study to further explore the role of oral insulin in delaying diabetes in relatives not significantly different than those in the subgroup that had apparent benefit in DPT-1.

The DPT-1 oral insulin trial enrolled relatives who were positive for islet cell antibodies by immunofluorescence and positive for insulin autoantibodies by radioimmunoassay, had first phase insulin release on intravenous glucose tolerance test above threshold, and had a normal oral glucose tolerance test . Since the DPT-1 oral study was conducted, there have been changes in the assay for insulin autoantibodies, resulting in an assay requiring much less blood volume, now commonly referred to as the micro insulin autoantibody or mIAA assay (3).

Thus, TrialNet screened participants for eligibility for this protocol using a strategy of initially testing samples for the presence of micro insulin autoantibodies and antibodies to glutamic acid decarboxylase and insulinoma associated antigen-2, with subsequent testing for islet cell autoantibodies only in antibody positive participants 4. This trial, therefore, differed from the DPT-1 oral study in both the substitution of the micro insulin autoantibody assay for the previous radioimmunoassay for insulin autoantibodies, and in initial testing for micro insulin autoantibodies, glutamic acid decarboxylase autoantibodies, and insulinoma associated antigen-2 autoantibodies, as compared to initial testing for islet cell autoantibodies and subsequent testing for insulin autoantibodies using the radioimmunoassay in islet cell autoantibody positive participants. Additionally, to test whether the outcome would extend to micro insulin autoantibody positive individuals not eligible for enrollment in the previous DPT-1 trial, this study included four separate strata according to additional antibodies and first phase insulin release status.

8. Study Objectives

The primary objective of the TrialNet Oral Insulin Trial was to determine whether intervention with repeated oral administration of recombinant human insulin, the potential autoantigen, prevented or delayed the development of clinical Type 1 Diabetes Mellitus (T1DM) in non-diabetic relatives of patients with T1DM who were positive for insulin autoantibodies but who did not have a metabolic defect (as the Primary Analysis Stratum). This intervention was compared with placebo given in a double-masked fashion.

Secondary objectives included the description of the effects of treatment with oral insulin versus placebo in other categories of subjects defined using different combinations of autoantibodies and metabolic status (the Secondary Analysis Strata) and an assessment of the consistency of treatment effect among strata. Secondary objectives also included the assessment of the effects of treatment on immunologic and metabolic markers, and the association of these markers with the risk of diabetes onset, among other possible risk factors.

The operational objectives were to recruit, screen, randomize, and follow sufficient numbers of subjects to provide adequate statistical power to determine whether T1DM can be delayed through the administration of oral insulin.

9. Investigational Plan

9.1 Overall Study Design and Plan – Description

This was a double-masked, randomized, placebo controlled trial with two arms, experimental and control groups. The primary outcome was development of T1DM. There was both primary and secondary study groups.

Recruitment and initial screening to identify subjects was done through the TrialNet Natural History Study of the Development of Type 1 Diabetes protocol. As part of this protocol, subjects will then undergo additional testing, and if eligible and willing, were randomized and followed as described.

Eligible subjects were non-diabetic relatives of patients with T1DM, who had normal glucose tolerance on an OGTT, who were confirmed to be mIAA positive on two samples (collections), and who also met the criteria for the following primary and secondary study strata based on other autoantibodies and metabolic characteristics:

Primary Analysis Stratum:
Either ICA (>= 10 JDF units) positive confirmed on two samples, or, if not confirmed for ICA, both GAD65ab and ICA512 positive on the same sample with confirmation of at least one of these autoantibodies on a separate sample.

Subjects must also have first phase insulin release (FPIR) above the threshold determined from the sum of the 1 and 3 minute insulin values from an intravenous glucose tolerance test (IVGTT). For participants age 3-7 or parents of T1DM proband the threshold is ≥ 60 μU/ml. For siblings or offspring age 8-45 or other relatives age 8-20, the threshold is ≥ 100 μU/ml.

The primary objective of the study was to assess the effects of treatment within this stratum.

Secondary objectives entail the assessment of treatment effects within additional strata:

Secondary Stratum 1:
Either ICA (>= 10 JDF units) positive confirmed on two samples, or, if not

confirmed for ICA, both GAD65ab and ICA512 positive on the same sample with confirmation of at least one of these autoantibodies on a separate sample.

Subjects must also have first phase insulin release *below* the FPIR thresholds defined in the Primary Stratum above.

Secondary Stratum 2:
ICA, or GAD65ab or ICA512 positive. Confirmation of either GAD65 or ICA512 on a separate sample (those confirmed for ICA are in primary stratum).

Subjects must also have first phase insulin release *above* the FPIR thresholds defined in the Primary Stratum above.

Secondary Stratum 3:
ICA, or GAD65ab or ICA512 positive. Confirmation of either GAD65 or ICA512 on a separate sample (those confirmed for ICA are in secondary stratum 1).

Subjects must also have first phase insulin release *below* the FPIR thresholds defined in the Primary Stratum above.

After participants signed the consent form, completed the screening visit(s), met all of the inclusion criteria and none of the exclusion criteria, and completed the baseline procedures participants was randomized to receive either oral insulin (7.5 mg of recombinant human insulin crystals) or placebo daily.

All subjects took one capsule of study medication daily for the duration of the study. Study medication was dispensed at each 6-month visit. Subjects remained on the same dose of insulin/placebo throughout the trial.

All participants randomized into this study were seen at a study site for a follow-up evaluation 3 and 6 months after randomization, and every 6 months thereafter. Participants were contacted by phone between 6-monthly clinic visits to assess changes in diabetes status, medication compliance and adverse events. These phone contacts occurred approximately 3 months from the date of the participants previous clinic visit.

Interim analyses was conducted periodically during the study and will be reviewed by the TrialNet Data and Safety Monitoring Board (DSMB) for assessment of effectiveness and safety.

The DSMB was given the ability to terminate the trial prematurely if a statistically significant effect was observed and it was considered that all major trial objectives have been met. The DSMB was also able to 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.

9.2 Discussion of Study Design, including Choice of Control Groups

This study was designed to further explore a suggested benefit seen in the DPT-1 oral insulin trial. The study design and control group were selected to replicate the previous study.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

1. Have a proband with T1DM.
2. If the proband is a sibling, parent or a child, the study participant must be 3 - 45 years of age. If the proband is a second or third degree relative (i.e. Niece, Nephew, Aunt, Uncle, Grandparent, Cousin), the study participant must be 3-20 years of age.
3. Willing to sign Informed Consent Form.
4. Has normal glucose tolerance on an OGTT performed within 7 weeks prior to randomization. If previous abnormal glucose tolerance, has had two consecutive OGTT with normal glucose tolerance.
5. mIAA confirmed positive within the previous six months.
6. At least one other antibody present on two separate samples, one of which was drawn within the past six months.

9.3.2 Exclusion Criteria

1. Does not satisfy the above inclusion criteria.
2. Has severe active disease, e.g. chronic active hepatitis, severe cardiac, pulmonary, renal, hepatic, immune deficiency and/or disease that is likely to limit life expectancy or lead to therapies such as immunosuppression during the time of the study.
3. Prior participation in a clinical trial for secondary prevention of T1DM.
4. History of treatment with insulin or oral hypoglycemic agent.
5. History of therapy with immunosuppressive drugs or non-physiologic glucocorticoids within the past two years for a period of more than three months.
6. Ongoing use of medications known to influence glucose tolerance, i.e. sulfonylureas, growth hormone, metformin, anticonvulsants, thiazide or potassium depleting diuretics, beta adrenergic blockers, niacin. Subjects on such medications should be changed to a suitable alternative, if available, and will become eligible one month after medication is discontinued.
7. Pregnant or intends to become pregnant while on study or lactating.
8. Deemed unlikely or unable to comply with the protocol.
9. OGTT that reveals abnormal glucose tolerance unless two subsequent consecutive OGTT have normal glucose tolerance. Abnormal glucose tolerance is defined as:
10. fasting plasma glucose ≥ 110 mg/dL (6.1 mmol/l), AND/OR
11. 2 hour plasma glucose ≥ 140 mg/dL (7.8 mmol/l) AND/OR
12. 30, 60, or 90 minute plasma glucose ≥200 mg/dL (11.1 mmol/l)
13. Subject has HLA DQA1*0102, DQB1*0602 haplotype.

9.3.3 Removal of Patients from Therapy or Assessment

Subjects may have been discontinued from treatment due to adverse effects of treatment that in the judgment of the investigator were related to the study medication. Subjects were also discontinued from treatment who revoke consent to be treated.

Subjects were not discontinued from treatment due to non-compliance or the apparent lack of preliminary beneficial effect, so-called treatment failure.

9.4 Treatments

9.4.1 Treatments Administered

All subjects took one capsule of study medication (7.5 mg of recombinant insulin or placebo) daily by mouth for the duration of the study. Study medication was dispensed at each 6-month visit. Subjects remained on the same dose of insulin/placebo throughout the trial.

9.4.2 Identity of Investigational Product

Participants were assigned to receive capsules of either oral insulin, 7.5 mg of recombinant human insulin crystals (Eli Lilly, Indianapolis, IN), or matched placebo. This was the same dose used in the DPT-1 study. Capsules were prepared with methylcellulose filler at a compounding pharmacy (Eminent Services Corporation, Frederick, Maryland) and masked bottles were shipped to the clinical sites.

9.4.3 Method of Assigning Patients to Treatment Groups

After participants signed the consent form, completed screening visits, met all of the inclusion criteria and none of the exclusion criteria, and completed the baseline procedures, participants were randomized in equal allocations to each treatment group via a computerized random number generator. Randomization was stratified by study site, and block size was a variation of size 2 and 4. Randomization was not stratified by stratum. Treatment assignment was double masked. Outcome assessments were conducted without knowledge of treatment assignment.

9.4.4 Selection of Doses in the Study

Because this study was undertaken to replicate the DPT-1 subgroup finding, the same 7.5 mg daily dose of oral insulin as in DPT-1 was used.

9.4.5 Selection and Timing of Dose for Each Patient

Participants were randomized in equal allocations to each treatment group via a computerized random number generator. Randomization was stratified by study site, and block size was a variation of size 2 and 4. Participants were instructed to take one capsule of study drug by mouth per day, either by swallowing the capsule whole, or by opening the capsule and emptying the contents into juice or soft food, if they could not swallow the capsule whole. The time of day for dosing was not specified. Dosing instructions were provided to participants in the Participant Handbook.

9.4.6 Blinding

The oral insulin and placebo capsules were manufactured to be identical in appearance, taste, and smell. The study drug was packaged in identical bottles with masked labels. The central pharmacy possessed the randomization table, and were equipped to unblind participants to their treatment assignment on a case-by-case basis, following defined unblinding procedures, if needed for adverse events or medical emergencies. Laboratory values were blinded for subjects while the study was ongoing, except in the case of a confirmed diabetes diagnosis or safety concern. The DSMB was not blinded during the review of the interim analysis.

9.4.7 Prior and Concomitant Therapy

History of any treatment with insulin or oral hypoglycemic agent, therapy with immunosuppressive drugs or non-physiologic glucocorticoids within the past two years for a

period of more than three months was considered exclusionary. Ongoing use of medications known to influence glucose tolerance, i.e. sulfonylureas, growth hormone, metformin, anticonvulsants, thiazide or potassium depleting diuretics, beta adrenergic blockers, and niacin was also prohibited during study participation. Subjects on such medications were changed to a suitable alternative, if available, and became eligible one month after medication is discontinued.

9.4.8 Treatment Compliance

Study drug accountability was performed at each follow-up study visit, and study subjects were counseled on treatment compliance, as necessary. Study subjects were provided with weekly pill counters and pill calendars to help facilitate treatment compliance.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed

	TN NH	Oral Trial Initial Visit	Baseline			1YR		2YR		3YR		4YR		5YR		6YR[6] …	
	Monitoring	I	0	3	6	12	18	24	30	36	42	48	54	60	66	72…	END
METABOLIC STUDIES																	
OGTT	X[1]				X	X	X	X	X	X	X	X	X	X	X	X	X
IVGTT		X	(X)[2]														
HbA1C	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
IMMUNOLOGIC STUDIES																	
Islet autoantibodies	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
DNA (Including HLA)	X																
Samples for Mechanistic/future studies[3]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CLINICAL MEASURES																	
Medical History/AE assessment		X[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Family history		X[4]															

Urine pregnancy test if applicable		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam including lifestyle assessments		X[4]				X		X		X		X		X		X	
Limited Physical Exam[5]				X	X		X		X		X		X		X		X
Dispense medication			X		X	X	X	X	X	X	X	X	X	X	X	X	
Assess medication compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1]OGTT must be within 7 weeks of randomization and result must be NGT. If previous abnormal OGTT, subject must have two consecutive OGTT with NGT

[2]Second IVGTT required only if first FPIR is below threshold.

[3]Samples may include serum, plasma, whole blood, and PBMC. Total blood draw volume in adults ≤150 ml at each visit. For children, no more than 5 ml/kg will be drawn at any single visit and no more than 9.5 ml/kg over an 8-week period. Thus, mechanistic samples and/or islet autoantibodies scheduled at initial visit may be omitted due to blood volume limitations.

[4]May be performed either at initial or baseline visit.

[5]Height, weight, BP, abdominal circumference (abdominal circumference not done at 3 month visit).

[6]Participants continue every 6 month visits until development of diabetes or study end (see Section 8.4 of OIT Protocol: Study Power and Maximum Information Design)

Participants were seen every 6 months, and at those visits, an oral glucose tolerance test was performed to assess whether diabetes had developed, the primary study end point. Criteria for diabetes onset were, as defined by the American Diabetes Association (ADA), based on glucose testing, or the presence of unequivocal hyperglycemia with acute metabolic decompensation 6. Specific criteria for diabetes onset is defined by the ADA as the presence of symptoms of diabetes plus casual plasma glucose ≥ 200 mg/dL or fasting plasma glucose ≥ 126 mg/dL or 2 hour plasma glucose ≥ 200 mg/dL. The criteria must have been met on two occasions as soon as possible but no less than one day apart for diabetes to be defined. It was preferred that at least one of the two testing occasions involve an oral glucose tolerance test. Tolerance tests were performed after an overnight fast. Samples were drawn through a temporary indwelling intravenous catheter. For the oral glucose tolerance test, the oral glucose dose was 1.75 g/kg (maximum 75 g).

Adverse events were reported to the TrialNet Coordinating Center in accordance with the TrialNet Adverse Event Monitoring Plan. They were graded as to severity according to common toxicity criteria or study-specific criteria and the investigator made a determination as to the relation to therapy. Events were assessed and reported in accordance with the ICH Guidelines for Good Clinical Practice and per the guidance of the DHHS Office for Human Research Protections (OHRP).

The adverse event case report form was required to be completed for all adverse events greater or equal to Grade 2 of the NCI CTCAE. For reporting serious adverse events (SAE), the TrialNet MedWatch Form was also required to be completed and faxed to the TNCC within 24 hours of when the site was notified of the event. These events reviewed by the TrialNet Medical Monitor, the TrialNet Safety Monitoring Committee, and the DSMB as appropriate. Deaths were required to be reported immediately. Event outcome and other follow-up information regarding the

treatment and resolution of the event was obtained and reported when available, if not known at the time the event is reported.

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

9.5.2 Appropriateness of Measurements

Clinical outcomes were standardized by use of a central laboratory for testing.

A TrialNet Diabetes Onset Adjudication Committee reviewed all relevant information for each subject diagnosed as having developed diabetes who does not meet the defined diabetes onset criteria. The Committee determined whether the diagnosis of diabetes in each such subject is sufficiently sound so as to include that subject among the cases who have reached the primary outcome in the statistical analysis. The Committee reviewed each case masked to treatment assignment.

9.5.3 Primary Efficacy Variable(s)

The primary outcome was the elapsed time from random treatment assignment to the development of diabetes among those enrolled in the primary analysis cohort consisting of subjects with insulin autoimmunity and absence of metabolic abnormalities.

Criteria for diabetes onset were, as defined by the American Diabetes Association (ADA), based on glucose testing, or the presence of unequivocal hyperglycemia with acute metabolic decompensation (diabetic ketoacidosis). One of the following criteria must have been 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.

OR

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

OR

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 75 g anhydrous glucose dissolved in water.

9.5.4 Drug Concentration Measurements

Study drug concentration measurements were not conducted in this study.

9.6 Data Quality Assurance

The case report forms for this study were designed with constraints and logic to facilitate real time validation of data as it was entered. Participating sites were audited annually, and data quality was reviewed at these audits. The TrialNet Coordinating Center reviewed data quality on an ongoing basis via reports, and conducting site trainings, as needed. A data error verification

system was utilized in preparation for the database lock and data analysis, in order to resolve any outstanding errors.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

Analyses of study data was 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 were conducted under the intention-to-treat principle whereby all outcome data in all randomized subjects was included in all analyses as appropriate.

The primary objective of the study was to assess the effect of oral insulin therapy versus placebo on the risk of diabetes onset in the population of subjects in the Primary Analysis Stratum as defined based on the previously defined eligibility criteria.

The cumulative incidence of diabetes onset over time since randomization within each group will be estimated from a modified Kaplan-Meier estimate of the "diabetes-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, one-sided, using the Mantel-logrank test. The estimates of cumulative incidence and the test will adjust for periodic outcome assessment visits to assess diabetes status. A one-sided test is employed since the objective is to confirm a preliminary finding from the prior DPT-1 Oral Insulin Trial. The relative risk of diabetes onset between groups will be estimated from the discrete Cox Proportional Hazards (PH) model. The critical value for the test statistic, and confidence intervals, in this primary analysis will be determined by the group-sequential procedure.

A variety of secondary analyses were planned that included the following:

1 The effects of treatment with oral insulin versus placebo will be described in the Secondary Analysis Strata defined in Section 3.3, each consisting of other categories of subjects defined using different combinations of autoantibodies and metabolic status. This will entail the same analyses as above for the Primary Analysis within each of the three secondary strata. An additional analysis will assess the effect of treatment within the Secondary strata combined using a Cox PH model stratified by the three secondary cohort strata, with separate estimates of the hazard ratio for oral insulin versus placebo within each stratum, and with a likelihood ratio test of the oral insulin treatment effect among all Secondary strata combined. Such analyses will be largely descriptive because the study is not designed to provide adequate power to detect an effect of oral insulin treatment within these secondary cohorts individually or combined.

2 The overall effect of oral insulin versus placebo treatment in the combined strata will be assessed by an analysis as described above using all subjects in a Cox PH model analyses stratified by the four analysis strata (Primary plus three Secondary), with a likelihood ratio test of the oral insulin treatment effect among all strata combined. If the magnitude of the oral insulin treatment effect within the secondary analysis cohorts approaches that in the primary cohort, then the power

of the study to detect an overall effect in all combined cohorts will be increased.

3 The consistency of the oral insulin versus placebo treatment effect will be assessed among strata. This will entail an analysis stratified by each of the four analysis strata (Primary plus three Secondary) and with a test of homogeneity of the treatment effect among strata, i.e. a group by stratum interaction, in a Cox PH Model.

4 Subgroup analyses will be conducted comparing the effects of oral insulin versus placebo on the risk of diabetes within subsets of the study cohort, such as among men versus among women. Such analyses will be conducted separately within the primary analysis stratum alone, and within the combined cohort stratified by analysis strata (Primary and three Secondary), with a test of the group by subgroup factor interaction in a Cox PH Model. Subgroups of the population will be classified by age (children <= 12 years of age, adolescents 13-17 years and adults >= 18 years), gender, race/ethnicity, specific antibody status at baseline, and above versus below threshold FPIR at baseline. Differences in the treatment effect between subgroups will be tested using a covariate by group effect in a Cox PH model (12).

Similar analyses will be conducted using the values of quantitative baseline factors including weight, BMI, and the immunologic and metabolic factors described in Section 2.3 that include the autoantibody titers, basal C-peptide, stimulated C-peptide (peak and AUC mean), measures of insulin resistance modeled from the OGTT, and the FPIR. 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. Such an analysis will also be conducted to assess the effects of age and FPIR as quantitative covariates.

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.

5. Longitudinal analyses will assess the effects of oral insulin versus placebo treatment on immunologic and metabolic markers over time up to the onset of diabetes. Differences between groups in the mean levels of quantitative factors over time will be assessed using a normal errors linear model for repeated measures (13). Differences between groups in the prevalence of qualitative factors over time will be assessed using generalized estimating equations for categorical measures (13). Generalized estimating equations may also be employed for the analysis of quantitative factors when the normal errors assumptions are violated.

Once a subject develops diabetes, that subject will no longer be followed for longitudinal assessment of these factors. Thus, these analyses will describe the differences between groups in factors among those who remain free of diabetes.

6. The association of demographic, genetic, immunologic, metabolic, and lifestyle factors, among others, both at baseline and over time, with the risk of diabetes onset will be assessed in Cox PH Models over time. If the proportional hazards assumption does not apply, an appropriate parametric regression model may be employed. The effects of changes in longitudinal factors on diabetes risk will be assessed using time-dependent covariates for these factors. Analyses will be conducted separately within the oral insulin 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.

9.7.2 Determination of Sample Size

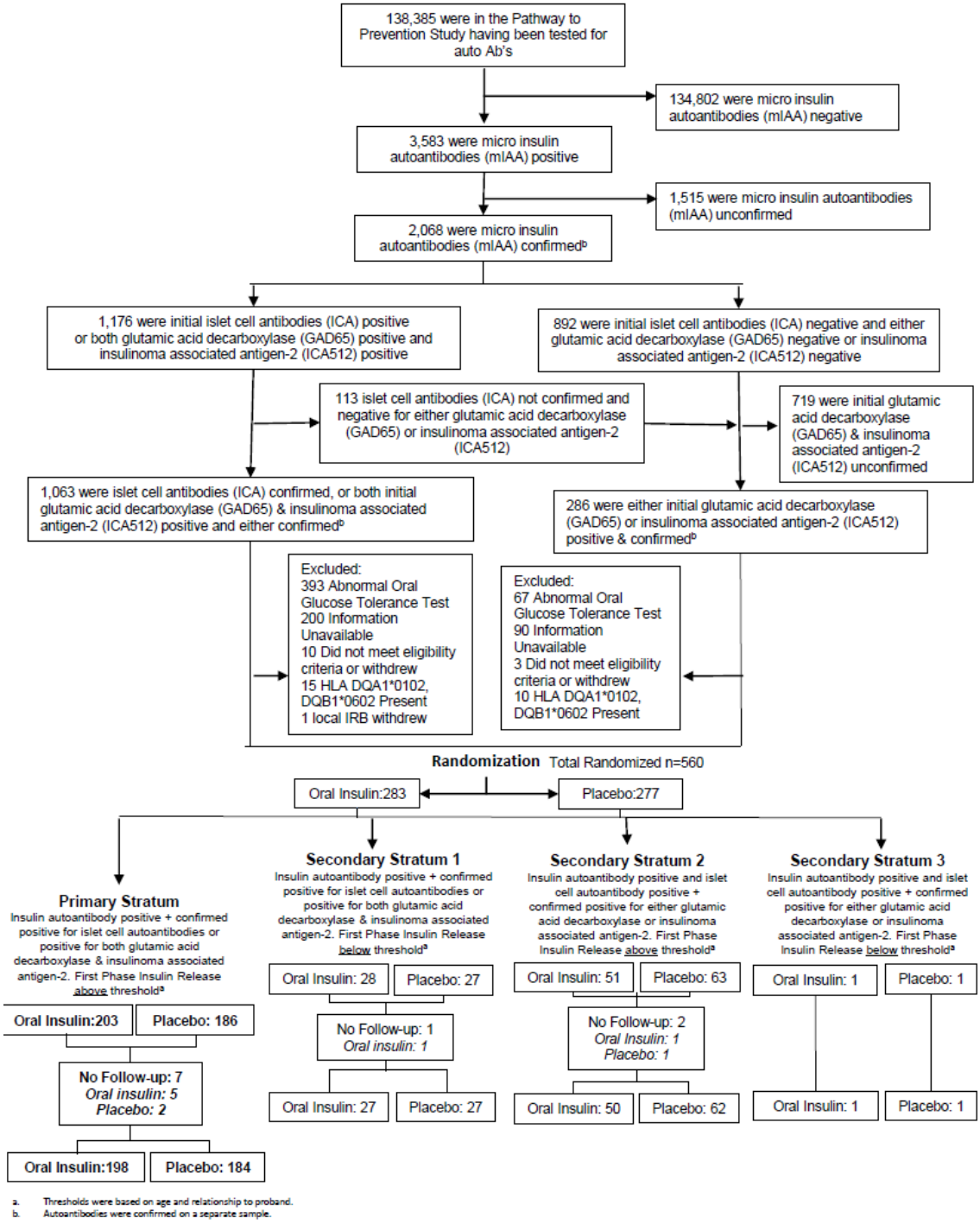
A fixed target sample size was not specified. Rather, the study was designed as a maximum information trial, in which subjects were recruited and followed until the required amount of statistical information was achieved that provided 85% power to detect a 40% risk reduction using a one-sided logrank test at the 0.05 level.

9.8 Changes in the Conduct of the Study or Planned Analyses

There were no changes made in the conduct of the study or in the planned analyses.

10. Study Patients

10.1 Disposition of Patients



10.2 Protocol Deviations

Protocol deviations were recorded throughout the conduct of the study. Overall, there were 2 deviations recorded for an ineligible subject entering the study. There were 728 deviations recorded for the protocol-specified collection or procedures not being followed. There were 599

deviations recorded for study visits either missed, or conducted outside of the allowable study visit window.

11. Efficacy Evaluation

11.1 Data Sets Analyzed

This study was designed and implemented under the intention-to-treat principle in which all subjects randomized were included in all analyses.

11.2 Demographic and Other Baseline Characteristics

	Entire Cohort		**Primary Stratum**		**Secondary Stratum 1**		**Secondary Strata 2 & 3**	
Participant Characteristic and Descriptive Statistic[a] Presented	**Oral Insulin N=283**	**Placebo N=277**	**Oral Insulin N=203**	**Placebo N=186**	**Oral Insulin N=28**	**Placebo N=27**	**Oral Insulin N=52**	**Placebo N=64**
Age – years (Median)	8.2 (5.9 – 12.5)	8.2 (5.4 – 11.5)	8.6 (6.1 - 12.8)	8.2 (5.5 – 11.8)	9.1 (5.9 – 13.7)	8.5 (6.5 – 10.8)	7.3 (5.1 - 10.3)	8.3 (5.1 – 11.5)
Male sex – Number of participants	170 (60.1)	170 (61.4)	128 (63.1)	117 (62.9)	19 (67.9)	19 (70.4)	23 (44.2)	34 (53.1)
Race - Number of participants[b]								
White	252 (95.5)	249 (94.3)	181 (95.3)	172 (94.5)	25 (96.2)	25 (100.0)	46 (95.8)	52 (91.2)
African American	8 (3.0)	9 (3.4)	6 (3.2)	4 (2.2)	0 (0.0)	0 (0.0)	2 (4.2)	5 (8.8)
Asian/Pacific Islander	4 (1.5)	6 (2.3)	3 (1.6)	6 (3.3)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity (Non-Hispanic) - Number of participants	256 (90.5)	252 (91.0)	182 (89.7)	171 (91.9)	26 (92.9)	26 (96.3)	48 (92.3)	55 (85.9)
Body Mass Index[d] (kg/m^2) (Median)	17.1 (15.3 – 19.5)	16.9 (15.5 – 19.2)	17.4 (15.5 – 20.0)	17.1 (15.6 – 19.6)	16.2 (15 – 18.1)	16.9 (15.5 – 17.8)	16.4 (15.0 – 18.4)	16.8 (15.3 – 19.2)
Family member(s) with T1D - Number of participants								
Sibling(s)	153 (54.1)	162 (58.5)	110 (54.2)	111 (59.7)	15 (53.6)	19 (70.4)	28 (53.8)	32 (50.0)
Identical twin	6 (2.1)	3 (1.1)	3 (1.5)	2 (1.1)	2 (7.1)	1 (3.7)	1 (1.9)	0 (0.0)
Offspring	3 (1.1)	7 (2.5)	2 (1.0)	5 (2.7)	0 (0.0)	0 (0.0)	1 (1.9)	2 (3.1)
Parent	71 (25.1)	57 (20.6)	45 (22.2)	40 (21.5)	7 (25.0)	3 (11.1)	19 (36.5)	14 (21.9)
Parent and Sibling	10 (3.5)	13 (4.7)	9 (4.4)	6 (3.2)	1 (3.6)	3 (11.1)	0 (0.0)	4 (6.2)
Offspring and another first degree relative	2 (0.7)	0 (0.0)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Second degree relative	33 (11.7)	30 (10.8)	27 (13.3)	18 (9.7)	3 (10.7)	1 (3.7)	3 (5.8)	11 (17.2)
Third degree or further removed relative	5 (1.8)	5 (1.8)	5 (2.5)	4 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Autoantibodies Positive -Number of participants								

glutamic acid decarboxylase (GAD65)	235 (83.0)	236 (85.2)	171 (84.2)	156 (83.9)	21 (75.0)	23 (85.2)	43 (82.7)	57 (89.1)
insulinoma associated antigen-2 (ICA512)	157 (55.5)	146 (52.7)	131 (64.5)	126 (67.7)	20 (71.4)	18 (66.7)	6 (11.5)	2 (3.1)
Micro Insulin Autoantibodies (mIAA)	253 (89.4)	241 (87.0)	186 (91.6)	163 (87.6)	24 (85.7)	24 (88.9)	43 (82.7)	54 (84.4)
Islet cell autoantibodies (ICA)	198 (70.0)	178 (64.3)	171 (84.2)	152 (81.7)	25 (89.3)	22 (81.5)	2 (3.8)	4 (6.2)
Glycated hemoglobin[c] (HbA1c) - percent (Median)	5.0 (4.8 – 5.2)	5.1 (4.8 – 5.2)	5.0 (4.8 – 5.2)	5.1 (4.8 – 5.2)	5.1 (4.9 - 5.3)	5.2 (5.0 – 5.5)	5.0 (4.9 – 5.2)	5.0 (4.9 – 5.1)
First Phase Insulin Release – micro-units/ml (Median)	145 (102 – 221)	150 (98.4 – 232)	153 (112 – 230)	152 (106 – 236)	50.8 (45.4 – 67.1)	57.8 (44.8 – 71.9)	163 (119 – 243)	174 (132 – 285)
C-peptide Area Under the Curve (AUC) Mean, Oral Glucose Tolerance Test[e] (nmol/L) (Median)	1.35 (1.00 – 1.81)	1.34 (1.03 – 1.82)	1.42 (1.04 – 1.91)	1.34 (1.04 – 1.96)	1.02 (0.93 -1.3)	1.1 (0.76 – 1.52)	1.36 (1.06 – 1.75)	1.43 (1.11 – 1.8)
Human Leukocyte Antigen (HLA) alleles present - number of participants (%)								
DR3[f]	119 (42.2)	102 (37.0)	88 (43.3)	74 (39.8)	9 (32.1)	9 (33.3)	22 (43.1)	19 (30.2)
DR4[f]	199 (70.6)	182 (65.9)	144 (70.9)	135 (72.6)	22 (78.6)	18 (66.7)	33 (64.7)	29 (46.0)

[a] The primary stratum included participants with normal glucose tolerance, above threshold first phase insulin release, and the presence of microinsulin autoantibodies, as well as islet cell autoantibodies on two separate samples or both glutamic acid decarboxylase and insulinoma associated antigen-2 autoantibodies on the same sample. Secondary stratum 1 included participants identical to those in the primary stratum, with the exception of below threshold first phase insulin release. Secondary stratum 2 participants had normal glucose tolerance, above threshold first phase insulin release, and the presence of microinsulin autoantibodies, as well as islet cell autoantibodies on one sample or glutamic acid decarboxylase or insulinoma associated antigen-2 autoantibodies on two separate samples. Secondary stratum 3 included participants who were identical to those in secondary stratum 2, with the exception of below threshold first phase insulin release.

[b] Parenthetical value(s): The interquartile range is displayed with the median, standard deviation is displayed with the mean, and percent is displayed with the number of participants.

[c] Self Reported: Race was not provided for 32 participants

[d] HbA1c missing for 1 participant

[e] body mass index within 2 months prior to study entry not reported for 3 participants

[f] C-peptide from OGTT not available for 1 participant

[g] HLA alleles not available for 2 participants

11.3 Measurements of Treatment Compliance

Treatment compliance was measured overtime via study drug accountability at follow-up study visits. Overall, average treatment compliance primarily fell between 70% - 100% over the course of the study.

11.4 Efficacy Results and Tabulations of Individual Patient Data

11.4.1 Analysis of Efficacy

In the primary stratum, diabetes was diagnosed in 120 participants—58 in the oral insulin group and 62 in the placebo group (Figure 2A). The annualized rate of diabetes was not significantly different between the two groups: 8.8% (95% CI: 6.7%, 11.2%) with oral insulin and 10.2% (95% CI: 7.8%, 12.9%) with placebo (hazard ratio 0.87 (95% CI: 0, 1.2) p=0.21). Treatment site was not a significant factor when tested either as a fixed effect in a mixed effects model or in the Cox Proportional Hazards model.

In secondary stratum 1 with first phase insulin release below threshold (n=55), diabetes was diagnosed in 32 participants—13 in the oral insulin group and 19 in the placebo group (Figure 2B). Annualized rate of diabetes in this stratum was 18.1% (95% CI: 9.6%, 29.1%) with oral insulin and 34.1% (95% CI: 20.6%, 51.1%) with placebo (hazard ratio 0.45 (95% CI: 0, 0.82), p=0.006). Thus, in this stratum median time to diabetes in the oral insulin group was 55.3 months (interquartile range: 19.2 – 67.5), and in the placebo group was 24.3 months (interquartile range: 13.3 – 47.3), a difference of 31.0 months.

In secondary strata 2 and 3 (combined), diabetes was diagnosed in 21 participants—11 in the oral insulin group and 10 in the placebo group. Annualized rate of diabetes in these strata was 5.1% (95% CI: 2.6%, 8.6%) with oral insulin and 4.7% (95% CI: 2.2%, 8.0%) with placebo (hazard ratio 1.03 (95% CI: 0, 2.11), p=0.53)

In the entire cohort, diabetes was diagnosed in 173 participants—82 in the oral insulin group and 91 in the placebo group. The annualized rate of diabetes was 8.7% (95% CI: 6.9%, 10.7%) and 10.4% (95% CI: 8.3%, 12.6%) in the oral and placebo treatment groups, respectively (hazard ratio 0.83 (95% CI: 0, 1.07) p=0.11).

Since the primary stratum in this study was designed to be consistent with the DPT-1 Study subgroup with baseline radioimmunoassay insulin autoantibodies > 80, a post hoc analysis of the hazard ratio of the primary stratum in the current study to the DPT-1 subgroup was conducted (DPT-1 to Oral Insulin: 1.04 (95% CI: 0.71, 1.52)) which was not statistically different at p=0.84, 2-sided. Thus, the entry criteria succeeded in replicating the risk seen in the DPT-1 cohort.

11.4.2 Statistical/Analytical Issues

The cumulative incidence of diabetes onset over time since randomization within each group was estimated from a modified Kaplan-Meier estimate of the "diabetes-free" survival function. The difference between groups in the cumulative incidence functions, and the associated hazard functions, was tested using the Mantel-logrank test on discrete time to T1D (6 month intervals). The relative risk of diabetes onset between groups was estimated from the discrete Cox Proportional Hazards model. The critical value for the test statistic, p=0.047, and confidence intervals, in the primary analysis is adjusted for a single interim analysis based on Lan and DeMets spending function.

The effect of treatment with oral insulin versus placebo was tested using the intention-to-treat principle in the primary and secondary analysis strata, each consisting of participants defined using different combinations of autoantibodies and metabolic status using the same analyses as above for the primary analysis. An additional analysis assessed the effect of treatment within all strata combined using a Cox Proportional Hazards model stratified by strata. Significance was based on a 1-sided threshold of .05 and 1-sided 95% confidence intervals.

The study was designed as a maximum information trial, which did not include a fixed sample size. Instead, participants were recruited and followed until the required amount of statistical information was achieved. At any point in time during the study, the information in the data for a logrank test is provided by I =(DOI•DC)/(DOI+DC), where DOI and DC refer to the number of participants who have developed diabetes in the oral insulin and control groups, respectively. The information required to provide 85% power to detect a 40% risk reduction (identical to the DPT-1 Oral Insulin Trial) with a one-sided logrank test at the 0.05 significance level is I = 27.551.

No attempt was made to impute missing data and no adjustment has been made for multiple comparisons, excepting the interim monitoring and multivariate analyses. Consequently, all but the primary analysis should be considered exploratory.

11.4.2.1 Adjustment for Covariates

Exploratory analyses were planned and developed by the TrialNet protocol committee and finalized before the study results were unblinded, and included analyses that incorporate factors such as duration of oral insulin use, age of enrollment, specific autoantibody pairs, year of enrollment, site of enrollment, sex, time to dysglycemia as a time dependent covariate, baseline insulin autoantibody titer, time to dysglycemia, changes in autoantibody levels or positivity, HbA1c as an outcome, c-peptide at diagnosis, the presence of symptoms at the time of diagnosis, consistency of hazard rates, and the effect of adherence to oral insulin on results.

11.4.2.2 Handling of Dropouts or Missing Data

All but 7 participants contributed to the analysis in the primary stratum. No attempt was made to impute missing data and no adjustment was made for multiple comparisons, excepting the interim monitoring and multivariate analyses.

11.4.2.3 Interim Analyses and Data Monitoring

An interim analysis of the primary study endpoint was conducted and reviewed by the DSMB to examine safety and futility. The DSMB was not blinded during the review of the interim analysis;

however, the review was conducted during a closed session with only DSMB members privy to the data and analysis.

11.4.2.4 Multicentre Studies

Treatment site was not a significant factor when tested either as a fixed effect in a mixed effects model or in the Cox Proportional Hazards model.

11.4.2.5 Multiple Comparisons

No attempt was made to impute missing data and no adjustment has been made for multiple comparisons, excepting the interim monitoring and multivariate analyses. Consequently, all but the primary analysis should be considered exploratory. Except for the post hoc hazard rate comparison with the DPT-1 study, all analyses were prespecified.

11.4.2.6 Use of an 'Efficacy Subset' of Patients

This study was designed and implemented under the intention-to-treat principle in which all subjects randomized were included in all analyses.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

11.4.2.8 Examination of Subgroups

In a prespecified, secondary analysis, a significant protective effect was found in the stratum consisting of 55 individuals in whom the first phase insulin response was below the threshold needed for entry into the primary stratum. The placebo group in this stratum had a 3-fold higher rate of progression to T1D than the placebo primary stratum, attesting to the added diabetes risk in those with diminished first phase insulin release. However, because there was no adjustment for multiple comparisons, this analysis must be considered exploratory and hypothesis generating.

11.4.3 Tabulation of Individual Response Data

The individual response data is available in appendix 16.2.6.

11.4.4 Drug dose, drug concentration, and relationships to response

All participants in this trial received 7.5mg of oral insulin or placebo by mouth daily.

11.4.5 Drug-drug and drug-disease interactions

There was no found relationship between response and concomitant therapy or between response and past and/or concurrent illness.

11.4.6 By-patient displays

Not applicable.

11.4.7 Efficacy Conclusions

Among 560 randomized participants (median age at enrollment was 8.2 years, inter-quartile range (IQR): 5.7 – 12.1; 170 (60%) were male; 90.7% were white/non-Hispanic; 57.6% with a sibling diagnosed with type 1 diabetes), 550 completed the trial. In the main study group of 389 participants (median age, 8.4; 245 (63%) male), 382 (96%) completed the trial. During a median follow-up of 2.7 years (Inter-quartile range (IQR): 1.5-4.6) in the main study group, diabetes was diagnosed in 58 (28.5%) participants in the oral insulin group and 62 (33%) in the placebo group. Time to diabetes was not significantly different between the two groups: hazard ratio (HR) =0.87

(95% CI 0, 1.2) p=0.21. In secondary stratum 1 (n=55), diabetes was diagnosed in 13 (48.1%) participants in the oral insulin group and 19 (70.3%) in the placebo group, and time to diabetes was significantly longer with oral insulin: HR=0.45 (95% CI 0, 0.82), p=0.006. In the other secondary stratum (n=116), and the entire cohort (n=560), the between group time to diabetes was not significantly different: HR=1.03 (95% CI 0, 2.11), p=0.53 and HR= 0.83 (95% CI: 0, 1.07), p=0.11, respectively.

12. Safety Evaluation

12.1 Extent of Exposure

Duration: Study participants were followed for a median of 2.7 years for the entire cohort.

Dose: All study participants received 7.5mg of oral insulin or placebo by mouth once daily.

12.2 Adverse Events (AEs)

There were no serious adverse events. There were no reported episodes of severe hypoglycemia. The most common adverse event was categorized as infection, with 134 and 120 events reported in this category in the oral insulin and placebo arms, respectively, over the duration of the study. Details of adverse events are provided below.

Severity (Grade)	Treatment Group	
	Oral Insulin No. of participants (%)	Placebo No. of participants (%)
0/1	133 (47.0)	144 (52.0)
2	114 (40.3)	104 (37.5)
3	35 (12.4)	29 (10.5)
4	1 (0.4)	0 (0)
5	0 (0.0)	0 (0.0)
Total	283 (100.0)	277 (100.0)

Adverse Effect Category	Oral Insulin		Placebo	
	No. of events	No. of participants N= 283 (%)	No. of events	No. of participants N = 278 (%)
Ocular/Visual	4	4 (1.4)	4	4 (1.4)
Infection	134	67 (23.7)	120	62 (22.4)
Pulmonary/Upper Respiratory	51	30 (10.6)	37	30 (10.8)
Endocrine	18	18 (6.4)	12	12 (4.3)
Musculoskeletal/Soft Tissue	45	38 (13.4)	20	18 (6.5)
Allergy/Immunology	18	17 (6.0)	11	11 (4.0)

Dermatology/Skin	29	25 (8.8)	20	18 (6.5)
Cardiac Arrhythmia	2	2 (0.7)	1	1 (0.4)
Gastrointestinal	30	28 (9.9)	34	25 (9.0)
Constitutional Symptoms	13	10 (3.5)	18	12 (4.3)
Surgery/Intra-Operative Injury	7	7 (2.5)	3	3 (1.1)
Neurology	15	13 (4.6)	17	12 (4.3)
Auditory/Ear	14	12 (4.2)	15	11 (4.0)
Hemorrhage/Bleeding	2	2 (0.7)	1	1 (0.4)
Metabolic/Laboratory	0	0 (0.0)	4	4 (1.4)
Pain	14	11 (3.9)	11	11 (4)
Syndromes	4	4 (1.4)	2	2 (0.7)
Renal/Genitourinary	1	1 (0.4)	5	3 (1.1)
Blood/Bone Marrow	1	1 (0.4)	2	2 (0.7)
Hepatobiliary/Pancreas	3	2 (0.7)	0	0 (0.0)
Sexual/Reproductive Function	1	1 (0.4)	2	2 (0.7)
Cardiac General	0	0 (0.0)	0	0 (0.0)
Lymphatics	1	1 (0.4)	1	1 (0.4)
Total Events	407	---	340	---

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no serious adverse events or deaths during this study.

12.4 Clinical Laboratory Evaluation

A marketing application for oral insulin is not being made. Clinical laboratory data will be made available upon request.

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

There were no adverse events related to study drug, and therefore no findings related to vital signs, physical findings or other observations related to safety. Oral insulin, and placebo, were found to be safe and well tolerated in study participants.

12.6 Safety Conclusions

There were no significant study-related adverse events in this study.

13. Discussion and Overall Conclusions

Oral insulin was safe and well tolerated in all strata. In the Primary Stratum, and in Secondary Strata 2 and 3, oral insulin did not prevent or delay the onset of type 1 diabetes. In Secondary Stratum 1, oral insulin delayed the onset of type 1 diabetes by an average of 31 months. These findings further support the understanding that not everyone develops type 1 diabetes in the same way.

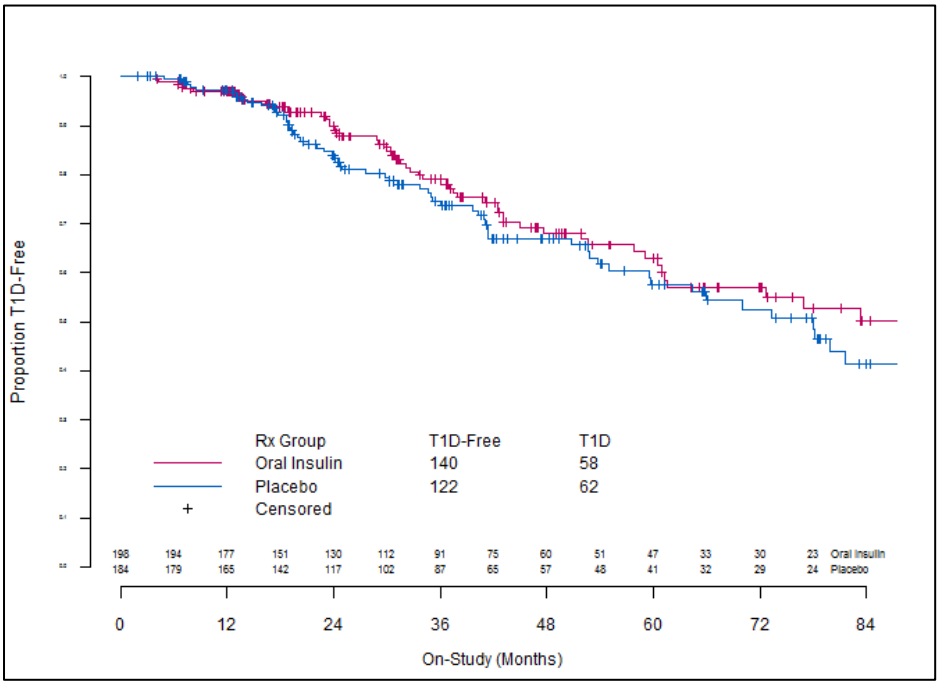
14. Tables, Figures, and Graphs Referred To But Not Included in the Text

14.1 Demographic Data

Please see section 11.2.

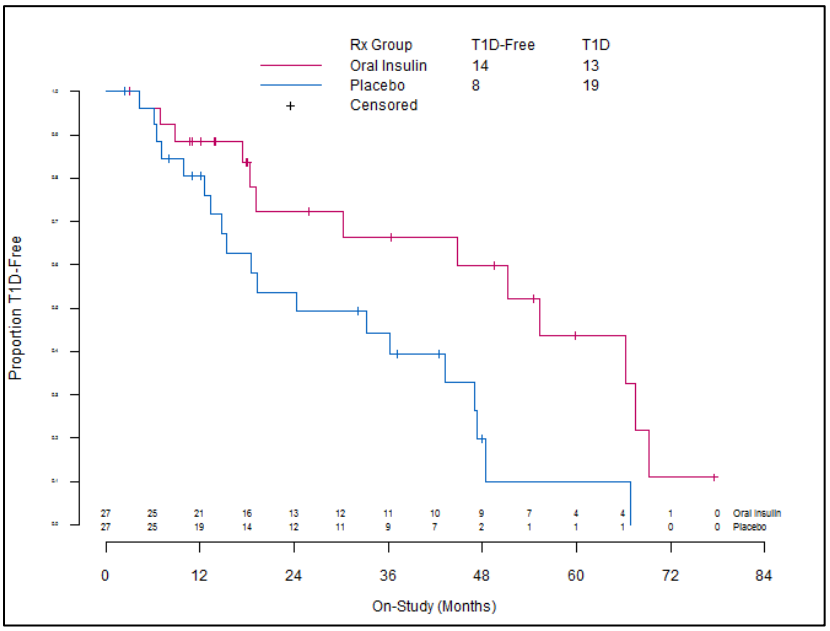
14.2 Efficacy Data

A – Primary Stratum



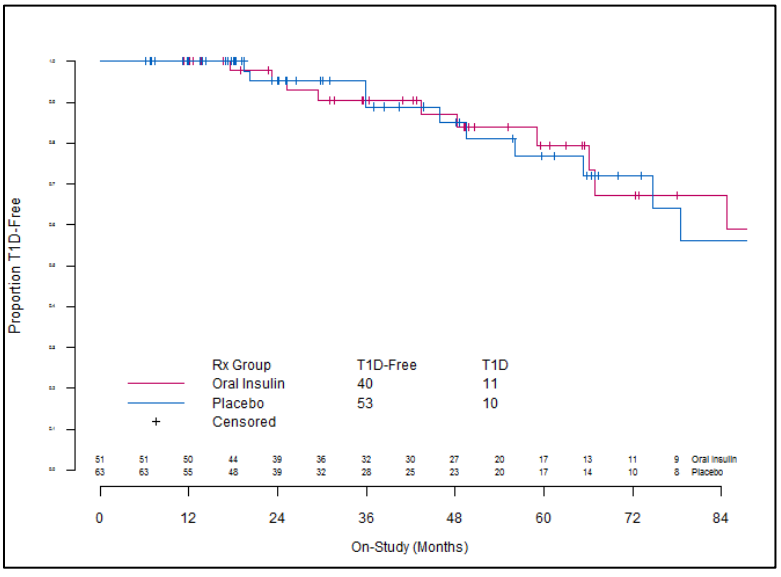
The quartiles of time to diabetes were 18.4, 31.9, and 55.1 months for oral insulin and 18.9, 32.7, and 54.4 months for placebo. Of those in the oral insulin group, 140 participants did not develop type 1 diabetes and 58 did. Of those in the placebo group, 122 participants did not develop type 1 diabetes and 62 did. The median months of follow-up was 32.0 (1.87-114).

B. Secondary Stratum 1



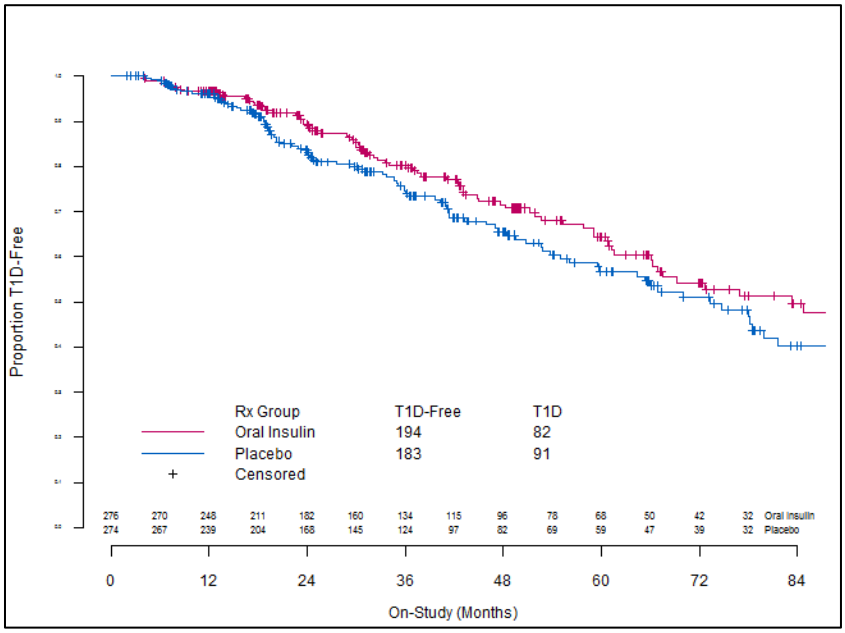
The quartiles of time to diabetes were 12.9, 19.2, and 52.8 months for oral insulin and 10.5, 18.5, and 39.8 months for placebo. Of those in the oral insulin group, 14 did not develop type 1 diabetes and 13 did. Of those in the placebo group, 8 did not develop type 1 diabetes and 19 did. The median months of follow-up was 18.9 (2.33-77.5).

C. Secondary Strata 2 and 3



The quartiles of time to diabetes were 25.3, 49.2, and 65.8 months for oral insulin and 18.1, 30.2, and 63.3 months for placebo. Of those in the oral insulin group, 40 participants did not develop type 1 diabetes and 11 did. Of those in the placebo group, 53 participants did not develop type 1 diabetes and 10 did. The median months of follow-up was 39.4 (6.21-115).

D. All Participants



The quartiles of time to diabetes were 18.4, 34.9, and 59.7 months for oral insulin and 17.8, 31.2, and 54.0 months for placebo. Of those in the oral insulin group, 194 participants did not develop type 1 diabetes and 82 did. Of those in the placebo group, 183 participants did not develop type 1 diabetes and 91 did. The median months of follow-up was 32.4 (1.87-115).

14.3 Safety Data

14.3.1 Displays of Adverse Events

Please see section 12.2

14.3.2 Listings of deaths, other serious and significant adverse events

Not Applicable. There were no deaths or serious adverse events during this study.

14.3.3 Narratives of deaths, other serious and significant adverse events

Not Applicable. There were no deaths or serious adverse events during this study.

15. References

1. Diabetes Prevention Trial - Type 1 Diabetes Study Group. Effects of Insulin in Relatives of Patients with Type 1 Diabetes Mellitus. *New England Journal of Medicine.* 2002;346(22):1685-1691.
2. Skyler JS, Krischer JP, Wolfsdorf J, et al. Effects of Oral Insulin in Relatives of Patients With Type 1 Diabetes. The Diabetes Prevention Trial–Type 1. *Diabetes Care.* 2005;28(5):1068-1076.
3. Williams AJK, Bingley PJ, Bonifacio E, Palmer JP, Gale EAM. A Novel Micro-assay for Insulin Autoantibodies. *Journal of Autoimmunity.* 1997;10(5):473-478.

16. Appendices

The following appendices are included with this report. Other appendices will be made available upon request.

16.1.1 Protocol and protocol amendments

16.1.2 Sample Case Report Form(s)

16.1.7 Randomization Scheme and Codes

16.1.11 Publications Based on the Study

16.2.6 Individual Response Data

16.2.7 Adverse Event listings (each patient)

Appendix 16.1.1 Protocol and Protocol Amendments

ORAL INSULIN FOR PREVENTION OF DIABETES IN RELATIVES AT RISK FOR TYPE 1 DIABETES MELLITUS

(Protocol TN-07)

VERSION: November 1, 2012

IND #: 76,419

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

PREFACE

The Type 1 Diabetes TrialNet Protocol TN-07, *Oral Insulin For Prevention Of 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 at the University of South Florida 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.

Table of Contents

1 STUDY OVERVIEW

This protocol describes the background, design, and organization of the Type 1 Diabetes TrialNet Protocol TN-07 entitled "*Oral Insulin For Prevention Of Diabetes In Relatives At Risk For Type 1 Diabetes Mellitus*." The protocol was written by Dr. Desmond Schatz, Chair of the TrialNet Oral Insulin Protocol Committee, the TrialNet Chairman's Office at Benaroya Research Institute and University of Miami, and the TrialNet Coordinating Center. 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 the equivalent at international sites.

The following table presents a summary of the study design:

Title	*Oral Insulin For Prevention Of Diabetes In Relatives At Risk For Type 1 Diabetes Mellitus*
IND Sponsor	TrialNet
Conducted By	TrialNet
Protocol Chair	Desmond Schatz, M.D.; University of Florida, Gainesville FL.
Subjects	A fixed target sample size has not been specified. Rather, the study is designed as a maximum information trial in which subjects are recruited and followed until the required amount of statistical information is achieved that provides 85% power to detect a 40% risk reduction using a one-sided logrank test at the 0.05 level.
Study Design	The study is a 2-arm, multicenter, randomized, double-masked, placebo-controlled clinical trial.
Treatment Description	Subjects will receive oral insulin 7.5 mg of recombinant human insulin crystals or placebo in capsules.
Objective	The primary objective is to determine whether intervention with repeated oral administration of recombinant human insulin will prevent or delay the development of clinical Type 1 Diabetes Mellitus (T1DM) in subjects at risk for T1DM.
Primary Outcome	The primary outcome is the elapsed time from random treatment assignment to the development of diabetes among those enrolled in the primary analysis cohort consisting of subjects with insulin autoimmunity and absence of metabolic abnormalities. Criteria for diabetes onset are as defined by the American Diabetes Association (ADA) based on glucose testing, or the presence of symptoms and unequivocal hyperglycemia.
Major Inclusion Criteria	(1) Relatives of T1DM proband with mIAA and at least one other islet autoantibody present (2) Normal OGTT performed within 7 weeks prior to randomization. The primary analysis stratum and secondary analysis strata are defined based on combinations of other autoantibodies present, and presence or absence of first phase insulin response on IVGTT.

2 BACKGROUND AND SIGNIFICANCE

2.1 Rationale for Study

2.1.1 Type 1 diabetes (T1DM)

Type 1 diabetes mellitus is an immune-mediated disease in which insulin-producing beta cells are 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). Unfortunately, the increase in type 1 diabetes is the greatest in children under age five years (2).

Current management of T1DM is not optimal. To avoid long-term complications, patients must maintain near normal glycemic control by frequent glucose monitoring throughout the day, by multiple daily insulin injections or use of an insulin pump, and by adjusting insulin doses for variation in diet and exercise. Such strict glycemic control can rarely be achieved with current management and overly aggressive therapy results in severe hypoglycemia which can be life threatening. It is not possible to fully mimic the function of the beta cell, and there are no established treatments that can prevent its destruction. Thus, despite advances in diabetes care and treatment, individuals with diabetes remain at risk for early mortality and a high rate of morbidity due to complications such as retinopathy leading to blindness, neuropathy and vascular disease leading to amputations and heart disease, and nephropathy leading to renal failure. The costs of caring for diabetes and its complications are currently greater than $100 billion a year (3).

Much is known about the natural history of the type 1 diabetes disease process. Beta cell destruction generally begins years before clinical onset as identified by the presence of circulating autoantibodies for disease relevant antigens. Though impairment in beta cell function is detected prior to clinical diagnosis, at the time of diagnosis, patients with Type 1 diabetes retain a significant amount of beta cell function as measured by C-peptide responses to a mixed meal tolerance test (MMTT) (4;5). Affected individuals often enter a honeymoon or remission phase where this insulin secretion is also seen. However, beta cell function deteriorates after diagnosis, eventually becoming undetectable and necessitating increasing reliance on exogenous insulin replacement.

2.1.2 Oral Insulin for prevention of T1DM

In the non-obese diabetic (NOD) mouse model of Type 1 Diabetes Mellitus (T1DM), it has been demonstrated that the oral administration of islet autoantigens is effective in delaying the onset of T1DM (6-10). Repeated ingestion of insulin by young, prediabetic NOD mice has been shown to inhibit their development of diabetes. It also has been shown that ingestion of glutamic acid decarboxylase (GAD), another putative β-cell antigen, by prediabetic NOD mice inhibits the development of diabetes. The results suggest that tolerance provoked by oral insulin or GAD administration can attenuate pancreatic islet autoimmunity, leading to a delay in the onset of the disease.

The hypothesis that oral insulin could delay the clinical onset of T1DM in humans was tested in the oral arm of the Diabetes Prevention Trial – type 1 diabetes (DPT-1) in which antibody positive relatives were randomized in a double-masked placebo-controlled trial (11). In the primary analysis of relatives selected and randomized in this trial on the basis of islet cell antibody (ICA) positivity with

insulin autoantibodies (IAA) ≥40 nU/ml, oral insulin did not delay or prevent development of diabetes. There was however evidence of heterogeneity of effect within the study cohort according to level of IAA. The subgroup with confirmed IAA ≥80 nU/ml not only progressed to diabetes at a faster rate than those subjects who did not have confirmed IAA ≥80 nU/ml, but also showed a potential beneficial effect of oral insulin (p=0.015). This effect was observed both in the group of subjects with IAA≥80 nU/ml as a whole, and in those recruited before a protocol change in 1997 that lowered the IAA threshold for eligibility. The presence of IAA ≥80 nU/ml was also found to be associated with other risk characteristics that suggest more rapid evolution to diabetes, including younger age, greater likelihood of presence of other autoantibodies, and greater loss of beta cell function (as suggested by lower levels of C-peptide in response to several provocative challenges).

The *post hoc* analysis suggesting a potential beneficial effect in the subgroup with baseline confirmed IAA >80 nU/ml can be deemed only to be hypothesis generating and not as a positive confirmatory analysis. The successor group to DPT-1, the Type 1 Diabetes TrialNet clinical trials network, has therefore designed this study to explore the potential role of oral insulin in delaying or preventing Type 1 diabetes in the subgroup of IAA positive relatives in whom the apparent benefit was observed in DPT-1.

During the intervening years since the DPT-1 oral study was conducted there have been changes in methods used to assay for IAA. Improvements in technique have resulted in an assay that requires much less blood volume, now commonly referred to as the micro or mIAA assay. As well, the field has progressed to screening for other diabetes-associated autoantibodies with much less reliance on ICA. Thus, the TrialNet Natural History Study for the Development of Type 1 Diabetes, which will screen subjects for eligibility for this protocol, uses a strategy of initially testing samples for the presence of GAD65ab, ICA512 and mIAA with subsequent testing for ICA only in antibody positive subjects. This trial therefore, is different from the DPT-1 oral study in both the substitution of mIAA for the previous IAA assay (pegIAA) and in initial testing for GAD65ab, ICA512 and mIAA (with testing for ICA in antibody positive subjects) as compared to initial testing for ICA and subsequent testing for peg IAA in ICA positive subjects. However, the metabolic criteria for insulin secretion and glucose tolerance will be the same in this TrialNet study as those that were used in DPT-1. All subjects will have normal glucose tolerance determined by oral glucose tolerance testing. The primary analysis will also be restricted to subjects with a first phase insulin response (FPIR) to intravenous glucose infusion above a specified threshold. Other secondary strata will be defined based on other combinations of autoantibodies present and/or FPIR below threshold.

To partially examine the effects of these changes, 329 of 372 ICA positive samples from the DPT-1 oral study were re-analyzed using current assays, specifically, GAD65ab, ICA512, and mIAA. Importantly, among those with high titer pegIAA (>80 nU/ml), 66% (168/253) were positive for mIAA; while among those with lower titer pegIAA as identified by the original DPT-1 study 89% (68/76) were mIAA negative in the current assay.

Consistent with the DPT-1 results, the effect of oral insulin is seen among those with normal glucose tolerance who were positive for mIAA and ICA whether or not other antibodies (ICA512, GAD65ab) were present. [Figure 1]

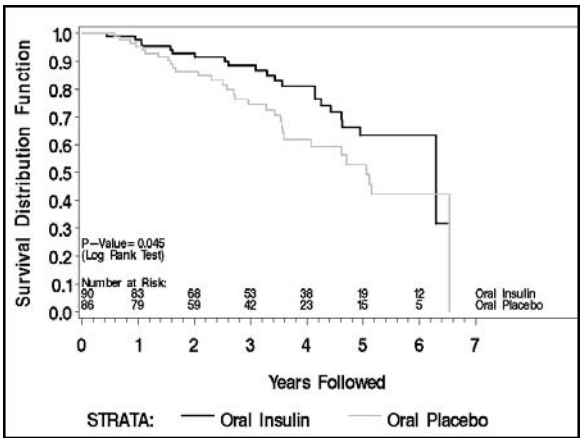


Figure 1: Effect of oral insulin on mIAA and ICA positive subjects enrolled in DPT-1Trial.

Further analysis of data from the DPT-1 Oral Study suggests that subjects with mIAA, and additionally either ICA512, or GAD65ab, also demonstrate an advantage from oral insulin treatment. [Figure 2]

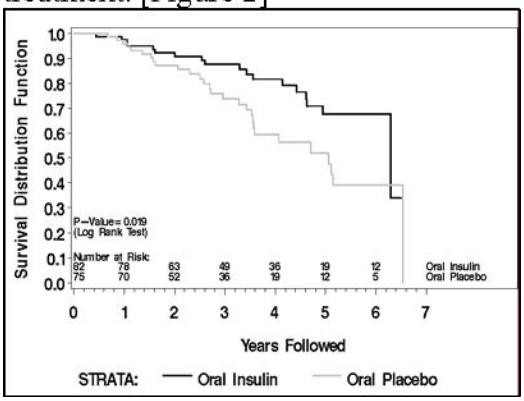


Figure 2: Effect of oral insulin on mIAA and ICA positive subjects who additionally have either ICA512 or GAD65ab enrolled in DPT-1 Trial.

Using the DPT-1 dataset, there are insufficient numbers of subjects who are ICA negative but GAD65ab and ICA512 positive to determine whether they have the same risk of progression as those ICA positive; however, emerging data from other studies suggest that this is likely true.

Therefore, the primary objective will be tested within the **Primary Analysis Stratum** consisting of those with normal glucose tolerance, above threshold FPIR, and mIAA. In addition, subjects must either have ICA, or have both GAD65ab and ICA512in the absence of ICA.

2.2 Rationale for Additional Cohorts

A secondary question is whether a beneficial effect observed in the Primary Analysis Stratum extends to other populations at different risk of diabetes. As described above, post-hoc analysis of the DPT-1 cohort indicated that the effect of oral insulin was most pronounced in those with higher pegIAA titers, now corresponding to a positive mIAA titer. This observation has led to the hypothesis that tolerance with oral insulin would be more likely in those individuals with insulin directed immune activity as indicated by the presence of mIAA. Thus, oral insulin therapy may be of benefit in

individuals with mIAA but with different combinations of ICA positivity, other autoantibody positivity and metabolic features than those in the primary cohort.
These additional secondary strata are:

Secondary 1:
mIAA confirmed, ICA confirmed with loss of FPIR

OR mIAA confirmed, ICA not confirmed, ICA512+ AND GAD65ab+ with loss of FPIR

Secondary 2:
mIAA confirmed, ICA not confirmed, ICA512+ OR GAD65ab+ with preserved FPIR

Secondary 3:
mIAA confirmed, ICA not confirmed, ICA512+ OR GAD65ab+ with loss of FPIR

The OGTT and genetic eligibility criteria would be the same as in the primary study cohort.

The study design provides adequate power to assess the main objective within the primary stratum but does not provide power to assess this objective within the secondary strata individually or in combination. Thus, the study will provide a preliminary assessment of the effects of oral insulin therapy in subjects with different risk characteristics, and will be used to provide a preliminary assessment as to whether treatment effectiveness is similar among these different categories of subjects.

2.3 Rationale for additional outcome measures

Immune function
The underlying hypothesis of this trial is the concept of induction of immunologic tolerance to the insulin secreting beta cell through the presentation of the autoantigen (insulin) orally. Animal studies have suggested that tolerance is accompanied by characteristic changes in immune phenotypes; however, whether these changes are associated with tolerance induction in humans is unknown. A goal of this study therefore, will be to study immune function through studies of B and T cell phenotype and function including antigen specific responses. The various autoantibodies to insulin or its byproducts will also be measured longitudinally.

Genetics
While there are strong associations with particular HLA genotypes and type 1 diabetes, other genes are also thought to contribute to the disease process. These include those associated with autoimmunity per se such as PTPN22 and those associated with diabetes such as insVNTR. It is unknown whether the response to oral insulin will relate to genotype, but typing will be performed on genes related to type 1 diabetes.

Insulin secretion and insulin resistance

Type 1 diabetes is primarily thought of as a disease of islet cell destruction leading to the declining ability to secrete endogenous insulin in sufficient amounts to maintain metabolic homeostasis. While insulin secretion cannot be measured directly due to its rapid metabolism, a by-product of insulin secretion, C-peptide, can be measured in response to a meal. This measurement may be obtained in an Oral glucose tolerance test (OGTT) conducted periodically during follow-up.

Glucose homeostasis also depends on the degree of insulin resistance, or the degree of resistance of the peripheral tissues to insulin action. Recent data suggests that modeling of data obtained during the OGTT can provide a reliable estimate of the degree of insulin resistance.

These data may be correlated with fasting insulin levels as well as body weight and abdominal circumference since these are often associated with insulin resistance.

3 STUDY DESIGN

3.1 Overview

This is a double-masked, randomized, placebo controlled trial with two arms, experimental and control groups. The primary outcome is development of T1DM. There will be both primary and secondary study groups.

3.2 Objectives

The primary objective of the TrialNet Oral Insulin Trial is to determine whether intervention with repeated oral administration of recombinant human insulin, the potential autoantigen, will prevent or delay the development of clinical Type 1 Diabetes Mellitus (T1DM) in non-diabetic relatives of patients with T1DM who are positive for insulin autoantibodies but who do not have a metabolic defect (as the Primary Analysis Stratum). This intervention will be compared with placebo given in a double-masked fashion.

Secondary objectives include the description of the effects of treatment with oral insulin versus placebo in other categories of subjects defined using different combinations of autoantibodies and metabolic status (the Secondary Analysis Strata) and an assessment of the consistency of treatment effect among strata. Secondary objectives also include the assessment of the effects of treatment on immunologic and metabolic markers, and the association of these markers with the risk of diabetes onset, among other possible risk factors.

The operational objectives are to recruit, screen, randomize, and follow sufficient numbers of subjects to provide adequate statistical power to determine whether T1DM can be delayed through the administration of oral insulin.

3.3 Study Population

Recruitment and initial screening to identify subjects will be done through the TrialNet Natural History Study of the Development of Type 1 Diabetes Protocol. As part of this protocol, subjects will then undergo additional testing, and if eligible and willing, will be randomized and followed as described. Subjects determined during screening to be ineligible or unwilling to be randomized to this

protocol will be followed under the Natural History Study Protocol.

Eligible subjects are non-diabetic relatives of patients with T1DM, who have normal glucose tolerance on an OGTT, who are confirmed to be mIAA positive on two samples (collections), and who also meet the criteria for the following primary and secondary study strata based on other autoantibodies and metabolic characteristics:

Primary Analysis Stratum:
Either ICA (>= 10 JDF units) positive confirmed on two samples, or, if not confirmed for ICA, both GAD65ab and ICA512 positive on the same sample with confirmation of at least one of these autoantibodies on a separate sample.

Subjects must also have first phase insulin release (FPIR) above the threshold determined from the sum of the 1 and 3 minute insulin values from an intravenous glucose tolerance test (IVGTT). For participants age 3-7 or parents of T1DM proband the threshold is $\geq$ 60 μU/ml. For siblings or offspring age 8-45 or other relatives age 8-20, the threshold is $\geq$ 100 μU/ml.

The primary objective of the study is to assess the effects of treatment within this stratum (see Section 8).

Secondary objectives entail the assessment of treatment effects within additional strata:

Secondary Stratum 1:
Either ICA (>= 10 JDF units) positive confirmed on two samples, or, if not confirmed for ICA, both GAD65ab and ICA512 positive on the same sample with confirmation of at least one of these autoantibodies on a separate sample.

Subjects must also have first phase insulin release *below* the FPIR thresholds defined in the Primary Stratum above.

Secondary Stratum 2:
ICA, or GAD65ab or ICA512 positive. Confirmation of either GAD65 or ICA512 on a separate sample (those confirmed for ICA are in primary stratum).

Subjects must also have first phase insulin release *above* the FPIR thresholds defined in the Primary Stratum above.

Secondary Stratum 3:
ICA, or GAD65ab or ICA512 positive. Confirmation of either GAD65 or ICA512 on a separate sample (those confirmed for ICA are in secondary stratum 1).

Subjects must also have first phase insulin release *below* the FPIR thresholds defined in the Primary Stratum above.

Subjects identified through the TN Natural History Study and who satisfy all eligibility criteria and no exclusion criteria (see below) will be eligible for this protocol.

3.3.1 Inclusion Criteria

4. Have a proband* with T1DM.
2. If the proband is a sibling, parent or a child, the study participant must be 3 - 45 years of age. If the proband is a second or third degree relative (i.e. Niece, Nephew, Aunt, Uncle, Grandparent, Cousin), the study participant must be 3-20 years of age.
3 Willing to sign Informed Consent Form.
4. Has normal glucose tolerance on an OGTT performed within 7 weeks prior to randomization. If previous abnormal glucose tolerance, has had two consecutive OGTT with normal glucose tolerance.
5. mIAA confirmed positive within the previous six months.
6. At least one other antibody present on two separate samples, one of which was drawn within the past six months.

* A proband is an individual diagnosed with diabetes before age 40 and started on insulin therapy within 1-year of diagnosis. Probands considered to have type 1 diabetes by their physician who do not meet this definition will be referred to the TrialNet Eligibility Committee.

3.3.2 Exclusion Criteria

1 Does not satisfy the above inclusion criteria.
2 Has severe active disease, e.g. chronic active hepatitis, severe cardiac, pulmonary, renal, hepatic, immune deficiency and/or disease that is likely to limit life expectancy or lead to therapies such as immunosuppression during the time of the study.
3 Prior participation in a clinical trial for secondary prevention of T1DM.
4 History of treatment with insulin or oral hypoglycemic agent.
5 History of therapy with immunosuppressive drugs or non-physiologic glucocorticoids within the past two years for a period of more than three months.
6 Ongoing use of medications known to influence glucose tolerance, i.e. sulfonylureas, growth hormone, metformin, anticonvulsants, thiazide or potassium depleting diuretics, beta adrenergic blockers, niacin. Subjects on such medications should be changed to a suitable alternative, if available, and will become eligible one month after medication is discontinued.
7 Pregnant or intends to become pregnant while on study or lactating.
8 Deemed unlikely or unable to comply with the protocol.
9 OGTT that reveals abnormal glucose tolerance unless two subsequent consecutive OGTT have normal glucose tolerance. Abnormal glucose tolerance is defined as:
    - fasting plasma glucose ≥ 110 mg/dL (6.1 mmol/l), AND/OR
    - 2 hour plasma glucose ≥ 140 mg/dL (7.8 mmol/l) AND/OR
    - 30, 60, or 90 minute plasma glucose ≥200 mg/dL (11.1 mmol/l)
10 Subject has HLA DQA1*0102, DQB1*0602 haplotype.

3.4 Description of Treatment Groups

Subjects will be randomized to receive either oral insulin (7.5 mg of recombinant human insulin crystals) or placebo daily.

3.5 Treatment Assignment and Double Masking

After participants sign the consent form, complete the screening visit(s), meet all of the inclusion criteria and none of the exclusion criteria, and complete the baseline procedures participants will be randomized to receive either oral insulin or placebo.

Participants will be randomized in equal allocations to each group. The randomization method will be stratified by the major TrialNet study site. This approach ensures that study site will not be a potential confounder.

This treatment assignment will be double masked. Outcome assessments will be conducted without knowledge of treatment assignment.

3.6 Study Assessments

The intervention protocol will be conducted at Centers and approved Affiliates with a General Clinical Research Center (GCRC) or equivalent facility. During the course of the study, participants will frequently undergo assessments of their insulin production, immunologic status, and overall health and well-being (see Figure 3, Schedule of Assessments). All blood and serum samples for outcome determinations will be sent to the TrialNet Core Laboratories for analysis.

The primary outcome is the development of clinical T1DM. Therefore, subjects will be followed until their development of T1DM or the conclusion of the study.

During the course of the study, samples will be drawn for storage at the National Institute for Diabetes and Digestive and Kidney Disease (NIDDK) Repository and at TrialNet Sites for future analysis. These samples will be collected only with the subject's permission. Subjects who decline consent for these sample collections will still be eligible to participate in this study (see Section 10.4).

3.7 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 central laboratories.

3.8 Study Timeline

A fixed target sample size has not been specified and the date on which the study will terminate has not been fixed in advance. Rather, the study is designed as a *maximum information trial* in which subjects are recruited and followed until the required amount of statistical information is achieved that provides 85% power to detect a 40% risk reduction using a one-sided logrank test at the 0.05 level. The required information number is $I = D_O * D_C / (D_O + D_C) = 27.6$; where D_O, D_C are the observed numbers developing diabetes in the oral insulin and control groups, respectively. Thus, the exact total sample size and study duration are unknown.

However, projections as to the expected total sample size and end date can be conducted based on assumed values of the rate of enrollment, the control group hazard rate and the rate of losses-to-follow-up. As the study progresses, these projections can be updated based on interim estimates of these parameters.

The TrialNet Natural History Study is projected to screen 20,000 or more subjects each year to identify subjects who may be eligible for this prevention study. Preliminary estimates show that this will yield between 50 and 60 subjects annually who will meet these eligibility criteria for the primary

study stratum, and who will consent for the trial. Further, from supplemental analyses of the DPT-1, it is projected that subjects in the primary analysis stratum will have a 50% 5 year risk (cumulative incidence) of diabetes. If 50 subjects are entered each year over 6 years (N = 300 total), using the expressions in Lachin and Foulkes (15), with allowance for some losses to follow-up, it is projected that a total study duration of 7.6 years would be required to achieve I = 27.6. If 60 subjects are entered each year over 5.5 years (N = 330), a total study duration of 6.8 years would be required. A total of D_T = 115 subjects are expected to have developed diabetes by study end.

4 SUBJECT MANAGEMENT

4.1 Screening Visit and Eligibility Assessment

Subjects potentially eligible for the Oral Insulin Trial will be identified through the TrialNet Natural History Study. They will be notified of their eligibility by TrialNet Investigators at an Affiliate clinical site or the associated Clinical Center.

The initial testing for mIAA and other autoantibodies will be done as part of Natural History screening. Those individuals who are mIAA positive will then be eligible for additional tests as part of the Natural History Monitoring visit. Those with normal glucose tolerance will be eligible for enrollment into either the Primary or one of the Secondary Analysis Strata of the Oral Insulin Trial depending on their test results from both the Natural History and Oral Insulin Trial assessments.

Figure 4 summarizes the flow of subjects from the Natural History Study into the Oral Insulin initial visit and randomization.

4.2 Natural History Monitoring Visit

As described in the TrialNet Natural History Study Protocol, mIAA positive individuals will undergo a Monitoring visit consisting of oral glucose tolerance testing, confirmation of autoantibody status, and HLA evaluation. At this visit, the Oral Insulin Trial will be described to the potential participant, initiating the process of informed consent for the Oral Insulin Trial. The subject will have up to 7 weeks from the time of the OGTT until randomization.

4.3 Oral Insulin Initial Visit

The participant will be asked to sign an informed consent document describing the purpose, risks, and benefits of the Oral Insulin Trial. A participant's signature indicates that he/she understands the potential risks and benefits of study participation. During the first visit, an IVGTT will be performed.

Assignment to study stratum will depend upon both antibody results and results from their IVGTT. Classification as "above threshold FPIR" will require only one IVGTT with this result. Subjects whose initial FPIR is below threshold will undergo repeat IVGTT no later than the day of randomization. If the second IVGTT is "above threshold", this classifies the subject in the "above threshold" category for stratum determination. Thus, classification as "below threshold" requires two "below threshold" IVGTT results. This process is to address the first-test effect observed in the DPT-1 whereby a "below threshold" FPIR on the initial visit was often not-confirmed.

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

4.4 Randomization

The participant will be eligible for randomization in one of the study strata if they satisfy all of the following:

1 mIAA positive on two separate samples
2 Positive for at least one other autoantibody on two samples
3 Does not meet the HLA exclusion criteria
4 Has normal glucose tolerance by OGTT, and if previous abnormal glucose tolerance, has two consecutive OGTTs with normal glucose tolerance.
5 Age $\geq$ 3 years.

Randomization must occur within 7 weeks of an OGTT in order to ensure that participants have normal glucose tolerance at time of randomization.

Prior to randomization, all entry criteria will be reviewed to ensure subject eligibility.

After randomization, study medication will be dispensed to the participant.

4.5 Administration of Study Medication

All subjects will take one capsule of study medication (7.5 mg of recombinant insulin or placebo) daily for the duration of the study. Study medication will be dispensed at each 6-month visit. Subjects will remain on the same dose of insulin/placebo throughout the trial.

4.6 Treatment Discontinuation

Subjects may be discontinued from treatment due to adverse effects of treatment that in the judgment of the investigator are related to the study medication. Subjects will also be discontinued from treatment who revoke consent to be treated.

Subjects will not be discontinued from treatment due to non-compliance or the apparent lack of preliminary beneficial effect, so-called treatment failure.

4.7 Intent-to-Treat Design

This study is designed and will be implemented under the intention-to-treat principle in which all subjects randomized will be included in all analyses. To minimize bias under this principle, this requires adoption of an intent-to-treat design. To the extent possible, all subjects randomized into the study should continue all scheduled follow-up assessments until the time of onset of diabetes, death, or the declared end of the study. All subjects discontinued from treatment by the investigator, or who refuse to continue treatment, or who fail to comply with treatment, should continue to be followed under this policy.

A subject whose follow-up lapses during the study will be termed *inactive*. No subject will be

designated as a study dropout. Inactive subjects will not be permanently withdrawn from the study and will be allowed to return to follow-up, and continue with randomized treatment, at any time provided that the subject has not developed diabetes. Those still inactive at the end of the study will be classified as lost to follow-up, and the date so lost will be that at which the subject was last known to be free of diabetes.

5 STUDY VISIT ASSESSMENTS

Participants will be seen at a study site and contacted by phone during follow-up to collect study data, perform required blood testing, determine changes in diabetes status and monitor study related adverse events and treatment compliance.

The schedule of evaluations and laboratory studies is presented in Figure 3, Schedule of Assessments (refer to Section 3.6). A summary of assessments for the protocol is given below.

All assessments will be performed on samples or data obtained from either the Natural History Study or this trial.

All participants randomized into this study will be seen at a study site for a follow-up evaluation three and six months after randomization and every six months thereafter. Participants will be contacted by phone between 6-monthly clinic visits to assess changes in diabetes status, medication compliance and adverse events. These phone contacts will occur approximately 3 months from the date of the participants previous clinic visit.

5.1 General Assessments

General assessments for this Protocol will include:

- Informed consent
- Inclusion/exclusion criteria
- Medical history including lifestyle assessment
- Physical examination including height/weight, abdominal circumference
- Concomitant medications
- Adverse events
- Treatment compliance

5.2 Laboratory Assessments

The following laboratory assessments will be performed during the study:

- Islet Autoantibodies

5.3 Mechanistic Outcome Assessments

Mechanistic assessments may include:

- DNA for testing other diabetes or immune associated genetic markers.
- RNA for the evaluation of immune cell frequency and function by gene expression analysis.
- Peripheral Blood Mononuclear Cells (PBMCs) for the evaluation of immune cell number and function.
- Serum and plasma for assays such as the evaluation of islet autoantibody epitope, affinity,

isotyping and proteomics based assessment of immune responses.

5.4 Metabolic Outcome Assessments

Metabolic assessments may include:
- HbA1c l
- OGTT
- Insulin secretion
- Insulin sensitivity
- IVGTT

5.5 Visit Windows

Randomization and initial treatment administration should begin within 7 weeks (no more than 52 days) from the OGTT. The subsequent treatment visits should be conducted within 6 weeks before or after the scheduled date based on each subject's date of randomization.

6 ADVERSE EVENT REPORTING AND SAFETY MONITORING

6.1 Adverse Event Definitions

6.1.1 Adverse Event
In this clinical trial, an adverse event is any occurrence or worsening of an undesirable or unintended sign, symptom or disease.

Throughout the study, the investigator must record adverse events on source documents, regardless of the severity. The investigator should treat participants with adverse events appropriately and observe them at suitable intervals until the events resolve or stabilize.

Adverse events may be discovered through:
- observation of the participant;
- questioning the participant;
- unsolicited complaint by the participant

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

6.1.2 Serious Adverse Event
For this trial, an adverse event associated with the treatment or study procedures that suggest a significant hazard, contraindication, side effect or precaution (as described below) is to be reported as a serious adverse event (SAE).

A serious adverse event (experience) or reaction is any untoward medical occurrence that:
- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,

- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

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

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

6.1.4 Grading Event Severity
TrialNet has adopted usage of the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) and/or study-specific criteria for classification to describe the severity of adverse events.

6.2 Adverse Event Reporting and Monitoring

Adverse events will be reported to the TrialNet Coordinating Center in accordance with the TrialNet Adverse Event Monitoring Plan (see Manual of Operations). They will be graded as to severity according to common toxicity criteria or study-specific criteria and the investigator will make a determination as to the relation to therapy. Events will be assessed and reported in accordance with the ICH Guidelines for Good Clinical Practice 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 greater or equal to Grade 2 of the NCI CTCAE. For reporting serious adverse events (SAE), the TrialNet MedWatch Form should also be completed and faxed to the TNCC *within 24 hours of when the site was notified of the event.* This will be reviewed by the TrialNet Medical Monitor, the TrialNet Safety 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 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 and adjudicated, if required, by the TrialNet Medical Monitor. The DSMB will conduct regular safety reviews approximately every three to six months (and, as needed) of adverse events by treatment group assignment. Serious adverse events as well as adverse events leading to study discontinuation will be reviewed by the DSMB.

6.3 Protecting Against or Minimizing Potential Treatment Risks

Subjects will not be enrolled who have other active serious medical problems. Regular monitoring of subjects and active inquiry will allow for early identification of adverse events.

7 PARTICIPANT SAFETY

7.1 Expected Side Effects and Adverse Events

There were no side effects or adverse events associated with oral insulin during the DPT-1 which consisted of the same study population and same dose of drug. Subjects did occasionally have mild expected adverse events associated with study procedures such as fainting and bruising with phlebotomy. Although unlikely, it is possible that oral insulin could accelerate disease.

7.2 Pregnancy

Pregnant and lactating women will not be included in this study. Females must have a negative pregnancy test prior to enrolling in the study and will be required to use birth control during the study. At every study visit the sexual activity of female participants of reproductive age will be re-assessed. If a subject who was previously sexually inactive becomes sexually active, she will be counseled about the need to use a reliable form of birth control. Female subjects will undergo urine pregnancy tests at regular intervals.

8 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. Such analyses may also entail the use of data from other studies in combination with data from this study. Likewise, data from this study may be used in combination with data from another study to address objectives of that 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.

8.1 Primary Outcome

The primary outcome is the elapsed time from random treatment assignment to the development of diabetes among those enrolled in the primary analysis cohort consisting of subjects with insulin autoimmunity and absence of metabolic abnormalities.

Criteria for diabetes onset are, as defined by the American Diabetes Association (ADA), 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.

OR

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

OR

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 75 g 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 and documentation of symptoms was performed by TrialNet study personnel.

A **TrialNet Diabetes Onset Adjudication Committee** will review all relevant information for each subject otherwise diagnosed as having developed diabetes who does not meet the above criteria. The Committee will determine whether the diagnosis of diabetes in each such subject 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 review each case masked to treatment assignment.

8.2 Primary Analysis

The primary objective of the study is to assess the effect of oral insulin therapy versus placebo on the risk of diabetes onset in the population of subjects in the Primary Analysis Stratum as defined on the basis of the eligibility criteria elaborated in Section 3.3.

The cumulative incidence of diabetes onset over time since randomization within each group will be estimated from a modified Kaplan-Meier estimate of the "diabetes-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, one-sided, using the Mantel-logrank test. The estimates of cumulative incidence and the test will adjust for periodic outcome assessment visits (12) to assess diabetes status. A one-sided test is employed since the objective is to confirm a preliminary finding from the prior DPT-1 Oral Insulin Trial. The relative risk of diabetes onset between groups will be estimated from the discrete Cox Proportional Hazards (PH) model (12). The critical value for the test statistic, and confidence intervals, in this primary analysis will be determined by the group-sequential procedure (Section 8.5 below).

8.3 Secondary Outcomes and Analyses

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

1 The effects of treatment with oral insulin versus placebo will be described in the Secondary Analysis Strata defined in Section 3.3, each consisting of other categories of subjects defined using different combinations of autoantibodies and metabolic status. This will entail the same analyses as above for the Primary Analysis within each of the three secondary strata. An additional analysis will assess the effect of treatment within the Secondary strata combined using a Cox PH model stratified by the three secondary cohort strata, with separate estimates of the hazard ratio for oral insulin versus placebo within each stratum, and with a likelihood ratio test of the oral insulin treatment effect among all Secondary strata combined. Such analyses will be largely descriptive because the study is not designed to provide adequate power to detect an effect of oral insulin treatment within these

secondary cohorts individually or combined.

2 The overall effect of oral insulin versus placebo treatment in the combined strata will be assessed by an analysis as described above using all subjects in a Cox PH model analyses stratified by the four analysis strata (Primary plus three Secondary), with a likelihood ratio test of the oral insulin treatment effect among all strata combined. If the magnitude of the oral insulin treatment effect within the secondary analysis cohorts approaches that in the primary cohort, then the power of the study to detect an overall effect in all combined cohorts will be increased.

3 The consistency of the oral insulin versus placebo treatment effect will be assessed among strata. This will entail an analysis stratified by each of the four analysis strata (Primary plus three Secondary) and with a test of homogeneity of the treatment effect among strata, i.e. a group by stratum interaction, in a Cox PH Model.

4 Subgroup analyses will be conducted comparing the effects of oral insulin versus placebo on the risk of diabetes within subsets of the study cohort, such as among men versus among women. Such analyses will be conducted separately within the primary analysis stratum alone, and within the combined cohort stratified by analysis strata (Primary and three Secondary), with a test of the group by subgroup factor interaction in a Cox PH Model. Subgroups of the population will be classified by age (children <= 12 years of age, adolescents 13-17 years and adults >= 18 years), gender, race/ethnicity, specific antibody status at baseline, and above versus below threshold FPIR at baseline. Differences in the treatment effect between subgroups will be tested using a covariate by group effect in a Cox PH model (12).

Similar analyses will be conducted using the values of quantitative baseline factors including weight, BMI, and the immunologic and metabolic factors described in Section 2.3 that include the autoantibody titers, basal C-peptide, stimulated C-peptide (peak and AUC mean), measures of insulin resistance modeled from the OGTT, and the FPIR. 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. Such an analysis will also be conducted to assess the effects of age and FPIR as quantitative covariates.

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.

5. Longitudinal analyses will assess the effects of oral insulin versus placebo treatment on immunologic and metabolic markers over time up to the onset of diabetes. Differences between groups in the mean levels of quantitative factors over time will be assessed using a normal errors linear model for repeated measures (13). Differences between groups in the prevalence of qualitative factors over time will be assessed using generalized estimating equations for categorical measures (13). Generalized estimating equations may also be employed for the analysis of quantitative factors when the normal errors assumptions are violated.

Once a subject develops diabetes, that subject will no longer be followed for longitudinal assessment of these factors. Thus, these analyses will describe the differences between groups in

factors among those who remain free of diabetes.

6. The association of demographic, genetic, immunologic, metabolic, and lifestyle factors, among others, both at baseline and over time, with the risk of diabetes onset will be assessed in Cox PH Models over time. If the proportional hazards assumption does not apply, an appropriate parametric regression model may be employed. The effects of changes in longitudinal factors on diabetes risk will be assessed using time-dependent covariates for these factors. Analyses will be conducted separately within the oral insulin 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.

8.4 Study Power and Maximum Information Design

The prior DPT-1 Oral Insulin Trial was designed to detect a 50% reduction in risk of diabetes overall. However, among those in the "high IAA intermediate risk" stratum, the observed relative risk was 0.566, corresponding to a 43.4% risk reduction. Thus, this study has been designed to provide 85% power to detect a 40% risk reduction using a one-sided test at the -0.05 level.

The study is designed as a maximum information trial in which subjects are recruited and followed until the required amount of statistical information is achieved.

At any point in time during the study, the information in the data for a logrank test is provided by $I = (D_O D_C)/D_T$. where D_O and D_C refer to the number of subjects who have developed diabetes in the oral insulin and control groups, respectively, and D_T refers to the total number of such subjects (14). The information required to provide 85% power to detect a 40% risk reduction with a one-sided logrank test at the 0.05 significance level is $I = 27.551$. Under this design the study will be terminated when the observed numbers of events (D_O, D_C, D_T) provides $I \geq 27.551$.

The final test of significance will employ the group sequential critical value 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.

Under a maximum information design, the exact total sample size and study duration are unknown, although projections of each can be generated a priori, and then monitored as the study progresses (14). At this time we project that the study will be able to enroll 50-60 subjects per year into the primary analysis stratum who will have a 50% 5 year risk of diabetes (see Section 3.8). During the DPT-1 oral insulin trial, 3 of 186 subjects were lost to follow-up of diabetes status over 4 years. With this information it is possible to use the expressions in Lachin and Foulkes (15) to make a projection as to the total study duration needed to accrue the information $I = 27.6$ needed to provide 85% power to detect a 40% risk reduction. If 50 subjects are entered each year over 6 years ($N = 300$ total), it is projected that a total study duration of 7.6 years would be required. If 60 subjects are entered each year over 5.5 years ($N = 330$), a total study duration of 6.8 years would be required. In each case, a total of $D_T = 115$ subjects are expected to have developed diabetes by study end.

However, the exact rate of recruitment, control hazard rate (or 5 year risk) and rate of losses to follow-

up are unknown. Thus, no specific time has been specified at which the study will end. Rather, the study will end when the accrued numbers of subjects developing diabetes provide I = 27.551. As the study progresses, projections of the study end will be computed based on the observed rate of enrollment, the observed hazard rate and the observed rate of loss-to-follow-up.

8.5 Interim Monitoring Plan

Interim analyses will be conducted periodically during the study and will be reviewed by the TrialNet Data and Safety Monitoring Board (DSMB) for assessment of effectiveness and safety. The Lan-DeMets (16) 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. Kim, Boucher and Tsiatis (17) describe the application of such group-sequential procedures in a maximum information design.
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 (18). Stopping for futility may inflate the type II error probability. The methods described in Lachin (19) will be employed to ensure that the type II error probability under the original design assumptions is not inflated beyond 0.20, or power reduced below 0.80, by a decision to terminate for futility.

9 ETHICAL CONSIDERATIONS AND COMPLIANCE WITH GOOD CLINICAL PRACTICE

9.1 Statement of Compliance

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

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

9.2 Participating Centers

Participating TrialNet clinical sites must have an appropriate assurance, such as a Federal-wide Assurance (FWA) 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 at each of the participating clinical sites. HIPAA regulations will be followed by each participating institution in accordance with each institution's requirements. The participating international sites will obtain approval from their corresponding review boards in accordance with their local procedures and institutional requirements.

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

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

9.3 Informed Consent

The process of assuring that individuals (and parent/guardian if less than 18 years of age) are making an informed decision about participating in this study includes both verbal and written communication. Written material includes a Patient Handbook and written consent forms. The consent form describes the procedures, risks, and benefits for the study. The consent form will be reviewed with participants (and their guardian in the case of participants under 18 years of age) and the participant will be given time to review the written consent form and ask questions. An assent form has also been developed for participants less than 18 years of age (unless local IRB requirements differ in procedure).

As part of the informed consent process, the participant and/or parent or guardian (if the participant is less than 18 years of age) will also complete a short, written Volunteer Understanding Quiz 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 ongoing consent of participants should be assessed on a continual basis as part of the informed consent process per Good Clinical Practice.

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

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

9.4 Study Subject Confidentiality

Study records with the study subject's information for internal use at the clinical sites will be secured at the study site during the study. At the end of the study, all records will continue to be kept in a

secure location. There are no plans to destroy the records.

Study subject data, which is for reporting purposes, will be stored at the University of South Florida 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. All paper copies of the forms will ultimately be destroyed after the data is transferred.

Genetic and other biological material will be stored for future use with the permission of the study subject as described in Section 10.4. The results of these future analyses will not be made known to the participant.

9.5 Risks, Benefits, and Inclusion of Children

The risks of this study are presented in the informed consent form and are described in Chapter 7. While there is no guaranteed benefit, there is the prospect of direct benefit to the individual subjects for their participation in the study. These potential benefits include that the diagnosis of diabetes will likely be made earlier via close monitoring, decreasing the risk of life threatening diabetic keto-acidosis.

The study procedures are minor increase over minimal risk and offer the possibility of benefit in the close monitoring and thus early detection of disease for all children. Further, the intervention may have direct benefit to a given subject and is likely to yield general knowledge about T1DM which is of importance for the understanding and amelioration of T1DM in children. Assent of children along with consent of the parents will be obtained prior to any study procedures. This research proposal in children is therefore consistent with United States Department of Health and Human Services, Protection of Human Subjects, Subpart D, Section 46.405 (Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects) and with Subpart D 50.52 (Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects).

10 STUDY ADMINISTRATION

10.1 Organizational Structure

This study is part of Type 1 Diabetes TrialNet, which is funded by the National Institutes of Health, principally the National Institute of Diabetes, Digestive and Kidney Diseases. Funding will cover the costs of administration and laboratory tests associated with this study during the participant's period of follow-up. Eli Lilly and Company will provide oral insulin crystals free of charge.

10.2 Groups and Committees

10.2.1 Oral Insulin Trial Protocol Committee

The Oral Insulin Trial Committee, the TrialNet Clinical Monitoring Group, Laboratory Monitoring Group, Steering Committee and Data and Safety Monitoring Board will receive periodic reports from the TrialNet Coordinating Center on the progress of the study. These will include accrual rates and

baseline demographic characteristics. Throughout the study, the Oral Insulin Trial Protocol Committee and the Laboratory Monitoring Group will review various indices of the performance of the TrialNet central laboratories including the reproducibility of results, within assay coefficients of variation, autoantibody rates of positivity and confirmation.

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

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

10.2.3 Clinical Sites
Each Principal Investigator at the participating TrialNet clinical site will oversee all operations. The clinical sites will forward all laboratory and data collection form information to the Coordinating Center for analysis. Conference calls and site visits, as needed, will facilitate evaluation of the trial management.

10.2.4 TrialNet Laboratories
TrialNet core laboratories will be utilized to perform tests and assays for this trial. All laboratory results will be forwarded to the TrialNet Coordinating Center for analysis.

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

10.2.6 Data and Safety Monitoring Board (DSMB)
The DSMB will meet approximately 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 Coordinating Center. The DSMB will independently evaluate whether there are grounds to discontinue the study.

10.3 Partnering with Industry

The proposed study medication, oral insulin, is not commercially available. Eli Lilly and Company is providing the oral insulin crystals for this study.

10.4 Sample and Data Storage

Stored samples, including genetic material, 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.

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

Data collected for this study will be sent to the TrialNet Coordinating Center at the University of South Florida. After the study is completed, de-identified data will be stored at the NIDDK Repository, under the supervision of the NIDDK/NIH, for use by researchers including those outside of TrialNet.

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

10.5 Preservation of the Integrity of the Study

The scientific integrity of the trial dictates that results be reported on a study-wide basis; thus, an individual clinical site will not report the data collected from its site alone. All presentations and publications using TrialNet data must protect the main objectives of the trial. Data that could be perceived as threatening the masking will not be presented prior to release of the primary study outcomes. The TrialNet Publications and Presentations Committee will approve the timing of presentations of data and the meetings at which they might be presented, and the publication of results and the selection of the journal to which each paper will be submitted for publication. Study results should be discussed with the news media only upon authorization of the Executive Committee, but never before the results are presented. Any written statements about this study that are shared with national media should be approved by the Executive Committee and the National Institute of Diabetes, Digestive and Kidney Diseases before release.

10.6 Participant Reimbursement and Compensation

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

Oral Insulin Study: Schedule of Assessments

	TN NH	Oral Trial Initial Visit	Baseline			1YR		2YR		3YR		4YR		5YR		6YR[6] …	
	Monitoring	I	0	3	6	12	18	24	30	36	42	48	54	60	66	72…	END
METABOLIC STUDIES																	
OGTT	X[1]				X	X	X	X	X	X	X	X	X	X	X	X	X
IVGTT		X	(X)[2]														
HbA1C	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
IMMUNOLOGIC STUDIES																	
Islet autoantibodies	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
DNA (Including HLA)	X																
Samples for Mechanistic/future studies[3]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CLINICAL MEASURES																	
Medical History/AE assessment		X[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Family history		X[4]															
Urine pregnancy test if applicable		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam including lifestyle assessments		X[4]				X		X		X		X		X		X	
Limited Physicalexam[5]				X	X		X		X		X		X		X		X
Dispense medication			X		X	X	X	X	X	X	X	X	X	X	X	X	
Assess medication compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1]OGTT must be within 7 weeks of randomization and result must be NGT. If previous abnormal OGTT, subject must have two consecutive OGTT with NGT

[2]Second IVGTT required only if first FPIR is below threshold.

[3]Samples may include serum, plasma, whole blood, and PBMC. Total blood draw volume in adults ≤150 ml at each visit. For children, no more than 5 ml/kg will be drawn at any single visit and no more than 9.5 ml/kg over a 8 week period. Thus mechanistic samples and/or islet autoantibodies scheduled at initial visit may be omitted due to blood volume limitations.

[4]May be performed either at initial or baseline visit.

[5]Height, weight, BP, abdominal circumference (abdominal circumference not done at 3 month visit).

[6]Participants continue every 6 month visits until development of diabetes or study end (see Section 8.4 of OIT Protocol: Study Power and Maximum Information Design)

Figure 4: Oral Insulin Trial Flow Chart

Study Stage

Natural History Study Screening Stage

First, second, or third degree relative

Autoantibody determination (s)

Criteria to move on**:** mIAA **and** one other antibody positive

If eligible ↓

Natural History Study Monitoring Stage Procedures	
Criteria to move on to Oral Trial	Confirmation of autoantibody status[1], OGTT, HLA, **Age 3-45 at time of randomization if proband 1st degree relative** **or** **Age 3-20 at time of randomization if proband second or third degree relative** **Autoantibodies (AA)** mIAA confirmed At least one other antibody positive on two samples **OGTT**[2] Fasting Plasma Glucose < 110 mg/dL (6.1 mmol/l) 2-hr Plasma Glucose < 140 mg/dL (7.8 mmol/l) 30, 60, 90 minute Plasma Glucose < 200 mg/dL (11.1 mmol/l) **HLA** Subject without HLA DQB1*0602

If eligible[3] ↓

Oral Trial Initial Visit Procedures: IVGTT[4], History[5], PE[5], volunteer quiz

If eligible ↓

Oral Insulin Randomization and Baseline[6]

Procedures (IVGTT)[7], Study medication dispensed

1 If autoantibodies are not confirmed positive on the second test done as part of Natural History, a tiebreaker draw will be required.
2 If Diabetes on first OGTT, confirmatory OGTT will be offered for subject information; however, if first OGTT is consistent with Diabetes, the subject is NOT eligible for oral trial regardless of results of subsequent OGTT.
3 Subjects not eligible for Oral Insulin Trial will be eligible for follow-up in Natural History study.
4 IVGTT may be done as soon as 24 hours after OGTT in which meter glucose values are consistent with NGT while formal results are pending.
5 History, PE, may be done at IVGTT initial visit or at baseline.
6 Randomization must occur within 7 weeks of OGTT.
7 If first IVGTT is below threshold, repeat IVGTT will be done at randomization/baseline visit.

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Appendix 16.1.2 Sample Case Report Forms

Site Number: ___ ___ ___ ___ | Participant ID: _____-___ ___-___ ___ -___ ___ ___ ___ - ___ **Int'l** | Participant Letters: ___ ___ ___

The Study Coordinator should complete this form during the Initial Visit.

A. VISIT INFORMATION

1. Date Initial Visit completed (*e.g. 05/Jan/2007*): ___ ___ / ___ ___ ___ / ___ ___ ___ ___ (DAY / MONTH / YEAR)
2. Did the visit occur at a site other than at the primary study site? Y N
   a. If YES, Record Site Number for reimbursement: ___ ___ ___ ___

   ***Note**: Site Number **must** correspond to a TrialNet Clinical Center, Affiliate, or Participating Physician*

B. INFORMED CONSENT

1. Date written informed consent obtained: ___ ___ / ___ ___ ___ / ___ ___ ___ ___ (DAY / MONTH / YEAR)
2. On the consent form, did the participant give permission to store samples for future testing? (*Check one)*
   - ☐ 1 YES, permission was given to store all samples including genetic samples.
   - ☐ 2 YES, permission was given to store all samples except genetic samples.
   - ☐ 3 NO, permission was not given to store any samples.

C. FAMILY HISTORY

1. Have any of your first or second degree relatives been diagnosed with Type 1 Diabetes (T1D) since the completion of the **Natural History Family History Form (NH01F)?** Y N

If YES, complete the following table:

2. Relative with Type 1 Diabetes	3. Sex of Relative	4. Current Age of Relative	5. Age of T1D Onset in Relative	6. Age Relative Started Insulin	Comments
See codes below	**CHECK ONE**	**Age in Years**	**Age in Years**	**Age in Years**	*Comments*
a. ___ ___	☐1 Male ☐2 Female	___ ___	___ ___	___ ___	_____
b. ___ ___	☐1 Male ☐2 Female	___ ___	___ ___	___ ___	_____
c. ___ ___	☐1 Male ☐2 Female	___ ___	___ ___	___ ___	_____
d. ___ ___	☐1 Male ☐2 Female	___ ___	___ ___	___ ___	_____
e. ___ ___	☐1 Male ☐2 Female	___ ___	___ ___	___ ___	_____
f. ___ ___	☐1 Male ☐2 Female	___ ___	___ ___	___ ___	_____
g. ___ ___	☐1 Male ☐2 Female	___ ___	___ ___	___ ___	_____

Use the letter codes below to record the type of relative:

P=Parent	**IT**=Identical Twin	**FS**=Brother/Sister	**AU**=Aunt/Uncle	**C**=Cousin
GP=Grandparent	**NT**=Non-identical Twin	**HS**=Half Brother/Sister	**N**=Niece/Nephew	**CH**=Child

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

C. FAMILY HISTORY (CONTINUED)

2. Autoimmune Disease History

Has anyone in your family (first or second degree relatives only) ever been diagnosed with an autoimmune disease(s)? Y N

If YES, Record the code that corresponds with the diagnosis. *(Refer to table below for diagnosis codes)*

a. __ __ If OTHER, 1) Specify:

b. __ __ If OTHER, 1) Specify:

c. __ __ If OTHER, 1) Specify:

Codes for Autoimmune Diseases:

01 Addison's Disease (Adrenal Insufficiency)
02 Alopecia
03 Celiac Disease (Gluten Allergy or Celiac Sprue)
04 Grave's Disease (Hyperthyroidism)
05 Immune Thyroid Disease
06 Rheumatologic Disease
07 Inflammatory Bowel Disease
08 Hypogonadism or Premature Menopause
09 Hypoparathyroidism
10 Pernicious Anemia
11 Vitiligo
12 Psoriasis
13 Lupus
14 Multiple Sclerosis
99 Other Autoimmune Disease

D. MEDICAL HISTORY

1. Have you ever been diagnosed with an autoimmune disease(s)? Y N

If YES, Record the code that corresponds with the diagnosis. *(Refer to table above for diagnosis codes)*

a. __ __ If OTHER, 1) Specify:

b. __ __ If OTHER, 1) Specify:

c. __ __ If OTHER, 1) Specify:

2. Do you have asthma or seasonal allergies? Y N

E. PREGNANCY MONITORING (If participant is male, proceed to Section F.)

1. If FEMALE, does the participant have reproductive potential? Y N
2. If FEMALE, is the participant sexually active? Y N

IF YES to BOTH questions E1. and E2. above, continue *(If not, proceed to **Section F.**)*

a. Does she currently use a form of birth control? *(Females of reproductive age are expected to use a form of birth control)* Y N

b. Does she plan on becoming pregnant in the next year? Y N

c. Was a urine pregnancy test completed at this visit? Y N

1) If YES, was the test result positive? Y N

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ | Participant ID: _____-___ ___- ___ ___ -___ ___ ___ ___ - ___ **Int'l** | Participant Letters: ___ ___ ___

If the **pregnancy test** result was **positive**, **STOP** here.
Initial and date this form and send the white copy to The TrialNet Coordinating Center.
The subject is **NOT eligible** to be randomized.

F. CONCOMITANT MEDICATIONS (Past or Current Usage)

1. Have you taken in the past, or are you currently taking immunosuppressive or steroid drugs? Y N
2. Have you taken in the past, or are you currently taking insulin, or other drugs to treat glucose? Y N
3. Have you taken in the past, or are you currently taking growth hormone, anti-convulsants, thiazide or potassium-sparing diuretics, beta-blockers, or niacin? Y N
4. Have you taken in the past, or are you currently taking any non-prescription medications including vitamin or herbal supplements? Y N

G. GENERAL PHYSICAL EXAM

1. Was a physical exam performed at this initial visit? Y N

   a. IF NO, date performed: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

2. Collect the following physical assessments:
   Note: *Have the participant rest for 5 minutes before doing these assessments.*

   a. Seated arm blood pressure: __ __ __ mmHg / __ __ __ mmHg (Systolic / Diastolic)

   b. Weight: __ __ __.__ kg or __ __ __. __ __ lbs

   c. Height: __ __ __.__ cm or __ __. __ __ in

   d. Abdominal circumference: __ __ __.__ cm or __ __. __ __ in

3. Record whether the following systems are reported as normal or abnormal by the participant and normal or abnormal upon examination: *(if not done, write "*")*:

Review of Systems	1) Participant Reported Normal?	2) Normal on Exam?	If Either is ABNORMAL, a) Explain:
a. HEENT	Y N	Y N	_____
b. Neck	Y N	Y N	_____
c. Thyroid	Y N	Y N	_____
d. Lungs	Y N	Y N	_____
e. Chest/Breasts	Y N	Y N	_____
f. Heart/Circulatory	Y N	Y N	_____
g. Abdomen	Y N	Y N	_____
h. Musculoskeletal	Y N	Y N	_____

G. GENERAL PHYSICAL EXAM (CONTINUED)

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

3. Record whether the following systems are reported as normal or abnormal by the participant and normal or abnormal upon examination: *(if not done, write "*")*:

Review of Systems	1) Participant Reported Normal?	2) Normal on Exam?	If Either is ABNORMAL, a) Explain:
i. Neurologic	Y N	Y N	_____
j. Genitourinary/Testes	Y N	Y N	_____
k. Skin/Nails	Y N	Y N	_____
l. Lymph nodes	Y N	Y N	_____
m. Other	Y N	Y N	_____
If OTHER, 3) Specify:	_____		

4. For subjects less than 18 years of age, record the participant's sexual development using the Tanner Scale:
*If the subject is 18 years of age or older, skip to **Section H**.*

Tanner Stage *(complete a. **OR** b. **AND** c.)*	*(check one)*		
a. Breast **(female)**	☐ 1 Stage 1	☐ 2 Stage 2	☐ 3 Stage 3 or greater
b. Genitalia **(male)**	☐ 1 Stage 1	☐ 2 Stage 2	☐ 3 Stage 3 or greater
c. Pubic Hair **(both)**	☐ 1 Stage 1	☐ 2 Stage 2	☐ 3 Stage 3 or greater

H. SPECIMENS DRAWN/ PROCEDURES PERFORMED/FORMS COMPLETED

The following specimens/procedures/forms should be drawn/performed/completed during this visit:

	a. Performed on this visit date?	**b. If NOT performed at this visit, specify date performed:**
1. IVGTT	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR
2. Serum for autoantibodies	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR
3. Samples for storage	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR
4. Volunteer Understanding Assessment	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR
5. Lifestyle Questionnaire	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR

Initials (first, middle, last) of person completing this form: __ __ __ F M L

Date form completed: __ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR

Site Number: ___ ___ ___ ___ Participant ID: ____-___ ___-___ ___ -___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

The Study Coordinator should complete this form at the Baseline Visit (Week 0) or prior to randomization.

A. VISIT INFORMATION

1. Visit Date: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

B. ELIGIBILITY

1. Inclusion Criteria

a. Is the participant between 3 and 45 years of age and a sibling, offspring or parent of an individual with Type 1 Diabetes?
OR
Is the participant between 3 and 20 years of age with another relative with Type 1 Diabetes? — Y N

b. Is the participant willing to accept random assignment? — Y N

c. Does the participant have a confirmed positive mIAA within the past 6 months? — Y N

d. Does the participant have at least one other antibody present on two separate samples, ONE of which was drawn within the past six months? — Y N

e. Does the participant have a normal glucose tolerance test within in the past 7 weeks and if more than one glucose tolerance test has been performed, are the two most recent tests normal? — Y N

2. Exclusion Criteria

a. Does the participant have Type 1 Diabetes? — Y N

b. Has the participant previously been enrolled in another clinical trial for Type 1 Diabetes prevention? — Y N

c. Is the participant immunodeficient? — Y N

d. Does the participant have a disease which would limit his/her ability to participate in the study? — Y N

e. Has the participant been treated with immunosuppressive drugs or glucocorticoids within the past 2 years for a period of more than 3 months? — Y N

f. Does the participant have the HLA DQA1*0102, DQB1*0602 haplotype? — Y N

g. Is the participant taking any medications that affect glucose homeostasis? — Y N

h. Does the participant have a history of treatment with insulin or any oral hypoglycemic agents? — Y N

i. Is the participant pregnant or planning on becoming pregnant during the course of the study? — Y N

Site Number: ___ ___ ___ ___ Participant ID: ____-___ ___-___ ___ -___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

C. HOUSEHOLD PARTICIPATION IN ORAL INSULIN STUDY

1. Is there anyone in your immediate family or living in your household who is currently randomized in the Oral Insulin Trial? Y N
   a. If YES**,** how many individuals? ___
   Record the Participant ID(s) and relationship(s) below.

Participant ID:		**Relationship:** *(Use the letter codes below)*	
1) Participant ID:	___-___ ___-___ ___-___ ___ ___ ___-___	a)	___ ___
2) Participant ID:	___-___ ___-___ ___-___ ___ ___ ___-___	b)	___ ___
3) Participant ID:	___-___ ___-___ ___-___ ___ ___ ___-___	c)	___ ___

Use the letter codes below to record the type of relative:

P=Parent	**IT**=Identical Twin	**FS**=Brother/Sister	**AU**=Aunt/Uncle	**C**=Cousin
GP=Grandparent	**NT**=Non-identical Twin	**HS**=Half Brother/Sister	**N**=Niece/Nephew	**CH**=Child

STOP AND DOUBLE CHECK ELIGIBILITY

Double-check Sections B1 and B2. To proceed, you must have:

Answered YES to *every* question in Section B1

AND Answered NO to *every* question in Section B2

IF **NOT** ELIGIBLE, **STOP HERE and do not continue with any further assessments**.
Initial and date this form, and send the white copy of this form to the TrialNet Coordinating Center.

If **ELIGIBLE,** proceed with randomization and complete this form.

D. RANDOMIZATION

1. Was the participant randomized? Y N

IF YES,

a. Date of randomization: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

b. Randomization Number: __ __ __ __ __ - __ __

IF NO,

c. Explain: _____

IF NO, **STOP HERE.** Initial and date this form and send the white copy to the TrialNet Coordinating Center.

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

E. SPECIMENS DRAWN/ PROCEDURES PERFORMED

The following specimens/procedures should be drawn/performed during this visit:

	a. Performed on this visit date?	**b. If NOT performed on this date, specify date collected:**
1. IVGTT (if needed)	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR
2. Dispensation of study drug. If YES, complete the ***Study Drug Dispensation and Return Form (OT14)***	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR

Initials (first, middle, last) of person completing this form: __ __ __ F M L

Date form completed: __ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates. Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number:	___ ___ ___ ___	Participant ID:	____-___ ___- ___ ___ -___ ___ ___ ___ - ___ **Int'l**	Participant Letters:	___ ___ ___

The Study Coordinator should complete this form at the 3-Month Follow-up Visit.

A. VISIT INFORMATION

1. Visit Date: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)
2. Did the visit occur at a site other than at the primary study site? Y N

   a. If YES, Record Site Number for reimbursement: __ __ __ __
   ***Note**: Site Number **must** correspond to a TrialNet Clinical Center, Affiliate, or Participating Physician*

B. MEDICAL HISTORY

1. Have there been any changes in health since the last scheduled visit? Y N

   If YES, refer to CTCAE criteria for grading definitions

   If Grade 1 adverse event, record on source document.
   *If Grade 2 or greater, complete **Adverse Event Report Form (OT08)** and source document.*

2. Have there been any changes in concomitant medications since the last scheduled visit? Y N
   If YES, complete a **Concomitant Medication Form (OT18)**

C. LIMITED PHYSICAL EXAM

1. Collect the following physical assessments:
   ***Note**: Have the participant rest for 5 minutes before doing these assessments.*

   a. Seated arm blood pressure: __ __ __ mmHg (Systolic) / __ __ __ mmHg (Diastolic)

   b. Weight: __ __ __ . __ kg or __ __ __ . __ __ lbs

   c. Height: __ __ __ . __ cm or __ __ __ . __ __ in

D. PREGNANCY MONITORING (If participant is male, proceed to Section E.)

1. If FEMALE, does the participant have reproductive potential? Y N
2. Is the female participant sexually active? Y N

   IF YES to BOTH questions D1 and D2 above, continue *(If not, proceed to **Section E.**)*

   a. Does she currently use a form of birth control? *(Females of reproductive age are expected to use a form of birth control)* Y N

   b. Does she plan on becoming pregnant in the next 6 months? Y N

   c. Was a urine pregnancy test completed at this visit? Y N

   1) If YES, was the test result positive? Y N

If the **pregnancy test** result was **positive**, **discontinue study drug** and complete a **Pregnancy Confirmation Report** (**OT10**) and a **Change of Status Form (OT12).** The TrialNet Coordinating Center must be notified within 24 hours of clinic notification of an active pregnancy in a study participant.

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates. Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ Participant ID: _____-___ ___-___ ___ -___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

E. COMPLIANCE (The Study Coordinator should assess the participant's study drug compliance and record on Source Document)

1. Record the date that the participant took his/her initial dose of study drug: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)
2. Is the participant currently taking study drug? Y N

   If NO, Complete a **Change in Study Drug Form (OT07).**

The Study Coordinator should reinforce the importance of taking the study drug every day.

F. SPECIMENS DRAWN/ PROCEDURES PERFORMED

The following specimens/procedures should be drawn/completed during this visit:

	a. Completed on this visit date?	b. If NOT done at this visit, specify date completed:
1. HbA1c	Y N	__ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)
2. Serum for autoantibodies	Y N	__ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)
3. Samples for storage	Y N	__ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

Initials (first, middle, last) of person completing this form: __ __ __ (F M L)

Date form completed: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates. Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ Participant ID: _____-___ ___- ___ ___ -___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

The Study Coordinator should complete this form at the Month 6, 18, 30, 42, 54, 66 follow-up visits.

A. VISIT INFORMATION

1. Visit Date: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

2. For which visit is this form being completed? *(check one)*

☐ 6 Month 6 ☐ 18 Month 18 ☐ 30 Month 30 ☐ 42 Month 42 ☐ 54 Month 54 ☐ 66 Month 66 ☐ 99 Other

a. If OTHER, specify: _____

3. Did the visit occur at a site other than at the primary study site? Y N
   a. If YES, Record Site Number for reimbursement: __ __ __ __
   ***Note**: Site Number **must** correspond to a TrialNet Clinical Center, Affiliate, or Participating Physician.*

B. MEDICAL HISTORY

1. Have there been any changes in health since the last scheduled visit? Y N

   If YES, refer to CTCAE criteria for grading definitions

   If Grade 1 adverse event, record on source document.
   *If Grade 2 or greater, complete **Adverse Event Report Form (OT08)** as well as source document.*

2. Have there been any changes in concomitant medication since the last scheduled visit? Y N
   If YES, complete a **Concomitant Medication form (OT18)**

C. LIMITED PHYSICAL EXAM

1. Collect the following physical assessments:
   ***Note**: Have the participant rest for 5 minutes before doing these assessments.*

a. Seated arm blood pressure: __ __ __ mmHg (Systolic) / __ __ __ mmHg (Diastolic)

b. Weight: __ __ __.__ kg or __ __ __. __ __ lbs

c. Height: __ __ __.__ cm or __ __. __ __ in

d. Abdominal circumference: __ __ __.__ cm or __ __. __ __ in

D. PREGNANCY MONITORING (If participant is male, proceed to Section E.)

1. If FEMALE, does the participant have reproductive potential? Y N

2. Is the female participant sexually active? Y N
   If YES to BOTH questions D1 and D2 above, continue *(If not, proceed to **Section E**)*

   a. Does she currently use a form of birth control? *(Females of reproductive age are expected to use a form of birth control)* Y N

   b. Does she plan on becoming pregnant in the next 6 months? Y N

   c. Was a urine pregnancy test completed at this visit? Y N

      1) If YES, was the test result positive? Y N

If the **pregnancy test** result was **positive**, **discontinue study drug** and complete a **Pregnancy Confirmation Report** (**OT10**) and a **Change of Status Form (OT12).** The TrialNet Coordinating Center must be notified within 24 hours of clinic notification of an active pregnancy in a study participant.

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

E. COMPLIANCE (The Study Coordinator should assess the participant's study drug compliance and record on Source Document)

1. How many doses has the participant missed since the last study visit? __ __
2. Is the participant currently taking study drug? Y N

   If NO, Complete a **Change in Study Drug Form (OT07).**

The Study Coordinator should reinforce the importance of taking the study drug every day.

F. SPECIMENS DRAWN/ PROCEDURES PERFORMED

The following specimens/procedures should be drawn/performed during this visit:

	a. Performed on this visit date?	**b. If NOT performed at this visit, specify date performed:**
1. HbA1c	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR
2. OGTT	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR
3. Serum for autoantibodies	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR
4. Samples for storage	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR
5. Dispensation/return of study drug (*If YES, complete the **Study Drug Dispensation and Return Form - OT14***)	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR

Initials (first, middle, last) of person completing this form: __ __ __ F M L

Date form completed: __ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ Participant ID: _____-___ ___-___ ___ -___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

The Study Coordinator should complete this form at the Month 12, 24, 36, 48, 60, and 72 follow-up visits.

A. VISIT INFORMATION

1. Visit Date: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

2. For which visit is this form being completed? *(check one)*

☐ 12 Month 12 ☐ 24 Month 24 ☐ 36 Month 36 ☐ 48 Month 48 ☐ 60 Month 60 ☐ 72 Month 72 ☐ 99 Other

a. If OTHER, specify: _____

3. Did the visit occur at a site other than at the primary study site? Y N
   a. If YES, Record Site Number for reimbursement: __ __ __ __
   ***Note**: Site Number **must** correspond to a TrialNet Clinical Center, Affiliate, or Participating Physician.*

B. MEDICAL HISTORY

1. Have there been any changes in health since the last scheduled visit? Y N

   If YES, refer to CTCAE criteria for grading definitions
   If Grade 1 adverse event, record on source document.
   *If Grade 2 or greater, complete **Adverse Event Report Form (OT08)** as well as source document.*

2. Have there been any changes in concomitant medication since the last scheduled visit? Y N
   If YES, complete a **Concomitant Medication Form** (**OT18**)

C. GENERAL PHYSICAL EXAM

1. Collect the following physical assessments:
   ***Note**: Have the participant rest for 5 minutes before doing these assessments.*

a. Seated arm blood pressure:	__ __ __ mmHg (Systolic) / __ __ __ mmHg (Diastolic)		
b. Weight:	__ __ __.__ kg	or	__ __ __. __ __ lbs
c. Height:	__ __ __.__ cm	or	__ __. __ __ in
d. Abdominal circumference:	__ __ __.__ cm	or	__ __. __ __ in

2. Record whether the following systems are reported as normal or abnormal by the participant and normal or abnormal upon examination: *(if not done, write "*")*:

Review of Systems	1) Participant Reported Normal?	2) Normal on Exam?	If Either is ABNORMAL, a) Explain:
a. HEENT	Y N	Y N	_____
b. Neck	Y N	Y N	_____
c. Thyroid	Y N	Y N	_____
d. Lungs	Y N	Y N	_____
e. Chest/Breasts	Y N	Y N	_____
f. Heart/Circulatory	Y N	Y N	_____

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

C. GENERAL PHYSICAL EXAM (CONTINUED)

2. Record whether the following systems are reported as normal or abnormal by the participant and normal or abnormal upon examination: *(if not done, write "*")*:

Review of Systems	1) Participant Reported Normal?	2) Normal on Exam?	If Either is ABNORMAL, a) Explain:
g. Abdomen	Y N	Y N	_____
h. Musculoskeletal	Y N	Y N	_____
i. Neurologic	Y N	Y N	_____
j. Genitourinary/Testes	Y N	Y N	_____
k. Skin/Nails	Y N	Y N	_____
l. Lymph nodes	Y N	Y N	_____
m. Other	Y N	Y N	_____
If OTHER, Specify	_____		

3. For subjects less than 18 years of age, record the participant's sexual development using the Tanner Scale:
If the subject is 18 years of age or older, skip to Section D.

Tanner Stage *(complete a. **OR** b. **AND** c.)*	*(check one)*		
a. Breast **(female)**	☐ 1 Stage 1	☐ 2 Stage 2	☐ 3 Stage 3 or greater
b. Genitalia **(male)**	☐ 1 Stage 1	☐ 2 Stage 2	☐ 3 Stage 3 or greater
c. Pubic Hair **(both)**	☐ 1 Stage 1	☐ 2 Stage 2	☐ 3 Stage 3 or greater

D. PREGNANCY MONITORING (If participant is male, proceed to Section E.)

1. If FEMALE, does the participant have reproductive potential? Y N

2. Is the female participant sexually active? Y N

If YES to BOTH questions D1 and D2 above, continue (If not, proceed to **Section E**)

a. Does she currently use a form of birth control? *(Females of reproductive age are expected to use a form of birth control)* Y N

b. Does she plan on becoming pregnant in the next 6 months? Y N

c. Was a urine pregnancy test completed at this visit? Y N

If YES, 1) Was the test result positive? Y N

If the **pregnancy test** result was **positive**, discontinue therapy and complete a **Pregnancy Confirmation Report** (**OT10**) and a **Change of Status Form** (**OT12**). The TrialNet Coordinating Center must be notified within 24 hours of clinic notification of an active pregnancy in a study participant.

E. COMPLIANCE (The Study Coordinator should assess the participant's study drug compliance and record on Source Document)

1. How many doses has the participant missed since the last study visit? __ __
2. Is the participant currently taking study drug? Y N

   If NO, Complete a **Change in Study Drug Form (OT07).**

The Study Coordinator should reinforce the importance of taking the study drug every day.

F. SPECIMENS DRAWN/ PROCEDURES PERFORMED

The following specimens/procedures should be drawn/performed during this visit:

	a. Performed on this visit date?	**b. If NOT performed at this visit, specify date performed:**
1. HbA1c	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR
2. OGTT	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR
3. Serum for autoantibodies	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR
4. Samples for storage	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR
5. Lifestyle Questionnaire	Y N	__ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR
6. Dispensation/return of study drug (*If YES, complete the **Study Drug Dispensation and Return Form - OT14***)	Y N	_ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR

Initials (first, middle, last) of person completing this form: __ __ __ F M L

Date form completed: __ __ / __ __ __ / __ __ __ __ DAY MONTH YEAR

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ | Participant ID: _____-___ ___-___ ___ -___ ___ ___ ___ - ___ **Int'l** | Participant Letters: ___ ___ ___

The Study Coordinator should complete this form during the 3-Month interim phone contact visit.

A. VISIT INFORMATION

1. Visit Date: ___ ___ / ___ ___ ___ / ___ ___ ___ ___ (DAY / MONTH / YEAR)

☐ 9	Month 9	☐ 33	Month 33	☐ 57	Month 57
☐ 15	Month 15	☐ 39	Month 39	☐ 63	Month 63
☐ 21	Month 21	☐ 45	Month 45	☐ 69	Month 69
☐ 27	Month 27	☐ 51	Month 51	☐ 99	Other

2. Information gathered from: *(check one)*
   ☐1 Parent (Mother, Father) ☐ 2 Guardian ☐ 3 Participant

B. MEDICAL HISTORY

1. Have there been any changes in health since the last scheduled visit? Y N

   If YES, refer to CTCAE criteria for grading definitions
   If Grade 1 adverse event, record on source document.
   *If Grade 2 or greater, complete **Adverse Event Report Form (OT08)** as well as source document.*

2. Have there been any changes in concomitant medication since the last scheduled visit? Y N
   If YES, complete a **Concomitant Medication Form (OT18)**

C. PREGNANCY MONITORING (If participant is male, proceed to Section D.)

1. If FEMALE, does the participant have reproductive potential? Y N
   If YES, continue (otherwise, proceed to **Section D**)
   a. Does she currently use a form of birth control? *(Females of reproductive age are expected to use a form of birth control, or practice abstinence)* Y N
   b. Does she plan on becoming pregnant in the next 6 months? Y N

D. COMPLIANCE (The Study Coordinator should assess the participant's study drug compliance and record on Source Document)

1. How many doses has the participant missed since the last study visit? ___ ___
2. Is the participant currently taking study drug? Y N

   If NO, Complete a **Change in Study Drug Form (OT07).**

The Study Coordinator should reinforce the importance of taking the study drug every day.

Initials (first, middle, last) of person completing this form: ___ ___ ___ (F M L)

Date form completed: ___ ___ / ___ ___ ___ / ___ ___ ___ ___ (DAY / MONTH / YEAR)

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ Participant ID: ____ - ___ ___- ___ ___ -___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

Complete this form each time participant stops taking study drug, or re-starts study drug.

A. REPORT INFORMATION

1. Date of report: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)
2. Current visit or last attended scheduled visit *(check one)*:

☐ 2	Baseline	☐ 18	Month 18	☐ 42	Month 42	☐ 66	Month 66
☐ 3	Month 3	☐ 24	Month 24	☐ 48	Month 48		
☐ 6	Month 6	☐ 30	Month 30	☐ 54	Month 54		
☐ 12	Month 12	☐ 36	Month 36	☐ 60	Month 60		

B. CHANGE IN STUDY DRUG

1. Change in study drug status: ☐ 1 Discontinuing ☐ 2 Re-starting
2. Date change in study drug status effective: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)
3. Reason the study drug was stopped *(check one – **complete for discontinuation only**)*:

☐ 1	Self-discontinued by participant	☐ 4	Pregnancy
☐ 2	Development of T1D** **Complete Diabetes Onset Form (OT16)**	☐ 5	Study discontinuation
☐ 3	Adverse event	☐ 99	Other

a. IF OTHER, specify: _____

_____

4. Was the participant informed of his/her treatment group assignment? Y N

With the exception of a pregnancy, if the participant was told of his/her treatment group assignment the **Protocol Deviation Form (OT13)** must be completed

5. Did the participant return the remaining study drug? Y N
6. Is there a change in study status at this time? Y N

If **YES**, complete **Change in Status Form (OT12)**

Initials (first, middle, last) of person completing this form: __ __ __ (F M L)

Date form completed: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ | Participant ID: _____-___ ___- ___ ___ -___ ___ ___ ___ - ___ **Int'l** | Participant Letters: ___ ___ ___

For this study, only events Grade 2 and greater will be reported to the Coordinating Center.
The Study Coordinator should complete this form to report:

- **A new adverse event, or**
- **A change in intensity, frequency, or duration of a previously reported adverse event. If updating a previously reported adverse event, make the necessary changes to your site copy of the original report and send a copy of the updated pages to the Coordinating Center. Include a copy of the first page for updates so that changes can be linked to the original Adverse Event ID Number.**

Complete this form with as much information as is currently known regarding the adverse event.

A. REPORT INFORMATION

Adverse Event ID Number: # # # # #

1. Date of report (*e.g. 01/Jan/2007*): __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

2. Current visit or last attended scheduled visit (check one):

☐ 1	Initial Visit	☐ 18	Month 18	☐ 48	Month 48
☐ 2	Baseline	☐ 24	Month 24	☐ 54	Month 54
☐ 3	Month 3	☐ 30	Month 30	☐ 60	Month 60
☐ 6	Month 6	☐ 36	Month 36	☐ 66	Month 66
☐ 12	Month 12	☐ 42	Month 42		

3. Was the participant taking the study drug at the time of the event? Y N

4. How many separate adverse events are being reported at this time? __ __

IF MORE THAN 1 event, **each** adverse event requires the completion of a **separate Adverse Event Report Form (OT08)**.

B. EVENT DESCRIPTION

1. Date of onset of adverse event: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

2. Event Type *(check **one**)*

Accident

- ☐ 1 Accident requiring medical assistance, but no ER visit or hospital admission
- ☐ 2 Accident requiring ER visit, but not admission to hospital
- ☐ 3 Accident requiring admission to hospital

Pregnancy

- ☐ 4 Pregnancy*
- ☐ 5 Adverse pregnancy outcome

* Complete **Pregnancy Confirmation Form** (**OT10**) and **Pregnancy Outcome Report Form** (**OT11**)

Procedure Related

- ☐ 6 Vasovagal fainting
- ☐ 7 Nausea, Emesis
- ☐ 8 Excessive Bleeding
- ☐ 9 Blood clot
- ☐ 10 Infection

General

- ☐ 11 Diarrhea
- ☐ 12 Allergic Reaction (rash, urticaria)

☐ 99 Other, a. Specify: _____

3. Describe the event:

(*Include information leading up to the event, procedures or tests completed, date stopped study drug, etc.*):

_____
_____
_____
_____

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ Participant ID: _____-___ ___- ___ ___ -___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

B. EVENT DESCRIPTION (CONTINUED)

4. Intensity of reported event (*check one*): ☐ 2 Grade 2 ☐ 3 Grade 3 ☐ 4 Grade 4 ☐ 5 Grade 5
   NOTE: Refer to NCI CTCAE to grade intensity

5. Has the adverse event resolved? Y N

   a. If YES, date resolved: ___ ___ / ___ ___ ___ / ___ ___ ___ ___ (DAY / MONTH / YEAR)

C. RELATIONSHIP AND ACTIONS TAKEN

1. Actions taken for the adverse event:

a. Discontinued study drug?	Y N	d. Non-drug treatment?	Y N
b. Concomitant medication prescribed?	Y N	e. None?	Y N
c. Outpatient procedure?	Y N	f. Other?	Y N

   1) If OTHER, specify: _____

2. Did treatment require any of the following?

a. Visit to study site	Y N
b. Visit to emergency room	Y N
c. Doctor's visit	Y N
d. Admission to hospital	Y N
e. Admission to skilled nursing facility	Y N

   If treatment involved admission to hospital or skilled nursing facility,
   1) Record length of stay: ___ ___ Days

3. Relationship to study drug *(check one)*:

☐ 1 Not related ☐ 2 Unlikely ☐ 3 Possible ☐ 4 Probable ☐ 5 Definite

Not related:	No relationship (0% chance) that AE/SAE is related to study drug
Unlikely:	Relationship is possible, but not likely (1 – 19% chance) that AE/SAE is related to study drug
Possible	Reasonable likelihood that the study medication caused the adverse event with a chance (20-50%) the AE/SAE is related that cannot be excluded
Probable:	Relationship is quite likely (51 – 99% chance) that the AE/SAE is related to the study drug
Definite:	Unquestionable relationship (100% chance) that the AE/SAE is related to the study drug

Site Number: ___ ___ ___ ___ Participant ID: _____-___ ___- ___ ___ -___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

D. EVENT OUTCOME

1. What was the outcome of the adverse event? *(check one)*

- ☐ 1 Recovered, no residual effect
- ☐ 2 Residual effect, no treatment
- ☐ 3 Residual effect, being treated
- ☐ 4 Persistent, no treatment
- ☐ 5 Persistent, being treated
- ☐ 6 Death (**Complete OT09 Mortality Event Form)**

a. Date of death: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

b. Probable cause of death: _____

- ☐ 99 Other

c. If OTHER, specify: _____

Report all **Serious Adverse Events** to the TrialNet Coordinating Center **within 24 hours.**
Fax the completed **TrialNet MedWatch Form** to the TrialNet Coordinating Center at **(866) 804-6058** or **(301) 468-1676** within **24 hours** of clinic notification.

E. MEDWATCH *(Complete for serious adverse events only)*

1. Date the TrialNet MedWatch Form was faxed to the Coordinating Center: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

a. Time the TrialNet MedWatch Form was faxed (*24-hour clock*): __ __ : __ __ (Hour / Min)

Initials (first, middle, last) of person completing this form: __ __ __ (F M L)

Date form completed: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

Signature of Principal Investigator *(Required)***:** _____ **Signed?** Y N

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ Participant ID: _____-___ ___-___ ___ -___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

Complete this form in the event of a study participant fatality during the study, regardless of whether the death was related to the study drug. This form should be sent to the Coordinating Center within 24 hours of notification of the death. Once a death certificate has been obtained, a copy MUST be sent to the Coordinating Center.

Additional form(s) that need to be completed:	**Documentation required by the TNCC:**
- **Adverse Event Report Form** (**OT08**)	- Death Certificate *(when available)* - Autopsy report *(when available)*

A. REPORT INFORMATION

1. Date of report: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)
2. Date of death __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)
3. Type of report: ☐ 1 Initial ☐ 2 Follow-up

B. GENERAL EVENT CLASSIFICATION

1. Where did the death occur? *(check one)*

☐ 1	Hospital	☐ 4	Long-term care institution
☐ 2	Home	☐ 5	Unknown
☐ 3	School/Work	☐ 99	Other

a. IF OTHER, specify: _____

2. The death was *(check one)*:

☐ 1	Sudden, explained	☐ 3	Following illness
☐ 2	Sudden, unexplained		

3. At the time of onset of the terminal event, the participant was *(check one)*:

☐ 1	Asleep	☐ 4	Engaged in moderate physical activity
☐ 2	Awake, but sedentary	☐ 5	Engaged in heavy physical activity
☐ 3	Engaged in light physical activity	☐ 9	Unknown

4. Was the participant on study drug at the time of the death? Y N
5. Has an autopsy been performed at this point? Y N
   a. IF YES, Is the autopsy report available? Y N
6. Has a death certificate been obtained? Y N
   a. IF NO, Has one been requested? Y N
7. Indicate the sources of information that were used to complete this form: (*Circle all that apply*)

a. Death certificate?	Y	N	d. Interview of attending physician?	Y	N
b. Autopsy report?	Y	N	e. Interview of family member?	Y	N
c. Hospital report on fatal illness?	Y	N	f. Other?	Y	N

1. IF OTHER, specify: _____

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ Participant ID: ____-___ ___-___ ___-___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

C. SPECIFIC EVENT INFORMATION

1. Describe the immediate cause of death:

_____
_____
_____
_____
_____

2. Describe the underlying cause of death:

_____
_____
_____
_____
_____

3. Describe any contributory causes of death:

_____
_____
_____
_____
_____

4. Specify which of the immediate, underlying and/or contributory causes of death were present at randomization:

_____
_____
_____
_____
_____

Initials (first, middle, last) of person completing this form: ___ ___ ___ (F M L)

Date form completed: ___ ___ / ___ ___ ___ / ___ ___ ___ ___ (DAY / MONTH / YEAR)

Signature of Principal Investigator: _____ (Signature) Date

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___

Participant ID: ____-___ ___- ___ ___ -___ ___ ___ ___ - ___
Int'l

Participant Letters: ___ ___ ___

Complete this form upon confirmation that a study participant is pregnant, regardless of assigned treatment group. Coded study medication *must* be stopped immediately.

Additional form(s) that need to be completed:
- **Change in Study Drug Form (OT07)**
- **Pregnancy Outcome Report Form (OT11)***
- **Change in Status Form (OT12)**
- **Adverse Event Report Form (OT08)**

* When pregnancy has ended

A. REPORT INFORMATION

Pregnancy Identification Number: ####

1. Report Date: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

2. Last attended study visit prior to the confirmed pregnancy:

☐ 2	Baseline	☐ 18	Month 18	☐ 42	Month 42	☐ 66	Month 66
☐ 3	Month 3	☐ 24	Month 24	☐ 48	Month 48		
☐ 6	Month 6	☐ 30	Month 30	☐ 54	Month 54		
☐ 12	Month 12	☐ 36	Month 36	☐ 60	Month 60		

B. PREGNANCY INFORMATION

1. Date of positive pregnancy test: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)
2. Date of last menstrual cycle: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)
3. Estimated date of delivery: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)
4. Is the participant planning on carrying the pregnancy to term? Y N
5. Has the coded study medication been stopped? Y N

IF YES, a **Change in Study Drug Form (OT07)** and **Change of Status Form (0T12)** must be completed.

6. Is the participant willing to continue with future follow-up visits? Y N
7. Has the participant's obstetric care provider been informed of her participation in this study? Y N

C. PREGNANCY HISTORY

1. Indicate total number of prior pregnancies (not including this one): __ __
2. Has the participant ever experienced a complication of pregnancy? Y N

IF YES,

a. Has the participant ever experienced a spontaneous miscarriage? Y N
b. Has the participant ever experienced a pregnancy that resulted in a stillbirth? Y N
c. Has the participant ever had a pregnancy result in neonatal death? Y N
d. Has the participant ever experienced a pre-term delivery (< 37 gestational weeks)? Y N
e. Has the participant ever experienced a post-term delivery (> 42 gestational weeks)? Y N

Initials (first, middle, last) of person completing this form: __ __ __ (F M L)

Date form completed: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ | Participant ID: _____-___ ___- ___ ___ -___ ___ ___ ___ - ___ **Int'l** | Participant Letters: ___ ___ ___

This form should be completed when the outcome of an active pregnancy becomes known. This form must be completed for all participants that become pregnant during the course of the trial.

A. PREGNANCY OUTCOME INFORMATION

1. Indicate the Pregnancy Identification Number: __ __ __ __

The *Pregnancy Identification Number* is located on the participant's initial **Pregnancy Confirmation Form** (**OT10**)

2. Is the outcome of the pregnancy unknown due to loss of participant to follow-up? Y N

IF YES, **STOP HERE**

3. Date pregnancy ended: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

4. Was the pregnancy terminated as a result of an induced abortion? Y N
   a. IF YES, was the reason for the abortion medically indicated? Y N
      1. IF YES*, specify reason: _____

5. Did the pregnancy result in a spontaneous miscarriage*? Y N

6. Did the pregnancy result in a live birth or multiple live births? Y N

7. Did the pregnancy result in a stillbirth? Y N
   a. IF YES*, did the stillbirth have any congenital malformations? Y N
      1. IF YES, specify: _____
   b. Did the stillbirth have any other complications? Y N
      1. IF YES, specify: _____

8. Indicate number of infants (both living and deceased) the birth resulted in: __ __

9. Were there any complications during the delivery? Y N

10. Was an HbA1c measured at any time during the pregnancy? Y N
    IF YES,
    a. Indicate HbA1c: __ __. __ %
    b. Date measured: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

11. Is the participant currently breastfeeding? Y N

* Requires completion of an **Adverse Event Report Form** (**OT08**)

B. INFANT INFORMATION

Complete Section B to record the details of any live birth(s).

1. Indicate the Pregnancy Identification Number: __ __ __ __

2. Birth Order:	__ __	__ __	__ __†
3. Indicate sex (M/F):	M F	M F	M F
4. Indicate gestational age:	__ __ wks	__ __ wks	__ __ wks

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ Participant ID: _____-___ ___- ___ ___ -___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

B. INFANT INFORMATION (CONTINUED)

Complete Section B to record the details of any live birth(s).

5. Indicate birth weight:	___ ___ ___ ___gm OR ___ ___ lbs ___ ___ oz	___ ___ ___ ___ gm OR ___ ___ lbs ___ ___ oz	___ ___ ___ ___ gm OR ___ ___ lbs ___ ___ oz
6. **1 minute** APGAR score:	___ ___	___ ___	___ ___
7. **5 minute** APGAR score:	___ ___	___ ___	___ ___
8. Was the infant born with any congenital malformations?	Y N	Y N	Y N
a. IF YES*, specify:	_____ _____	_____ _____	_____ _____
9. Was the infant born with other complications?	Y N	Y N	Y N
a. IF YES*, specify:	_____ _____	_____ _____	_____ _____
10. Was the infant admitted to the Neonatal Intensive Care Unit (NICU) at any time*?	Y N	Y N	Y N
11. Was the infant discharged from the hospital alive?	Y N	Y N	Y N
IF YES, a. Date discharged:	__ __/__ __ __/__ __ __ __ DAY MONTH YEAR	__ __/__ __ __/__ __ __ __ DAY MONTH YEAR	__ __/__ __ __/__ __ __ __ DAY MONTH YEAR
IF NO*, b. Date of death:	__ __/__ __ __/__ __ __ __ DAY MONTH YEAR	__ __/__ __ __/__ __ __ __ DAY MONTH YEAR	__ __/__ __ __/__ __ __ __ DAY MONTH YEAR
c. Specify cause of death:	_____ _____	_____ _____	_____ _____

* Requires completion of an **Adverse Event Report Form** (**OT08**)

† If more space is needed, attach additional copies of the second page of this form

Initials (first, middle, last) of person completing this form: ___ ___ ___ (F M L)

Date form completed: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ Participant ID: ___-___ ___-___ ___ -___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

The Study Coordinator should complete this form for every change in study status (inactivation or re-activation).

A. REPORT INFORMATION

Status Identification Number: # # # # #

1. Date of report *(e.g. 05/Sep/2007)*: ___ ___ /___ ___ ___ / ___ ___ ___ ___ (DAY MONTH YEAR)

2. Last attended study visit *before* change in status (*check one*):

☐ 1	Initial	☐ 12	Month 12	☐ 36	Month 36	☐ 60	Month 60
☐ 2	Baseline	☐ 18	Month 18	☐ 42	Month 42	☐ 66	Month 66
☐ 3	Month 3	☐ 24	Month 24	☐ 48	Month 48	☐ 72	Month 72
☐ 6	Month 6	☐ 30	Month 30	☐ 54	Month 54		

B. STATUS CHANGE INFORMATION – ACTIVE / INACTIVE

1. Effective date for change in status:
(*For inactivation, record date of last contact with participant*) ___ ___ /___ ___ ___ / ___ ___ ___ ___ (DAY MONTH YEAR)

2. Change in status that has occurred:

☐ 1 Change to active status following period of inactivity

☐ 2 Change to inactive status following period of active study participation

(Complete Change in Study Drug Form (OT07) if the participant re-starts or withdraws from study drug)

C. DESCRIPTION OF INACTIVATION

1. Record the primary reason for participant inactivation *(check one)*:

☐ 1 Adverse Event *

☐ 2 Death

☐ 3 Pregnancy **

☐ 4 Withdrew consent *(describe)*
1) Explain: _____

☐ 5 e. Lost to follow-up *(e.g. unable to contact)*

☐ 6 Ineligible

☐ 7 Development of T1D***

☐ 8 End of study

☐ 9 Complications with Study Drug *(describe)*
1) Specify: _____

☐ 10 Other *(describe)*
1) Specify: _____

2. Is the participant willing to be contacted in the future? Y N

* *Complete an **Adverse Event Report Form (OT08)** as required*
** *Complete a **Pregnancy Confirmation Form (OT10)** and a **Pregnancy Outcome Report Form (OT11)***
*** *Complete a **Type 1 Diabetes Onset Form (OT16)**.*

Initials (first, middle, last) of person completing this form: ___ ___ ___ (F M L)

Date form completed: ___ ___ /___ ___ ___ / ___ ___ ___ ___ (DAY MONTH YEAR)

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ Participant ID: ___-___ ___- ___ ___ -___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

Complete this form for each protocol deviation that occurs. A protocol deviation is defined as any action taken that is counter to the specific instructions given in the protocol.

A. REPORT INFORMATION

Deviation ID Number: #####

1. Date of report: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

2. For which study visit is this form being completed?

☐ 1	Initial Visit	☐ 12	Month 12	☐ 36	Month 36	☐ 60	Month 60
☐ 2	Baseline	☐ 18	Month 18	☐ 42	Month 42	☐ 66	Month 66
☐ 3	Month 3	☐ 24	Month 24	☐ 48	Month 48	☐ 72	Month 72
☐ 6	Month 6	☐ 30	Month 30	☐ 54	Month 54		

B. PROTOCOL DEVIATION INFORMATION

1. Date protocol deviation occurred __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

2. Protocol deviation (*check one)*:

☐ 1 Randomization of ineligible subject
a. If checked, approved by Eligibility Committee? Y N

☐ 2 Participant randomized more than 52 days after OGTT performed

☐ 3 Study procedure required by protocol not completed

☐ 4 Protocol-specified assay collection schedule not followed

☐ 5 Study visit occurred outside of window

☐ 99 Other

If OTHER,
b. Specify deviation: _____

3. Describe deviation and circumstances: _____

4. Corrective action taken *(if necessary)*: _____

Signature of PI: **Signed?** Y N

Date signed: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

Initials (first, middle, last) of person completing this form: __ __ __ (F M L)

Date form completed: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: __ __ __ __ Participant ID: ____ - ___ ___- ___ ___ -___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

The Study Coordinator should complete this form for every dispensation and return of study drug.

A. REPORT INFORMATION

1. Report date *(e.g. 05/Jan/2007)*: __ __ / __ __ ___/ __ __ __ __ (DAY / MONTH / YEAR)

2. Current visit or last attended scheduled visit *(check one)*:

☐ 2	Baseline	☐ 18	Month 18	☐ 42	Month 42	☐ 66	Month 66
☐ 3	Month 3	☐ 24	Month 24	☐ 48	Month 48		
☐ 6	Month 6	☐ 30	Month 30	☐ 54	Month 54		
☐ 12	Month 12	☐ 36	Month 36	☐ 60	Month 60		

B. RETURN OF STUDY DRUG

1. Was study drug returned? Y N
   *If NO, skip to **Section C.***

2. Date study drug returned: __ __ / __ __ ___/ __ __ __ __ (DAY / MONTH / YEAR)

3. Number of capsules returned (including full bottles): __ __ __ capsule(s)

C. DISPENSATION OF STUDY DRUG

1. Was study drug dispensed? Y N
   *If NO, skip to **Section D.***

2. Date study drug dispensed: __ __ / __ __ ___/ __ __ __ __ (DAY / MONTH / YEAR)

   a. Number of capsules dispensed (including bottles that were returned): __ __ __ capsule(s)

   b. How did the participant receive the study drug?

   ☐ 1 At Clinical Center ☐ 2 By Courier

3. Record the Randomization Number used for study drug dispensation: __ __ __ __ __ - __ __

4. Labels and dates of study drug bottles dispensed to the participant:

Attach Second Part of Bottle Label

a. 

Attach Second Part of Label From Bottle 1 Here

b. 

Attach Second Part of Label From Bottle 2 Here

1) Date bottle dispensed:

__ __ / __ __ __ / __ __ __ __
DAY MONTH YEAR

__ __ / __ __ __ / __ __ __ __
DAY MONTH YEAR

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ Participant ID: ___ - ___ ___- ___ ___ -___ ___ ___ ___ -___ **Int'l** Participant Letters: ___ ___ ___

C. DISPENSATION OF STUDY DRUG (CONTINUED)

4. Labels and dates of study drug bottles dispensed to the participant:

Attach Second Part of Bottle Label

1) Date bottle dispensed:

c. 

DAY ___ ___ / **MONTH** ___ ___ ___ / **YEAR** ___ ___ ___ ___

d. 

DAY ___ ___ / **MONTH** ___ ___ ___ / **YEAR** ___ ___ ___ ___

e. 

DAY ___ ___ / **MONTH** ___ ___ ___ / **YEAR** ___ ___ ___ ___

f. 

DAY ___ ___ / **MONTH** ___ ___ ___ / **YEAR** ___ ___ ___ ___

g. 

DAY ___ ___ / **MONTH** ___ ___ ___ / **YEAR** ___ ___ ___ ___

D. ADDITIONAL INFORMATION

1. Were there any unusual circumstances? *(For example, did the participant experience any difficulties taking the study drug, such as, did the participant lose the study drug or require a larger quantity than normal dispensed?)* Y N

If YES,

a. Describe:

Initials (first, middle, last) of person completing this form: ___ ___ ___ (F M L)

Date form completed: ___ ___ / ___ ___ ___/ ___ ___ ___ ___ (DAY / MONTH / YEAR)

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ Participant ID: ____-___ ___- ___ ___ -___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

This form should be completed when an expected visit is missed and a visit form will not be completed.

A. VISIT INFORMATION

1. Report Date: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

2. Which visit did the participant miss?

☐ 2	Baseline	☐ 18	Month 18	☐ 42	Month 42	☐ 66	Month 66
☐ 3	Month 3	☐ 24	Month 24	☐ 48	Month 48	☐ 72	Month 72
☐ 6	Month 6	☐ 30	Month 30	☐ 54	Month 54		
☐ 12	Month 12	☐ 36	Month 36	☐ 60	Month 60		

3. Was the participant contacted? Y N

a. If YES, is there a change in the participant's status? Y N

If YES, complete **Change of Status Form (OT12)**

4. Provide additional information about the reason the visit was missed, if known:

_____
_____
_____
_____
_____

Initials (first, middle, last) of person completing this form: ___ ___ ___ (F M L)

Date form completed: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates. Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number: ___ ___ ___ ___ Participant ID: ____-___ ___- ___ ___ -___ ___ ___ ___ - ___ **Int'l** Participant Letters: ___ ___ ___

E. OTHER LABORATORY VALUES

Laboratory Values	a. Result	Reference Range (if available) b. Low	c. High	d. Date
1. HbA1c *(only if obtained outside of TrialNet)*	___ ___ . ___ %	___ ___ . ___ %	___ ___ . ___ %	___ ___ / ___ ___ ___ / ___ ___ ___ ___ DAY MONTH YEAR

Signature of Physician reviewing this form: _____

Initials (first, middle, last) of person completing this form: ___ ___ ___ F M L

Date form completed: ___ ___ / ___ ___ ___ / ___ ___ ___ ___ DAY MONTH YEAR

Site Number: ___ ___ ___ ___ | Participant ID: _____-___ ___- ___ ___ -___ ___ ___ ___ - ___ **Int'l** | Participant Letters: ___ ___ ___

The Study Coordinator should complete this form when it is necessary for a participant to transfer to a new site. The yellow copy of this form should also be sent to the new site.

A. REPORT INFORMATION

1. Report Date: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

2. What is the last visit that the participant will complete at the current site before the transfer?

☐ 1	Initial Visit	☐ 12	Month 12	☐ 36	Month 36	☐ 60	Month 60
☐ 2	Baseline	☐ 18	Month 18	☐ 42	Month 42	☐ 66	Month 66
☐ 3	Month 3	☐ 24	Month 24	☐ 48	Month 48	☐ 72	Month 72
☐ 6	Month 6	☐ 30	Month 30	☐ 54	Month 54		

3. Date of last completed study visit: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

B. CONTACT CHANGE/SITE TRANSFER INFORMATION

1. Date change to be implemented: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

2. Is the participant transferring to another site? Y N

   If YES,

   a. Current Site Number: ___ ___ ___ ___

   b. New Site Number: ___ ___ ___ ___

Initials (first, middle, last) of person completing this form: ___ ___ ___ (F M L)

Date form completed: __ __ / __ __ __ / __ __ __ __ (DAY / MONTH / YEAR)

On all questions write "?" if the desired information is currently unavailable, but is being checked and will be known in future updates.
Write "" if the desired information is permanently unavailable (i.e. will not be known in any future updates).*

Site Number:
Date of Initial Assessment:
Person Completing Form:

Participant ID:
Participant Letters:

Assess Date	Medication	Dose	Units (mg, ml)	Frequency (BID, TID)	Interval (QD, QOD)	Route (PO, IV, etc.)	Indication	Start Date	Continuing?	If no, Stop Date
									O Y O N	
									O Y O N	
									O Y O N	
									O Y O N	
									O Y O N	
									O Y O N	
									O Y O N	
									O Y O N	
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									O Y O N	
									O Y O N	
									O Y O N	

Appendix 16.1.7 Randomization Scheme and Codes

TN07 Oral Insulin Appendix 16.1.7 – Randomization Scheme and Codes

Participant ID	Treatment	Randomization #
104548	Placebo	05007-2
104641	Placebo	05-034
105068	Placebo	05004-5
106297	Active	05002-4
106673	Active	05008-1
107924	Placebo	05-012
108374	Active	05-014
154059	Active	05-015
164092	Placebo	05-038
189107	Placebo	05-026
191668	Active	05-025
199045	Placebo	05-028
207345	Active	05-055
257186	Placebo	05-046
264860	Placebo	05-047
292670	Active	05-056
340020	Placebo	05-061
108436	Active	05-013
105102	Placebo	05-019
106031	Placebo	05-029
109000	Placebo	05011-8
178056	Placebo	04-069
216583	Active	05-050
106979	Active	05-045
107410	Active	05010-2
295400	Placebo	05-054
108131	Active	05-024
185281	Placebo	05-020
185285	Placebo	05-042
186748	Active	05-022
209027	Active	05-039
153128	Placebo	13-001
153248	Active	20-002
154032	Active	13-002
216704	Placebo	20-001
136433	Placebo	09002-6
136806	Placebo	09003-1
137702	Active	09001-0
171406	Active	09-004
171411	Placebo	09-008

Participant ID	Treatment	Randomization #
181847	Active	09-006
191656	Active	09-009
193059	Active	09-007
207413	Placebo	09-010
221640	Placebo	09-013
248060	Active	09-020
248773	Active	09-017
298583	Active	09-021
133591	Active	11001-2
134428	Active	11003-7
134482	Placebo	11006-1
147111	Active	11005-8
170035	Active	11-012
178903	Active	11-009
211676	Active	09-011
217665	Placebo	09-014
232903	Placebo	09-015
309784	Active	09-026
140808	Active	03002-1
141125	Placebo	03009-9
141479	Placebo	03001-5
142210	Active	03003-6
145077	Placebo	03-014
145569	Active	03010-4
153861	Placebo	03007-4
184285	Active	03-018
220284	Active	03-023
235303	Placebo	03-026
245361	Placebo	03-028
234883	Placebo	03-025
144158	Placebo	03004-8
144420	Active	03006-2
144825	Active	03008-3
212215	Active	03-021
203974	Active	03-019
253821	Active	03-030
146504	Active	04-028
146952	Placebo	04004-0
147185	Placebo	04001-2
147201	Active	04005-4

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Participant ID	Treatment	Randomization #
147239	Placebo	04008-6
147335	Placebo	04020-3
147711	Active	04003-3
148202	Active	04011-3
148528	Placebo	04-034
150595	Placebo	04015-0
155264	Active	04018-5
180854	Placebo	04-050
189432	Placebo	04-033
200991	Placebo	04-045
202163	Active	04-044
203110	Placebo	04-056
206031	Active	04-047
208401	Placebo	04-063
210883	Placebo	04-053
210965	Placebo	04-064
213313	Active	04-054
219630	Placebo	04-057
221040	Active	04-067
229552	Active	04-074
234740	Active	04-066
235141	Active	04-065
238841	Placebo	04-077
255747	Active	04-075
286966	Active	04-084
287768	Active	04-080
340305	Placebo	04-083
345822	Active	04-085
350068	Placebo	04-086
518507	Placebo	04-070
101498	Placebo	02001-6A
146069	Placebo	04-035
149316	Placebo	04-029
151806	Placebo	04-023
158976	Placebo	04-030
159024	Active	04-032
168561	Placebo	04-072
173990	Placebo	04-040
176150	Placebo	04-049
191959	Active	04-038

Participant ID	Treatment	Randomization #
203609	Active	04-058
212554	Placebo	04-060
217024	Active	04-061
288477	Active	04-073
154712	Placebo	07-006
154752	Active	07001-4
154999	Placebo	07003-0
155537	Placebo	07002-7
156088	Active	07004-2
172030	Active	07-008
241237	Placebo	07-020
517728	Placebo	07-017
154527	Active	07-012
154955	Placebo	07-007
156817	Placebo	07-010
171974	Active	07-009
184068	Placebo	02-039
190402	Placebo	04-037
230191	Active	07-018
237704	Placebo	07-019
301743	Placebo	07-024
503001	Active	07-014
519439	Active	07-021
201422	Placebo	07-015
101597	Active	02001-6
101854	Active	02007-3
102756	Placebo	02004-9
102758	Active	02004-9A
102841	Active	02006-1
103811	Placebo	02018-1
104207	Placebo	02-014
104306	Active	02-041
138006	Placebo	02-024
162540	Placebo	02-042
169235	Active	02-026
171203	Active	02-032
175960	Placebo	02-028
206864	Active	02-040
212260	Active	02-049
212600	Active	02-038

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Participant ID	Treatment	Randomization #
230382	Active	02-043
236509	Placebo	02-044
254522	Active	02-050
260222	Placebo	02-047
288057	Active	02-051
101858	Active	02-056
166212	Placebo	02-025
168458	Active	02-036
197113	Placebo	02-037
304068	Placebo	02-057
103336	Placebo	02012-4
103888	Placebo	02017-2
101307	Active	02003-7
183153	Placebo	02-035
294727	Placebo	02-053
300134	Active	02-055
103688	Active	02015-9
166317	Active	02-027
234791	Active	02-045
132805	Placebo	11-008
165583	Placebo	11-011
214401	Placebo	11-015
109239	Active	12002-2
110266	Placebo	12001-9
110454	Placebo	12-004
183456	Placebo	09-005
190195	Placebo	12-006
200178	Active	12-008
500340	Placebo	12-007
218374	Placebo	12-009
168672	Placebo	11-007
216293	Active	12-010
241141	Active	12-012
300046	Active	12-014
300051	Placebo	12-015
107042	Placebo	08-009
111188	Active	08001-8
111736	Placebo	08002-3
111779	Placebo	08-007
112040	Active	08003-9

Participant ID	Treatment	Randomization #
112129	Placebo	08004-6
112931	Active	08-015
113280	Active	08-013
140791	Active	03-029
157899	Placebo	08-011
159348	Active	02-029
168183	Active	08-010
169136	Active	08-012
191652	Placebo	08-014
196502	Active	08-016
205749	Placebo	08-017
213955	Placebo	08-025
282440	Placebo	08-024
298211	Active	08-023
299910	Active	06-029
515635	Active	08-020
110956	Active	08-008
242383	Active	08-019
242507	Placebo	08-018
113488	Active	14004-7
115226	Placebo	14-009
116554	Active	14-012
117163	Placebo	14-005
184372	Placebo	14-017
207650	Active	14-016
216121	Active	14-019
277201	Placebo	14-026
114938	Placebo	14-011
164043	Active	14-010
157990	Active	14-014
176743	Placebo	14-013
115711	Placebo	14-006
220089	Placebo	14-018
114772	Active	14003-8
219687	Placebo	14-020
247044	Placebo	14-024
272310	Active	14-028
188769	Active	14-031
224296	Active	14-025
118256	Placebo	06001-1

TN07 Oral Insulin Appendix 16.1.7 – Randomization Scheme and Codes

Participant ID	Treatment	Randomization #
119286	Placebo	06003-2
120460	Active	06-008
161542	Active	06-012
188017	Placebo	06-014
192103	Placebo	06-010
198828	Placebo	06-032
200258	Active	06-020
209379	Placebo	06-021
212464	Active	06-015
234535	Placebo	06-034
253138	Active	06-024
297115	Placebo	06-028
314740	Active	06-030
703145	Active	06-033
118347	Active	06002-5
237285	Placebo	06-025
117432	Placebo	06-022
158675	Active	06-006
208409	Active	06-017
123011	Active	06-019
170778	Active	06-009
183678	Placebo	06-018
510142	Active	06-026
121278	Placebo	01005-6
121544	Active	01006-3
121669	Active	01001-9
122255	Placebo	01009-8
122338	Active	01-011
122664	Placebo	01004-7
122707	Active	01003-5
170901	Placebo	01-012
188584	Active	01-017
188767	Placebo	01-020
190897	Placebo	01-018
191384	Active	01-019
211441	Active	01-024
214675	Placebo	01-031
215575	Active	01-021
238533	Active	01-023
286704	Placebo	01-026

Participant ID	Treatment	Randomization #
290560	Active	01-028
347740	Active	01-032
122274	Active	01010-0
123470	Active	01008-4
180595	Placebo	01-016
122752	Placebo	01007-0
125600	Placebo	10-009
125912	Active	10-014
126006	Active	10-007
126267	Active	10003-5
139956	Placebo	04-059
166581	Placebo	10-013
169495	Active	10-006
240231	Active	10-020
277980	Active	10-016
282701	Placebo	10-019
124690	Placebo	10001-4
126687	Placebo	10-005
192313	Active	10-008
211189	Active	10-012
300592	Active	10-021
244386	Active	10-015
100308	Active	15-021
100508	Placebo	15-002
170925	Placebo	15-006
176409	Placebo	15-008
187158	Active	15-011
187159	Active	15-011
221718	Placebo	15-007
286095	Placebo	15-015
158891	Active	16-001
213204	Placebo	16-005
195463	Placebo	07-013
296701	Active	16-011
236554	Placebo	16-006
241508	Active	16-009
127694	Placebo	16-002
209105	Active	16-003
209106	Active	16-003
129175	Active	17-002

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Participant ID	Treatment	Randomization #
129220	Active	17-003
239046	Placebo	17-011
130849	Placebo	17-006
237513	Placebo	17-010
294420	Active	17-015
347143	Active	17-019
225359	Placebo	17-008
162254	Active	17-017
139273	Active	17-013
223717	Placebo	17-016
263065	Active	17-014
170446	Placebo	17-001
220081	Active	05-036
236744	Active	05-040
237435	Placebo	05-041
239945	Placebo	05-044
254077	Placebo	05-048
288465	Active	05-052
149090	Active	04010-7
168009	Active	04-027
180512	Active	04-036
191712	Placebo	04-039
191736	Active	04-042
227373	Active	04-062
292855	Active	04-087
334300	Placebo	04-082
212102	Active	05-037
296577	Placebo	05-057
170515	Active	04-046
189367	Active	15-010
236322	Placebo	15-012
242554	Active	16-008
258622	Placebo	15-016
287120	Active	15-013
287122	Placebo	15-014
287123	Placebo	15-014
302960	Active	15-020
315734	Placebo	15-019
354120	Active	15-023
354180	Active	15-024

Participant ID	Treatment	Randomization #
104381	Active	05-016
106430	Active	05003-8
150689	Active	04016-9
173564	Placebo	05-018
174596	Placebo	19-001
181598	Active	19-002
197368	Placebo	19-020
198997	Active	19-005
206142	Placebo	19-004
207653	Placebo	19-011
212933	Placebo	19-007
229729	Active	19-012
243578	Active	19-013
276602	Placebo	19-015
293487	Placebo	19-019
294397	Active	19-017
297940	Placebo	19-018
506633	Placebo	05-017
195507	Active	05-027
247720	Placebo	19-014
213274	Placebo	18-005
219382	Active	18-009
227676	Placebo	18-006
243301	Active	18-011
245441	Active	18-012
131998	Active	18-001
243472	Placebo	18-010
248457	Placebo	18-013
251162	Placebo	18-014
270063	Active	18-016
296706	Active	18-017
104397	Placebo	05001-7
104616	Active	05005-9
191632	Placebo	05-023
241843	Active	05-049
219460	Active	05-059
106033	Active	05-030
285785	Active	05-051
200279	Placebo	05-033
134454	Placebo	11002-9

TN07 Oral Insulin Appendix 16.1.7 – Randomization Scheme and Codes

Participant ID	Treatment	Randomization #
169650	Active	11-010
700195	Active	09-016
157332	Placebo	03-011
208258	Active	03-024
146482	Placebo	04006-5
146608	Active	04-055
147887	Placebo	04-081
149087	Active	04-051
162299	Active	02-023
101925	Placebo	02002-0
103320	Active	02010-3
188999	Placebo	02-033
301719	Active	02-054
103655	Active	02-021
300122	Active	02-055
103865	Active	02016-0
173995	Placebo	02-030
134786	Placebo	11004-6
187126	Placebo	11-014
186965	Active	12-005
209452	Active	19-006
113482	Active	14-015
159200	Placebo	14-007
303393	Placebo	14-029
316640	Active	14-030
228298	Active	14-022
199618	Placebo	06-016
201136	Active	06-013
243038	Active	06-031
194164	Placebo	06-011
122293	Placebo	01002-2
162636	Active	01-014
172586	Placebo	01-013
121974	Active	01-015
302121	Active	01-030
100116	Active	15-001
239468	Placebo	12-011
213839	Active	16-004
216868	Placebo	16-007
199541	Active	05-032

Participant ID	Treatment	Randomization #
306801	Placebo	05-058
149847	Placebo	04013-4
294368	Active	15-018
106271	Placebo	05006-0
215403	Placebo	18-008
132267	Placebo	18-002
298800	Placebo	18-015
154160	Placebo	05-060
172438	Active	05-031
186415	Active	05-021
233839	Placebo	05-053
106433	Placebo	05009-6
271837	Active	20-003
214522	Active	09-012
296734	Active	09-023
298188	Placebo	09-022
207312	Placebo	09-018
271858	Placebo	02-048
702445	Placebo	09-024
702781	Placebo	09-025
112103	Placebo	03005-7
140365	Active	03-017
142062	Placebo	03-016
159857	Active	03-012
205979	Placebo	03-020
231085	Placebo	03-027
145894	Active	03-013
157083	Placebo	03-015
219189	Placebo	03-022
148025	Active	04-026
148776	Active	04002-9
148980	Active	04-022
150443	Active	04-031
151583	Placebo	04-043
196581	Active	04-078
208843	Active	04-048
214511	Active	04-068
250853	Active	04-079
181049	Active	04-041
148129	Placebo	04019-2

TN07 Oral Insulin Appendix 16.1.7 – Randomization Scheme and Codes

Participant ID	Treatment	Randomization #
148565	Placebo	04012-8
149549	Active	04-024
150110	Active	04021-7
150730	Placebo	04017-6
152085	Placebo	04-025
167809	Placebo	04-052
252527	Placebo	04-071
156327	Active	07005-1
156345	Placebo	07-011
242790	Active	07-022
287965	Placebo	07-023
182144	Active	07-016
102767	Placebo	02008-2
102865	Placebo	02-022
103323	Placebo	02009-5
103522	Active	02011-7
103524	Active	02011-7
179384	Active	02-034
192883	Placebo	02-046
103474	Placebo	02-031
103238	Placebo	02020-7
103949	Active	02019-6
289753	Placebo	02-052
101548	Placebo	02-035
102367	Placebo	02005-8
103691	Active	02013-8
179399	Placebo	12-013
184658	Active	11-013
292328	Placebo	09-019
110829	Active	08005-5
112832	Placebo	08006-4
165332	Placebo	08-022
243339	Placebo	08-021
114820	Active	14-008
114876	Active	14001-1
216122	Active	14-019
235033	Placebo	14-021
190927	Active	14-023
230976	Placebo	14-027
119387	Placebo	06-007

Participant ID	Treatment	Randomization #
119799	Placebo	06004-4
237034	Placebo	06-023
158762	Active	06-005
219353	Placebo	06-027
229387	Placebo	01-022
262976	Placebo	01-025
299414	Placebo	01-029
242694	Placebo	01-027
277365	Placebo	10-018
126387	Placebo	10004-9
220473	Placebo	10-011
242901	Placebo	10-017
100736	Placebo	15-003
100780	Active	15-005
176822	Active	15-004
290747	Active	15-017
277600	Placebo	16-010
129419	Active	17-005
233459	Active	17-009
170304	Active	17-007
174059	Placebo	17-012
186529	Placebo	17-004
338560	Placebo	17-018
201622	Active	05-043
149034	Active	04007-7
150556	Active	04014-1
151042	Placebo	04-076
218080	Placebo	05-035
241304	Active	15-009
352763	Placebo	15-022
187884	Active	19-009
195928	Placebo	19-010
197962	Placebo	19-003
206943	Active	19-008
279389	Active	19-021
293496	Active	19-016
193248	Active	18-004
227916	Active	18-007
177368	Active	18-003
115222	Placebo	14002-5
126429	Placebo	10-010

Appendix 16.1.11 Publications

JAMA | Original Investigation

Effect of Oral Insulin on Prevention of Diabetes in Relatives of Patients With Type 1 Diabetes
A Randomized Clinical Trial

Writing Committee for the Type 1 Diabetes TrialNet Oral Insulin Study Group

IMPORTANCE Type 1 diabetes requires major lifestyle changes and carries increased morbidity and mortality. Prevention or delay of diabetes would have major clinical effect.

OBJECTIVE To determine whether oral insulin delays onset of type 1 diabetes in autoantibody-positive relatives of patients with type 1 diabetes.

DESIGN, SETTING, AND PARTICIPANTS Between March 2, 2007, and December 21, 2015, relatives with at least 2 autoantibodies, including insulin autoantibodies and normal glucose tolerance, were enrolled in Canada, the United States, Australia, New Zealand, the United Kingdom, Italy, Sweden, Finland, and Germany. The main study group (n = 389) had first-phase insulin release on an intravenous glucose tolerance test that was higher than the threshold. The 55 patients in the secondary stratum 1 had an identical antibody profile as the main study group except they had first-phase insulin release that was lower than the threshold. Secondary strata 2 (n = 114) and strata 3 (n = 3) had different autoantibody profiles and first-phase insulin release threshold combinations. Follow-up continued through December 31, 2016.

INTERVENTIONS Randomization to receive 7.5 mg/d of oral insulin (n = 283) or placebo (n = 277), including participants in the main study group who received oral insulin (n = 203) or placebo (n = 186).

MAIN OUTCOME AND MEASURES The primary outcome was time to diabetes in the main study group. Significance was based on a 1-sided threshold of .05, and 1-sided 95% CIs are reported.

RESULTS Of a total of 560 randomized participants (median enrollment age, 8.2 years; interquartile range [IQR], 5.7-12.1 years; 170 boys [60%]; 90.7% white non-Hispanic; 57.6% with a sibling with type 1 diabetes), 550 completed the trial including 389 participants (median age, 8.4 years; 245 boys [63%]), 382 (96%) in the main study group. During a median follow-up of 2.7 years (IQR, 1.5-4.6 years) in the main study group, diabetes was diagnosed in 58 participants (28.5%) in the oral insulin group and 62 (33%) in the placebo group. Time to diabetes was not significantly different between the 2 groups (hazard ratio [HR], 0.87; 95% CI, 0-1.2; $P = .21$). In secondary stratum 1 (n = 55), diabetes was diagnosed in 13 participants (48.1%) in the oral insulin group and in 19 participants (70.3%) in the placebo group. The time to diabetes was significantly longer with oral insulin (HR, 0.45; 95% CI, 0-0.82; $P = .006$). The HR for time to diabetes for the between-group comparisons for the 116 participants in the other secondary stratum was 1.03 (95% CI, 0-2.11; $P = .53$) and for the entire cohort of 560 participants was 0.83 (95% CI, 0-1.07; $P = .11$), which were not significantly different. The most common adverse event was infection (n = 254), with 134 events in the oral insulin group and 120 events in the placebo group, but no significant study-related adverse events occurred.

CONCLUSIONS AND RELEVANCE Among autoantibody-positive relatives of patients with type 1 diabetes, oral insulin at a dose of 7.5 mg/d, compared with placebo, did not delay or prevent the development of type 1 diabetes over 2.7 years. These findings do not support oral insulin as used in this study for diabetes prevention.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00419562

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Supplemental content

CME Quiz at jamanetwork.com/learning

Group Information: Writing Committee for the Type 1 Diabetes TrialNet Oral Insulin Study Group members and trial collaborators are listed at the end of this article.

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In the Diabetes Prevention Trial-Type 1 (DPT-1),[1,2] oral insulin compared with placebo did not show a reduction in the development of diabetes, but a post hoc analysis identified an at-risk subgroup with higher insulin autoantibody titers that suggested benefit.[2] Consequently, the Type 1 Diabetes TrialNet clinical trials network, which succeeded the DPT-1 trial group, sought to further explore the role of oral insulin in delaying diabetes among relatives who were not significantly different from those in the subgroup who had experienced apparent benefit from oral insulin in DPT-1.

The DPT-1 oral insulin trial enrolled relatives who were positive for islet cell antibodies by immunofluorescence and positive for insulin autoantibodies by radioimmunoassay, had first-phase insulin release on intravenous glucose tolerance test higher than threshold (defined below), and had a normal oral glucose tolerance test result. Since the DPT-1 oral study was conducted, the microinsulin autoantibody assay, which requires much less blood volume, was developed.[3]

Thus, TrialNet screened participants for eligibility for this protocol using a strategy of initially testing samples for the presence of microinsulin autoantibodies and antibodies to glutamic acid decarboxylase and insulinoma-associated antigen-2, with subsequent testing for islet cell autoantibodies among patients who had tested positive for the antibody.[4] This trial, therefore, differed from the DPT-1 oral study by using the microinsulin autoantibody assay instead of the radioimmunoassay to detect insulin autoantibodies and by initially testing for microinsulin autoantibodies, glutamic acid decarboxylase autoantibodies, and insulinoma-associated antigen-2 autoantibodies compared with initial testing for islet cell autoantibodies and subsequent testing for insulin autoantibodies using the radioimmunoassay in islet cell autoantibody-positive participants. Additionally, to test whether the outcome would extend to microinsulin autoantibody-positive individuals not eligible for enrollment in the previous DPT-1 trial, this study included 4 separate strata according to additional antibodies and first-phase insulin release status.

Key Points

Question Can oral insulin delay or prevent clinically diagnosed type 1 diabetes?

Findings In this randomized clinical trial that included 389 participants in the primary analysis who were first- and second-degree relatives of patients with type 1 diabetes, oral insulin compared with placebo did not significantly reduce the risk of diabetes onset over a median of 2.7 years (insulin group, 28.5% and placebo group, 33%; hazard ratio, 0.87).

Meaning Oral insulin as used in this study was not effective in prevention of type 1 diabetes.

Methods

Protocols for this trial were approved by institutional review boards or ethics committees at all 87 participating locations in the United States, Canada, Sweden, Finland, Italy, United Kingdom, Australia, Germany, and New Zealand. Study coordination, laboratory tests, and data management were conducted centrally. Participants, their parents, or both provided written informed consent.

Screening and Eligibility

Potential participants were identified through participation in the TrialNet Natural History Study (subsequently renamed the TrialNet Pathway to Prevention Study).[5] Nondiabetic relatives of probands with type 1 diabetes were screened at institutional review board-approved sites after informed consent was obtained. These included first-degree relatives (sibling, parent, or child) who were aged 3 through 45 years, as well as second- or third-degree relatives (niece, nephew, aunt, uncle, cousin) who were aged 3 through 20 years. Initial screening was for diabetes autoantibodies—antibodies to microinsulin, glutamic acid decarboxylase, and insulinoma-associated antigen-2. Islet cell autoantibodies were measured if at least 1 other antibody tested positive. Race/ethnicity was included as part of federal reporting requirements, based on participant self-report of fixed categories determined by the National Institutes of Health.

Eligible participants were nondiabetic relatives of patients with type 1 diabetes, who had normal glucose tolerance on an oral glucose tolerance test, who were confirmed to have tested positive for the microinsulin autoantibody on 2 sample collections, who did not have the diabetes-protective human leukocyte antigen haplotypes *DQA1*0102* and *DQB1*0602*, and who met criteria for the following primary and secondary study strata based on other autoantibodies and metabolic characteristics.

Primary Analysis Stratum

The primary objective of the study was to assess the effects of treatment within this stratum.

Eligible participants had to have either islet cell autoantibodies (≥10 juvenile diabetes foundation units) confirmed positive on 2 sample collections, or if not confirmed for islet cell autoantibodies, both glutamic acid decarboxylase and insulinoma-associated antigen-2 autoantibody tested positive on the same sample with confirmation of at least 1 of these autoantibodies required on a separate sample. Participants had to have first-phase insulin release higher than the threshold determined from the sum of the 1- and 3-minute insulin values from an intravenous glucose tolerance test. For participants aged 3 through 7 years or parents of probands with type 1 diabetes, the threshold was 60 μU/mL or higher. For siblings or offspring aged 8 through 45 years or other relatives aged 8 through 20 years, the threshold was 100 μU/mL or higher. These were the same thresholds used in the DPT-1 study.[1,2]

The secondary objectives were to assess the effects of treatment in each stratum and in the entire group enrolled (the 4 strata combined).

Secondary Stratum 1: Identical to the primary stratum except participants had first-phase insulin release *lower than* the thresholds defined above.

Secondary Stratum 2: Islet cell autoantibodies not confirmed, or glutamic acid decarboxylase or insulinoma-associated antigen-2 autoantibody positive and confirmed on a separate sample (those confirmed for islet cell autoantibodies are in the primary stratum). In this stratum, participants also had first-phase insulin release *higher than* the thresholds defined in the primary stratum.

Secondary Stratum 3: Identical to secondary stratum 2 except participants had first-phase insulin release *lower than* the thresholds defined in the primary stratum above. Other entry criteria included normal glucose tolerance by oral glucose tolerance test, or if they had a previous abnormal glucose tolerance, 2 consecutive oral glucose tolerance tests with normal glucose tolerance. Abnormal glucose tolerance was defined as it was in DPT-1[1,2] using the standard criteria in effect at the initiation of DPT-1: fasting plasma glucose of more than 110 mg/dL; and/or 2-hour plasma glucose of more than 140 mg/dL; and/or 30-, 60-, or 90-minute plasma glucose of more than 200 mg/dL (to convert glucose from mg/dL to mmol/L, multiply by 0.0555).

Full exclusion criteria are available in the protocol (Supplement 1).

Randomization and Masking

After participants signed the consent form, completed screening visits, met all of the inclusion criteria and none of the exclusion criteria, and completed the baseline procedures, they were randomized in equal allocations to each treatment group via a computerized random-number generator. Randomization was stratified by study site, and block size was a variation of size 2 and 4. Randomization was not stratified by stratum. Treatment assignment was double masked. Outcome assessments were conducted without knowledge of treatment assignment.

Intervention

Participants were assigned to receive capsules of either oral insulin, 7.5 mg of recombinant human insulin crystals (Eli Lilly), or matched placebo. This was the same dose used in the DPT-1 study.[2] Capsules were prepared with methylcellulose filler at a compounding pharmacy (Eminent Services Corp) and masked bottles were shipped to the clinical sites. All participants were requested to take 1 capsule of study medication daily for the duration of the study. Study medication was dispensed at each 6-month visit. Participants consumed the capsule as a single daily dose, either by taking the capsule or, if the participant could not swallow capsules, sprinkling its contents in juice or on food.

Assessments

Participants were seen every 6 months. At those visits, an oral glucose tolerance test was performed to assess whether diabetes had developed. Criteria for diabetes onset were, as defined by the American Diabetes Association (ADA), based on glucose testing or the presence of unequivocal hyperglycemia with acute metabolic decompensation.[6] Specific criteria for diabetes onset is defined as the presence of symptoms of diabetes plus casual (random) plasma glucose of 200 mg/dL or higher or fasting plasma glucose of 126 mg/dL or higher, or 2-hour plasma glucose of 200 mg/dL or higher. The criteria must have been met on 2 occasions as soon as possible but no less than 1 day apart for diabetes to be diagnosed. It was preferred that at least 1 of the 2 testing occasions involved an oral glucose tolerance test. Tolerance tests were performed after an overnight fast. Blood samples were drawn through a temporary indwelling intravenous catheter. For the oral glucose tolerance test, the oral glucose dose was 1.75 g/kg (maximum, 75 g).

Outcomes

The primary outcome was the elapsed time from random treatment assignment to the development of diabetes among those enrolled in the primary analysis stratum, consisting of participants with insulin autoimmunity and first-phase insulin release that was higher than the threshold. Secondary outcomes included the effects of oral insulin treatment vs placebo in each stratum and in all strata combined, the consistency of oral insulin vs placebo treatment effect among strata, various subgroup analyses, and longitudinal analyses to assess the effects of oral insulin vs placebo over time. Other secondary outcomes such as the association of demographic, genetic, immunologic, metabolic, and lifestyle factors are not reported herein.

Additional exploratory analyses were planned and developed by the TrialNet protocol committee and finalized before the study results were unblinded and included analyses that incorporates factors such as duration of oral insulin use, age of enrollment, specific autoantibody pairs, year of enrollment, site of enrollment, sex, time to dysglycemia as a time-dependent covariate, baseline insulin autoantibody titer, time to dysglycemia, changes in autoantibody levels or positivity, hemoglobin A_{1c} as an outcome, C-peptide levels at diagnosis, the presence of symptoms at the time of diagnosis, consistency of hazard rates, and association between adherence to oral insulin and results. Of these additional analyses, the relationship between adherence to oral insulin and results is reported herein and in eFigure 2 in Supplement 2. Additionally, a post hoc hazard rate comparison with the DPT-1 study was also completed and is reported herein.

Statistical Methods

Diabetes Risk

The cumulative incidence of diabetes onset over time since randomization within each group was estimated from a modified Kaplan-Meier estimate of the "diabetes-free" survival function. The difference between groups in the cumulative incidence functions and the associated hazard functions was tested using the Mantel log-rank test on discrete time to type 1 diabetes (6-month intervals). The relative risk of diabetes onset between groups was estimated from the discrete Cox proportional hazards model.[7] The critical value for the test statistic, $P = .047$, and CIs in the primary analysis were adjusted for a single interim analysis based on the Lan-DeMets spending function.[8]

The effect of treatment with oral insulin vs placebo was tested using the intention-to-treat principle in the primary and

secondary analysis strata, each consisting of participants defined using different combinations of autoantibodies and metabolic status using the same analyses as above for the primary analysis. An additional analysis assessed the effect of treatment within all strata combined using a Cox proportional hazards model stratified by stratum. Significance was based on a 1-sided threshold of .05, and 1-sided 95% CIs are reported.

The study was designed as a maximum information trial, which did not include a fixed sample size. Instead, participants were recruited and followed up until the required amount of statistical information was achieved.[9] At any point during the study, the information in the data for a log-rank test is provided by $I = (D_{OI} \times D_C)/(D_{OI}+D_C)$, for which D_{OI} and D_C refer to the number of participants who developed diabetes in the oral insulin and control groups, respectively. The information required to provide 85% power to detect a 40% risk reduction (identical to the DPT-1 Oral Insulin Trial)[2] with a 1-sided log-rank test at the .05 significance level is $I = 27.551$. All but 7 participants contributed to the analysis in the primary stratum. No attempt was made to impute missing data and no adjustment has been made for multiple comparisons, except the interim monitoring and multivariate analyses. Consequently, all but the primary analysis should be considered exploratory. Except for the post hoc hazard rate comparison with the DPT-1 study, the primary and secondary analyses were prespecified, and the exploratory analyses were preplanned.

Statistical analyses were performed using TIBCO Spotfire S+ 8.2 (PerkinElmer). Data on adverse events and efficacy were evaluated twice yearly by an independent data and safety monitoring board with predefined stopping rules.

Results

Participants in this study were relatives of patients with type 1 diabetes who tested positive for multiple autoantibodies and had normal glucose tolerance at the time of randomization. Screening of 138 385 individuals for potential enrollment began in March 2004. The first participant was randomized March 2, 2007, and the last participant, December 21, 2015. For the entire cohort, the randomization rate was a mean of 5 participants per month, and for the primary stratum, 3.5 participants per month. The database for this report was locked January 20, 2017.

Of those screened, 3583 (2.56%) tested positive for microinsulin autoantibodies so were potentially eligible for this study. Of these, 2068 tested positive for microinsulin autoantibodies (**Figure 1**). A total of 560 participants were randomized, including 389 in the primary stratum. In the secondary strata, 55 participants were randomized in secondary stratum 1, 114 participants in secondary stratum 2, and 2 participants in secondary stratum 3. In the entire cohort, the median age at enrollment was 8.2 years (IQR, 5.7-12.1 years), 60% were boys, more than 90.7% were non-Hispanic white, and 57.6% had a sibling diagnosed with type 1 diabetes. The **Table** shows the baseline participant characteristics by treatment group for the entire cohort, for the primary stratum, and for the secondary strata. There were no substantial imbalances between treatment groups.

Follow-up

Participants were followed up for a median of 2.7 years (IQR, 1.5-4.7 years) for the entire cohort; a median of 2.7 years (IQR, 1.5-4.6 years) for the primary stratum. A total of 173 participants (31%) were diagnosed with type 1 diabetes in the entire cohort and 120 (31%) in the primary stratum, were diagnosed with type 1 diabetes. Based on the number of participants diagnosed with type 1 diabetes, study design parameters were met ($I = 30.0$).

Lost or Withdrawn From Study

The lost-to-follow-up rate was 4.0% per year. Ten randomized participants were never evaluated for type 1 diabetes and never underwent an oral glucose tolerance test after randomization (7 in the oral insulin; 3 in the placebo group; 5 and 2, respectively, for just the primary stratum). If these participants are removed, the rate of lost to follow-up was 3.3% per year.

Outcome Data

In the primary analysis stratum, diabetes was diagnosed in 120 participants—58 in the oral insulin group and 62 in the placebo group (**Figure 2**A). The annualized rate of diabetes was not significantly different between the 2 groups: 8.8% (95% CI, 6.7%-11.2%) with oral insulin and 10.2% (95% CI, 7.8%-12.9%) with placebo (hazard ratio [HR], 0.87; 95% CI, 0-1.2; $P = .21$). Treatment site was not a significant factor when tested either as a fixed effect in a mixed-effects model or in the Cox proportional hazards model.

Of the 55 patients in secondary stratum 1 (ie, with first-phase insulin release lower than threshold), diabetes was diagnosed in 32 participants—13 in the oral insulin group and 19 in the placebo group (Figure 2B). The annualized rate of diabetes was 18.1% (95% CI, 9.6%-29.1%) for the oral insulin group and 34.1% (95% CI, 20.6%-51.1%) for the placebo group (HR, 0.45; 95% CI, 0-0.82; $P = .006$). Thus, the median time to diabetes for the oral insulin group was 55.3 months (IQR, 19.2-67.5 months) and was 24.3 months (IQR, 13.3-47.3 months) for the placebo group, a difference of 31.0 months.

In secondary strata 2 and 3 (combined), diabetes was diagnosed in 21 participants—11 in the oral insulin group and 10 in the placebo group. The annualized rate of diabetes for this combined stratum was 5.1% (95% CI, 2.6%-8.6%) in the oral insulin group and 4.7% (95% CI, 2.2%-8.0%) for the placebo group (HR, 1.03; 95% CI, 0-2.11; $P = .53$; Figure 2C).

In the entire cohort, diabetes was diagnosed in 173 participants—82 in the oral insulin group and 91 in the placebo group. The annualized rate of diabetes was 8.7% (95% CI, 6.9%-10.7%) and 10.4% (95% CI, 8.3%-12.6%) in the oral and placebo treatment groups, respectively (HR, 0.83; 95% CI, 0-1.07; $P = .11$; Figure 2D).

Because the primary stratum in this study was designed to be consistent with the DPT-1 Study subgroup with baseline radioimmunoassay insulin autoantibodies of more than 80, a post hoc analysis of the HR of the primary stratum in the

Figure 1. Participant Flow Through Type 1 Diabetes TrialNet Study

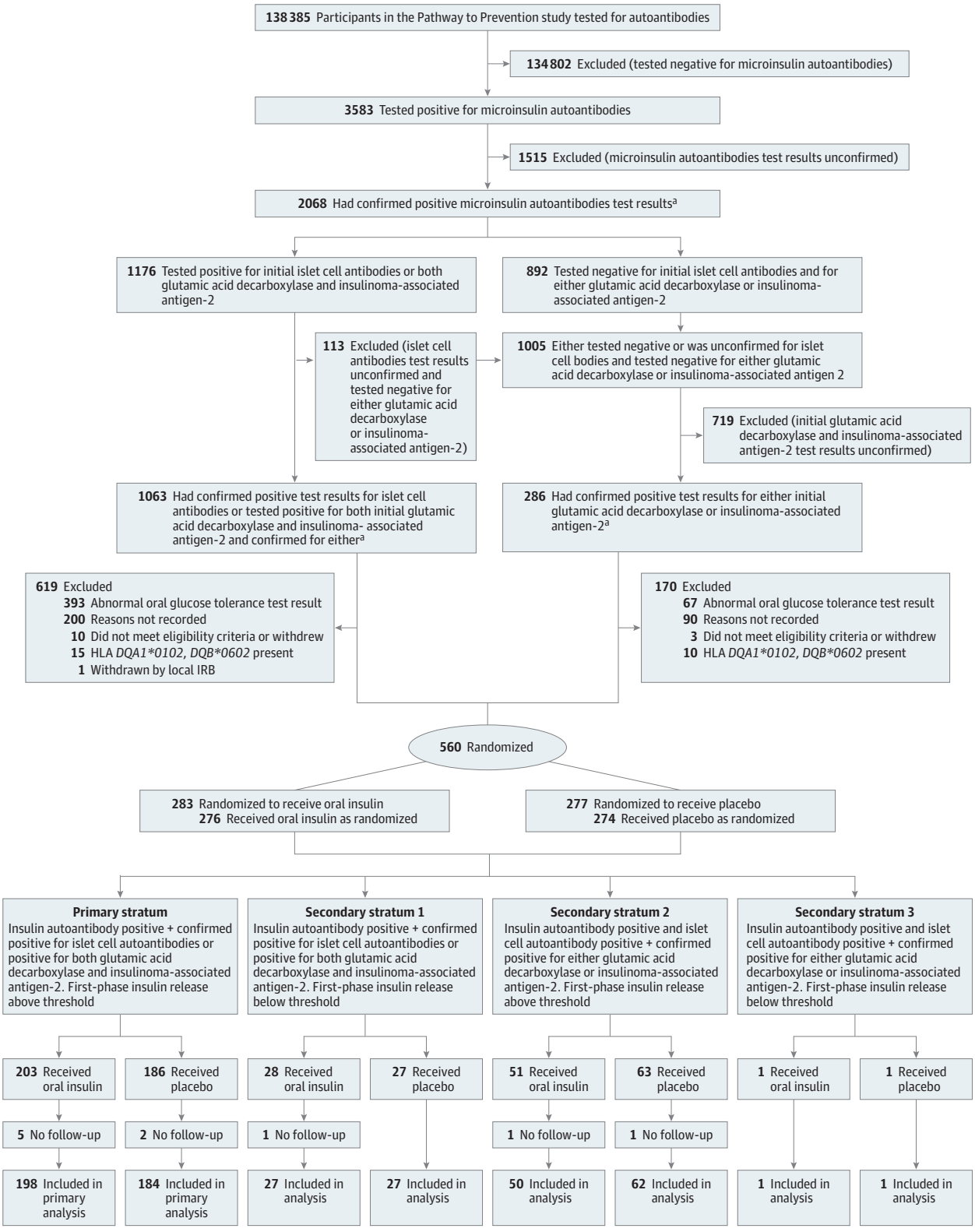


Table. Distribution of Participant Characteristics by Treatment Group and Strata

Participant Characteristics[a]	Entire Cohort		Primary Stratum		Secondary Stratum 1		Secondary Strata 2 and 3	
	Oral Insulin (n = 283)	Placebo (n = 277)	Oral Insulin (n = 203)	Placebo (n = 186)	Oral Insulin (n = 28)	Placebo (n = 27)	Oral Insulin (n = 52)	Placebo (n = 64)
Age, median (IQR), y	8.2 (5.9-12.5)	8.2 (5.4-11.5)	8.6 (6.1 -12.8)	8.2 (5.5-11.8)	9.1 (5.9-13.7)	8.5 (6.5-10.8)	7.3 (5.1 -10.3)	8.3 (5.1-11.5)
Boys, No. (%)	170 (60.1)	170 (61.4)	128 (63.1)	117 (62.9)	19 (67.9)	19 (70.4)	23 (44.2)	34 (53.1)
Race/ethnicity, No. (%)[b]								
White	252 (95.5)	249 (94.3)	181 (95.3)	172 (94.5)	25 (96.2)	25 (100.0)	46 (95.8)	52 (91.2)
Black	8 (3.0)	9 (3.4)	6 (3.2)	4 (2.2)	0	0	2 (4.2)	5 (8.8)
Asian/Pacific Islander	4 (1.5)	6 (2.3)	3 (1.6)	6 (3.3)	1 (3.8)	0	0	0
Non-Hispanic, No. (%)	256 (90.5)	252 (91.0)	182 (89.7)	171 (91.9)	26 (92.9)	26 (96.3)	48 (92.3)	55 (85.9)
BMI, median (IQR)[c]	17.1 (15.3-19.5)	16.9 (15.5-19.2)	17.4 (15.5-20.0)	17.1 (15.6-19.6)	16.2 (15-18.1)	16.9 (15.5-17.8)	16.4 (15.0-18.4)	16.8 (15.3-19.2)
Family members with type 1 diabetes, No. (%)								
Sibling	153 (54.1)	162 (58.5)	110 (54.2)	111 (59.7)	15 (53.6)	19 (70.4)	28 (53.8)	32 (50.0)
Identical twin	6 (2.1)	3 (1.1)	3 (1.5)	2 (1.1)	2 (7.1)	1 (3.7)	1 (1.9)	0
Offspring	3 (1.1)	7 (2.5)	2 (1.0)	5 (2.7)	0	0	1 (1.9)	2 (3.1)
Parent	71 (25.1)	57 (20.6)	45 (22.2)	40 (21.5)	7 (25.0)	3 (11.1)	19 (36.5)	14 (21.9)
Parent and sibling	10 (3.5)	13 (4.7)	9 (4.4)	6 (3.2)	1 (3.6)	3 (11.1)	0	4 (6.2)
Offspring and another first-degree relative	2 (0.7)	0	2 (1.0)	0	0	0	0	0
Second-degree relative	33 (11.7)	30 (10.8)	27 (13.3)	18 (9.7)	3 (10.7)	1 (3.7)	3 (5.8)	11 (17.2)
Third-degree or further removed relative	5 (1.8)	5 (1.8)	5 (2.5)	4 (2.2)	0	0	0	1 (1.6)
Autoantibodies positive, No. (%)								
Glutamic acid decarboxylase	235 (83.0)	236 (85.2)	171 (84.2)	156 (83.9)	21 (75.0)	23 (85.2)	43 (82.7)	57 (89.1)
Insulinoma-associated antigen-2	157 (55.5)	146 (52.7)	131 (64.5)	126 (67.7)	20 (71.4)	18 (66.7)	6 (11.5)	2 (3.1)
Micro insulin autoantibodies	253 (89.4)	241 (87.0)	186 (91.6)	163 (87.6)	24 (85.7)	24 (88.9)	43 (82.7)	54 (84.4)
Islet cell autoantibodies	198 (70.0)	178 (64.3)	171 (84.2)	152 (81.7)	25 (89.3)	22 (81.5)	2 (3.8)	4 (6.2)
Hemoglobin A_{1c}, median (IQR), %[d]	5.0 (4.8-5.2)	5.1 (4.8-5.2)	5.0 (4.8-5.2)	5.1 (4.8-5.2)	5.1 (4.9-5.3)	5.2 (5.0-5.5)	5.0 (4.9-5.2)	5.0 (4.9-5.1)
First-phase insulin release, median (IQR), μU/mL	145 (102-221)	150 (98.4-232)	153 (112-230)	152 (106-236)	50.8 (45.4-67.1)	57.8 (44.8-71.9)	163 (119-243)	174 (132-285)
C-peptide, median (IQR), nmol/L[e]	1.35 (1.00-1.81)	1.34 (1.03-1.82)	1.42 (1.04-1.91)	1.34 (1.04-1.96)	1.02 (0.93 -1.3)	1.1 (0.76-1.52)	1.36 (1.06-1.75)	1.43 (1.11-1.8)
Human leukocyte antigen alleles, No.(%)[f]								
DR3	119 (42.2)	102 (37.0)	88 (43.3)	74 (39.8)	9 (32.1)	9 (33.3)	22 (43.1)	19 (30.2)
DR4	199 (70.6)	182 (65.9)	144 (70.9)	135 (72.6)	22 (78.6)	18 (66.7)	33 (64.7)	29 (46.0)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; IQR, interquartile range.

[a] The primary stratum included participants with normal glucose tolerance, first-phase insulin release higher than threshold, the presence of microinsulin autoantibodies, and islet cell autoantibodies on 2 separate samples or both glutamic acid decarboxylase and insulinoma-associated antigen-2 autoantibodies on the same sample. Secondary stratum 1 included participants with the same profile as those in the primary stratum except they had first-phase insulin release that was lower than threshold. Secondary stratum 2 participants had normal glucose tolerance, first-phase insulin release higher than threshold, the presence of microinsulin autoantibodies, and islet cell autoantibodies on 1 sample or glutamic acid decarboxylase or insulinoma-associated antigen-2 autoantibodies on 2 separate samples. Secondary stratum 3 included participants whose profiles were identical to those in secondary stratum 2 except for their first-phase insulin release was lower than threshold, defined in the Methods section.

[b] Self-reported race was not provided by 32 participants.

[c] Not reported for 3 participants.

[d] Values were missing for 1 participant.

[e] C-peptide from oral glucose tolerance test not available for 1 participant. Area under the curve (AUC) mean, oral glucose tolerance test.

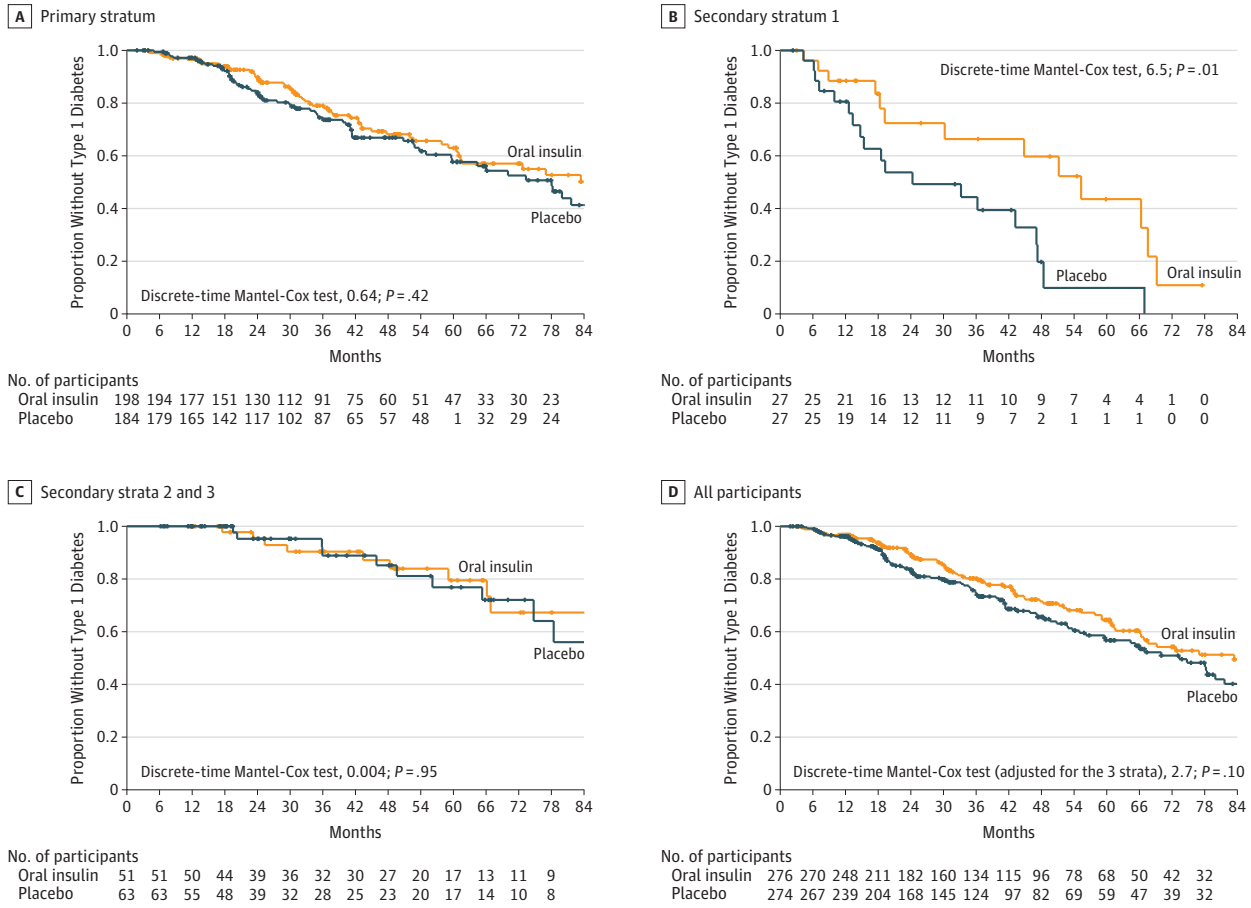
[f] Not available for 2 participants.

current study to the DPT-1 subgroup was conducted (DPT-1 to oral insulin, 1.04; 95% CI, 0.71-1.52; eFigure 2 in Supplement 2), which was not statistically different at $P = .84$, 2-sided. Thus, the entry criteria succeeded in replicating the risk seen in the DPT-1 cohort.

Analysis of Additional Preplanned Exploratory Outcomes

In an exploratory analysis of the primary stratum that included participants with 85% or more adherence with treatment (n = 215), the annualized rate of diabetes was 6.9% with oral insulin and 9.7% with placebo (HR, 0.69; 95% CI,

Figure 2. The Proportion of Study Individuals Who Had Not Developed Type 1 Diabetes as a Function of Follow-up



The plus marks indicate that the participants were censored.

A, The quartiles of time to diabetes were 18.4, 31.9, and 55.1 months for oral insulin and 18.9, 32.7, and 54.4 months for placebo. Of those in the oral insulin group, 140 participants did not develop type 1 diabetes and 58 did. Of those in the placebo group, 122 participants did not develop type 1 diabetes and 62 did. The median months of follow-up was 32.0 (1.87-114).

B, The quartiles of time to diabetes were 12.9, 19.2, and 52.8 months for oral insulin and 10.5, 18.5, and 39.8 months for placebo. Of those in the oral insulin group, 14 did not develop type 1 diabetes and 13 did. Of those in the placebo group, 8 did not develop type 1 diabetes and 19 did. The median months of follow-up was 18.9 (2.33-77.5).

C, The quartiles of time to diabetes were 25.3, 49.2, and 65.8 months for oral insulin and 18.1, 30.2, and 63.3 months for placebo. Of those in the oral insulin group, 40 participants did not develop type 1 diabetes and 11 did. Of those in the placebo group, 53 participants did not develop type 1 diabetes and 10 did. The median months of follow-up was 39.4 (6.21-115).

D, The quartiles of time to diabetes were 18.4, 34.9, and 59.7 months for oral insulin and 17.8, 31.2, and 54.0 months for placebo. Of those in the oral insulin group, 194 participants did not develop type 1 diabetes and 82 did. Of those in the placebo group, 183 participants did not develop type 1 diabetes and 91 did. The median months of follow-up was 32.4 (1.87-115).

0-1.04; P = .06). In examining Kaplan-Meier curves for the primary stratum that included participants with varying degrees of adherence among more adherent participants, there was separation between the oral insulin and placebo groups during the first 24 months after randomization. Therefore, in an analysis of the first 24 months' follow-up of adherent participants in the primary stratum, a protective association was observed among those taking oral insulin with fewer participants progressing to diabetes than among those taking placebo—the annualized rate of diabetes was 2.4% with oral insulin and 6.9% with placebo (HR, 0.348; 95% CI, 0-0.855; P = .02). This exploratory analysis is included in the eAppendix in Supplement 2.

Adverse Events

There were no serious adverse events and no reported episodes of severe hypoglycemia. The most common adverse event was categorized as infection, with 134 and 120 events reported in this category in the oral insulin and placebo groups, respectively, over the duration of the study (eTable 1 and 2 in Supplement 2).

Discussion

In this randomized clinical trial, oral insulin at a dose of 7.5 mg/d did not prevent the development of clinical type 1

diabetes in antibody-positive relatives of patients with type 1 diabetes in the primary stratum or in the entire randomized group.

Oral antigen administration has had small and inconsistent benefits in clinical trials involving patients with multiple sclerosis and rheumatoid arthritis, despite success in animal models of those autoimmune diseases. Among patients who have been newly diagnosed with type 1 diabetes, oral insulin, at the same or lower doses than the dose levels studied in this trial, failed to preserve pancreatic islet β-cell function.[10] In the DPT-1 study, 7.5 mg/d of oral insulin failed to delay or prevent type 1 diabetes in the study as a whole.[2] However, a post hoc analysis of data from DPT-1 revealed that autoantibody-positive relatives with higher confirmed radioimmunoassay insulin autoantibody titers progress to diabetes at a faster rate than participants with lower or unconfirmed insulin autoantibodies, and this subgroup may have benefitted from oral insulin.[2] Participants with insulin autoantibodies that were 80 nU/mL or higher and who were treated with 7.5/d of oral insulin had an apparent 4- to 5-year delay in the onset of disease.

Because this study was undertaken to replicate the DPT-1 subgroup finding, the same 7.5-mg/d of oral insulin was used. However, immunomodulatory effects were reported with higher doses of oral insulin in preclinical studies and in a small-dose escalation study of children early in the disease process. The Pre-Point study[11] found potentially protective immunomodulatory effects only in the 6 children who received the highest dose of oral insulin studied (67.5 mg/d). Therefore, as a companion study to the clinical trial reported herein, TrialNet has recently completed enrollment of more than 90 antibody-positive relatives in a study aimed at determining whether higher doses of oral insulin administered daily or every other week have measurable immunomodulatory effects (NCT02580877).

In a prespecified, secondary analysis in the current trial, a significant protective effect was found in the stratum consisting of 55 individuals in whom the first-phase insulin response was lower than the threshold needed for entry into the primary stratum. The placebo group in this stratum had a higher rate of progression to type 1 diabetes than participants taking placebo in the primary stratum (34.1%-10.2%), attesting to the added diabetes risk among those with diminished first-phase insulin release. However, because there was no adjustment for multiple comparisons, this analysis must be considered exploratory and hypothesis generating.

Although requiring a large, multicenter network, this trial emphasizes the feasibility of identifying and treating individuals early in the type 1 diabetes disease process. Individuals with 2 or more antibodies are destined (>80% risk at 10 years) to develop clinical type 1 diabetes, albeit at various rates of progression.[24] Individuals with 2 or more antibodies and normal glucose tolerance are now considered to have stage 1 type 1 diabetes.[12] Without intervention, most of these individuals will develop stage 2 type 1 diabetes, manifested by abnormal glucose tolerance and eventually clinically apparent, or stage 3 type 1 diabetes. As noted in this study, the overall rate of progression from stage 1 to stage 3 was approximately 9.5% per year; not significantly different from the rate of progression in genetically at-risk infants who were followed up from birth.[12]

Thus, trials of disease-modifying therapies among individuals with multiple antibodies could be considered treatment trials, in which the therapy aims to treat early type 1 diabetes or islet autoimmunity as distinct from prevention trials, which implies testing of therapies in healthy individuals to prevent disease. Most randomized clinical trials investigating type 1 diabetes-modifying therapy have been conducted among individuals with clinically overt disease. Disease-modifying therapies including the anti-CD3 monoclonal antibody, [13-19] rituximab,[18-21] abatacept,[22] and alefacept[23] significantly preserved insulin production (as measured by C-peptide levels) as well having immunological effects in the first 1 to 2 years after diagnosis of clinical disease. As demonstrated in the Diabetes Control and Complications Trial (DCCT),[24,25] improved short-term diabetes control associated with sustained C-peptide production decreased the risk of complications. However, an effect at earlier stages of the disease in delaying onset of clinical diagnosis of diabetes would have a much more profound effect in relieving the burden of disease. Despite marked advances in insulin delivery and glucose monitoring, there are still significant unmet needs for disease modifying therapy in type 1 diabetes.

Limitations

This study has several limitations. First, there was a change in insulin autoantibody assay methods from the DPT-1 Oral Insulin study. The change in assay may have contributed to an inability to replicate previous results from the study using a 7.5-mg fixed dose of oral insulin because the selected study population for this trial may differ slightly from the population in the previous study that showed apparent benefit. Second, as in other type 1 diabetes prevention trials, there is the limited knowledge about and the ability to incorporate heterogeneity in the pathogenesis of disease. This trial enrolled participants based on evidence of autoimmunity but did not take into account genetic background, age at onset, and type of first-appearing diabetes-related autoantibody. The emerging literature now suggests that future trials need to consider these factors, and this trial adds to that, suggesting that first-phase insulin release status and treatment adherence should also be incorporated into study designs. Third, due to lack of adjustment for multiple comparisons, all secondary analyses need to be interpreted as exploratory.

Conclusions

Among autoantibody-positive relatives of patients with type 1 diabetes, oral insulin at a dose of 7.5 mg/d, compared with placebo, did not delay or prevent the development of type 1 diabetes over 2.7 years. These findings do not support oral insulin as used in this study for diabetes prevention.

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Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
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Other - leading trial network from inception until 2015: Skyler.

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Appendix 16.2.7 Adverse Events by Participant

TN07 Oral Insulin – Appendix 6.2.7 Adverse Events by Participant

PID	Age	Race	Sex	Date	SOC	PT	Primary/Secondary AE	AE Duration (Days)	Expectedness	Severity	Causality by Reporter	Details	Treatment
100116	22	White	Male	08/20/2016	Ocular/Visual	Ocular/Visual - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Foreign body removed from right eye in the Emergency Department.	Active
100736	5	White	Female	05/25/2010	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Varicella, the participant developed Chicken Pox lesions on the 25-05-10.	Placebo
100736	6	White	Female	03/04/2011	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	43	Not Expected	2	Definitely not related	Purulent Rhinitis	Placebo
100736	9	White	Female	06/23/2014	Endocrine	Pancreatic endocrine: glucose intolerance	Primary	0	Expected	3	Definitely not related	On 05-05-2014 a 9 year old female participant had a scheduled OGTT with a 2 hour glucose reading of 218mg/dL. A confirmatory OGTT was scheduled however the participants mother performed random blood glucose checks at home. These readings were between 140 and 330. She contacted her paediatric diabetologist who decided to start insulin therapy.	Placebo
100780	10	White	Male	12/18/2011	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Scarlet Fever	Active
100780	10	White	Male	02/05/2012	Infection	Infection with unknown ANC	Primary	7	Not Expected	2	Definitely not related	Tonsillitis	Active
101307	16	White	Female	06/12/2010	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	16	Expected	2	Probably not related	Participant felt run down for about 1 week with fever, headache, possibly flu per family physicians consult with mother of participant given	Active
101307	17	White	Female	06/12/2011	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	0	Expected	2	Definitely not related	Participant reported sore muscles	Active

101307	18	White	Female	11/15/2011	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	15	Not Expected	2	Definitely not related	Participant reported nasal congestion, rash, swelling of hands when they get a cold ********** Participant reported nasal congestion	Active
101307	18	White	Female	01/30/2012	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	Participant reported allergic reaction, swelling of hands, hives	Active
101498	16	White	Male	07/01/2010	Dermatology/Skin	Rash: acne/acneiform	Primary	.	Expected	2	Definitely not related	Participant began to develop acne in ~July 2010; the severity increased in February 2012 and intervention was started at that time.	
101498	17	White	Male	07/20/2011	Cardiac Arrhythmia	Vasovagal episode	Primary	0	Expected	3	Definitely related	Shortly after placement of IV and completion of baseline draw (39 ml), ppt felt queasy, with the need to vomit. The participant then passed out (while lying in bed) and had a few muscle twitches in the participant's right arm and leg (possibly myoclonic jerks). The participant regained consciousness within a few seconds and had some dry heaves. Afterwards, the participant felt normal. MD evaluated the participant~10 minutes after this episode and neurological exam was normal. Given the brevity of the syncope, the normal neuro exam and the lack of a post-ictal episode, MD felt this episode was unlikely to represent a seizure	
101498	18	White	Male	07/30/2012	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	While dermatologist was evaluating subject in regards to starting Accutane for acne vulgaris, he discovered a suspicious nevus on his neck. A	

												biopsy was performed and melanoma was ruled out.	
101597	6	White	Male	02/01/2009	Musculoskeletal/Soft Tissue	Fracture	Primary	28	Not Expected	2	Definitely not related	Participant fell off a spinning-type bar stool when he was reaching for a stuffed animal on a high shelf; fall resulted in the fracture of his left wrist.	Active
101597	7	White	Male	05/14/2010	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	10	Expected	2	Definitely not related	Participant had an accidental fall in his school classroom, which resulted in him hitting his head on the corner of a desk. The laceration required suture repair.	Active
101597	8	White	Male	03/21/2011	Cardiac Arrhythmia	Vasovagal episode	Primary	0	Expected	3	Definitely related	As RN was placing IV, participant (who was reclined on the bed) chose to watch the process and lost consciousness. He revived quickly, and felt fine after the head of his bed was lowered completely and a cold compress applied to his forehead.	Active
101858	25	White	Female	01/02/2016	Musculoskeletal/Soft Tissue	Extremity-lower (gait/walking)	Primary	.	Not Expected	2	Definitely not related	Subject sprained her right ankle playing recreational soccer. Slightly limited ability to walk with noticeable ecchymosis and decreased range of motion.	Active
101858	26	White	Female	03/24/2017	Metabolic/Laboratory	Metabolic/Laboratory - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Subject diagnosed with Vitamin D deficiency by primary care physician.	Active
102367	13	White	Female	05/03/2011	Pulmonary/Upper Respiratory	Cough	Primary	5	Expected	1	Definitely not related	Participant reported cough/congestion	Placebo
102767	4	White	Female	10/31/2007	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)		7		2	Definitely not related	./ While trick-or-treating, participant's father tripped and fell onto her resulting on abrasions, brusing and a mild concussion.	Placebo

102841	12	White	Male	05/29/2012	Musculoskeletal/Soft Tissue	Fracture	Primary	47	Expected	2	Definitely not related	Fractured growth plate in right arm while pitching at a baseball game. Right arm was in a cast for 6 weeks.	Active
102841	16	White	Male	12/02/2016	Dermatology/Skin	Rash/desquamation	Primary	.	Not Expected	2	Definitely not related	Subject developed a rash on arms and trunk, which pediatrician diagnosed as guttate psoriasis. (Subject's mother mentions that she developed psoriasis at about the same age as the subject, but hers went away after her first pregnancy.) MD prescribed prednisone (20 mg bid x 3 days), plus a cortisone cream. About a week after starting treatment, subject's rash had improved somewhat. Treatment with cortisone cream continues.	Active
102865	11	White	Female	12/31/2014	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	1	Not Expected	2	Definitely not related	Participant's mother reports that participant vomited every half-hour for 15 hours, then every two hours for the next 15 hours. Provider categorized as gastroenteritis.	Placebo
102865	11	White	Female	01/12/2015	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Upper respiratory infection, with symptoms severe enough to cause participant to miss two days of school. No treatment sought or given.	Placebo
102865	11	White	Female	04/11/2015	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	Contact Dermatitis: Subject was picking flowers in a field when their hands made contact with yarrow root plants. Subsequent swelling of bilateral hands resolved within a couple of hours of treatment with one 25 mg dose of benadryl.	Placebo
102865	11	White	Female	04/18/2015	Endocrine	Thyroid function, low (hypothyroidism)	Primary	.	Not Expected	2	Definitely not related	Subject began to experience "mental fogginess," hair loss, fatigue, depression and constipation. MD was skeptical	Placebo

												that hypothyroidism was the cause, but eventually agreed to blood work, which confirmed diagnosis. Since institution of levothyroxine, all symptoms have been improving.	
103238	4	White	Male	02/04/2010	Infection	Infection - Other (Specify in Event Details)	Primary	10	Expected	1	Definitely not related	pharyngitis	Placebo
103238	4	White	Male	03/01/2010	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	1	Expected	1	Possibly related	abdominal pain	Placebo
103238	5	White	Male	07/16/2010	Infection	Infection - Other (Specify in Event Details)	Primary	6	Expected	1	Definitely not related	upper respiratory infection	Placebo
103238	5	White	Male	07/18/2010	Constitutional Symptoms	Fatigue (asthenia, lethargy, malaise)	Primary	.	Not Expected	1	Definitely not related	mild fatigue noted by parent	Placebo
103238	5	White	Male	03/15/2011	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	sinus infection, date is estimated as reported as March 2011	Placebo
103320	8	White	Female	07/23/2008	Surgery/Intra-Operative Injury	Intra-operative Injury - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	Extraction of front lower tooth	Active
103320	8	White	Female	07/23/2008	Gastrointestinal	Dental: teeth		0		2	Definitely not related	Other, Specify: / Extraction of front lower primary tooth./ As tooth was loose for nine months, but would not fall out and adult tooth had grown in taller (behind the primary tooth), dentist planned extraction of primary.	Active
103320	9	White	Female	02/25/2009	Neurology	Mood alteration	Primary	.	Expected	2	Probably not related	Mother of participant called site on 3/25/2009 to report that participant began to suffer "bouts of anxiety" while the family was on vacation. Upon returning home in mid-March, they took her to an emergency room for treatment and have since seen a pediatric	Active

												endocrinologist for evaluation. Ativan was started on 3/24/2009.	
103320	10	White	Female	07/15/2010	Endocrine	Pancreatic endocrine: glucose intolerance	Primary	2	Expected	3	Definitely not related	Hospitalization for new diagnosis of type 1 diabetes	Active
103323	5	White	Male	12/17/2008	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	20	Expected	2	Definitely not related	Bronchitis: satrted as a runny nose and cough; when symptoms persisted, ppt saw MD and was diagnosed with bronchitis and treated with amoxicillin (31Dec2008-6Jan2009, 250 mg tid)	Placebo
103323	8	White	Male	07/01/2011	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	6	Expected	2	Definitely not related	Participant developed fever and was diagnosed with right ear infection.	Placebo
103323	8	White	Male	07/16/2011	Ocular/Visual	Ocular/Visual - Other (Specify in Event Details)	Primary	8	Expected	2	Definitely not related	Corneal abrasion developed while participant was playing in a swimming pool and was accidentally bumped.	Placebo
103323	8	White	Male	11/29/2011	Infection	Infection - Other (Specify in Event Details)	Primary	4	Expected	2	Definitely not related	'Strep throat' (pharyngitis), diagnosed by MD and treated with oral antibiotics	Placebo
103323	9	White	Male	01/16/2012	Musculoskeletal/Soft Tissue	Fracture	Primary	43	Not Expected	2	Definitely not related	Ppt fell while snowboarding and sustained a left distal radial fracture. Three attempts were required for a successful reduction, followed by six weeks in a long arm cast.	Placebo
103323	9	White	Male	03/01/2012	Hemorrhage/Bleeding	Hemorrhage, pulmonary/upper respiratory	Primary	19	Expected	2	Definitely not related	Participant suffered multiple episodes of epistaxis. Pediatrician evaluated ppt, and cauterized left nostril. This treatment was effective.	Placebo
103323	9	White	Male	03/27/2012	Infection	Infection - Other (Specify in Event Details)	Primary	5	Expected	2	Definitely not related	'Strep throat' (pharyngitis), diagnosed by MD and treated with oral antibiotics	Placebo
103323	11	White	Male	10/26/2014	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	8	Not Expected	2	Probably not related	Participant reported that the subject couldn't hear out of their right ear and that the pain	Placebo

												was '10 out of 10.' MD diagnosed a right ear infection, which was treated with a Z-Pack.	
103323	11	White	Male	10/26/2014	Infection	Infection - Other (Specify in Event Details)	Primary	8	Not Expected	2	Probably not related	Participant developed a cough which "sounded like a bark." MD diagnosed sinusitis, which was treated with a Z-Pack.	Placebo
103323	12	White	Male	05/09/2015	Infection	Infection with unknown ANC	Primary	9	Not Expected	2	Definitely not related	Participant was bit on the left hand by the family dog on 5/9/2015 and diagnosed with cellulitis by an MD on 5/12/2015. The subject was prescribed 250 mg Zithromax/day for 10 days. By their last dose on 5/18/2015, the cellulitis had resolved.	Placebo
103323	12	White	Male	05/16/2015	Infection	Infection - Other (Specify in Event Details)	Primary	6	Not Expected	2	Definitely not related	Upper respiratory infection developed while on an antibiotic for cellulitis (caused by a dog bite). Symptoms included a cough, congestion and sore throat.	Placebo
103323	12	White	Male	09/16/2015	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	20	Not Expected	2	Definitely not related	Subject is on two football teams so had been practicing on a nearly-daily basis. Sprained right ankle on the field; this was treated with ibuprofen (200 mg bid), icing and a brace. Subject also switched to high-top football cleats.	Placebo
103323	13	White	Male	01/29/2016	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	Dysplastic nevus on left upper back - subject's mother noticed a mole, so took subject to dermatologist for evaluation. She was told it showed "mild dysplasia." No treatment is planned, but subject will undergo annual skin checks. ********** Dysplastic nevus on left upper back - subject's mother noticed	Placebo

												a mole, so took subject to dermatologist for evaluation. She was told it showed "mild dysplasia."	
103323	13	White	Male	07/27/2016	Infection	Infection - Other (Specify in Event Details)	Primary	11	Not Expected	2	Definitely not related	On 26Jul2016, family's pet dog was upset and, as subject tried to calm him, the dog bit two of the fingers on subject's right hand. Subject's mother (who attends nursing school) washed the puncture wound, applied antibiotic ointment, and thought it looked "good." By later on the next day, the bite appeared infected and cellulitis was diagnosed. [Occurrence date above reflects progression of AE to Grade 2. Provider evaluated bite (prior to development of cellulitis) as Grade 1.] Doxycycline (100 mg bid) was started on 27Jul2016, with course completed on 02Aug2016.	Placebo
103336	6	White	Male	06/19/2009	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	13	Expected	2	Possibly related	Infection; symptoms included sinus congestion and sore throat.	Placebo
103336	6	White	Male	08/01/2009	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	.	Not Expected	2	Possibly related	lip swelling	Placebo
103474	14	White	Female	12/05/2016	Neurology	Neurology - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	A sequelae to an elective outpatient surgery, the participant experienced parasthesia on the lower quarter of her left hand palmar surface, proximal to the wrist. Per guardian, the participants overseeing physician states they expect a full recover and the	Placebo

												participant is scheduled for post-operative check up.	
103474	14	White	Female	12/05/2016	Surgery/Intra-Operative Injury	Intra-operative Injury - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	Research participant held a planned outpatient surgery for the removal of a ganglion cyst on the left wrist/forearm. The participant was discharged the same day and is recovering with sequelae. Per guardian, the participant is experiencing parasthesia on bottom quarter of her left hand palmer surface, proximal to the wrist as a complication of the surgery. Guardian states a full recovery is expected and a post-operative check up is scheduled.	Placebo
103474	14	White	Female	02/26/2017	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	5	Not Expected	1	Definitely not related	Subject developed influenza with low grade fever and missed one week of school.	Placebo
103522	8	White	Male	05/20/2008	Gastrointestinal	Dental: teeth		10		2	Definitely not related	./ Participant fell while riding a bicycle suffering dental trauma: Lost a tooth and chipped a tooth.	Active
103522	8	White	Male	06/15/2008	Infection	Infection with normal ANC or Grade 1 or 2 neutrophils		7		2	Definitely not related	./ Cellulitis of left axilla, following spinder bite.	Active
103522	9	White	Male	02/14/2009	Allergy/Immunology	Allergic reaction/hypersensitivity (including drug fever)	Primary	6	Expected	2	Definitely not related	urticaria; evaluated by primary MD, who noted no etiology	Active
103522	10	White	Male	03/04/2010	Endocrine	Pancreatic endocrine: glucose intolerance	Primary	2	Expected	2	Definitely not related	Participant was found to have an OGTT in the diabetic range (at 120 minute timepoint) at his Month 24 Visit on Feb 22, 2010. The family did not report any	Active

												symptoms at that time but, upon reflection, participant's mother feels he has become more impatient when he is hungry, "like his blood sugar is low." Confirmatory OGTT was done March 4, 2010, and this again showed values in the range diagnostic for diabetes.	
103524	5	White	Female	04/16/2011	Musculoskeletal/Soft Tissue	Fracture	Primary	30	Expected	2	Definitely not related	Subject fell off the monkey bars at the park and suffered a buckle fracture of the right ulna and radius. Arm was splinted that day, and a cast was placed on 19April2011.	
103524	9	White	Female	10/01/2014	Infection	Infection - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	Subject developed a headache, fever of 101.7 (F), pharyngitis, stomach pain and rhinitis. Subject did not see a provider for care, but missed school. Treatment was within Children's Tylenol.	
103655	9	White	Male	02/23/2012	Auditory/Ear	Auditory/Ear - Other (Specify in Event Details)	Primary	13	Not Expected	2	Definitely not related	Participant had ear infection causing dizziness.	Active
103691	4	White	Male	01/03/2009	Pulmonary/ Upper Respiratory	Cough	Primary	4	Not Expected	1	Definitely not related	Subject developed a common cold. Recovered by 4 days.	Active
103691	4	White	Male	02/07/2009	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	1	Definitely not related	Subject's mother reports subject had the "flu".	Active
103691	5	White	Male	02/01/2010	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	.	Not Expected	1	Probably not related	Intermittent nocturnal leg cramps - Subject's mother reports since 2/1/10, the subject will periodically wake up at night becuase of the cramps in his lefgs. A Chem 13 and magnesium panel was run, with no abnormal results. Subject was referred to his pediatrican.	Active

103811	4	White	Male	09/30/2008	Infection	Infection with unknown ANC	Primary	15	Expected	2	Definitely not related	Symptoms of upper respiratory infection (sore throat, runny nose) first appeared 30 September 2008. On 6 October 2008, participant saw an MD, who diagnosed a sinus infection and prescribed antibiotics.	Placebo
103811	7	White	Male	03/05/2012	Neurology	Cognitive disturbance	Primary	.	Expected	2	Definitely not related	Diagnosis of Attention Deficit Hyperactivity Disorder was made based on teacher/parent questionnaire.	Placebo
103865	18	White	Male	01/04/2011	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	0	Expected	2	Definitely not related	Deviated Septum surgical repair	Active
103888	5	White	Male	12/19/2008	Infection	Infection - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Strep throat	Placebo
103888	7	White	Male	03/15/2011	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	sinus infection, date estimated.	Placebo
103888	12	White	Male	05/18/2015	Metabolic/Laboratory	Glucose, serum-high (hyperglycemia)	Primary	.	Expected	3	Probably not related	Participant referred to Seattle Children's by PCP when presented with high BG. Participant admitted in DKA and hospitalized for standard 3 day admission.	Placebo
103949	6	White	Female	08/01/2009	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	.	Not Expected	2	Possibly related	Lip swelling	Active
104207	11	White	Male	06/02/2012	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	3	Expected	2	Definitely not related	Participant went camping and suffered insect bites on his left forearm and right shoulder which became inflamed. Primary physician evaluated these and prescribed a steroid cream, which was applied twice in 48 hours and was followed by resolution.	Placebo
104306	5	White	Female	03/01/2013	Infection	Infection - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Subject had Otitis Media starting on 3/1/13, treated with amoxicillin for five days. Subject	Active

												reported pain resolution and completed amoxicillin dose on 3/6/15.	
104306	6	White	Female	06/10/2013	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Laceration on head from metal object. Participant was taken to the emergency room and treated (no stitches required) and no concussion reported. Medical records have been requested.	Active
104381	12	White	Female	05/03/2013	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Participant had sinus pressure and rhinorrhea for 1 week. Mother thought it was allergies, however when symptoms did not resolve they went to their pediatrician. Participant diagnosed with a sinus and ear infection. MD prescribed a Z pack for 5 days.	Active
104381	14	White	Female	11/18/2014	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	27	Not Expected	2	Definitely not related	Sinusitis diagnosed at pcp 20NOV2014. Prescribed Omnicef x10 days. Sinusitis unresolved after Omnicef. Returned to pcp 11DEC2014 and started Z-pack. Sinusitis resolved with Z-pack.	Active
104381	14	White	Female	12/18/2014	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Influenza diagnosed at pcp on 18DEC2014. Given Tamiflu. Resolved completely.	Active
104381	15	White	Female	12/02/2015	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	14	Not Expected	2	Definitely not related	Thyroglossal Duct Cyst	Active
104381	16	White	Female	02/15/2017	Neurology	Mood alteration	Primary	13	Not Expected	4	Definitely not related	Study staff notified by mother on 07MAR2017 of suicide attempt that occurred on 15FEB2017. Subject taken to local ER with altered mental status and presumed polysubstance ingestion. Subject was found to be	Active

												agitated and tachycardic with erratic behavior and was subsequently intubated / sedated. Subject was hospitalized at local children's hospital for 4 days and then sent to inpatient psychiatric facility for 10 days. Per hospital medical records, subject reported to be "stressed out and aggravated " and took pills to commit suicide.	
104397	11	White	Male	02/01/2008	Infection	Infection with normal ANC or Grade 1 or 2 neutrophils		9		2	Probably not related	./ Subject developed right ear infection 2/1/08, went to MD who prescribed 2-pack one PO QD x 7 days. Ear infection resolved by 2/10/08.	Placebo
104397	12	White	Male	05/12/2009	Infection	Infection with unknown ANC	Primary	7	Not Expected	2	Definitely not related	Developed ear infection in left ear on 05/12/2009. Went to family physician. Started on Amoxicillin 1 Twice a day (unable to recall exact mg). Completed course of Amoxicillin 05/19/2009	Placebo
104397	13	White	Male	01/04/2010	Infection	Infection with unknown ANC	Primary	10	Not Expected	2	Definitely not related	Had Left ear discomfort. Went to physican. Started on Amoxicillin 1 PO BID 01/04/2010. Completed 10 day course. Infection resolved.	Placebo
104397	14	White	Male	06/15/2011	Endocrine	Pancreatic endocrine: glucose intolerance	Primary	.	Expected	1	Definitely not related	On 6/2/11, 14 yo male participant had an OGTT with a 2 hr glucose > 200 mg/dL. 2 hr glucose value for confirmatory OGTT on 6/13/11 was over 200 mg/dL. Participant is asymptomatic, however based on ADA criteria was diagnosed with Type 1 Diabetes.	Placebo
104548	7	White	Male	05/02/2008	Infection	Infection with unknown ANC		10		2	Probably not related	./ On 05/02/08 subject had a sore throat. Mother took him to MD. Dx of Strep Throat.	Placebo

												Started on Amoxicillin BID for ten days.	
104641	21	White	Female	05/07/2015	Pain	Pain	Primary	0	Not Expected	2	Definitely not related	5/7/15, participant woke up at 5 am with migraine associated with nausea, photosensitivity, and "spinning". Participant took Tylenol 325mg and Advil 400 mg, but neither intervention helped. 14 hours later, participant drank a cup of coffee and migraine resolved. Occurrence most likely related to emotional and hormonal stress. The participant also has a family history of migraines	Placebo
104641	23	White	Female	01/16/2017	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Participant reported "sore throat and feeling awful" on 1/16/17. Went to doctor who put participant on a Z-pack. Resolved by 1/20/17.	Placebo
105068	10	White	Male	03/05/2010	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	6	Not Expected	2	Definitely not related	Participant began having a fever 03/05/2010. Went to the physician office 03/06/2010. tested positive for FLU. Highest temp 103.7. treated with Tylenol, motrin and tamiflu. Fever resolved 03/11/2010. Returned to school 03/12/2010	Placebo
105068	11	White	Male	07/27/2010	Infection	Infection with unknown ANC	Primary	8	Not Expected	2	Definitely not related	Mother took participant to pediatrician on 07/27/2010. Dx with ear infection. Started on Ceftin 250mg PO BID on 07/27/2010	Placebo
105068	11	White	Male	01/11/2011	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	13	Not Expected	1	Probably not related	experienced fever, cold like symptoms for six days and then went to MD and took zithromax for 5 days and went back to school on the 19th	Placebo
105068	12	White	Male	07/04/2011	Infection	Infection with unknown ANC	Primary	3	Not Expected	3	Definitely not related	Bug bite on right leg. Area became red, swollen, tender, and warm. Accompanied with red streak to groin and inguinal	Placebo

												lymphadema. Participant was afebrile. Went to urgent care. Received rocephin shot x 1. Started Biaxin tabs twice daily for 10 days. Symptoms resolved after 3 days of antibiotics. Completed antibiotics.	
105068	12	White	Male	11/21/2011	Infection	Infection - Other (Specify in Event Details)	Primary	5	Not Expected	1	Definitely not related	11/21/11 started having symptoms of a sinus infection including a cough and nasal congestion. 11/23/11 was seen by MD and received antibiotics IM x 1. Symptoms resolved 11/26/11.	Placebo
106297	11	White	Male	06/24/2010	Neurology	Personality/behavioral	Primary	1662	Not Expected	2	Definitely not related	In 2009 the particpant witnessed some very bad storms that resulted in flooding to their home. Following this experience, the participant developed anxiety related to storms and weather. Behavioral therapy was unsuccessful and the participant was prescribed an antidepressant for anxiety. The anxiety regarding storms was alleviated, however the participant remained on anti-depressants for depression. Multiple antidepressants have been used. All anxiety/depression medications were discontinued 1/11/2015.	Active
106297	11	White	Male	12/05/2010	Pain	Pain	Primary	0	Not Expected	3	Definitely not related	Participant was taken to the ER on 12/05/2010 for a migraine. Was treated with one dose of Tylenol, Reglan, Benedryl and one other IV medication (unknown at this time). Migraine subsided and paticipant was sent home.	Active

106297	12	White	Male	06/15/2011	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	7	Not Expected	1	Definitely not related	Non descript rash- no vesicles or pustules. Located on face, scalp, and trunk. Accompanied by pruritis. No other symptoms. Visited pediatrician- viral infection.Spontaneously resolved.	Active
106673	11	White	Male	01/13/2008	Gastrointestinal	Vomiting		0		2	Definitely not related	./ Upon insertion of IV, subject became nauseated and vomited. Once stable (after 30min) IVGTT was completed. After 15 mins subject vomited again. After I had subject stable and went home.	Active
106673	11	White	Male	03/23/2008	Neurology	Personality/behavioral		28		2	Probably not related	Other, Specify: / Behavioral changes including not talking to people, doing poorly @school/ Family physician discontinued attenol + all meds including oral insulin. Now doing better according to mother "he is back to his old self.	Active
107042	16	White	Male	06/20/2011	Surgery/Intra-Operative Injury	Intra-operative injury	Primary	45	Not Expected	1	Definitely not related	Participant had severe over-bite that needed surgical repair. The participant was admited to the hospital on 6/20/2011 and had surgery later that afternoon. The participant spent one night in the hosptial and was released the next day on 6/21/2011. The participant had the lower portion of the jaw moved forward and the upper portion moved back to allow upper and lower teeth to align properly.	Placebo

107042	17	White	Male	04/13/2012	Neurology	Seizure	Primary	.	Not Expected	3	Definitely not related	Participant "passed out and had a seizure" and currently at Good Shephard hospital. ********** Participant "passed out and had a seizure" and currently at Good Shephard hospital. 5/11/12-Mother states seizure could be the result of tumor or blood clot. Additional blood work will be drawn in 3 weeks. Blood sugar was normal and not related to hypoglycemia. Participant was not diagnosed with seizure disorder. 5/14/12-full medical record requested ********** Participant "passed out and had a seizure" and currently at Good Shephard hospital. 5/11/12-Mother states seizure could be the result of tumor or blood clot. Additional blood work will be drawn in 3 weeks. Blood sugar was normal and not related to hypoglycemia. Participant was not diagnosed with seizure disorder. 5/14/12-full medical record requested 6/2/12-unable to obtain medical record 7/9/12-Participant was seen by neurologist who repeated MRI. Mother states the clot was dissolving in the sinus cavity and instructed to keep ppt on ASA for 6 more months. Recommeded seeing a cardiac MD for a TILT test, mother states unsure why they are having her son see a cardiologist. Mother states no	Placebo

												symptoms or problems that she knows of. No additional seizures noted. ********** Participant "passed out and had a seizure" and currently at Good Shephard hospital. 5/11/12-Mother states seizure could be the result of tumor or blood clot. Additional blood work will be drawn in 3 weeks. Blood sugar was normal and not related to hypoglycemia. Participant was not diagnosed with seizure disorder. 5/14/12-full medical record requested 6/2/12-unable to obtain medical record 7/9/12-Participant was seen by neurologist who repeated MRI. Mother states the clot was dissolving in the sinus cavity and instructed to keep ppt on ASA for 6 more months. Recommeded seeing a cardiac MD for a TILT test, mother states unsure why they are having her son see a cardiologist. Mother states no symptoms or problems that she knows of. No additional seizures noted.	
107042	18	White	Male	06/05/2013	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	.	Not Expected	3	Definitely not related	Torn ligament in L thumb. Injury occurred in 3/2013 was not diagnosed until 5/2013. Subsequent surgery scheduled 6/5/2013.	Placebo
107410	21	White	Female	05/09/2016	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	84	Expected	1	Definitely not related	Participant stated that she had two bouts of bloody stool and that she was going to the gastroenterologist over the summer for evaluation. If she is	Active

												told to be removed from the study, she call. Did not have any contact with participant until 8/1/16 where she stated that she was continuing the study and that the doctor felt that the bleeding could be stress related.	
107924	10	White	Male	02/18/2014	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	On 2/18/14, participant was diagnosed with psoriasis on eyelids and elbows bilaterally. Prescribed mometasone furoate ointment 0.1% to be applied three times a day.	Placebo
107924	11	White	Male	05/03/2014	Ocular/Visual	Ocular/Visual - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	On May 3, 2014 participant was diganosed with myopia and prescribed glasses	Placebo
108131	46	White	Male	10/31/2014	Pain	Pain	Primary	4	Expected	2	Probably not related	The participant reported that the site where the IV catheter was placed in the right antecubital vein became bruised and painful. The pain was described as a deep tissue pain that extended into the elbow. No local or systemic signs of infection were present. Bruising was noted to be approximately 7.5cm	Active
108374	8	White	Female	06/07/2010	Infection	Infection with unknown ANC	Primary	10	Not Expected	2	Definitely not related	06/07/2010 developed sinus infection with a cough. Started on Augmentin, prednisolone and proventil. Resolved 06/17/2010	Active
108374	10	White	Female	12/02/2011	Endocrine	Pancreatic endocrine: glucose intolerance	Primary	.	Expected	1	Definitely not related	on 11/21/11, a 10 yo participant had an OGTT with a 2 hr glucose value over 200 mg/dL. On 11/28/11, participant's mother stated participant recently started exhibiting an increase in nocturnal enuresis, polyuria, polydipsia, and lethargy. On 11/30/11 2hr pp on home	Active

												glucose meter was 266 mg/dL. On 12/2/11, pediatric endocrinolgist diagnosed with Type 1 Diabetes based on 2hr OGTT glucose over 200 mg/dL, symptoms, and home blood glucose values. Was not started on insulin.	
109239	12	White	Female	09/21/2009	Pulmonary/ Upper Respiratory	Bronchospasm, wheezing	Primary	.	Not Expected	1	Definitely not related	Subject was diagnosed via medical history with excercise induced asthma on Sept 21, 2009. She would get sometimes get short of breath at the beginning of basketball games. She was prescribed an albuterol inhaler from which she is to take one puff prior to games.	Active
109239	12	White	Female	10/02/2009	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	On 10/3/2009, subject developed fever, sore throat, and difficulty swallowing. The subject was brought to her primary MD where a diagnosis of strep pharyngitis was made. The subject was started on penicillin, but quickly developed a rash. They went back to MD and the penicillin was discontinued and benedryl PRN for the rash and azithromycin were started. The pharyngitis resolved improved and resolved by 10/9/09.	Active
109239	12	White	Female	10/04/2009	Allergy/Immunology	Allergic reaction/hypersensitivity (including drug fever)	Secondary	0	Not Expected	2	Definitely not related	Subject developed rash in lower back, torso, and front of legs as a result of penicillin. The rash resolved with the discontinuation of penicillin and the administration of benadryl.	Active
109239	12	White	Female	06/01/2010	Infection	Infection with unknown ANC	Primary	3	Not Expected	2	Definitely not related	Subject diagnosed with bilateral ear infections via otoscope. Treated with azithromycin 500	Active

												mg x 1 day followed by 250 mg x 4 days.	
109239	12	White	Female	06/01/2010	Neurology	Personality/behavioral	Primary	.	Not Expected	2	Definitely not related	Subject diagnosed with ADHD and started on Concerta.	Active
109239	13	White	Female	02/24/2011	Gastrointestinal	Vomiting	Primary	2	Not Expected	2	Definitely not related	Subject developed food poisoning during a school field trip to Washington DC. Vomited 4-5 times.	Active
109239	13	White	Female	03/13/2011	Neurology	Neurology - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	The subject suffered a blow to the left elbow during a basketball game with resulting pain, tingling, and numbness of the arm. The subject parents took her to an emergency room where the diagnosis of a bruised ulnar nerve was made. The subject was advised to rest the arm. The symptoms subsided over the following week.	Active
110266	7	White	Male	12/13/2008	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	mild cold symptoms	Placebo
110266	7	White	Male	03/22/2009	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Cold symptoms	Placebo
110266	7	White	Male	04/09/2009	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	3	Not Expected	1	Definitely not related	Cold symptoms	Placebo
110266	8	White	Male	01/14/2010	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Common cold symptoms	Placebo
110266	9	White	Male	11/25/2010	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	Cold symptoms	Placebo

110266	9	White	Male	06/12/2011	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	1	Not Expected	2	Definitely not related	Subject sprained left small finger playing ball	Placebo
110266	9	White	Male	08/08/2011	Neurology	Neurology - Other (Specify in Event Details)	Primary	1	Not Expected	2	Definitely not related	Headache	Placebo
110266	10	White	Male	01/07/2012	Pain	Pain - Other (Specify in Event Details)	Primary	0	Not Expected	2	Probably not related	Subject suffered headache	Placebo
110266	10	White	Male	03/22/2012	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	Cold	Placebo
110266	10	White	Male	04/18/2012	Neurology	Neurology - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	Headache	Placebo
110454	12	White	Male	05/25/2011	Infection	Infection - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	The subject, along with 2 siblings, came down with chicken pox (varicella) starting around 5/25/11. Symptoms began with malaise, followed by a rash to the torso, face, and upper arms. The symptoms resolved by 4/1/11. At the time of the study visit, the mother noted that the subject still had some scars in the chest area that were healing.	Placebo
110454	16	White	Male	03/30/2015	Infection	Infection - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Subject had upper respiratory tract infection. Missed school x 1 day. No treatment. Did not stop study drug.	Placebo
110454	17	White	Male	11/17/2015	Infection	Infection - Other (Specify in Event Details)	Primary	3	Not Expected	1	Definitely not related	Subject had a cold from 11-17-15 to 11-20-15. Subject missed school for 1 day. No treatment given. No medications. Mild.	Placebo
110956	9	White	Female	05/01/2011	Musculoskeletal/Soft Tissue	Fracture	Primary	.	Not Expected	3	Definitely not related	Participant broke right arm while doing a front handspring at gymnastics on May 1, 2011. Participant has a closed reduction preformed as an out	Active

												patient on May 2nd, 2011. The participant had cast placed to the right arm and continues to have cast at this time.	
112931	15	White	Male	11/15/2012	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Fell and hit his forehead hard. Has a cut in his right eyebrow requiring stitches. Would is clean now. Placed on Antibiotic.	Active
113280	6	White	Male	01/18/2011	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	4	Not Expected	2	Definitely not related	Mother states fever of 103.0 degrees F. Diagnosed with Influenza A at PCP office. TamiFlu given for 5 days	Active
113280	6	White	Male	01/28/2011	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	4	Not Expected	2	Definitely not related	Mother states fever of 102-103 degrees F with cough/congestion. Seen by PCP, negative for strep. Diagnosed as viral infection. No abx given. OTC meds for symptosm of cough/congestion.	Active
113280	6	White	Male	03/04/2011	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	9	Not Expected	2	Definitely not related	Mother states participant c/o bilateral ear pain with fever of 102 degrees F. Seen by PCP and diagnosed with otitis media to bilateral ears.	Active
113488	10	White	Female	01/23/2008	Infection	Infection with unknown ANC		11		2	Probably not related	Other, Specify: / Bronchitis/ Participant experienced runny nose cough and low-grade fever for 5 days. Prescribed Biaxin 500 mg OD for 10 days.	Active
113488	11	White	Female	01/12/2009	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Probably not related	Subject experienced low grade fever, cold symptoms and body ache. Missed 3 days of school. Took cough syrup (Delsym), Advil for fever and asthma puffer (Salbutamol and Flovent). Was on the puffer only when she had a cough and cold.	Active

113488	12	White	Female	10/18/2009	Syndromes	Flu-like syndrome	Primary	5	Not Expected	2	Definitely not related	Subject started feeling ill on Oct/18/09. Missed school from Oct/19-09-Oct/23/09, went back to school the following week (Oct/26/09). Had gone into a walk in clinic where the doctor prescribed antibiotics for pneumonia and cold like symptoms. Subject was on antibiotics for 5 days as instructed by doctor along with flovent, ventolin for her breating problems. Subject has asthma and takes singulair everyday and has taken flovent on some occasions prior to this event. Symptoms were: fever, dry cough, aches &pain, headache, dizziness, pneumonia (subject may have had H1N1)	Active
114772	6	White	Female	10/31/2009	Syndromes	Flu-like syndrome	Primary	3	Not Expected	2	Definitely not related	Subject received H1N1 shot on Thursday (Oct/29/09). Flu like symptoms started on Saturday (Oct/31/09)evening, with a fever at 9pm. Had fever all day on Sunday (Nov/01/09) which kept getting higher between doses of Motrin. Subject's fever went up to 104C when parents had decided to take the subject to the Emergency. Emergency doctor suspects that the subject has H1N1 and had prescribed Tamiflu 2x30mg/day for 5 days. She missed school on Nov/02/09, felt better and was symptom free by November 3rd. Her mom kept her out of school until November 5th. Subjects flu like symptoms were; fever, tiredness,	Active

												persistent cough and sore throat.	
114772	6	White	Female	02/08/2010	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	3	Not Expected	2	Probably not related	Subject was off from school on Feb/08/10 with a stuffy nose and cough. Mother gave subject Buckley's Jack & Jill decongestant twice a day for two days. Subject recovered from symptoms by Feb/11/10.	Active
114772	7	White	Female	03/15/2011	Infection	Infection - Other (Specify in Event Details)	Primary	8	Not Expected	2	Definitely not related	Subject was sick from March 15-22/11, had a fever for 3 days (March 15-18) and vomiting (March 19-22). She was prescribed Amoxicillin chewable tablets for 7 days but, she took it for 3 days (March 19-22). She also had PRN Pedialyte PO (March 19-22) and PRN Advil 200 mg. PO (March 16- 19). Symptoms resolved on March 23/11. Subject was on March break, but mother stated that participant would have missed one week of school.	Active
114820	6	White	Male	11/05/2009	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	3	Not Expected	1	Probably not related	Subject developed fever symptoms 3 weeks ago. Had fever for 2 days and had missed one day of school. Mother gave subject 4 doses of Motrin over a 24 hour period.	Active
114820	7	White	Male	05/29/2011	Infection	Infection - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	Subject was sick from May 29 - May 31/2011; had cold like symptoms, fever 102 degree Fahrenheit and cough. Took Tylenol liquid 160 mg.PRN; subject missed 3 days of school	Active

												May 29,30 and 31. Symptoms resolved on June 1/2011.	
114820	11	White	Male	12/30/2014	Gastrointestinal	Vomiting	Primary	1	Not Expected	2	Definitely not related	Subject was sick on Dec. 30, 14 with vomiting (X5), diarrhea (X5) and fever (not measured). Took Gravol kids PRN, did not seek any medical attention. Would have missed 1 day of school. Symptoms resolved on Dec. 31, 14.	Active
114820	13	White	Male	12/13/2016	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	1	Not Expected	2	Definitely not related	On Dec. 13, 2016 subject was not feeling well, felt tired and missed 1 day of school (Dec. 13th, 2016). Did not take any meds, did not seek any MD attention. Back to normal on Dec. 14th, 2016.	Active
114820	13	White	Male	12/29/2016	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	On Dec. 29, 2016 subject was sick with flu-like symptoms, felt feverish, had upset stomach and vomited x 4. Took caps. Advil PRN x5 on Dec. 29th and 30, 2016. Did not seek MD attention. Would have missed 4 days of school Dec. 29, 2016-Jan. 01, 2017 (subject was on break). Back to normal on Jan. 02, 2017.	Active
114876	13	White	Female	12/01/2007	Infection	Infection with unknown ANC		7		2	Probably not related	Other, Specify: / viral infection/ c/o sore throat, cough, runny nose. Missed 2 days of school.	Active
114876	14	White	Female	11/18/2008	Musculoskeletal/Soft Tissue	Fracture	Primary	32	Not Expected	2	Definitely not related	Subject fractured her right foot on November 18, 2008 during gymnastics, was taken to the emergency - temporary cast for 1 week. Subject visited family doctor on November 25, 2008 as instructed by the emergency doctor, x-rays were done again - permanent cast on foot	Active

												fracture until December 20, 2008.	
114876	14	White	Female	03/01/2009	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	22	Not Expected	1	Definitely not related	Subject sprained ankle at a gymnastics competition on March 1st while warming up on the beam. Subject did not say anything until after competing on the beam, floor and vault. When subject went to the physiotherapist on March 2nd, physiotherapist looked at it and indicated it was a grade 1 sprain. Sprain had healed completely as of March 23. Subject had also aggravated knees at the same competition. They were not taped properly. Subject was in a great deal of pain on March 3rd. Was given extra sessions of physiotherapy that week and has been restricted training until March 30th.	Active
114876	14	White	Female	04/23/2009	Musculoskeletal/Soft Tissue	Fracture	Primary	42	Not Expected	2	Definitely not related	Subject fractured her right foot during gymnastics (while tumbling) on April 23, 09 and was taken to the emergency. Was in a cast for 6 weeks. The cast was taken off on June 4th at which time it was completely healed. Subject missed one day of school.	Active
114876	14	White	Female	06/13/2009	Syndromes	Flu-like syndrome	Primary	6	Not Expected	2	Probably not related	Subject began having flu symptoms on June 13, 2009 and missed 2 days of school. Symptoms were; cough, sneezing, congestions, fatigue, and achiness. She was better by June 19, 2009.	Active

114876	15	White	Female	02/20/2010	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Subject experienced cold like symptoms- stuffy nose, cough and fever on Feb/20/2010. Missed one day of school. Subject took Buckleys complete 1x per day for 4 days, and Tylenol for cold 1x per day for 4 days. Recovered without sequelae by Feb/24/2010	Active
114876	16	White	Female	12/01/2010	Infection	Infection - Other (Specify in Event Details)	Primary	20	Not Expected	2	Definitely not related	Participant was sick beginning Dec.1st/10; had a cough, headache, was congested and had a fever for 2 days. She missed one day of school. Subject took Tylenol Cold tablets 500 mg. PRN for 5 days (Dec.1 - Dec.6 /10) and Tylenol Menstrual caplets 500 mg PRN for 2 days.	Active
114876	16	White	Female	02/17/2011	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Participant was sick beginning Feb. 17/11; she felt feverish (temperature not measured), had sore throat, mild headache and stuffy nose. Subject stated: "had low energy and did not feel well in general". Took Tylenol Cold tablets 500 mg. PRN and Vitamin C tablets 500 mg. PRN. She missed one day of school. Felt well on Feb. 21/11.	Active
114876	16	White	Female	04/19/2011	Constitutional Symptoms	Fatigue (asthenia, lethargy, malaise)	Primary	1	Not Expected	2	Definitely not related	Subject returned from a 10 day trip abroad; felt unwell and tired and fainted while in the shower. Subject did not injure self but stayed at home on April 19/11. Symptoms resolved on April 20/11.	Active
114876	17	White	Female	08/08/2011	Infection	Infection - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	On August 8/11 subject had cold like and allergy symptoms: cough, stuffy nose, watery and itchy eyes and felt feverish. Took PRN Tylenol tablets 500	Active

												mg and PRN Reactin tablets 10 mg. Missed 1 day of work. Symptoms resolved on August 10/11.	
114876	17	White	Female	11/14/2011	Infection	Infection - Other (Specify in Event Details)	Primary	41	Not Expected	2	Definitely not related	Subject had runny nose/sniffles, cough and was "generally feeling run down", as per subject's parent due to stress of heavy workload of grade 12 curriculum, from Nov. 14th.-Dec.24th./11. Had fever (not measured) on Nov.14th./11.Took PRN Buckley's cold and sinus from Nov. 14th. - Dec. 24th. /11. Participant missed two days of school Nov.14th. and Nov. 23rd./11. Did not seek medical attention. Symptoms resolved on Dec. 25th./11.	Active
114876	18	White	Female	11/13/2012	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Subject was sick from Nov. 13th to Nov. 16th /12, had a fever (not measured), stuffy nose and headache; did not take any meds. Missed one day of school Nov.14th /12. Symptoms resolved on Nov. 17th /12.	Active
114876	21	White	Female	02/01/2016	Neurology	Neurology - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	Subject had a concussion on Feb. 01, 2016 (at cheerleading event) with mild headache. Seen by MD in the ER, tablets Tylenol # 3 PRN given and rest recommended. No other symptoms present, no additional tests done. Missed 2 days of school, Feb. 01 and Feb. 02, 2016. Back to normal on Feb. 03, 2016.	Active
115222	15	White	Male	03/20/2008	Pain	Pain		1		2	Probably not related	Other, Specify: / Migrane/ Participant experienced severe headache hich is common for him. missed one day of school.	Placebo

115222	16	White	Male	07/21/2008	Infection	Infection with normal ANC or Grade 1 or 2 neutrophils		11		2	Probably not related	Other, Specify: / Infection to groin on (R) leg/ Participant c/o redness and swelling to groin on (R) leg. Family doctor prescribed antibiotic x 10 days.	Placebo
115226	12	White	Male	01/17/2011	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	Participant had cold symptoms from Jan 17 to Jan 23 /11 with cough, sore ears, sinus pain and headache. Did not seek medical attention, took Buckley's night cough mixture for 5 days (Jan 17 - Jan 21/11), Advil Cold & Sinus PRN and Acetaminophen Tablets 200 mg. PRN for 3 days (Jan 20 - Jan 22/11). He also took Ventolin puffer x 2 (Jan.20 and 21/11) 2 puffs at bed time. Subject missed 4 days of school (Jan 17, 19, 20 & 21/11). He felt well on Jan. 24/11.	Placebo
115226	13	White	Male	12/22/2011	Infection	Infection - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	Subject had headache and stuffy nose on Dec. 22nd and Dec. 23rd, 2011. Took PRN Advil Cold and Sinus Plus tablets 200mg. (2 doses). Missed 2 days of school Dec. 22nd and Dec. 23rd , 2011. Symptoms resolved on Dec. 24th. 2011.	Placebo
115226	14	White	Male	11/03/2013	Gastrointestinal	Vomiting	Primary	3	Not Expected	2	Definitely not related	Subject was not feeling well on Nov. 3rd, 13; vomited X3 during the night. On Nov. 4th and 5th still not feeling well - with low energy level and tired. Did not seek any medical attention, did not take any medications. Missed two days of school Nov. 4th. and 5th. Symptoms resolved on Nov. 6th./13.	Placebo
115226	15	White	Male	12/12/2013	Infection	Infection - Other (Specify in Event Details)	Primary	374	Not Expected	2	Definitely not related	Subject was sick from Dec. 12th to Dec. 20th, 13 with stuffy nose, cough, snezeeing and mild sore throat. Did not seek any	Placebo

												medical attention; OTC medication taken: PRN Benylin extra strength cough & cold and PRN Tylenol extra strength tablets. Missed four days of school, Dec. 13th. to Dec. 17th/ 13. Symptoms resolved on Dec. 21st/13.	
115226	15	White	Male	10/03/2014	Infection	Infection - Other (Specify in Event Details)	Primary	6	Not Expected	2	Definitely not related	Subject had mild cold with runny nose, nasal congestion and mild headache that started on Oct. 3rd, 14. Missed two days of school: Oct 6th and Oct. 7th, 14. Did not seek any medical attention. Took Benylin Extra Strength Cough & Cold Syrup 2 tsp. (10 ml) on Oct. 4th, 14; and Benadryl Tabl. 25mg. X1 on Oct. 5th, 6th and 7th, 14. Symptoms resolved on Oct. 9th, 14.	Placebo
115226	17	White	Male	03/12/2016	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Subject has had abdominal pain since Mar. 12, 16; "on and off" as per subject report. Missed days of school Nov. 17 & Nov. 18th.16. On Nov. 21st subject had nausea and moderate abdominal pain and went to ER. Seen by MD, blood tests done (normal results), no meds given. Would have missed a day of school (Nov. 21st,16), went to ER after school. Subject has scheduled ultrasound abdomen on Dec. 05, 16.	Placebo
115711	8	White	Female	02/24/2011	Musculoskeletal/Soft Tissue	Fracture	Primary	20	Not Expected	3	Probably not related	While horseback riding ppt fell off and was thrown against a post. PPt suffered a broken arm along with facial injuries and lost 3 teeth. PPt was in ER for 7 hours and was anesthetized for facial repair and the arm set in a	Placebo

												cast. The ppt was discharged home under the care of her parents. In 4 days had returned to school but was on a liquid progressing to a soft diet for 2 weeks and then resumed a full diet. The cast was removed on March 16th. The participant has a plate and false teeth but has full recovery. An X-ray is booked for April 27th as Follow-up.	
115711	9	White	Female	08/28/2011	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	10	Not Expected	2	Probably not related	Amoxil 5 ml TID x 10 days	Placebo
115711	9	White	Female	09/11/2011	Renal/Genitourinary	Cystitis	Primary	11	Not Expected	2	Probably not related	Fever with vomiting and wetting self dx with UTI	Placebo
115711	9	White	Female	11/09/2011	Renal/Genitourinary	Cystitis	Primary	11	Not Expected	2	Probably not related	One day sick with fever and vomiting (belly pain). Suprax x10 days for UTI	Placebo
115711	9	White	Female	12/19/2011	Renal/Genitourinary	Cystitis	Primary	17	Not Expected	2	Probably not related	abdominal pains started on Dec 19th and was checked by physician for UTI. Urine sample showed few bacteria but no treatment given. Belly pains increased and a urine sample on Dec 25th, 2011 showed bacteria, blood and white blood cells. Dec 26,2011, prescription given for suprax 10ml (100mg/5ml) OD	Placebo
115711	9	White	Female	04/11/2012	Auditory/Ear	Hearing: patients without baseline audiogram and not enrolled in a monitoring program	Primary	.	Not Expected	2	Probably not related	Past number of years, Mom has noticed child having difficulty hearing. Treated with antibiotics for frequent ear infections and with nasonex for nasonal congestion with no noted improvement in hearing. Assessed April 11, 2012 by audiologist and diagnosed with mild hearing loss in the left ear	Placebo

												and mild to moderate hearing loss in the right ear.	
115711	9	White	Female	06/09/2012	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	dislocated left elbow while doing a cartwheel. To ER for re-location, anesthetic used for procedure. Sent home after re-location and child is recovering. Arm is slightly swollen and unable to completely straighten elbow.	Placebo
116554	7	White	Male	11/08/2011	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	Subject was sick from Nov. 8th - Nov.10th /11, had stomach pain and slight decrease in appetite/energy level. Vomited X1 and had a fever (not measured) on Nov.9th. Took PRN Advil tabl.100 mg. Missed one day of school on Nov.10th /11. Symptoms resolved on Nov.11th /2011.	Active
116554	7	White	Male	01/27/2012	Gastrointestinal	Vomiting	Primary	3	Not Expected	2	Definitely not related	Subject was sick from Jan. 27th - Jan. 30th. 2012. Had fever(not measured) on Jan. 27th and 28th; and vomited (x 5) on Jan. 27th.12. Did not seek medical attention. Advil tablets 100 mg. PRN taken. Missed one day of school Jan. 27th. 12. Symptoms resolved on Jan. 30th. 12.	Active
116554	7	White	Male	04/09/2012	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	On Apr. 9/12 participant broke out in all over body rash, itchy, red, some hive like swelling. As per participant's parent, " it might be an allergic reaction to oil of oregano", parent gave it to the subject 5ml P.O X1 on Apr.7 and Apr. 8th. Seen by MD, Benadryl prescribed x 3 (Apr.9 - Apr. 12/12). Missed days of school Apr.10 and 11/12.	Active

												Symptoms resolved on Apr.12/12.	
116554	7	White	Male	04/09/2012	Infection	Infection - Other (Specify in Event Details)	Primary	46	Not Expected	2	Definitely not related	On Apr. 9/12 participant broke out in all over body rash, itchy, red, some hive like swelling. As per participant's parent, " it might be an allergic reaction to oil of oregano", parent gave the subject 5ml P.O X1 on Apr.7 and Apr. 8th. Seen by MD, Benadryl prescribed x 3 (Apr.9 - Apr. 12/12). Missed days of school Apr.10 and 11/12. Subject's rash resolved on Apr.12/12. Participant also had a mild cough and cold that increased slightly since Apr. 13/12. Seen by MD on May 3rd/12 told had sinus infection and started antibiotics Novamox 50 mg/5ml. 3X100 ml P.O for 2 weeks May 3 - 17/12. Symptoms resolved on May 25/12.	Active
116554	8	White	Male	02/01/2013	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	Subject was slightly injured on Feb 1st. /13 during a hockey game, hurt left hip; had difficulty with full range of motion and pain for that day. Taken to the hospital on Feb. 2nd./ 13, seen by MD and x-ray done. The x-ray result was o.k. only slight soreness remained. No additional tests or follow up required. Missed one day of hockey practice; as per subject's parent : "1.5 day missed normal activities". Symptoms resolved completely by Monday Feb. 4th. /13.	Active

116554	8	White	Male	03/26/2013	Renal/Genitourinary	Renal/Genitourinary - Other (Specify in Event Details)	Primary	11	Not Expected	2	Definitely not related	Subject had scheduled a same - day surgery (circumcision) on Mar.26th. under general anesthesia. Woke up from the surgery well; was very nauseous but did not vommit. Participant had 2 Acetaminophen chewable's X 1 on Mar. 26th.; and on Mar. 27th 1 dose Acetaminophen and Morphine liquid 2 mg. BID. Missed one day of school March 26th. inclusive. Symptoms resolved on April 6th./13.	Active
116554	9	White	Male	03/08/2014	Infection	Infection - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Subject was sick from Mar. 8th - 13th with cold symptoms: slight fever on Mar. 9th and mild cough. As per subject's parent, subject "might have missed one day of school if there had been school (was March break). Two tablets Children's Advil PRN given, Mar. 8th and 9th. Symptoms resolved on Mar. 13th.	Active
117163	7	White	Female	04/05/2009	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	3	Not Expected	2	Possibly related	Subject experienced belly ache the week of April 05, 09. Missed 2 days of school and the belly ache resolved 2-3 days after onset.	Placebo
117432	11	White	Male	03/04/2014	Gastrointestinal	Nausea	Primary	1	Not Expected	1	Definitely not related	nausea for 1 day, no treatment	Placebo
118256	16	White	Female	12/08/2009	Gastrointestinal	Ulcer, GI	Primary	.	Not Expected	2	Probably not related	Participant had been complaining of nausea; working with Gastroenterologist; initial diagnostic studies negative including US, labs,and HIDA scan. EGD completed on 12/08/2009 and mother was told that there was a small duodenal ulcer and contacted	Placebo

												the Study Coordinator. The PI contacted the Gastroenterologist who believed that it was not related to study drug. Was also negative for H. Pyloria.	
119387	13	White	Male	10/15/2010	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	31	Not Expected	2	Definitely not related	Injured wrist in fall in gym. Had x-ray, not in ER.	Placebo
119387	14	White	Male	12/27/2011	Infection	Infection - Other (Specify in Event Details)	Primary	10	Expected	2	Possibly related	On Dec 27 2011 started an antibiotic 2 x a day for 10 days for a cold and cough. Fo rthe same illness took sungulair once a day at night for 7 days,	Placebo
119387	16	White	Male	04/29/2014	Blood/Bone Marrow	Blood/Bone Marrow - Other (Specify in Event Details)	Secondary	.	Not Expected	3	Probably not related	Subject was first diagnosed with pneumonia based on fever x3 days, coughing and chest x-ray that showed "spots on his lungs" per subjects mother. Cough continuted until trip to doc on April 28th for weakness, SOB. WBC at hospital measured 164,000. Had 4units of blood transfused, 2 units of platelets. Spinal tap was clear, bone marrow biopsy done, no transplan needed. Medications: clarithromycin ER 500mg started april1 for pneumonia (to be a secondary event). Cefepime give first 14 days starting April 28th, allopurinol, raspuricase, prednisone for first 28 days starting April 30th, rantidine, insulin. chemo drugs, cytarabine, vincristine, daunorubicin, asparaginase, methotrexate.	Placebo

120460	6	Black/ African American	Female	06/30/2010	Infection	Infection - Other (Specify in Event Details)	Primary	10	Expected	2	Probably not related	strep throat, treated with amoxicillin for 10 days	Active
121278	16	White	Female	01/01/2010	Infection	Infection - Other (Specify in Event Details)	Primary	6	Not Expected	1	Probably not related	Patient with Step throat and HINI. Patient went to MD and took penicillin for 7 days, 2 tabs daily. Patient improved and feeling well.	Placebo
121544	.	White	Male	.	Dermatology/Skin	Rash/desquamation		.		2	Probably not related	Other, Specify: / (unknown origin) small rash or skin irritation./ Pt noted circuler rash 1X .5 x0 on LUQ just above umbilicus. pink. No itch, no pain. Pt states he is putting "cream on it". Not sure what.	Active
121544	25	White	Male	09/01/2012	Constitutional Symptoms	Weight loss	Primary	53	Expected	1	Definitely not related	Subject reported weight loss of approximately 4 kg attributed to beginning a new residency and moving to a new city. The subject is adjusting to a new stressful, demanding schedule. ********** Subject reported weight loss of approximately 4 kg attributed to beginning a new residency and moving to a new city. He is adjusting to a new stressful, demanding schedule. ********** Subject reported weight loss of approximately 4 kg attributed to beginning a new residency and moving to a new city. He is adjusting to a new stressful, demanding schedule.	Active
121669	.	White	Female	.	Neurology	Neurology - Other (Specify in Event Details)		.		2	Probably not related	Other, Specify: / Raynauds like sx/ Cool hands/feet, c/o burning sensation and hands/feet "turning purple." MD states it	Active

												may be r/t Adderall. Tapering off. Starting Strattera.	
121669	21	White	Female	06/25/2014	Hepatobiliary/Pancreas	Pancreatitis	Primary	9	Not Expected	2	Probably not related	21 year old subject, with a history of alcohol abuse admitted to the hospital on 6/25/14 for severe abdominal pain for 2 days found to have pancreatitis. Had some nausea, no fever, diarrhea or vomiting. Drinks half pint whiskey and 6 beers daily. Medications are Trazadone and Adderall and oral insulin/placebo. Hospital day #1 on 6/26/14 the subject was stable on bowel rest. Abdominal pain controlled on iv dilauded. No signs of alcohol withdrawal. ********** 21 year old subject, with a history of alcohol abuse admitted to the hospital on 6/25/14 for severe abdominal pain for 2 days found to have pancreatitis. Had some nausea, no fever, diarrhea or vomiting. Drinks half pint whiskey and 6 beers daily. Medications are Trazadone and Adderall and oral insulin/placebo. Hospital day #1 on 6/26/14 the subject was stable on bowel rest. Abdominal pain controlled on iv dilauded. No signs of alcohol withdrawal. Hospital day #8 Pancreatitis No clinical improvement, continued pain with po liquid, - continued NPO, iv pain meds Repeat CT scan showed "small phlegmon" Transferred from community hospital to tertiary care	Active

												hospital. ********** 21 year old subject, with a history of alcohol abuse admitted to the hospital on 6/25/14 for severe abdominal pain for 2 days found to have pancreatitis. Had some nausea, no fever, diarrhea or vomiting. Drinks half pint whiskey and 6 beers daily. Medications are Trazadone and Adderall and oral insulin/placebo. Hospital day #1 on 6/26/14 the subject was stable on bowel rest. Abdominal pain controlled on iv dilauded. No signs of alcohol withdrawal. Hospital day #8 Pancreatitis No clinical improvement, continued pain with po liquid, - continued NPO, iv pain meds Repeat CT scan showed "small phlegmon" Transferred from community hospital to tertiary care hospital. Hospital discharge: Abdominal pain resolved. Patient able to tolerate regular diet. Amylase and lipase normalized. Patient advised counseling about alcohol abuse and discharged home. Diagnosis: alcoholic pancreatitis.	
121669	23	White	Female	03/17/2016	Gastrointestinal	Dental: teeth	Primary	0	Not Expected	2	Definitely not related	wisdom teeth extraction	Active
122293	9	White	Male	07/19/2008	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)		0		2	Definitely not related	./ Pt was at karate class and was kicked in abdomen. Increased pain. Went to ER. No N/V/D. No medications given. Blood work done and discharged.	Placebo

122338	17	White	Male	11/01/2011	Infection	Infection with unknown ANC	Primary	61	Not Expected	2	Definitely not related	Multiple sinus infections, start 11/1/2011, Augmentin prescribed by primary MD, resolved 1/1/2012.	Active
122338	18	White	Male	12/01/2011	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Patient was diagnosed with asthma by their primary care physician and started on Albuterol and Q-Var inhalers.	Active
122338	18	White	Male	07/01/2012	Pain	Pain	Primary	.	Not Expected	2	Definitely not related	Participant has a history of Left shoulder pain starting 7/1/12 for which the participant had physically therapy for x 1 year until 1/6/14 and on 1/6/14 recieved a cortisone shot intra-articular in the Left shoulder.	Active
122338	18	White	Male	10/15/2012	Infection	Infection - Other (Specify in Event Details)	Primary	12	Not Expected	2	Definitely not related	Subject reports sinus infection that was treated with Avelox 400mg daily for a week.	Active
122338	19	White	Male	11/30/2012	Infection	Infection - Other (Specify in Event Details)	Primary	6	Not Expected	2	Definitely not related	Subject reports bacterial throat infection treat with Amoxicillin daily for a week.	Active
122338	19	White	Male	04/01/2013	Infection	Infection - Other (Specify in Event Details)	Primary	19	Not Expected	2	Definitely not related	Subject reports sinus infection that was treated with Augmentin.	Active
122338	19	White	Male	05/01/2013	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Subject reports sinus infection that was treated with Augmentin 875 mg for 10 days.	Active
122338	19	White	Male	06/01/2013	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Subject reports right foot abscess that was treated with Amoxicillin for 10 days.	Active
122338	19	White	Male	07/13/2013	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	55	Not Expected	2	Definitely not related	Subject reports a rectal fissure that occurred after falling backwards on to a hard railing while lifting heavy boxes. Subject took flagyl 500 mg for one week and canasa 1000 mg for inflammation.	Active
122338	19	White	Male	09/10/2013	Infection	Infection - Other (Specify in Event Details)	Primary	22	Not Expected	2	Probably not related	Participant noticed rash on hands and feet as well as a sore throat that started on 9/10/13, and went to health center on college campus 9/12/13.	Active

												Participant reports taking one dose each of Sudafed 120 mg and Benadryl 25 mg at college campus health center on 9/12/13. The college campus health center also started the participant on Amoxicillin 875 mg BID on 9/12/13 which was stopped on 9/17/13. Participant had lab work done at Quest on 9/13/13 and was positive for Coxsackie Virus.	
122338	19	White	Male	11/22/2013	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	43	Not Expected	2	Definitely not related	Sinus infection.	Active
122338	20	White	Male	01/27/2014	Dermatology/Skin	Urticaria (hives, welts, wheals)	Primary	10	Not Expected	3	Definitely not related	Rash requiring hydrocortisone cream	Active
122338	20	White	Male	03/08/2014	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Sinus infection	Active
122338	20	White	Male	03/22/2014	Ocular/Visual	Ocular/Visual - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	eye infection requiring tobramycin opth drops.	Active
122338	20	White	Male	04/18/2014	Musculoskeletal/Soft Tissue	Fracture	Primary	8	Not Expected	2	Definitely not related	broken scaphoid related to basketball injury, surgery performed outpatient, antibiotics and pain medication administered, resolved	Active
122338	20	White	Male	07/13/2014	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Participant reports having a strep throat, which required taking amoxicillin .	Active
122338	20	White	Male	09/01/2014	Infection	Infection - Other (Specify in Event Details)	Primary	8	Not Expected	2	Definitely not related	Participant reports strep throat that was diagnosed by MD at school. Participant took amoxicillin prescribed by MD to treat strep throat.	Active
122338	21	White	Male	12/01/2014	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Strep throat diagnosed Dec 1, 2014, treated with Amoxicillin for 10 days.	Active

122338	21	White	Male	04/03/2015	Infection	Infection with unknown ANC	Primary	6	Not Expected	2	Definitely not related	Treated outpatient. Omnicept taken daily from april 3rd to april 9th, 2015	Active
122338	21	White	Male	07/27/2015	Infection	Infection - Other (Specify in Event Details)	Primary	14	Not Expected	2	Definitely not related	Upper Respiratory Infection, not related per study team, grade 2, start 7/27/15, stopped 8/10/15, treated with Amoxicillin 875 mg PO BID x 10 days	Active
122664	4	White	Male	10/31/2008	Infection	Infection - Other (Specify in Event Details)	Primary	7	Not Expected	1	Probably not related	Pt with ear infection. Went to PCP and prescribed amoxicillin x 7 days. No fever, n/v. Pt feeling fine. No further interventions.	Placebo
122707	3	White	Male	09/06/2007	Allergy/Immunology	Allergic reaction/hypersensitivity (including drug fever)		0		3	Definitely not related	./ Pt had a low grade fever on 9/6/07 and took dye free liquid motrin. He then developed Laryngeal edema + (L) eye swelling with hives. Resolved with benadryl.	Active
122707	3	White	Male	09/11/2007	Infection	Infection with unknown ANC		0		2	Definitely not related	./ Diagnosed with GAS on 9/11/07	Active
122707	4	White	Male	02/13/2008	Infection	Infection with unknown ANC		13		2	Probably not related	Other, Specify: / Fever 102.5./ Pt with fever for 3days, body aches, tylenol every 4 hrs. Followed by congestion tll 2/25/08 Benadryl every evening. Resolved. Pt feeling well.	Active
122707	5	White	Male	04/08/2009	Allergy/Immunology	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Primary	.	Not Expected	1	Definitely not related	patient with allergy signs and symptoms: itchy throat, itchy eyes, nasal stuffiness, sneezing, and cough. Has had seasonal allergy symptoms beginning in April.	Active
123011	16	White	Male	12/01/2013	Musculoskeletal/Soft Tissue	Fracture	Primary	50	Not Expected	3	Definitely not related	Participant suffered a fracture of right first metacarpal bone while working out in gym. Participant was treated by pin insertion to stabilize the fracture in outpatient procedure under general anaesthesia. There was no	Active

												inpatient hospitilization for the event and participant was discharged immediatey on antibiotics (Anacef) and painkillers. The condition has resolved and participant reports no compliants on the day of event report.	
123470	15	White	Female	11/16/2010	Pain	Pain	Primary	.	Not Expected	2	Definitely not related	Experiencing pain during ovulation, PMD prescribed oral contraceptives	Active
123470	18	White	Female	12/17/2012	Pain	Pain	Secondary	28	Expected	2	Definitely not related	Patient was experiencing chest pain with sternal swelling and high blood pressure and was seen at an immediate care center. Patient was later diagnosed with cholecystitis, which was believed to have produced the chest pain and associated symptoms.	Active
123470	18	White	Female	01/14/2013	Hepatobiliary/Pancreas	Cholecystitis	Primary	0	Not Expected	3	Definitely not related	Participant had to have gall bladder removed due to stones. Prior to surgery, the subject reported abdominal pain and high blood pressure, which resolved after surgery.	Active
123470	18	White	Female	01/25/2013	Hepatobiliary/Pancreas	Pancreatitis	Secondary	2	Not Expected	3	Definitely not related	Patient was brought back into the hospital due to abdominal pain, and was treated for pancreatitis	Active
123470	19	White	Female	05/20/2014	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Patient was diagnosed with bacterial infection in throat.	Active
123470	19	White	Female	08/20/2014	Endocrine	Endocrine - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Patient was diagnosed with Polycystic Ovarian Syndrome	Active

123470	20	White	Female	09/11/2015	Pulmonary/ Upper Respiratory	Dyspnea (shortness of breath)	Primary	6	Not Expected	2	Definitely not related	Patient was seen in Emergency room for shortness of breath on 9/11/2015. The subject received a "breathing treatment" and was discharged the same day with a Medrol dose pack and a Ventolin inhaler. Patient reported that provider told the subject that they had inflammation of the lungs, likely due to an infection. We are requested medical records to confirm details. ********** Patient was seen in Emergency room for shortness of breath on 9/11/2015. Patient received a "breathing treatment" and was discharged the same day with a Medrol dose pack and a Ventolin inhaler. Patient reported that provider explained that there was inflammation of the lungs, likely due to an infection. We requested medical records to confirm details. After receiving the medical reports from the Emergency Room, we changed the diagnosis to shortness of breath, as physical exam and chest x-ray were normal.	Active
125600	7	White	Male	10/02/2011	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	1	Probably not related	sore throat and swollen neck glands	Placebo
125600	12	White	Male	06/26/2016	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	8	Not Expected	2	Definitely not related	Fell from hammock and injured head. Required ER visit and stitches for laceration.	Placebo
126006	8	White	Male	06/22/2010	Neurology	Cognitive disturbance	Primary	.	Not Expected	2	Definitely not related	Diagnosed with ADD on 6/22/10. Started Concerta 18mg daily on 6/22/10.	Active

126006	8	White	Male	09/20/2010	Infection	Infection - Other (Specify in Event Details)	Primary	17	Not Expected	2	Probably not related	Diagnosed with strep throat in September 2010. Took amoxicillin for one week, did not resolve. Starting in October took Omnicef for one week, and resolved.	Active
126006	8	White	Male	11/24/2010	Infection	Infection - Other (Specify in Event Details)	Primary	5	Not Expected	2	Probably not related	conjunctivitis	Active
126006	11	White	Male	06/17/2013	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Otitis Media treated with 10 day course of amoxicillin; follow-up examination with family physician indicated infection was resolved	Active
126006	12	White	Male	02/05/2015	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Probably not related	pharyngitis/strep throat	Active
126006	13	White	Male	03/23/2015	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Probably not related	strep throat	Active
126006	13	White	Male	06/02/2015	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	4	Not Expected	2	Probably not related		Active
126267	.	White	Male	.	Pulmonary/ Upper Respiratory	Cough		.		2	Definitely not related	Other, Specify: / Bronchitis/ Mid-March diagnosed with bronchitis and prescribed antibiotics for 10 days. Study drug was not stopped.	Active
126267	10	White	Male	09/26/2009	Infection	Infection - Other (Specify in Event Details)	Primary	7	Not Expected	2	Probably not related	H1N1 Flu	Active
126267	11	White	Male	11/01/2010	Infection	Infection - Other (Specify in Event Details)	Primary	68	Not Expected	2	Probably not related	Reports symptoms of sinus infection started in November. Diagnosed with sinus infection 12/10/10 and started 10 day course of Augmentin. Did not resolve, and started another 10 day course of Augmentin.	Active
126267	12	White	Male	06/01/2011	Surgery/Intra-Operative Injury	Intra-operative Injury - Other (Specify in Event Details)	Primary	20	Not Expected	3	Definitely not related	Subject had surgery adenoids removed and sinuses resected due to recurrent sinus infections and per ENT	Active

												physician recommendation after scope showing blockage of sinuses and swelling	
126267	14	White	Male	09/01/2013	Pulmonary/ Upper Respiratory	Bronchospasm, wheezing	Primary	.	Not Expected	2	Probably not related	Mother reported at 69 M phone visit, subject had a chronic cough which the family thought was bronchitis; doctors diagnosed him as having an asthma flare; subject is currently taking prednisone and antibiotics routinely until further notice.	Active
126267	15	White	Male	05/08/2014	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	strep throat	Active
126267	16	White	Male	01/15/2016	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	15	Not Expected	2	Probably not related	Diagnosed with upper respiratory infection on 1/15/16	Active
126387	11	White	Male	10/14/2013	Pain	Pain - Other (Specify in Event Details)	Primary	0	Not Expected	2	Probably not related	participant developed headache (pain scale 6 out of 10) one hour into OGTT. Participant took 500mg Tylenol. Participant vomited 25 minutes later. Test stopped, snack given. blood glucose 102. Physical exam within normal limits. 2 hours after headache first developed, participant feeling well, discharged from CRU.	Placebo
126429	42	White	Female	02/01/2013	Infection	Infection - Other (Specify in Event Details)	Primary	37	Not Expected	2	Probably not related	Subject was diagnosed with strep throat 2/1/13 and completed a course of Amoxicillin which didn't resolve the issue; on 2/25/2013 subject completed a course of augmentin and symptoms resolved	Placebo
126429	43	White	Female	06/17/2014	Sexual/Reproductive Function	Sexual/Reproductive Function - Other (Specify in Event Details)	Primary	.	Not Expected	3	Definitely not related	Presented to ER with vaginal bleed. Spotting on Saturday, worsened on Sunday. c/o crampy, abdominal pain.	Placebo

												Diagnosis of miscarriage on endovaginal u/s with negative FHT. 8 weeks preg G9 with 2 past miscarriages which required D&C.	
126429	44	White	Female	03/28/2015	Infection	Infection - Other (Specify in Event Details)	Primary	6	Not Expected	2	Probably not related	Diagnosed with Flu B, treated with advil	Placebo
127694	14	White	Male	05/20/2013	Gastrointestinal	Heartburn/dyspepsia	Primary	3	Not Expected	2	Definitely not related	Sore throat and difficulty swallowing. Mother feels that it was due to anxiety and acid reflux prior to dental treatment	Placebo
129175	21	White	Male	08/17/2010	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	3	Not Expected	1	Definitely not related	Lifting weights-muscular strain to the back	Active
129220	15	White	Male	07/06/2013	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	1	Not Expected	3	Definitely not related	Participant accidentally put garden fork through left great toe.	Active
129419	16	White	Male	07/07/2014	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	0	Not Expected	1	Definitely not related	Participant sat in chair for 15minutes between 90 and 120minute timepoint of OGTT and fainted in chair. Participant helped to the floor, legs raised and regained consiousness, HR80 BP 100/60. Participant able to get back onto bed after 10minutes and felt fine for remainder of OGTT. Participant ate and drank before leaving the unit. ********** Participant sat in chair for 15minutes between 90 and 120minute timepoint of OGTT and fainted in chair. Participant helped to the floor, legs raised and regained consiousness, HR80 BP 100/60. Participant able to get back onto bed after 10minutes and felt fine for	Active

												remainder of OGTT. Participant ate and drank before leaving the unit.	
132805	10	White	Female	01/26/2012	Infection	Infection with unknown ANC	Primary	7	Not Expected	2	Definitely not related	Treated with oral antibiotics and resolved	Placebo
133591	11	White	Male	10/23/2010	Pulmonary/ Upper Respiratory	Cough	Primary	5	Not Expected	1	Definitely not related	had non-productive cough, no fever, from 10/23/10-10/28/10. Used only OTC medication for 3 doses. Resolved without difficulty.	Active
134428	5	White	Female	12/21/2008	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	13	Expected	2	Definitely not related	ear infection treated with oral antibiotic	Active
134454	7	No Selection Made	Female	12/02/2008	Endocrine	Endocrine - Other (Specify in Event Details)	Primary	16	Expected	3	Definitely not related	Participant had episodes of hyperglycemia at home and in office, but only on the glucose meter. No labs were drawn. PCP contacted endocrinologist who admitted participant into the hospital. Per, usual routine for new dx of diabetes. Patient had normal glucose levels on admission 12/02/08, and patient did not start insulin while hospitalized. Participant received a repeat OGTT 12/04; with no clinical alert. Participant did receive diabetes education. Mom will be monitoring participant to determine hyperglycemia.	Placebo
134454	7	No Selection Made	Female	02/02/2009	Infection	Infection - Other (Specify in Event Details)	Primary	7	Expected	2	Definitely not related	strep throat diagnosed 2/2/09	Placebo

134482	9	No Selection Made	Male	02/01/2009	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Secondary	.	Not Expected	1	Probably not related	somnambulation-has had six episodes in the past 3 months. Mother and Brother also had episodes when they were this particular age. Episodes last approx. 3 minutes then parents return pt. to bed. No physical harm has occurred during episodes.	Placebo
134482	9	No Selection Made	Male	02/01/2009	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	.	Not Expected	1	Probably not related	somnambulation-has had six episodes in the past 3 months. Mother and brother also had episodes when they were this particular age. Episodes last approx. 3 minutes then parents return pt. to bed. No physical harm has occurred during episodes.	Placebo
134482	10	No Selection Made	Male	01/26/2010	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	2	Not Expected	2	Probably not related	abdominal pain with vomiting x2. No reported diarrhea. No fever. Stayed home from school. No meds given, conservative management only.	Placebo
134482	11	No Selection Made	Male	06/15/2010	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	14	Not Expected	2	Definitely not related	pulled muscle in back while in a bounce house. Needed rest for two weeks. Took Motrin as needed	Placebo
134482	11	No Selection Made	Male	10/24/2010	Musculoskeletal/Soft Tissue	Joint-function	Primary	9	Not Expected	1	Definitely not related	while in a bounce house, sister landed on subject's left knee, which caused soreness and bruising. Did not see physician and did not take any medications. Knee was sore enough that subject did not want to go to water polo practice.	Placebo
134482	11	No Selection Made	Male	11/15/2010	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	vomited for 2 days, no fever, no URI, missed school for 2 days	Placebo

134482	11	No Selection Made	Male	12/13/2010	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	vomited for 2 days, no fever. Headache for 1 day. Missed four days school. Other people at home were ill.	Placebo
134482	11	No Selection Made	Male	02/01/2011	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	11	Not Expected	2	Definitely not related	upper respiratory symptoms, rhinorrhea with cough x 1 week. No fever. Did not miss school.	Placebo
134482	12	No Selection Made	Male	11/10/2011	Dermatology/Skin	Rash: acne/acneiform	Primary	.	Not Expected	2	Definitely not related	Facial acne had been getting worse. Saw dermatologist on 11/10/11, was prescribed antibiotic. ********** Per mother, facial acne has improved with OTC medications (see concomitant medication log).	Placebo
134482	13	No Selection Made	Male	09/25/2012	Pulmonary/ Upper Respiratory	Cough	Primary	3	Not Expected	1	Definitely not related	Cough lasted until 28SEP2012. Stayed home from school for 3 days. Ibuprofen and Dayquil administered by mother.	Placebo
134482	13	No Selection Made	Male	09/25/2012	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	3	Not Expected	1	Definitely not related	Nasal congestion lasted from 25SEP2012 until 28SEP2012. Stayed home from school for three days.	Placebo
134786	8	White	Male	02/12/2008	Syndromes	Flu-like syndrome		0		3	Definitely not related	Other, Specify: / Fever; ER visit/ Pt c flu-like symptoms @ home. Temp 105-F per parent report; not recoverying family taken ER, given antibiotics IM, c RX antibiotics for 5 days- possible zithromyan.	Placebo
134786	8	White	Male	06/01/2008	Metabolic/Laboratory	Glucose, serum-low (hypoglycemia)	Primary	0	Expected	2	Possibly related	Mom reported that subject woke up feeling dizzy and weak, she checked his blood sugar and it was 44. She gave him juice. She re-checked blood sugar and it was 80.	Placebo
134786	8	White	Male	08/01/2008	Neurology	Seizure	Primary	0	Not Expected	2	Probably not related	Subject was at a resort pool where he slipped in a puddle of water and fell onto his back, hitting his head. He got up,	Placebo

												walked a short distance and then had a tonic-clonic seizure per observation by father. Subject was taken via ambulance to the emergency department where he had a CT scan done and was discharged home.	
134786	10	White	Male	12/06/2010	Neurology	Seizure	Primary	0	Not Expected	2	Probably not related	Subject had seizure at home while sitting at table eating breakfast. Mom had her back turned to patient so unknown whether patient seized and fell to the floor or fell to the floor and then seized. Per mother patient had tonic-clonic seizure activity lasting approximately 15 seconds and then patient slept for 40 minutes. Subject was taken to ED via ambulance. Lab chemistry panel within normal limits. Hemoglobin A1c pending. Blood glucose in ED was 197 initially and then 83 three hours later. Subject was examined by PI- no focal neurologic findings. Subject was discharged home same day, plan to follow up with PMD.	Placebo
134786	11	White	Male	12/16/2011	Neurology	Seizure	Secondary	0	Not Expected	3	Probably not related	Subject has had several seizures in the past (2007 after fall and in 2010) The subject had one on December 16, 2011 where they became unaware of surroundings and had stiff movements of all extremities per Mom (tonic-clonic movements). Mom called 911 and they were seen in the emergency department of local hospital. The subject was diagnosed at this time with	Placebo

												epilepsy and started on Levatriacetan.	
134786	12	White	Male	08/22/2012	Neurology	Ataxia (incoordination)	Primary	.	Not Expected	1	Probably not related	When subject gets up, it is noted that his first step is slow and he is unable to balance well for first 1-3 seconds.	Placebo
136433	22	White	Male	02/15/2016	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Secondary	4	Not Expected	2	Definitely not related	Patient suffered severe road rash on shoulder and legs due to fall off motorcycle while dirt bike riding.	Placebo
136433	22	White	Male	02/15/2016	Neurology	Neurology - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Participant fell of motorcycle while dirt bike riding. Suffered concussion, had to be seen in urgent care and admitted to ER again a couple of days later for post-concussive syndrome (vomit and inability to stand up). Also patient suffered severe whiplash.	Placebo
136433	22	White	Male	08/09/2016	Neurology	Neurology - Other (Specify in Event Details)	Primary	45	Not Expected	2	Definitely not related	Participant was ride his motorcycle and got hit. He went to urgent care where they did a concussion test and also a CT scan. Patient states that doctor gave CT scan results as: "no visible trauma or bleeding". Originally he was cleared but when he went back for a follow up on 9/23/16 the sports medicine doctor did another test and concluded he did originally have a concussion. No medication or procedures were done during and after this visit since was not having any post-concussion syndrome symptoms.	Placebo

136433	22	White	Male	10/01/2016	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Participant was riding a bicycle and and had a pedal slip. The pedal pins puncture the patient in the left shin. The puncture bled consistently for about 8 hours before it stopped. Participant did not go to the hospital. Participant called the primary care physician who suggested a Tetanus vaccine booster. As of 10/19/2016 participant reports that wound is healing normal. The only medication he put on was Neosporin over the counter.	Placebo
136433	23	White	Male	11/24/2016	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	20	Not Expected	2	Probably not related	Patient reports that he had bronchitis and flu symptoms. He was treated by physician, prescribed Azithromycin for 5 days (see concomitant medications). Participant did not take any other medication.	Placebo
136806	12	White & Asian	Female	07/28/2014	Infection	Infection with unknown ANC	Primary	.	Not Expected	2	Probably not related	Patient was told by medical professional that she has a viral illness that caused her fever and a single genital ulcer. She was tested for Herpes and Epstein-Barr virus and both test came back negative. Medication was given as follow: Lidocaine gel 2% jelly to be applied to the ulcer every 2 hours for 1 week and 4 times a day for 4-5 days thereafter. Nystatin - Triamcinolone topical cream 4 times a day for 1 week. Ibuprofen during the first 4-5 days as needed.	Placebo
137702	6	White	Female	01/13/2009	Infection	Infection - Other (Specify in Event Details)	Primary	3	Not Expected	2	Probably not related	Participant experienced a rash all over body including neck and chest areas. Temperature of 101.5 F. Laboratory results	Active

												returned positive for strep cultures; participant diagnosed with scarlet fever. Prescribed Amoxycilin for 10 days. Condition resolved. ANC unknown. Dx: Scarlet Fever. Prescribed Amoxycilin for treatment.	
137702	8	White	Female	06/14/2010	Pulmonary/ Upper Respiratory	Pneumonitis/pulmonary infiltrates	Primary	2	Not Expected	2	Definitely not related	Began as a cold for about a week; fever for three days (99.0-102.0 F) sore throat and mild cough	Active
137702	8	White	Female	03/25/2011	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	.	Expected	2	Definitely not related	03/25: Participant ran a fever of 102.5 F in the evening 03/26: Fever went up to 103.9 F 03/27: Participant went to the doctor and was prescribed medication 03/28: Fever went down to 100.3 F	Active
139273	18	Unknown or Not Reported	Male	04/06/2016	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	Sore throat treated with antibiotics	Active
139273	18	Unknown or Not Reported	Male	07/01/2016	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	21	Not Expected	2	Definitely not related	Right big toe - infected ingrown toenail	Active
140365	10	White	Male	09/16/2014	Infection	Infection with unknown ANC	Primary	4	Not Expected	2	Probably not related	Participant/mother states that on September 16, 2014 patient went to see his PCP for an annual visit check up, and was found to have a sinus infection. The only symptoms were nasal congestion and cough. Treated with CeFalexin suspension 250 mg/ 5ml x 10 days. Participant recovered without sequelae.	Active
141479	14	White	Male	01/25/2016	Dermatology/Skin	Rash: acne/acneiform	Primary	.	Not Expected	2	Probably not related	Participant states having ACNE on face since 2 and half months. Participant noticed it getting	Placebo

												worse on frontal lobe and cheeks and decided to see a pediatric dermatologist who started treatment with SOLODYN 115 mg PO QD .	
144158	5	White	Female	03/28/2008	Pain	Pain		49		1	Definitely not related	Other, Specify: / 1.Non-specific abdominal pain 2.increased crams/ 1. 2 months crampy abdominal pain - no specific vatimin, no nausea, no exercise, no weight wss 2. increased frequency of cramps no specific type or timing.	Placebo
144158	7	White	Female	06/30/2010	Pulmonary/ Upper Respiratory	Cough	Primary	2	Not Expected	1	Definitely not related	Had cough with cold like symptoms (stuffy nose) - Family Doctor dx. Bronchitis	Placebo
145569	9	White	Male	07/29/2014	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Experienced sore throat on 7/28, mother took child to the pediatrician on 7/29/14 and child was diagnosed as having strep throat. Treated with course of antibiotics and recovered.	Active
146504	12	Unknown or Not Reported	Female	12/17/2009	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	4	Not Expected	1	Probably not related	Participant said she had cough and cold symptoms - most likely Common Cold. She did not have any medications for this event and it lasted less than one week.	Active
146504	15	Unknown or Not Reported	Female	05/26/2013	Infection	Infection with unknown ANC	Primary	10	Not Expected	2	Definitely not related	Went to doctors about sore throat. Doctor sent patient home with ten day course of Amoxicillin. She said that it strep throat came back on the second week of June after the 10 day course of Amoxicillin was done, however no medical intervention was done on the second case.	Active

146504	18	Unknown or Not Reported	Female	04/18/2016	Infection	Infection - Other (Specify in Event Details)	Primary	29	Not Expected	2	Definitely not related	vaginal infection with prolonged period and spotting; treated outpatient with Metronidazole for 10 days ********** vaginal infection with prolonged period and spotting; treated outpatient with Metronidazole for 7 days ********** vaginal infection with prolonged period and spotting; treated outpatient with Metronidazole for 7 days	Active
146504	18	Unknown or Not Reported	Female	06/01/2016	Gastrointestinal	Nausea	Primary	214	Not Expected	2	Definitely not related	subject experiences abdominal pain and nausea every morning; reports not eating anything until nausea subsides around noon	Active
146504	19	Unknown or Not Reported	Female	09/30/2016	Gastrointestinal	Vomiting	Primary	1	Not Expected	2	Definitely not related	vomiting x 10 episodes in 24 hrs, diarrhea, chills, no meds or IV fluids	Active
146608	13	White	Male	09/03/2012	Infection	Infection with unknown ANC	Primary	10	Not Expected	2	Definitely not related	Low grade fever, sore throat. Only had symptoms from 9/3/2012-9/8/2012.Ten days of Amoxicillin BID started on 4 SEP 2012.	Active
146608	17	White	Male	03/21/2016	Gastrointestinal	Vomiting	Primary	1	Not Expected	2	Definitely not related	vomited three times; experienced diarrhea; fever of 100F	Active
146608	17	White	Male	12/01/2016	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	bronchitis with cough, congestion and fever of 101F; diagnosed by PCP; prescribed unknown antibiotic 1 tab BID for 10 days	Active
146952	14	White	Female	03/02/2009	Infection	Infection - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	MOC reports participant is in 2nd week of 6wk program of antibiotics for a fungal infection. Believes it began about 3/2/09. More information to follow.	Placebo

147111	7	White	Male	02/14/2009	Neurology	Somnolence/depressed level of consciousness	Secondary	84	Not Expected	3	Definitely not related	involved in head on collision while on dirt bike. Suffered loss of conscious secondary to brain contusion. Airlifted to other area hospital. Stayed in hospital overnight 18 hrs for observation. Fully recovered	Active
147111	7	White	Male	02/14/2009	Neurology	Neurology - Other (Specify in Event Details)	Primary	84	Not Expected	3	Definitely not related	involved in head -on collision while on dirt bike. Suffered loss of consciousness, airlifted to other area hospital. Had brain contusion. Stayed in hospital overnight(18 hours) for observation. Doing well, fully alert, at home with full recovery expected. ********** involved in head -on collision while on dirt bike. Suffered loss of consciousness, airlifted to other area hospital. Had brain contusion. Stayed in hospital overnight(18 hours) for observation. Doing well, fully alert, at home with full recovery expected. New requested information: event was changed to reflect the brain contusion as primary event instead of somnolence	Active
147111	7	White	Male	02/14/2009	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Secondary	172	Not Expected	2	Definitely not related	one inch scalp laceration down to the bone with facial bruising and swelling due to dirt bike collision.	Active
147111	8	White	Male	08/08/2010	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	1	Not Expected	2	Definitely not related	vomiting	Active
147111	8	White	Male	11/06/2010	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	6	Not Expected	2	Definitely not related	on 11/6/10, mother noticed subject did not feel well and was having wheezing. Was seen by MD on 11/8/10 who made diagnosis of pneumonia based	Active

												on CXR and PE. Was started on Zithromax, albuterol inhaler and prednisone. Did well with treatment and recovered after 5 days.	
147111	9	White	Male	06/30/2011	Musculoskeletal/Soft Tissue	Fracture	Primary	21	Not Expected	2	Definitely not related	fell off scooter and fractured left fifth finger. Wore splint for 3 weeks	Active
147111	9	White	Male	08/01/2011	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	14	Not Expected	2	Definitely not related	was wrestling with father, hit head on the wall, had a occipital laceration requiring 6 staples	Active
147111	9	White	Male	08/17/2011	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	1	Not Expected	1	Definitely not related	Mild fever to 100 degrees Farenheit. No antipyretics, lasted 24 hours.	Active
147111	9	White	Male	08/17/2011	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	1	Not Expected	1	Definitely not related	had mild fever, no antipyretics given	Active
147111	9	White	Male	09/15/2011	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	fell off monkey bars at school previous day before study visit. Complaining of right elbow pain. Physical exam at study visit showed some swelling around right elbow with decreased range of motion, unable to fully pronate or flex elbow. PI recommended follow-up with PCP to obtain Xray to assess for fracture.	Active
147185	11	White	Male	11/24/2008	Infection	Infection - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	Went to MD's office on 11/24/08 for infection from a pencil accidentally jammed in finger, lead was dug out of finger. On Keflex for 7days.	Placebo

147185	11	White	Male	05/01/2009	Infection	Infection - Other (Specify in Event Details)	Primary	7	Not Expected	1	Definitely not related	MOC reports an ear infection 5/1/09 - 5/8/09. PCP prescribed antibiotic (Keflex) 2 pills per day for 7 days. Cleared after antibiotic. Did not miss any school.	Placebo
147185	12	White	Male	10/16/2009	Auditory/Ear	Auditory/Ear - Other (Specify in Event Details)	Primary	6	Not Expected	1	Probably not related	Robby had ear infection which lasted about one week.	Placebo
147201	9	White	Male	12/27/2008	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	MOC reported child falling at home on 12/27/08. This required a visit to Urgent Care and four stitches.	Active
147201	9	White	Male	12/27/2008	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	********** MOC reported child falling at home on 12/27/08. This required a visit to Urgent Care and four stitches.	Active
147201	9	White	Male	12/27/2008	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	********** MOC reported child falling at home on 12/27/08. This required a visit to Urgent Care and four stitches.	Active
147201	10	White	Male	03/10/2010	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	1	Not Expected	1	Probably not related	MOC says he has been fighting a mild virus for past four weeks which made him tired. Participant had very low-grade fevers (99-100) and vomited once. He was not hospitalized. He now seems fully recovered.	Active
147239	11	White	Male	11/05/2008	Gastrointestinal	Diarrhea	Primary	3	Not Expected	1	Definitely not related	MOC reports 2 bouts of diarrhea between Halloween and Thanksgiving. MOC gave one dose of pepto bismal for one day, symptoms resolved.	Placebo
147239	11	White	Male	11/20/2008	Gastrointestinal	Vomiting	Primary	5	Not Expected	2	Probably not related	MOC reported vomitting and nausea for four to five days. Child missed two days of school and went to the doctor. No medicationss were prescribed by physician.	Placebo

147239	14	White	Male	12/15/2011	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	Head Contusion. 7fott piece of lumber fell on patient's head. Left contusion. No concussion. Patient was tired and had headaches for a week.	Placebo
147239	15	White	Male	10/17/2012	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	30	Not Expected	2	Definitely not related	upper respiratory infection. PCP Prescribed z-pack from 1NOV2012-16NOV2012.	Placebo
147239	15	White	Male	04/02/2013	Infection	Infection with unknown ANC	Primary	14	Not Expected	2	Definitely not related	Ear infection antibiotics.Medication began on April 4th-April 14th. BID, everyday route PO.	Placebo
147335	17	White	Male	05/02/2010	Infection	Infection with unknown ANC	Primary	11	Not Expected	2	Definitely not related	Infection lasted 11 days. Took 500mg of Augmentin for sinus infection BID for ten days.	Placebo
147711	10	White	Male	08/09/2007	Pulmonary/ Upper Respiratory	Bronchospasm, wheezing		0		3	Definitely not related	Other, Specify: / Asthma attack (broncho spasm)/ Participant was taken to emergency room at 12:00 am on 08/09/07 for an asthma attack. Participant was given 7 breathing treatments (3 with albuterol and 4 with albuterol and atrovent). Also given predrisone and Zithromax.	Active
147711	11	White	Male	11/16/2007	Pulmonary/ Upper Respiratory	Bronchospasm, wheezing		0		2	Definitely not related	Other, Specify: / Asthma attack (bronchospasm)/ On 16/Nov/2007 participant was taken to the emergency room for am asthma attack. He was treated with Prednisone 40mg for 2days, 20 mg for 2 days, and Zithromax for 5 days.	Active
147711	11	White	Male	11/16/2007	Gastrointestinal	Heartburn/dyspepsia		2		2	Probably not related	Other, Specify: / Worsening of Gastroesophageal reflux disease (GERD)/ When participant was taken to ER for asthma attack, he was told by the physician that the GERD is getting worse and may have caused the asthma attack.	Active

147711	12	White	Male	10/03/2008	Gastrointestinal	Diarrhea	Primary	4	Not Expected	1	Probably not related	subject had diarrhea for three days.	Active
147711	12	White	Male	01/07/2009	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	MOC reported participant had bronchitis in early January. Child went to doctor and was prescribed rondac x6days 1 teasp every 6h prn, prednisone x3days 20mg qd, amoxicillin x3days 250mg 3x/day. Child also missed about a week of school. Fully recovered.	Active
147711	12	White	Male	08/06/2009	Pulmonary/ Upper Respiratory	Bronchospasm, wheezing	Primary	8	Not Expected	2	Definitely not related	MOC reports being at the doctors office for a scheduled visit and the doctor giving 2 nebulizer treatments and prescribing prednisone for 9 days (dose decreasing every three days - see concom med)	Active
147711	12	White	Male	08/21/2009	Infection	Infection - Other (Specify in Event Details)	Primary	8	Not Expected	2	Definitely not related	MOC reports taking participant into ER because his Asthma symptoms were increasing afer previous round of prednisone. MOC reports he had "some type of bacterial infection". ER prescribed zithromax and prednisone (see concom med)	Active
148129	7	White	Male	07/05/2011	Infection	Infection with unknown ANC	Primary	133	Not Expected	2	Definitely not related	Participant had an infection on this big toe and was prescribed Keflex, 250mg TID for 7 days, to treat.	Placebo
148776	6	White	Female	10/01/2007	Surgery/Intra-Operative Injury	Intra-operative Injury - Other (Specify in Event Details)	Primary	31	Not Expected	2	Definitely not related	Outpatient surgery for umbilical hernia.	Active
148776	8	White	Female	07/07/2009	Infection	Infection - Other (Specify in Event Details)	Primary	258	Not Expected	2	Definitely not related	MRSA infection in different parts of the body. [500mg Cephalexin 7 JUL 2009]. [SMZ/TMP(sulfamethoxazole/trimethoprim) reg strength tabs on 7 AUG 2009]. [Sulfameth/trimethoprim mg	Active

												800/160 tabs BID for 10 days on 19 OCT 2009] [Cephalexin 500mg BID for ten days on 23 OCT 2009]	
148980	3	White	Female	10/04/2008	Dermatology/Skin	Rash/desquamation	Primary	.	Not Expected	2	Definitely not related	Mother reported a skin rash (eczema like) on torso which began on 10/4/08 and was prior to subject starting study medication . Subject started study medication on 10/6/08. Mother also reports on 10/2 or 10/3 she changed the subject's chewable multivitamin to Flinestones brand and has since put the subject back on the original chewable multivitamin. Skin rash is persisting. Local PI suggested family see a pediatrician. Will follow-up when provided more information from the family. Subject remains on study medication.	Active
148980	4	White	Female	02/10/2009	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	5	Not Expected	2	Probably not related	MOC reported subject was treated for impetigo (skin infection). She was given an antibiotic for 10 days (2/10/09 - 2/20/09). MOC reports this cleared in five to six days of tx and is recovered.	Active
148980	5	White	Female	12/25/2009	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	0	Not Expected	1	Definitely not related	MOC alerted coordinator to potential allergic reaction on Christmas Day 2009. Child was given candy produced in factory that uses peanuts; child is allergic to peanuts. Child had little to no symptoms but MOC gave Benadryl "just in case."	Active

148980	5	White	Female	03/15/2010	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Secondary	10	Not Expected	2	Definitely not related	Participant had a cold that turned into "walking pneumonia" - Fever of 100-101 for four days at which time it was 104 for one hour. Subject went to urgent care on 3/15 for the day subject peaked at 104 and started Azithromycin. Subject went again on 3/20 and was diagnosed with walking pneumonia. By 3/25 subject symptoms cleared but subject was given Amoxicillin for seven days.	Active
148980	5	White	Female	03/15/2010	Infection	Infection with unknown ANC	Primary	10	Not Expected	2	Definitely not related	Extended family had all been ill with cold symptoms . Patient became ill and went to urgent care because doctor's office was closed. Urgent care visit resulted in "wait and see." There was no improvement so family went back to urgent care on 20th of March 2010, when she was diagnosed with "Walking Pneumonia." Was sent home with antibiotics that helped her get better.	Active
149034	4	White	Female	04/22/2008	Infection	Infection with normal ANC or Grade 1 or 2 neutrophils	Primary	7	Not Expected	2	Definitely not related	"Pt. was diagnosed with an ear infection on 4/22/2008 and was treated with an oral antibiotic for 5 days. More information to follow. Liquid 2-pack x5 days: 11/2 tablespoons on day 1. Days 2-5 (3/4 tablespoon)"	Active
149034	4	White	Female	04/22/2008	Infection	Infection with unknown ANC	Primary	7	Not Expected	2	Definitely not related	"strep throat/dx with strep throat, concurrently w/ AE # 0175 treated with liquid Z-pack: 11/2 teaspoon on day 1, days 2-5 3/4ths tablespoons-duration 5 days. Second round of 5-day 2-pack." by coordinator's AE report on 14/May/2008.	Active

149034	4	White	Female	04/22/2008	Infection	Infection with normal ANC or Grade 1 or 2 neutrophils		7		2	Probably not related	Other, Specify: / Ear infection/ Pt. was diagnosed with an ear infection on 4/22/08 and was treated with an oral antibiotic for 5 days. More information to follow. Liquid 2 - pack X5 days : 11/2 tablespoons on day 1, days 2-5 3/4 tablespoon.	Active
149034	4	White	Female	05/11/2008	Infection	Infection - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	"./ Pt had hand foot and mouth sores- viral infection. Tylenol every 4 hours x 3 days. Missed 2 days of school. Mom says misdiagnosed- on AEs #0175(AE ID: 2244) and #0176 (AE ID" 2242)." Was stated on the original AE that was not submitted by coordinator that performed interview.	Active
149034	4	White	Female	05/11/2008	Infection	Infection - Other (Specify in Event Details)		5		2	Probably not related	./ Pt had hand foot and mouth sores- viral infection. Tylenol every 4 hours x 3 days. Missed 2 days of school. Mom says misdiagnosed- on AEs #0175 and #0176.	Active
149034	4	White	Female	05/14/2008	Infection	Infection with unknown ANC		0		2	Probably not related	Other, Specify: / strep throat/ dx with strep throat, concurrently w/ AE # 0175 treated with liquid Z-pack: 11/2 tablespoon on day 1, days 2-5 3/4 tablespons- duration 5 days. Second round of 5-day 2-pack.	Active
149034	5	White	Female	04/01/2009	Infection	Infection - Other (Specify in Event Details)	Secondary	7	Not Expected	2	Definitely not related	MOC reports child had ear infection and was placed on antibiotic (amoxicilin) 2 doses per day for 7days. Unsure of dose. Also, reports was recently diagnosed with Eosinophilic Esophagitis (EE) - currently being treated with Prevacid (dissolvable tablet once a day)	Active

149034	5	White	Female	07/06/2009	Infection	Infection - Other (Specify in Event Details)	Primary	18	Not Expected	1	Definitely not related	MOC reports child had fifth's disease for about three weeks. No visit to the doctor and no medication. Also, reports continued diarrhea and stomach pain from allergies (EE). Has an appointment on 9/17 with a specialist regarding EE diagnosis.	Active
149034	6	White	Female	02/11/2010	Gastrointestinal	Esophagitis	Primary	3	Not Expected	3	Probably not related	Participant has a known diagnosis of Eosinophilic Esophagitis and had an upper GI endoscopy and biopsy visit. Four hours later, while eating lunch, she started to have right-sided neck pain, mild mid-abdominal pain, became pale, was breathing fast, and parents noted a low-grade fever. They took her to Emergency where she was given bolus of 20cc/kg NS. Chest X-Ray showed signs of airways disease without focal infiltrate, CBC had mild leukocytosis at 13. She was admitted to PICU for observation pending probable micro-perforation due to endoscopy. She was started on ampicillin, gentamicin and metronidazole therapy which lasted 48hrs. Then was switched to Augmentin for following ten days. Continued Flovent throughout treatment.	Active
149034	8	White	Female	10/10/2011	Infection	Infection with unknown ANC	Secondary	5	Not Expected	2	Definitely not related	Streptococcus, with a fever up to 102.7F for 24 hours and no other symptoms. Took Augmentin for 10 days.	Active
149034	9	White	Female	10/01/2012	Infection	Infection with unknown ANC	Secondary	9	Not Expected	2	Definitely not related	Strep throat. Mid-grade fever did not exceed 102 degrees F. Treated through October 10th	Active

												with 500mg for 10 days with amoxicillin.	
149034	9	White	Female	12/17/2012	Surgery/Intra-Operative Injury	Intra-operative Injury - Other (Specify in Event Details)	Primary	0	Expected	3	Definitely not related	Participant had frequent occasions of strep throat so had her tonsil and adenoid removed.	Active
149034	9	White	Female	01/01/2013	Infection	Infection with unknown ANC	Secondary	9	Not Expected	2	Definitely not related	Strep and bronchitis in January. Patient was treated with a ten day course of Amoxicillin .	Active
149034	9	White	Female	05/25/2013	Infection	Infection with unknown ANC	Secondary	11	Not Expected	2	Definitely not related	10 day course of Amoxicillin in May for ear infection.	Active
149034	11	White	Female	06/20/2015	Infection	Infection with normal ANC or Grade 1 or 2 neutrophils	Primary	.	Not Expected	3	Definitely not related	Fever, nausea, voining, abdominal pain for 24 hours when presented to ER. Ultrasound showed appendicitis so went to surgery, appenmdectomy performed and went home a few hours later.	Active
149034	11	White	Female	06/27/2015	Infection	Infection with unknown ANC	Primary	6	Not Expected	3	Definitely not related	While on family vacation when participant presented with fever, cough and fatigue taken to ER and was diagnosed with "pneumonia". The participant was prescribed Amoxicillin suspension TID. After completion of antibiotic symptoms has not reoccurred.	Active
149034	11	White	Female	07/23/2015	Infection	Infection with unknown ANC	Primary	6	Not Expected	2	Definitely not related	Complaint of ear pain and low grade fever	Active
149034	12	White	Female	12/04/2015	Infection	Infection with unknown ANC	Primary	4	Not Expected	2	Definitely not related	Sinus infection	Active
149034	13	White	Female	03/13/2017	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Diagnosed with Strep Throat	Active

149087	9	White	Male	07/30/2012	Dermatology/Skin	Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Primary	32	Not Expected	2	Possibly related	Rash started on arms and spread to entire body over time. Mother took child into pediatrician, who made the diagnosis of erythema multiforme. Not painful or itchy. Self-resolving with no sequalae.	Active
149087	9	White	Male	12/29/2012	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	1	Not Expected	2	Definitely not related	103 degree F fever Dec 29-30 as measured tympanically; mild cough and congestion followed resolution of fever. Mom reports it may have been the flu although participant did receive flu vaccination on December 13.	Active
149087	9	White	Male	01/29/2013	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Participant diagnosed with strep throat on 29/Jan/2013. Treated with amoxicillin for 10 days; bacteria responded to antibiotic treatment and participant is feeling better.	Active
149087	9	White	Male	05/06/2013	Gastrointestinal	Vomiting	Secondary	0	Not Expected	2	Definitely not related	Participant had 4 episodes of vomiting in a 12 hour period of time shortly before being diagnosed with Streptococcal pharyngitis. Participant did NOT require IV fluids, was prescribed a 10-day course of antibiotics to treat the bacterial infection, and reports feeling better now.	Active
149087	9	White	Male	05/06/2013	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Participant had a sore throat and fever. Was diagnosed with Streptococcus and took 10 days of antibiotics.	Active
149087	10	White	Male	01/07/2014	Endocrine	Pancreatic endocrine: glucose intolerance	Primary	1	Expected	3	Probably not related	Participant presented for 18-month follow-up visit and was found to have a fasting plasma glucose of >200. Participant was diagnosed with type 1 diabetes and admitted to the hospital for diabetes management teaching.	Active

149090	8	White	Female	03/30/2009	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Mother reports around 30 MAR 2009 participant was diagnoised with strepthroat by family physician and placed on antibiotic for 10 days. Resolved.	Active
149090	9	White	Female	07/23/2009	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	16	Not Expected	2	Definitely not related	Mother reporst 23 July, 2009 participant put on Zithromax for strep throat. did not get any better and received another round of Zithromax 04 AUG 2009.	Active
149090	9	White	Female	12/28/2009	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	Out patient tonsillectomy	Active
149090	11	White	Female	08/18/2011	Pain	Pain - Other (Specify in Event Details)	Primary	17	Not Expected	1	Definitely not related	18 Aug 2011 mandibular spacers placed by orthodontist causing pain. Mandibular braces were placed on 01 Sep 2011. Pain resolved 3 days after placement.	Active
149090	12	White	Female	02/22/2013	Musculoskeletal/Soft Tissue	Myositis (inflammation/damage of muscle)	Secondary	126	Not Expected	1	Definitely not related	o Participant is a fast pitch softball pitcher and had soreness/pain in right shoulder. MRI done to see if any soft tissue tears. Mom stated the participant never took pain meds. Mother stated the participant had physical therapy for 4 months and was taught how to pitch correctly.	Active
149090	13	White	Female	02/03/2014	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	28	Not Expected	2	Probably not related	Participant is a softball pitcher. Participant complained of pain in wrist and was diagnosed with wrist tendonitis on February 3, 2014. Participant and mother both stated no pain medications were taken for the tendonitis. The only treatment was a cast as therapy for 4 weeks. The cast was removed March 3, 2014.	Active

TN07 Oral Insulin – Appendix 6.2.7 Adverse Events by Participant

149090	14	White	Female	09/04/2014	Dermatology/Skin	Rash: acne/acneiform	Primary	.	Not Expected	2	Probably not related	15 year old female developed acne. Severity increased 19 Jun 2015	Active
149090	16	White	Female	12/22/2016	Cardiac Arrhythmia	Supraventricular and nodal arrhythmia	Primary	.	Not Expected	2	Definitely not related	Cardiologist diagnosed Inappropriate Sinus Tachycardia after subject had syncope episodes and palpitations	Active
149316	17	White	Male	01/11/2012	Infection	Infection - Other (Specify in Event Details)	Primary	3	Not Expected	3	Definitely not related	Appendicitis	Placebo
149549	7	White	Male	04/01/2012	Musculoskeletal/Soft Tissue	Fracture	Primary	142	Not Expected	2	Definitely not related	Participants broke their wrist playing with their sibling. The subject was diagnosed with a broken bone in their wrist near the growth plate at the base of their thumb at a local hospital. The subject's wrist was cast for 6 weeks and the subject had fully recovered from the fracture at the time this event was reported to the coordinator. The subject will follow-up with their doctor again in August to confirm the growth plate has completely healed.	Active
149549	8	White	Male	05/13/2013	Infection	Infection with unknown ANC	Primary	9	Not Expected	2	Definitely not related	Participant was diagnosed with strep throat on May 13; participant took 10 days of antibiotics and reports now feeling better.	Active
149549	11	White	Male	11/15/2015	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	0	Not Expected	2	Probably not related	Participant experienced a fever (104) with nausea, vomiting and headache for approximately 24 hours. Symptoms were treated with alternating doses of tylenol and ibuprofen every 3 hours. Mother reports she checked participant's BG during this time and it was normal.	Active

149549	11	White	Male	12/01/2015	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	Participant again experienced a fever (104 degrees) with headache, nausea and vomiting. Mother reports blood sugars were normal. She took participant in to see PCP--PCP ordered blood work and mother reports participant was found to have low white blood cell count and low hemoglobin (lab results not available). Participant was referred to an immunologist.	Active
149549	11	White	Male	01/04/2016	Endocrine	Pancreatic endocrine: glucose intolerance	Primary	.	Expected	3	Probably not related	Participant was found to have a 2-hour post OGTT blood glucose >300 at 84-month study visit. Participant referred to our diabetes urgent clinic where it was recommended to track BG for ~1 week. Blood sugars were in the high 200's post-meal pretty consistently, with a fasting blood sugar of ~200 on 04/JAN/2016. T1D was diagnosed and lantus was started. ********** UPDATE 10/18/2016: Please note, as this participant was not hospitalized at the time of this event, and this event is expected, this AE was submitted in error. Participant was found to have a 2-hour post OGTT blood glucose >300 at 84-month study visit. Participant referred to our diabetes urgent clinic where it was recommended to track BG for ~1 week. Blood sugars were in the high 200's post-meal pretty consistently, with a fasting blood sugar of ~200 on 04/JAN/2016. T1D was	Active

												diagnosed and lantus was started.	
150110	11	White	Female	09/07/2015	Musculoskeletal/Soft Tissue	Fracture	Primary	32	Not Expected	2	Definitely not related	Participant's cousin sat on participant's arm on 7/SEP/15. Participant complained of pain to parent but there was no apparent swelling of the area and pain was treated with alternating Tylenol and Ibuprofen Q3 hours. On 10/SEP/15 after no improvement, parent took participant to pediatrician's office to have an x-ray and fracture of the radius was noted. Participant's radius was placed in a cast. ********** Participant's cousin sat on participant's arm on 7/SEP/15. Participant complained of pain to parent but there was no apparent swelling of the area and pain was treated with alternating Tylenol and Ibuprofen Q3 hours. On 10/SEP/15 after no improvement, parent took participant to pediatrician's office to have an x-ray and fracture of the radius was noted. Participant's radius was placed in a cast. Follow-up: participant's cast was removed	Active

												on 9/OCT/2015 with no sequelae.	
150443	14	White	Female	05/19/2010	Infection	Infection with unknown ANC	Primary	11	Not Expected	2	Definitely not related	Prescribed Amoxicillin PO 1 tab daily May19-May31, 2010	Active
150443	18	White	Female	07/01/2014	Sexual/Reproductive Function	Irregular menses (change from baseline)	Primary	189	Not Expected	2	Definitely not related	Participant noted not having a period for 6 months so went to PCP and was prescribed Provera 1 Tab, QD, PO in which participant took 12/27/2014-1/6/2015. Participant unable to remember exact date of when event started, but stated that AE started sometime in June.	Active
150443	20	White	Female	04/01/2017	Neurology	Mood alteration	Primary	.	Not Expected	2	Definitely not related	diagnosed with anxiety by PCP, prescribed Zoloft 50mg PO QD	Active
150689	3	White	Male	10/01/2008	Auditory/Ear	Auditory/Ear - Other (Specify in Event Details)	Primary	10	Not Expected	1	Definitely not related	MOC reported around early October child had an ear infection and was prescribed amoxicillin for 10 days.	Active
151042	13	White	Female	04/27/2016	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	0	Not Expected	2	Probably not related	Fever of 103 degrees F for one day, no other symptoms. No medications taken for fever.	Placebo
151042	14	White	Female	04/01/2017	Infection	Infection - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Diagnosed with Influenza B	Placebo
152085	12	White	Female	04/18/2013	Infection	Infection - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	Patient diagnosed with sinus infection	Placebo

152085	12	White	Female	04/18/2013	Infection	Infection - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	Patient reports positive strep culture.	Placebo
152085	12	White	Female	07/07/2013	Pain	Pain - Other (Specify in Event Details)	Secondary	2	Not Expected	2	Definitely not related	Patient's parent reported participant had pharyngitis and had been diagnosed with a bacterial infection causing her sore throat since the last visit. Patient was prescribed antibiotics to treat the infection and took ibuprofen to treat the pain.	Placebo
152085	12	White	Female	07/07/2013	Infection	Infection - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Patient's parent reported at 3-month interim phone contact that patient was diagnosed with a bacterial infection following pharyngitis since her last visit with the site. Patient was prescribed antibiotics and took ibuprofen to treat pain.	Placebo
153128	16	White	Female	05/01/2014	Infection	Infection - Other (Specify in Event Details)	Primary	54	Not Expected	2	Probably not related	Pt diagnosed with mononucleosis after having swollen lymph nodes. Pt treated with viscous lidocaine. Pt recovered on 6/24/2014 with no sequelae.	Placebo
153248	17	White	Female	04/25/2015	Infection	Infection with unknown ANC	Primary	9	Not Expected	2	Definitely not related	Participant with streptococcal pharyngitis treated with 10 day course of oral antibiotics (cephalexin oral suspension) with complete resolution.	Active
154160	8	Black/ African American	Male	11/01/2015	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	15	Not Expected	2	Definitely not related	On 11/1/15 patient was attending an outdoor event and did an obstacle course where the subject injured their ankle. Doctor was seen, but unsure if injury was a break, sprain or fracture. Patient was placed in cast. Cast removed on 11/16/15. No further intervention was needed. This event occurred after study	Placebo

												enrollment, but prior to starting study drug.	
154527	16	White	Male	09/25/2012	Infection	Infection with unknown ANC	Primary	7	Not Expected	2	Probably not related	Infection on left ring finger	Active
154527	17	White	Male	10/25/2013	Musculoskeletal/Soft Tissue	Fibrosis-deep connective tissue	Primary	131	Not Expected	3	Definitely not related	Sustained a suspected seperated shoulder injury in football game on 10/25/13. Initial treatment of physical therapy did not resolve issue and surgery was performed to repair the torn labrum in his right shoulder on 11/25/13. Physical therapy was completed following surgery into January 2014.	Active
154752	13	White	Female	12/18/2010	Pain	Pain	Primary	7	Not Expected	2	Probably not related	prescription antacid given	Active
154752	14	White	Female	02/28/2012	Pulmonary/ Upper Respiratory	Cough	Primary	15	Not Expected	1	Definitely not related	Participant saw her doctor, c/o a "bad cold."	Active
154752	14	White	Female	03/16/2012	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	31	Not Expected	2	Definitely not related	Participant went to ER for c/o stomach pain.	Active
154752	16	White	Female	06/24/2014	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	11	Not Expected	2	Definitely not related	"puffy eye": right eye red and swollen, restricting vision. Possible dust irritation or allergic reaction to an unknown. Treated with steroid eye drops.	Active
154752	17	White	Female	07/21/2015	Pain	Pain	Primary	.	Not Expected	2	Probably not related	Participant has a history of stomach pains and diarrhea. Prescription antacid given.	Active
154955	16	White & Black/ African	Male	01/15/2013	Neurology	Somnolence/depressed level of consciousness	Primary	76	Not Expected	2	Definitely not related		Placebo

		American											
154999	10	White	Male	03/08/2010	Gastrointestinal	Dental: teeth	Primary	1	Not Expected	2	Probably not related	Participant was running, fell forward and broke his tooth. His dentist did a repair.	Placebo
155264	5	White	Male	06/01/2009	Infection	Infection - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	child was at dentist on 6/1 for a root canal and filing. he was placed on antibiotic and novacaine while at dentist, then given penicillin starting 6/2. instructed to finish the round of penicillin. also leading up to dentist visit c/o fever and toothache, ibuprofin was given prn (see concom meds)	Active
155537	7	White	Female	04/01/2009	Infection	Infection - Other (Specify in Event Details)	Primary	11	Not Expected	2	Definitely not related	Mother called to report subject with UTI. Medical doctor started her on 10 days of antibiotics.	Placebo
155537	7	White	Female	07/22/2009	Pain	Pain - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Tonsillitis. Placed on antibiotics.	Placebo
155537	8	White	Female	05/21/2010	Pulmonary/ Upper Respiratory	Obstruction/stenosis of airway	Primary	1	Not Expected	2	Definitely not related	elective tonsilectomy to resolve sleep apnea and snoring.	Placebo
155537	9	White	Female	04/14/2011	Gastrointestinal	Dental: teeth	Primary	0	Not Expected	2	Probably not related	Mom describes tooth pain, followed by extraction and antibiotics.	Placebo
155537	9	White	Female	07/25/2011	Auditory/Ear	Otitis, external ear (non-infectious)	Primary	9	Not Expected	2	Definitely not related	Diagnosed with ear infection on 7/25/11. Placed on amoxycillin, 500 mg bid. Fever persisted (103 on 7/28.) Seen for recheck on 7/28.	Placebo
155537	10	White	Female	02/24/2012	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	Participant bruised her elbow, treated as an outpatient with Ace bandage and sling.	Placebo

155537	13	White	Female	08/09/2014	Infection	Infection - Other (Specify in Event Details)	Primary	5	Not Expected	3	Definitely not related	viral meningitis	Placebo
156345	13	White	Male	04/07/2013	Musculoskeletal/Soft Tissue	Fracture	Primary	.	Not Expected	2	Definitely not related	Participant used his left arm to break his fall during a game with resulting fracture to both Ulna and Radius bones in his left arm.	Placebo
157332	11	White	Male	06/18/2009	Endocrine	Endocrine - Other (Specify in Event Details)	Primary	2	Expected	2	Definitely not related	Participant's mother contacted by phone one of our coordinators stating that she took her child to the ER because she noticed all of a sudden that the subject looked thinner than normal, was drinking a lot of fluids, overeating and urinating a lot. She tested their blood glucose at home and it read "HI" on the meter. In the ER their Blood glucose was 591mg/dl and the subject wasn't in DKA. Patient was started on IV and performed other labs. After a few hours and by protocol polices Patient was admitted to the hospital for treatment (Started Insulin) and Diabetes Education.	Placebo
157990	9	Black/ African American	Male	04/26/2011	Pain	Pain - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Sore throat started Apr. 26, 2011, of moderate severity. Was taken to family physician's office later that day, tested positive for strept throat. Amoxicillin given with good immediate effect.	Active
158675	7	White	Female	10/27/2011	Endocrine	Pancreatic endocrine: glucose intolerance	Primary	1	Expected	3	Probably not related	Mother reported increasing urination with ncturia every other night for past couple of months. Also noted increasing thirst. Did laboratory glucose at end of OGTT and was 303	Active

												mg/dl. Diagnosed with type 1 diabetes.	
158976	10	White	Female	07/15/2013	Pain	Pain	Primary	3	Not Expected	2	Definitely not related	Patient reports sore throat began 15/JUL/2013; followed by runny nose which began 16/JUL/2013. Resolved 18/JUL/2013	Placebo
159348	3	White	Male	08/28/2010	Infection	Infection - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	Pinworms was given Vermox once a week for 2 weeks	Active
159348	3	White	Male	09/08/2010	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Secondary	96	Not Expected	2	Probably not related	Participants mother reports wheezing, cough, fever, Physician diagnosed bronchitis and prescribed .25 tsp dimetap BID, .25 tsp. Delsym cough medicine BID and 2 puffs of Albuterol BID	Active
159857	12	White	Male	02/08/2015	Musculoskeletal/Soft Tissue	Fracture	Primary	120	Not Expected	3	Definitely not related	On February 8, 2015 participant loss control on his four wheeler hitting a tree, causing single fracture of his radius and ulnar bones. On the same day, participant was taken for surgery and placed on a cast for a month. Participant states that by the 4th months after the accident , he recovered without sequelae. Participant does not remember what medication took while recovering - No information available.	Active
161542	10	White	Female	09/26/2014	Endocrine	Thyroid function, low (hypothyroidism)	Primary	.	Not Expected	2	Possibly related	Subject's mother called on Sep 26 to report that the LMD ordered thyroid replacement based on abnormal lab values. Mother reports the subject had symptoms of fatigue and puffy eyes so she made the appointment with the LMD.	Active

162540	7	White	Female	05/25/2014	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Participant's mother reported that subject was crying when urinating so an appointment was made at their primary care physician's office and the MD prescribed antibiotics for a urinary tract infection.	Placebo
162636	4	White	Male	09/01/2011	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	335	Not Expected	2	Definitely not related	Patient had eczema in infancy and reported a flare to the torso and axilla that started during the change of seasons in September 2011. The mother reported applying Aquaphor to the effected area.	Active
162636	5	White	Male	05/01/2012	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	61	Not Expected	2	Definitely not related	molluscum on torso ********** molluscum on torso treated with Imiquimod 5%	Active
162636	6	White	Male	01/17/2013	Infection	Infection - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Subject's mother reported subject was diagnosed with influenza treated with Tamiflu x 5 days and fully recovered.	Active
162636	6	White	Male	09/01/2013	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	394	Not Expected	2	Definitely not related	Eczema bilateral AC space. Skin red and irritated. Family treating with hydrocortisone with good results.	Active
162636	7	White	Male	04/28/2014	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Mother reported subject having strep throat and tonsillitis, treated with Amoxicillin x 10 days.	Active
164043	4	White	Female	03/10/2010	Infection	Infection - Other (Specify in Event Details)	Primary	7	Not Expected	1	Definitely not related	Strep throat	Active
164043	4	White	Female	05/09/2010	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	2	Not Expected	2	Probably not related	hives	Active
164043	5	White	Female	01/15/2011	Pulmonary/Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	10	Not Expected	2	Probably not related	strep throat	Active

164092	8	White	Male	02/21/2016	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Patient came in for 36 month OGTT 2/21/16 and reported continuing non-productive cough that was treated with OTC medication. Mom could not remember drug name, so was asked to follow-up with medication name once home. On 2/27/16, Mom replied back that the medication was Singulair, which is a prescription drug. Co-I re-reviewed and changed to Grade 2 AE. Further contact with patient's mom revealed that the condition is possibly anxiety related and searching for alternative treatment options.	Placebo
165332	38	White	Female	07/01/2015	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	Had started having occasional diarrhea approx. July 1, 2015 with worsening symptoms over the past few months. Had colonoscopy on 1/29/16. Received results on 2/5/16 while here for 12 month OGTT, diagnosis lymphocytic colitis. Subject was told by outside MD that the condition is autoimmune and oral insulin would not be the cause. Will be placed on a steroid pack and an additional medication. Patient to call with name of drug	Placebo
165332	39	White	Female	11/30/2015	Pulmonary/Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	Had respiratory infection that required Augmentin and 5 day course of oral steroid	Placebo
165332	39	White	Female	02/22/2016	Metabolic/Laboratory	Metabolic/Laboratory - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	iron deficiency, labs had been done by new physician which revealed this deficiency. Prescribed iron supplement	Placebo

165332	39	White	Female	02/22/2016	Metabolic/Laboratory	Metabolic/Laboratory - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	vitamin B12 deficiency, labs had been done by new physician which revealed this deficiency. Prescribed vitamin B12 supplement	Placebo
165332	40	White	Female	11/11/2016	Cardiac General	Cardiac General - Other (Specify in Event Details)	Primary	.	Not Expected	1	Definitely not related	on 11/11/16, rheumatologist informed subject of systolic ejection murmur II/VI, On 1/9/17, TN PI also heard murmur on PE during Oral Insulin annual visit, no action to be taken at this time	Placebo
165332	40	White	Female	11/11/2016	Musculoskeletal/Soft Tissue	Arthritis (non-septic)	Primary	.	Not Expected	2	Definitely not related	Had joint pain in toes, knees and elbows, along with dry eyes and mouth, diagnosed with Sjogren's by rheumatologist on 11/11/16, started on Pacquenil	Placebo
165583	7	White	Male	06/15/2011	Gastrointestinal	Constipation	Primary	320	Not Expected	1	Definitely not related	Subject has history of intermittent constipation now with abdominal pain, nausea (without emesis) in evenings associated with recurrence of contipation	Placebo
165583	8	White	Male	03/26/2012	Pulmonary/Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	4	Expected	1	Definitely not related	Subject began upper respiratory infection with cough and congestion symptoms. Given musinex and improving.	Placebo
165583	8	White	Male	03/31/2012	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	1	Expected	1	Definitely not related	24-hour Stomach flu, no medication given	Placebo
165583	10	White	Male	04/02/2014	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	3	Not Expected	1	Definitely not related	Strep throat	Placebo
165583	11	White	Male	04/27/2015	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	flu symptoms. subject prescribed 10 day regime of tamiflu	Placebo
165583	11	White	Male	04/30/2015	Auditory/Ear	Auditory/Ear - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Ear infection. subject prescribed 10 day regime of amoxicillin	Placebo
165583	12	White	Male	12/15/2015	Infection	Infection with normal ANC or	Primary	16	Not Expected	2	Definitely not related		Placebo

						Grade 1 or 2 neutrophils							
165583	12	White	Male	03/21/2016	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	1	Definitely not related	mother reported subject was congested and PMD diagnosed with sinus infection	Placebo
165583	12	White	Male	04/18/2016	Allergy/Immunology	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Primary	12	Not Expected	2	Definitely not related	had a cough and tightness in chest when breathing	Placebo
165583	12	White	Male	04/18/2016	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	1	Definitely not related	subject had a sore throat and PMD diagnosed with strep throat	Placebo
165583	13	White	Male	03/17/2017	Infection	Infection - Other (Specify in Event Details)	Primary	42	Not Expected	2	Definitely not related	subject had a fever of 106 and went to the ER. The ER did blood work and everything was normal. Two weeks later subject still not feel well and was diagnosed with strep throat. He had 2 courses of antibiotic treatment	Placebo
166212	5	White	Male	03/09/2010	Renal/Genitourinary	Renal/Genitourinary - Other (Specify in Event Details)	Primary	0	Not Expected	1	Definitely not related	Participant had been diagnosed with phimosis prior to enrollment in trial, but pediatrician recommended waiting until ppt was five years old to have a circumcision performed. Circumcision was done on 09Mar2010.	Placebo
166317	9	White	Female	12/31/2011	Dermatology/Skin	Urticaria (hives, welts, wheals)	Primary	30	Not Expected	3	Probably not related		Active
166581	6	White	Male	11/30/2013	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	Subject was treated for pin worms	Placebo
168009	7	White	Female	05/21/2010	Infection	Infection - Other (Specify in Event Details)	Primary	11	Not Expected	2	Definitely not related	sore noted on back, Mother took participant to ER where sore was diagnoised as MRSA infection. Was treated with 10 day cource of Bactrim DS from 5-21-10 to 01 June 2010.	Active

168009	8	White	Female	03/20/2011	Infection	Infection - Other (Specify in Event Details)	Primary	12	Not Expected	2	Definitely not related	"bump" on right buttock - Septra prescribed for MRSA infection	Active
168009	8	White	Female	03/23/2011	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	3	Not Expected	1	Definitely not related	viral pharyngitis and headache	Active
168009	8	White	Female	08/24/2011	Infection	Infection - Other (Specify in Event Details)	Primary	7	Not Expected	1	Definitely not related	Participant had MRSA last year and the participant just had a break out last week until this week per mother. (August 24 to August 31) Participant " apparently is a carrier" per mother. ********** Participant had MRSA last year and the participant "just had a break out last week until this week per mother". (August 24 to August 31) Participant " apparently is a carrier" per mother. ********** Participant had MRSA last year and the participant "just had a break out last week until this week per mother". (August 24 to August 31) Participant " apparently is a carrier" per mother.	Active
168009	9	White	Female	09/01/2012	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Probably not related	Participant with medical history of frequent kidney and bladder infections was treated on September 1, 2012 with Bactrim DS BID x 10 days for kidney infection. Has resolved without sequelae.	Active
168009	10	White	Female	11/18/2012	Infection	Infection - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	Review of participant's medical record and external Rx history indicated the use of sulfamethoxazole tmp 55 (obtained from outside	Active

												pharmacy on 18 Nov 2012) for urinary tract/kidney infection.	
168183	6	White	Male	07/06/2010	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	1	Expected	1	Probably not related	Threw up once on way home.	Active
168183	6	White	Male	07/06/2010	Ocular/Visual	Ocular/Visual - Other (Specify in Event Details)	Primary	5	Expected	2	Definitely not related	Had red, swollen, and painful eye. Physician thought that he got something in it. Prescribed Tobramycin and Dexamethasone in drop form with 1 to 2 drops every 4 hrs. for 5 days.	Active
168183	10	White	Male	03/19/2014	Endocrine	Endocrine - Other (Specify in Event Details)	Primary	3	Expected	3	Definitely not related	participant was taken to ER with complaints "stomachache" and high glucose readings. Mother reports participant having more complaints of "stomachache" and recently started on medication. Participant was admitted and insulin therapy initiated-diagnosed with T1D	Active
168561	15	White	Female	07/10/2016	Infection	Infection - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Participant reports at 24-month visit on 21/JUL/2016 a history of not feeling well with swelling and tenderness in neck, just under the chin, in early June. Following worsening of swelling and tenderness, was seen by PCP and diagnosed with an infected lymphnode. Participant was started Augmentin on 10/JUL/2016 with no improvement and worsening of symptoms on 12/JUL/2016. Participant was seen again by PCP who discontinued Augmentin therapy and started Cefdinir same day. Participant feels much better today with slight	Placebo

												residual swelling, no tenderness.	
168561	15	White	Female	11/10/2016	Infection	Infection with unknown ANC	Primary	5	Not Expected	2	Definitely not related	Participant reports another lymphnode infection, similar to that previously reported (10/JUL/2016); treated with 10 day course of 600mg QD Cefdinir.	Placebo
168672	13	White	Male	10/01/2011	Pain	Pain - Other (Specify in Event Details)	Primary	4	Expected	1	Definitely not related	Intermittent headache	Placebo
168672	16	White	Male	12/20/2013	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	3	Expected	1	Definitely not related	fever max 102.0F	Placebo
168672	16	White	Male	12/20/2013	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	3	Expected	1	Definitely not related	Musculoskeletal achiness	Placebo
169235	6	White	Female	02/16/2010	Gastrointestinal	Dental: teeth	Primary	0	Expected	2	Definitely not related	Two primary incisors were extracted to make room for secondary teeth. Ppt experienced no pain after procedure, missed just on ehour of school.	Active
169235	6	White	Female	04/24/2010	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	2	Expected	2	Definitely not related	Participant entered study with a diagnosis of "reactive airway disease/asthma," experienced an exacerbation which required treatment with duoneb X 1.	Active
169235	7	White	Female	02/01/2011	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	36	Expected	2	Definitely not related	Upper respiratory infection (in ppt with history of asthma) treated with occasional doses of OTC until 3 weeks passed without resolution. Saw PMD on 22Feb2011, who prescribed	Active

												oral steroids for 4 days (unclear if beneficial); symptoms resolved 2 weeks after end of steroid course.	
169235	7	White	Female	03/16/2011	Infection	Infection - Other (Specify in Event Details)	Primary	14	Not Expected	3	Definitely not related	Asthma-exacerbated sinusitis: Initial symptom was a cough, which worsened quickly. Visit to the emergency department on 19Mar2011, where she received oral steroids. Ppt returned to the hospital 20Mar2011 and was admitted for treatment with albuterol, oral steroids and amoxicillin. Discharged on 22Mar2011.	Active
169495	11	White	Female	12/22/2014	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Influenza	Active
169495	12	White	Female	06/08/2015	Hemorrhage/Bleeding	Hemorrhage, GU	Primary	281	Not Expected	2	Definitely not related	Started Sprintec once a day in June to regulate menstrual cycle. Has increased dose to 2-3 tabs daily as well as adding Synthroid. C/o menses every 2 weeks lasting for 10 days. Bleeding increases with activity. Pelvic/back pain with bleeding.	Active
169495	12	White	Female	09/30/2015	Endocrine	Thyroid function, low (hypothyroidism)	Primary	.	Not Expected	2	Probably not related	On 11/8/15. mom reported that MD started participant on synthroid to see if this would help with the excessive menstrual bleeding. Thyroid antibodies were high (>600), but TSH normal. First does of synthroid taken on 11/30/15. Mom reports participant has responded well to treatment-decrease in menstrual bleeding, 5lb weight loss, and has grown an inch in height.	Active

169650	4	White	Female	11/18/2010	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	2	Not Expected	1	Definitely not related	had fever of 100.5 degrees F starting on 11/18/10. No other symptoms. Did not take any medications. Resolved completely by 11/20/10	Active
169650	4	White	Female	01/26/2011	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	15	Expected	2	Definitely not related	upper respiratory infection with rhinorrhea, no fever or cough	Active
170035	3	White & Hawaiian/Pacific	Male	07/12/2012	Infection	Infection - Other (Specify in Event Details)	Primary	15	Not Expected	2	Definitely not related	Experienced cold symptoms: runny nose, cough, and congestion. Used Triaminic 1/2 tsp BID for 3 days. Also used Hyland Homeopathic cold medicine 1 tsp BID to TID for 2 weeks. Did not see pediatrician at the time. Symptoms resolved on 27JUL2012 without sequelae.	Active
170035	4	White & Hawaiian/Pacific	Male	08/24/2012	Infection	Infection - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	On 24AUG2012 participant experienced a fever of 101.0 degrees Farenheit for two days. He took Children's Tylenol 1 tsp every 6 hours for two days. Fever resolved on 26AUG2012 without sequelae.	Active
170035	4	White & Hawaiian/Pacific	Male	08/24/2012	Infection	Infection - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	On 24AUG2012, participant had bilteral eye discharge. Not seen by pediatician but pediatrician called in a prescription for antibiotic eye drops Occuflox 0.3% on 27AUG2012, to be administered one drop in each eye twice a day for five days. Eye discharge resolved on 29AUG2012.	Active
170035	4	White & Hawaiian/Pacific	Male	08/28/2012	Allergy/Immunology	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Primary	4	Not Expected	2	Definitely not related	On 28 AUG2012 participant experienced sneezing, nasal congestion, and runny nose. Participant took Claritin 1 tsp	Active

												daily for four days. Symptoms resolved on 1SEP2012.	
170035	4	White & Hawaiian/Pacific	Male	06/14/2013	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	3	Not Expected	2	Definitely not related	103.0 degrees Fareheit fever from 14JUN2013 to 17JUN2013. Participant did not see MD; mother treated with Children's Tylenol and Children's Motrin. Resolved without sequelae.	Active
170035	5	White & Hawaiian/Pacific	Male	05/28/2014	Gastrointestinal	Constipation	Primary	.	Not Expected	2	Definitely not related	Has had constipation occurrences since 28MAY2014 on and off. Taken to pediatrician on 13JUN2013, x-ray showed constipation. Miralax PO was recommended.	Active
170446	16	White	Male	05/07/2013	Infection	Infection - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Probable bacterial sinus infection. Antibiotics prescribed.	Placebo
170515	9	White	Male	02/13/2015	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	Influenza A	Active
170515	10	White	Male	12/14/2015	Infection	Infection - Other (Specify in Event Details)	Primary	1	Not Expected	2	Definitely not related	common cold with fever	Active
170925	13	White	Male	11/20/2013	Gastrointestinal	Perforation, GI	Primary	4	Not Expected	3	Definitely not related	Participant presented in A.E. with nausea and severe abdominal pain. Underwent emergency appendectomy on 20/11/13.	Placebo
171406	4	White	Male	12/01/2010	Pulmonary/ Upper Respiratory	Cough	Primary	2	Not Expected	2	Probably not related	Participant had a cough, runny nose and fever (101) during 12/1/2010 - 12/3/2010. Tylenol OTC was indicated.	Active
171406	7	White	Male	05/09/2014	Ocular/Visual	Ocular surface disease	Primary	1103	Not Expected	2	Probably not related	Participant had conjunctivitis, needed eye drops for 7 days.	Active

172030	6	White	Male	03/27/2010	Hemorrhage/Bleeding	Hemorrhage, GI	Primary	1	Not Expected	1	Definitely not related	Blood in stool noted 3/27, this, the third episode in 2 months. First episode occurred prior to study entry. Practitioner seen, who recommended no intervention other than 'wait and see.' If another episode occurs, they will scope him. Hold oral ferrous solution. observe for constipation, abdominal c/o, changes in bowel habits, any further hemachezia.	Active
172030	7	White	Male	05/18/2011	Gastrointestinal	Constipation	Primary	0	Not Expected	2	Definitely not related	Presented to ER with c/o abd. pain.	Active
172030	8	White	Male	09/05/2012	Endocrine	Pancreatic endocrine: glucose intolerance	Primary	6	Expected	2	Definitely not related	FBS=139 with polyuria and fever.	Active
172438	3	White	Female	01/30/2012	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	On 1/30/12 was diagnosed with strep throat via culture and bilateral ear infection. Given Augmentin liquid orally twice daily for 10 days.	Active
172438	8	White	Female	01/16/2017	Infection	Infection - Other (Specify in Event Details)	Primary	28	Not Expected	2	Definitely not related	Participant's mother reports participant experienced fever, stomach pains and nausea starting on 1/16/17. Walk-in clinic originally reported strep test as negative. On 1/20/17 received call from clinic with + strep test and prescription for PCN 250 mg BID; started taking that day. 1/23/17 went to pediatrician with continued symptoms and 2nd test still + for strep. Physician changed prescription to Clindamycin 300 mg TID and started taking same day. 1/29/17 vomited, and again on 1/30/17 with no fever.	Active

												Again positive strep culture at pediatrician's office. Changed prescription to Cephalexin 500 mg BID. 2/3/17 rash appeared and returned to physician who felt it was a viral rash and that participant had concurrent virus with strep infection. (CBC with diff and Sed Rate normal) Participant's brother came down with apparently the same virus that night as he threw up. 2/4/17 participant "feeling better", still nauseated but eating again. Scheduled to finish antibiotics on 2/10/17 with appointment for lab work scheduled for 2/13/17.	
172438	9	White	Female	03/13/2017	Infection	Infection - Other (Specify in Event Details)	Primary	14	Not Expected	2	Definitely not related	Participant's mother sent an email on 3/13/17 that participant had a positive strep test and would have to cancel visit for next week to CRC for OGTT. Spoke to mother on phone 3/14/17 and she said participant went to school nurse with complaints of sore throat, fever, stomach ache and head ache on 3/13/17. Mother took participant to pediatrician that day. Strep test returned positive and participant was given prescription for Cephaxelin 500 mg BID X10 days. Took first dose evening of 3/13/17. ********** Participant's mother sent an email on 3/13/17 that participant had a positive strep test and would have to cancel visit for next week to CRC for OGTT. Spoke to mother on	Active

												phone 3/14/17 and she said participant went to school nurse with complaints of sore throat, fever, stomach ache and head ache on 3/13/17. Mother took participant to pediatrician that day. Strep test returned positive and participant was given prescription for Cephaxelin 500 mg BID X10 days. Took first dose evening of 3/13/17. Participant took complete 10 day course of Cephaxelin 500 mg BID. Took last dose on 3/23/17. Went to pediatrician on 3/27/17 and strep test returned negative. Symptoms all resolved.	
172438	9	White	Female	04/10/2017	Infection	Infection - Other (Specify in Event Details)	Primary	14	Not Expected	2	Definitely not related	On 5/30/17 mother of participant reported that on 4/10/17 participant didn't "feel good", complained of a sore throat and spiked a fever. Mother took participant to pediatrician and strep test returned positive. Participant started a 10 day course of Cephalexin 500 mg BID starting 4/10/17 and last dose taken on 4/20/17. Also started probiotics that day. Returned to pediatrician on 4/24/17 and strep test came back negative. All symptoms resolved.	Active
173990	8	White	Male	05/21/2016	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Participant had an allergic reaction to wasp venom after being stung below the eye. Both eyes swelled shut for several days. Participant was treated with benadryl around the clock from 21/MAY through 24/MAY and then BID 25/MAY	Placebo

												through 29/MAY. Swelling had resolved by 31/MAY/2016.	
173995	6	White	Male	07/15/2013	Musculoskeletal/Soft Tissue	Extremity-upper (function)	Primary	0	Not Expected	3	Definitely not related	Subject broke his right arm while jumping on a trampoline. The subject's arm was set and a cast was placed to help the bones align. Subject may still require surgery, this will be determined on Monay July 22nd at his follow-up appointment.	Placebo
174596	15	White	Female	10/24/2016	Pain	Pain - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	Intermittent Abdominal Pain had been previously reported as a grade 1 AE. Escalated event to grade 2 after episode of abdominal pain on 24OCT2016 and subject was referred to GI specialist for evaluation. GI visit on 15NOV2016 was followed by EGD with biopsy on 18NOV2016 and subject was diagnosed with celiac disease. No meds, will start gluten free diet.	Placebo
175960	4	White & Hawaiian/Pacific	Female	04/01/2011	Dermatology/Skin	Urticaria (hives, welts, wheals)	Primary	.	Expected	2	Probably not related	Hives, associated with "cold" temperature per Mom; resolve with 1-2 doses of Benadryl (5 mg), then recur x 3-4/week; allergy testing has not revealed any cause.	Placebo
176409	17	White	Male	01/10/2016	Neurology	Seizure	Primary	526	Not Expected	2	Definitely not related	Participant had a generalized seizure during Sunday lunch. He fell to the floor and according to his mother had a generalized convulsion. They called the ambulance and he was taken to the E.R. The seizure had stopped before the emergency services arrived and no drugs were administered. His blood glucose reading in the ER was 118mg/dL. He was admitted to	Placebo

												hospital for an MRI, EEG and ECG. We are awaiting the final reports of these tests.	
176409	18	White	Male	05/09/2016	Neurology	Mood alteration	Primary	406	Not Expected	3	Definitely not related	Participant had repeated anxiety attacks which commenced on the 9th of May 2016. He was unable to attend school for two weeks and did not want to leave the house unnaccompanied.	Placebo
176822	3	White	Male	11/20/2010	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	11	Not Expected	2	Definitely not related	Tonsillitis	Active
176822	4	White	Male	02/11/2011	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Varicella Zoster (Chickenpox) treated with antiviral agent.	Active
176822	5	White	Male	06/11/2012	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Tonsillitis	Active
178056	8	White	Male	03/02/2016	Gastrointestinal	Vomiting	Primary	3	Not Expected	2	Probably not related	Mother reports participant experienced nausea and vomiting (3-4 times each day) from March 2 through March 4. Participant's mother check BG on home meter, which read 105. After PI assessment at study visit, it was recommended urine ketones also be check in this situation as BG may not be elevated secondary to vomiting. Participant has since recovered and was well-appearing at study visit.	Placebo
178903	5	Unknown or Not Reported	Male	01/13/2011	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	upper respiratory infection with rhinorrhea, cough, no fever, no sore throat.	Active

178903	6	Unknown or Not Reported	Male	04/25/2011	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	1	Not Expected	2	Probably not related	vomiting 2 days.	Active
178903	6	Unknown or Not Reported	Male	04/27/2011	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	1	Not Expected	1	Definitely not related	Fever for two to three days, along with vomiting for 3 days. Seen by physician at an outpatient facility. Participant was prescribed Amoxicillin for ten days.	Active
178903	6	Unknown or Not Reported	Male	04/27/2011	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	9	Not Expected	2	Definitely not related	in April, had ear infection with fever 102 degrees. Treated with Amoxicillin for 10 days ********** in April, had ear infection with fever 102 degrees Farenheit. Treated with Amoxicillin for 10 days. Grade for fever: 2.	Active
178903	6	Unknown or Not Reported	Male	08/22/2011	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	dental work on lower left molar on 8/22/11. Drilled deep into tooth, cleaned it out, put in antibiotic, covered with amalgam. Lower right molar done on 8/26/11.	Active
178903	6	Unknown or Not Reported	Male	12/01/2011	Musculoskeletal/Soft Tissue	Fracture	Secondary	61	Not Expected	3	Definitely not related	On evening 12/1/11, was jumping on the bed and fell off, suffering displaced right supracondylar humerus fracture. Was seen in ER, then was admitted to hospital for closed reduction and percutaneous skeletal fixation right extension type 2b supracondyular humerus fracture. Discharged home evening of 12/2/11.	Active
178903	7	Unknown or Not Reported	Male	04/22/2012	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	White patches on skin	Active

178903	7	Unknown or Not Reported	Male	12/11/2012	Pulmonary/ Upper Respiratory	Cough	Primary	.	Not Expected	1	Definitely not related	Cough and runny nose developed today.	Active
179384	6	White	Female	02/15/2015	Infection	Infection - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	At some point in February 2015 (participant's father is unable to remember exact day, so start date was estimated as the middle of the month), participant began to experience "flu" symptoms including fever, vomiting and diarrhea. These symptoms were treated with three 500cc boluses of NS (administered at home by the subject's father, who is a paramedic), as well as Zofran and Tylenol liquid over a 3-4 day period.	Active
179384	7	White	Female	09/15/2015	Syndromes	Flu-like syndrome	Primary	2	Not Expected	2	Definitely not related	Subject's symptoms included nausea, vomiting, diarrhea, fever (~101.5 F). No medications were taken as treatment. Symptoms resolved completely after a couple of days.	Active
180512	10	White	Female	09/15/2013	Infection	Infection with unknown ANC	Primary	19	Not Expected	2	Definitely not related	Participant presents to Urgent care with runny nose, sore throat x1 day, Fever of 103 degrees Fahrenheit started this afternoon Sept 15, 2013 at 1400. Participant denies vomiting or diarrhea. Participant is drinking good fluids per mom. Denies ill contacts, smoke exposure Temperature at 20:29 was 38.3 degrees Celsius or 100.94 degrees Fahrenheit Neck: with mild cervical lymphadenopathy Ears, nose, mouth and throat:	Active

												Tympanic membranes clear moderate pharyngeal erythema with exudate. Respiratory: Lungs are clear to auscultation. respirations are non-labored. breath sounds are equal. Symmetrical chest wall expansion Acetaminophen 500 mg x one given at 23:59 The rapid strep test was positive. Prescription for cephalexin 500 mg oral one tablet, PO, BID, 20 tablet. Give Ibuprofen - 400 mg every 6 hours as needed for fever or discomfort.	
180854	4	White	Male	04/06/2014	Gastrointestinal	Vomiting	Primary	1	Not Expected	2	Definitely not related	Went to a local ED gave Zofran and local rehydration for GAE (stomach bug) and some dehydration. No labs or IV. Vomiting started 4/6/2014 with fruity odor to breath; no diarrhea, no polyuria, no polydispisa, no weight change noticed. Highest random BG yesterday was 129 with ketones 2.8. Fasting BG 4/7/2014 morning 119. Ketones down to 0.7. ********** Went to a local ED gave Zofran and PO rehydration for GAE (stomach bug) and some dehydration. No labs or IV. Vomiting started 4/6/2014 with fruity odor to breath; no diarrhea, no polyuria, no polydispisa, no weight change noticed. Highest random BG yesterday was 129 with ketones 2.8. Fasting BG 4/7/2014 morning 119. Ketones down to 0.7.	Placebo

180854	7	White	Male	06/18/2016	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	1	Not Expected	2	Definitely not related	vomiting x2 episodes in one day, no other symptoms, no treatment needed	Placebo
181598	17	White	Male	02/21/2014	Infection	Infection - Other (Specify in Event Details)	Primary	6	Not Expected	2	Definitely not related	Influenza positive at PCP visit 22FEB2014, treated with Tamiflu.	Active
181847	8	White	Male	01/13/2012	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	7	Not Expected	4	Definitely not related	Participant developed a fever of 104.7 degrees F on 13/JAN/2012 over 5-6 days. Missed school for one week. Participant's pediatrician advised to take Acetominophen, as needed.	Active
182144	3	White	Male	09/23/2012	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	0	Not Expected	2	Definitely not related	Left ear infecton treated with amoxicillin	Active
182144	3	White	Male	10/10/2012	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	19	Not Expected	2	Definitely not related	Recurrent ear infection treated with bilateral PE tube placement	Active
182144	3	White	Male	10/16/2012	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	13	Not Expected	2	Definitely not related	Adenotonsillar hypertrophy treated with tonsillectomy and adenoidectomy	Active
182144	4	White	Male	06/11/2013	Pulmonary/Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	Asthma exacerbation	Active
182144	4	White	Male	06/27/2013	Pain	Pain - Other (Specify in Event Details)	Primary	2	Not Expected	3	Definitely not related	25/Jun/2013 Subject began to complain of pain in their hands/wrists and legs (bilateral UE and LE), to the point that the subject was unable to ambulate or dress themself. There has been no known trauma. At its worst, the pain is severe. The subject responded to pain medications (Tylenol and Ibuprofen at home, Morphine in the ER). No fever, rash rhinorrhea, cough, vomiting, diarrhea or urinary changes noted. Lab work was within	Active

												normal limits, including inflammatory markers. The subject has a normal cardiac exam, no respiratory symptoms, and has no cardiorespiratory symptoms. The subject has had an exposure to Cefdinir about 2 weeks ago and serum sickness-like reacton is possible. Subject continues to improve after admission, pain decreased to moderate grade.	
182144	5	White	Male	01/28/2014	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Positive RSV treated with oral steroids and albuterol nebs	Active
182144	5	White	Male	02/10/2014	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Asthma exacerbation	Active
182144	5	White	Male	08/03/2014	Dermatology/Skin	Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	Primary	9	Not Expected	2	Probably not related	Treated with oral medication in the emergency room and then discharged home to continue on oral medication.	Active
184285	14	Unknown or Not Reported	Female	09/17/2014	Pain	Pain	Primary	0	Not Expected	2	Probably not related	Participant reports that on September 17, 2014 went to see her PCP because she had abdominal pain. Participant was taken to the emergency room with a possible diagnosis of appendicitis. All blood work and imaging (MRI and pelvic ultrasound) came back negative for that, but imaging showed polycystic ovaries. The abdominal pain went away by itself with no medication given to the patient. Participant was kept in observation for 4 hours in the ER and then discharged	Active

												with the recommendation to make a follow up appointment with ObGyn.	
184372	4	White	Male	12/11/2012	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	Participant was sick from Dec. 11th - Dec. 13th; complained of a sore tummy on Dec.11th and vomitted a few times on Dec. 12th. Also, the subject was very tired on Dec. 11th and Dec. 12th. Missed one day of school (Dec. 12) and one day of day care (Dec. 12th). Did not seek any medical attention. Symptoms resolved on Dec. 13th. 12.	Placebo
184372	4	White	Male	03/11/2013	Pain	Pain - Other (Specify in Event Details)	Primary	104	Not Expected	2	Probably not related	Subject has been experiencing stomach pains since Jan./2013. Seen by a family physician as well as pediatrician, no definite diagnose has been made yet. Participant was started on Losec 10 mg. on Jan. 26/13. On Feb. 16th taken to the ER (c/o stomach pain), a complete physical exam performed and sent home as not seen anything unusual. Losec stopped on Feb. 19th. On Feb. 22 subject was seen by a pediatrician, blood work done (tests for celiac disease and kidney function) all results came back normal. On March 11 subject vomited 5-6 times throughout the night, no fever noted, no medication given. Missed one day of day care Mar. 12, but was feeling "usual self" as per subject's	Placebo

												parent. Started on Pro-biotics on Apr. 1st./13.	
184372	4	White	Male	04/27/2013	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	8	Not Expected	2	Definitely not related	Subject was sick with a sore throat and a fever (101 F) on Apr. 27 /13. Seen by MD in the Walk-in-clinic on Apr. 28 ; sent home no meds given. Participant had not been feeling well, really tired and often with a mild fever, during the week Apr. 29th - May 3rd. Children's Advil 200 mg. PRN given. On May 3rd taken to the Children's ER, seen by MD and throat swab done. Started on Amoxicillin 250 mg. BID on May 3rd for 7 days. On May 4th the swab came back positive for strep throat. Symptoms resolved on May 5th /13. Missed 2 days of day care, May 2nd and 3rd/13.	Placebo
184372	6	White	Male	01/11/2015	Gastrointestinal	Vomiting	Primary	1	Not Expected	2	Definitely not related	Subject was sick on Jan. 11, 15; started vomiting early in the morning ~5 times. Complained of stomach pain after that but did not vomit. No other symptoms present. Had small meals in the afternoon, no vomiting. Did not take any meds or seek medical attention. On Jan. 12, 15 subject felt completely normal.	Placebo
184372	7	White	Male	01/30/2016	Gastrointestinal	Vomiting	Primary	2	Not Expected	2	Definitely not related	Subject was sick on Jan. 30th. and Jan. 31st, 16. C/o stomach pain, vomiting X 5 and diarrhea X 2. No meds given; did not seek any medical attention; no	Placebo

												other symptoms present. Subject did not participate in regular ADL on Jan. 30th and 31st. Symptoms resolved on Feb. 1st, 2016	
184372	7	White	Male	12/07/2016	Infection	Infection - Other (Specify in Event Details)	Primary	12	Not Expected	2	Definitely not related	Subject got minor skin abrasion on chin and nose (occurred during play) on Dec. 7, 2016. Healing scrape on chin and nose noted at 48 study visit on Dec. 13/16. On Dec. 14/16 family noticed spots around the abrasion. Participant seen by FD on Dec. 15/16 " some type of infection" as per MD. Cream Taro - Mupirocin 2% TID and Cephalexin 250mg TID for 5 days prescribed. Subject missed one day of school Dec. 15/16. Resumed regular activities on Dec. 16/16. Symptoms- skin abrasion and spots were completely gone on Dec. 19/16.	Placebo
184658	9	White & Black/ African American	Female	11/27/2011	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	.	Not Expected	1	Possibly related	ABDOMINAL PAIN (NO EMESIS,NAUSEA, DIARRHEA OR CONSTIPATION) 4-6 HOURS POST STUDY MEDICATION DOSE	Active
184658	13	White & Black/ African American	Female	11/22/2015	Auditory/Ear	Auditory/Ear - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Ear Infection	Active

184658	13	White & Black/ African American	Female	04/01/2016	Infection	Infection - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Influenza Type B	Active
184658	13	White & Black/ African American	Female	04/29/2016	Auditory/Ear	Auditory/Ear - Other (Specify in Event Details)	Primary	11	Not Expected	2	Definitely not related	ear infection	Active
185281	10	White & Black/ African American	Female	09/03/2011	Infection	Infection - Other (Specify in Event Details)	Primary	376	Not Expected	1	Definitely not related	Participant had impetigo right posterior thigh.	Placebo
185281	10	White & Black/ African American	Female	04/01/2012	Allergy/Immunology	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Primary	44	Not Expected	2	Definitely not related	Participant's mother reported that the participant developed seasnal allergies and took Claritin daily.	Placebo
185281	11	White & Black/ African American	Female	09/09/2012	Musculoskeletal/Soft Tissue	Fracture	Primary	24	Not Expected	2	Definitely not related		Placebo
186415	12	White	Male	08/10/2012	Musculoskeletal/Soft Tissue	Fracture	Primary	35	Not Expected	2	Definitely not related	Participant was playing football in the street. Fell backwards, resulting in a Jones fracture in their left foot. Went to Family doctor, who performed an xray. Xray confirmed fracture. Wore a boot cast for 5 weeks. Follow up	Active

												xray showed fracture had healed. Boot was removed.	
186529	7	Unknown or Not Reported	Female	10/02/2013	Auditory/Ear	Otitis, external ear (non-infectious)	Secondary	28	Not Expected	2	Definitely not related	Participants grandmother commented in last holidays participant had discharge from ear, when seen by Medical staff discovered eardrum had burst.	Placebo
186748	7	White	Male	07/05/2011	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	0	Expected	1	Definitely not related	Participant had a scheduled tonsilectomy and adenoidctomy	Active
186748	7	White	Male	02/10/2012	Gastrointestinal	Vomiting	Primary	1	Not Expected	1	Definitely not related	Participant had a stomach virus that members in his school class had as well as his siblings	Active
186965	7	White	Male	03/28/2012	Infection	Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infe	Primary	1	Not Expected	3	Definitely not related	Subject experienced fever of 101 degrees F with lethargy and poor appetite beginning evening of 3/28/12. Missed school the next day. No treatment given. Recovered without sequelae.	Active
186965	8	White	Male	02/26/2013	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Subject developed upper respiratory tract infection with congestion, cough, fever to 101 deg F. Missed school X 3 days. Tx with CVS Children's Cough and Cold liquid Q4 prn during the day and CVS Children's Cough and Cold liquid Q4 prn at night, along with Ibuprofen Childrens liquid prn and Tylenol Childrens Liquid prn for fever. Resolved 2-Mar-2013.	Active
186965	8	White	Male	06/30/2013	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	6	Not Expected	2	Definitely not related	Rash on arms from exposure to poison oak. Treated with OTC benadryl cream and OTC hydrocortisone	Active

186965	8	White	Male	07/28/2013	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	Starting the week of 7/28/13, the subject started to complain of almost daily stomach aches, usually occuring at night. The mother started watching the subjects diet and believes that the pains are related to dairy in the subject's diet. She started having the subject take lactase pills prn (900 units per pill, 1 pill per dose) with high diary meals and is seeing improvement in the pain.	Active
186965	9	White	Male	11/02/2013	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Upper respiratory tract infection with mild coughing. Treated with Delsym liquid prn.	Active
186965	9	White	Male	11/22/2013	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	Sore throat with fever to 101.7. Treated with Tylenol PRN. Subject missed 1/2 day of school.	Active
186965	9	White	Male	01/27/2014	Gastrointestinal	Diarrhea	Primary	0	Not Expected	1	Definitely not related	Subject experienced abdominal pain and diarrhea, < 4 stools over baseline. Missed school, but did not otherwise alter ADL. No treatment given. Did not miss any study drug doses.	Active
186965	9	White	Male	03/08/2014	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Upper respiratory tract infection with cough and congestion, no fever. Treated with over the counter cough and cold medications.	Active
186965	9	White	Male	03/18/2014	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Left otitis media treated with Amoxicillin and over the counter analgesics.	Active
186965	9	White	Male	03/21/2014	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	38	Not Expected	2	Definitely not related	Right Achilles tendonitis. Subject saw MD and physical therapist for treatment	Active
186965	9	White	Male	04/04/2014	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	24	Not Expected	2	Definitely not related	Left Achilles tendonitis. Subject saw physical therapist for treatment	Active

186965	10	White	Male	09/03/2014	Infection	Infection - Other (Specify in Event Details)	Primary	1	Not Expected	2	Definitely not related	Upper respiratory tract infection with rhinitis, sneezing, nasal congestion tx with over the counter CVS Children's Nightime Cough and Cold Liquid and over the counter CVS Children's Daytime Cough and Cold Liquid.	Active
186965	10	White	Male	03/01/2015	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	15	Not Expected	2	Definitely not related	Subject developed poison oak rash in both arms, both legs, face, and ears on 3/1/15. Rash was getting close to eyes, prompting MD to prescribe prednisone po.	Active
186965	10	White	Male	03/11/2015	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	Upper respiratory tract infection	Active
186965	10	White	Male	03/16/2015	Auditory/Ear	Auditory/Ear - Other (Specify in Event Details)	Secondary	5	Not Expected	2	Definitely not related	Bilateral ear infection	Active
187158	10	White	Male	01/15/2015	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Pharyngitis	
187159	6	White	Male	02/01/2015	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	1	Not Expected	2	Definitely not related	Viral gastroenteritis	Active
187159	8	White	Male	07/23/2016	Musculoskeletal/Soft Tissue	Fracture	Primary	32	Not Expected	2	Definitely not related	On the 23rd of July the subject sustained a non-displaced supracondylar fracture of his left distal humerus. Treated in the emergency room with an open splint. Reviewed on the 29th of July and had a full arm cast applied. The cast was removed on the 24th of August.	Active
187884	16	White	Male	10/15/2013	Dermatology/Skin	Rash: acne/acneiform	Primary	700	Not Expected	2	Definitely not related	Facial acne developed in October 2013. Subject was seen by a dermatologist 12DEC2013 and started on an oral antibiotic	Active

												for acne treatment on 12DEC2013.	
188769	8	White	Male	06/13/2016	Pulmonary/ Upper Respiratory	Cough	Primary	2	Not Expected	3	Definitely not related	Participant had an upper respiratory tract infection. He had a cough and missed school for two days.	Active
189107	8	White	Female	08/08/2016	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Participant diagnosed with left ear infection on August 8, 2016. Physician prescribed Amoxicillin 250 mg BID for 10 days. Resolved by end of antibiotic course.	Placebo
189107	8	White	Female	03/21/2017	Infection	Infection - Other (Specify in Event Details)	Primary	12	Not Expected	2	Definitely not related	Participant had abdominal pain starting on 3/21/17, then fever developed 3/22/17, but no sore throat. Physician diagnosed strep throat and prescribed a 10 day course of Amoxicillin 500 mg BID. Participants's mother said participant was "better with no symptoms by 3/26/17 and finished 10 day course of antibiotics on 4/2/17.	Placebo
189432	5	White	Female	07/15/2013	Infection	Infection with unknown ANC	Primary	7	Not Expected	2	Definitely not related	Doctor/Nurse visit prescribed 10days of MOC gave patient 1.5tsp of Children's Motrin for 3days for fevers alongside with Omnicef.	Placebo
189432	6	White	Female	05/20/2014	Pulmonary/ Upper Respiratory	Fistula, pulmonary/upper respiratory	Primary	14	Not Expected	2	Definitely not related	Identified by MOC as "walking pneumonia" no prescribed medication. Participant took Ibuprofen 2 tabs BID PO and Children's Robitussin 1 tab BID PO 5/20-6/3/2014	Placebo
189432	6	White	Female	06/27/2014	Renal/Genit ourinary	Cystitis	Primary	8	Not Expected	2	Definitely not related	UTI was prescribed Cephalexin	Placebo
189432	7	White	Female	04/01/2015	Infection	Infection with unknown ANC	Primary	9	Not Expected	2	Definitely not related	MOC took participant to PCP due to fever over 100F. PCP prescribed Keflex 2.5 tsp, BID, PO for 10 days for Strep throat.	Placebo

189432	7	White	Female	05/01/2015	Infection	Infection with unknown ANC	Primary	9	Not Expected	2	Definitely not related	MOC reported ear infection occurring at the same time as strep throat in the beginning of May with fever over 100F. PCP gave participants prescription of omnicef for ear infection and strep throat, 2tsp, BID, PO for 10 days.	Placebo
189432	7	White	Female	09/01/2015	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	10	Not Expected	2	Definitely not related	subject presented to PCP with ear pain and sore throat, was diagnosed with ear infection and prescribed cefdinir for 10 days; subject also took motrin for 5 days during the course of the illness	Placebo
190195	4	White	Male	07/24/2011	Endocrine	Pancreatic endocrine: glucose intolerance	Primary	.	Expected	3	Definitely not related	The subject started developing progressively increasing thirst around 7/22/11. On the night of 7/23/11, the father obtained a glucometer reading of 513. The father brought him into a hosspital ER. A blood glucose level of 400 ng/dL was obtained by the hospital lab and a diagnosis of T1D was made The subject was started on insulin and was hospitalized 7/24/11 and discharged 7/25/11.	Placebo
190402	3	White	Male	12/09/2011	Blood/Bone Marrow	Hemoglobin	Primary	101	Not Expected	3	Probably not related	Hemoglobin low at 6.7 g/dl - dx of iron deficiency anemia	Placebo
190897	5	White	Male	12/01/2011	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	grouping of warts under the arm pit and spreading to the underside of his bicep consistent with Molluscum contagiosum ********** grouping of warts under the arm pit consistent with Molluscum contagiosum	Placebo

190927	11	White	Female	02/22/2014	Gastrointestinal	Vomiting	Primary	2	Not Expected	2	Probably not related	No iv fluids required but participant vomited 5 times in 24hour period. Subject did not stop study drug. Vomiting stopped on Feb 23rd but felt a little queasy. resolved on Feb 24th, 2014	Active
191384	9	White	Male	09/15/2011	Endocrine	Thyroid function, low (hypothyroidism)	Primary	27	Not Expected	2	Definitely not related	patient's bloodwork indicated hypothyroid. Started on Synthroid. Feeling well.	Active
191632	10	White	Male	10/09/2011	Neurology	Neurology - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	Participant was hit with a baseball bat in the right temproal area. Negative LOC. Denied dizziness, headache, nausea, or vomiting. Seen in ED. CT scan was negative for brain injury. Per CT scan, diagnosed with chronic sinusitis. Prescribed 7 day course of antibiotics.	Placebo
191632	10	White	Male	01/01/2012	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Diagnosed with strepthroat. Prescribed oral antibiotics BID x 10 days. Infection resolved.	Placebo
191632	11	White	Male	01/29/2013	Infection	Infection - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Participant was hit in the face with a baseball bat at practice. They received 2 stiches on the inside of their mouth where their teeth went through their cheek and 2 stitches on their chin. They were started on prophylactic antibiotics. Cephalexin 250 mg capusles 3 times a day for 5 days.	Placebo
191632	11	White	Male	02/24/2013	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	On 2/24/13, the participant developed a cough. On 2/26/13, they went to their doctor due to difficulty breathing. They were diagnosed with Croup and prescribed prednisone. After 2 days of prednisone, they were feeling better and stopped taking the medication.	Placebo

TN07 Oral Insulin – Appendix 6.2.7 Adverse Events by Participant

191632	12	White	Male	12/13/2013	Musculoskeletal/Soft Tissue	Fracture	Primary	.	Not Expected	2	Definitely not related	Participant rolled right foot at PE. They were taken to urgent care, which performed an Xray confirming a fracture. Participant was given a boot and was put in a hard cast on 12/20/13. The cast was removed on 1/2/14. On 1/10, they re-injured their ankle and were put back in a boot.	Placebo
191668	3	Black/ African American	Female	07/26/2011	Dermatology/Skin	Burn	Primary	10	Not Expected	2	Definitely not related	Obtained a 2 x 1 cm second degree burn on right AC from placing arm under a moving treadmill. Saw pediatrician. Bacitracin ointment applied x 10 days. No debridement necessary. ********** Obtained a 2 x 1 cm second degree burn on right AC from placing arm under a moving treadmill. Saw pediatrician. Bactroban ointment applied x 10 days. No debridement necessary.	Active
191668	7	Black/ African American	Female	01/21/2016	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Participant had an ear infection that was diagnosed on 1/21/16 by the subject's physician, who prescribed Amoxicillin 10mL, two times daily for 10 days. Last dose was January 30, 2016.	Active
191668	7	Black/ African American	Female	02/12/2016	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Participant taken to physician on Friday, February 12, 2016, who diagnosed the subject with a sinus infection. She was prescribed Cefdinir 250 mg/5mL, 10 ML once daily for 10 days. Last dose taken 2/21/2016	Active

191668	7	Black/ African American	Female	03/11/2016	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Participant diagnosed with "strep throat" by physician and place on 10 days of antibiotics	Active
191668	8	Black/ African American	Female	05/31/2016	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Participant complained of ear pain and was taken to pediatrician who noted "fluid behind the ear drum" and prescribed antibiotics. (Augmentin 7.5 ml BID for 10 days). No purulent discharge, no fever. Participant has had no pain since one day after physician put on abx.	Active
191736	12	White	Male	11/14/2011	Infection	Infection with unknown ANC	Primary	5	Not Expected	2	Definitely not related	upper respitatory infection with cough requiring z-pak and NyQuil for treatment	Active
192313	10	White	Female	03/01/2014	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	In March 2014 participant told parents that she felt her chest tighten and had increased work of breathing whenever she ate chicken or turkey. Allergy tested, negative for chicken and turkey. Father has similar reaction when eating chicken and turkey. Participant removed these items from diet. No meds taken.	Active
192313	11	White	Female	05/11/2015	Neurology	Neurology - Other (Specify in Event Details)	Primary	2	Not Expected	2	Probably not related	5/11/15 developed migrane headache, treated at home with PO tylenol and advil alternating every 2 hours, appetite poor, attended school. 5/12/15 no change in symptoms or treatment, attended school only couple of hours. 5/13/15 same symptoms and treatment but vomited twice when tried to take food/water, did not attend school, able to perform basic ADLs (ambulate, use toilet) but	Active

												stayed in bed most of day, added exedrin headache med without relief of symptoms. Mother took to emergency department where participant received IV fluids and IV pain meds (mother thinks tylenol and advil but unsure). Headache resolved by midnight and has not returned. Family history of migraines in mother, maternal grandfather and maternal great grandfather.	
192883	9	White	Female	06/03/2015	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Participant reports upper respiratory infection beginning on June 3, 2015. Participant had cough, pharyngitis. No fever, nausea, vomiting, lymphadenopathy, or myalgias. Treat with Ibuprofen, chloraseptic spray, tylenol and cough drops as needed. Symptoms resolved on June 7, 2015.	Placebo
192883	10	White	Female	08/18/2016	Infection	Infection with unknown ANC	Primary	3	Not Expected	2	Definitely not related	Participant was diagnosed with "mycoplasma pneumonia" which, according to the family, lasted ~3 days and was treated in an outpatient setting. [Participant subsequently developed a 'rare immune response' which required hospitalization, so details of the pneumonia are somewhat vague and all dates are approximate. Participant's hospitalization will be reported on a separate AE Form, as a secondary event (start date = 21Aug2016).]	Placebo

192883	10	White	Female	08/21/2016	Dermatology/Skin	Ulceration	Secondary	58	Not Expected	3	Definitely not related	Participant was diagnosed with "mycoplasma pneumonia" which, according to the family, lasted ~3 days and was treated in an outpatient setting. The AE reported here is a 'rare immune response' to the mycoplasma, which caused vaginal ulceration and required hospitalization. Family was told that the vaginal ulceration may recur for up to one year. Details re. both AEs are somewhat vague and all dates are approximate (start and stop dates refer to dates of hospitalization). ********** Participant was diagnosed with mycoplasma pneumonia which, according to the family, lasted ~3 days and was treated in an outpatient setting. The AE reported here was initially categorized as a 'syndrome,' as the family described it as a rare immune response to the mycoplasma, which caused vaginal ulceration and required hospitalization. Family was told that the vaginal ulceration may recur for up to one year. Details re. both AEs were somewhat vague and all dates were approximate (start and stop dates reported [21Aug-23Aug 2016] referred to dates of hospitalization), so medical records were requested.	Placebo
195463	8	White	Male	06/01/2013	Pulmonary/ Upper Respiratory	Bronchospasm, wheezing	Primary	.	Not Expected	3	Definitely not related	pt. seen in ER for wheezing and difficulty breathing.	Placebo

195463	9	White	Male	11/03/2013	Allergy/Immunology	Allergic reaction/hypersensitivity (including drug fever)	Primary	.	Not Expected	3	Definitely not related	Participant displayed a severe reaction, probably to peanuts in a bar that was near or touching the nut-free treat that he consumed.	Placebo
195507	9	White	Male	02/06/2012	Infection	Infection with unknown ANC	Primary	13	Not Expected	2	Definitely not related	2/6/12 went to MD for cold symptoms (non productive cough, chest congestion, clear nasal discharge, and ear discomfort); afebrile. Diagnosed with ear infection. Started on 10 day course of oral Amoxicillin. Discontinued amoxicillin 2/16/12 for development of uticaria with pruritis. Cold symptoms resolved. Treating remaining uticaria and pruritis with oral Zyrtec and Benadryl as needed.	Active
195507	11	White	Male	07/23/2014	Infection	Infection with unknown ANC	Secondary	6	Not Expected	2	Definitely not related	On 7/23/14 the subject went to the MD for conjunctivitis. Started on 7 day course of Polymyxin B Sul-Trimethoprim Opthalmic drops.	Active
195507	11	White	Male	08/25/2014	Allergy/Immunology	Allergic reaction/hypersensitivity (including drug fever)	Secondary	18	Not Expected	2	Definitely not related	Dad reported on visit of 9/8/14 that patient had poision ivy rash(hives) starting two weeks ago(starting on 8/25/2014). The patient did not take medication for the rash and it was healing upon physical exam.	Active
195507	12	White	Male	08/04/2015	Allergy/Immunology	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Primary	4	Not Expected	2	Definitely not related	nasal congestion which was treated with sudafed for 5 days	Active
195928	5	White	Male	12/01/2013	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Strep Throat diagnosed at pcp and treated with oral antibiotic. Fully recovered. Family reported to study site at 18 month visit.	Placebo

195928	5	White	Male	08/25/2014	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Subject diagnosed with Upper Respiratory Infection at PCP visit on 25AUG2014. Treated at home with PRN albuterol nebulizer for 4 days.	Placebo
195928	7	White	Male	05/10/2016	Ocular/Visual	Watery eye (epiphora, tearing)	Primary	.	Not Expected	2	Probably not related	Watery eyes started 10MAY2016. Seen by PCP and Zyrtec started 15MAY2016.	Placebo
196502	14	White	Male	03/19/2014	Endocrine	Endocrine - Other (Specify in Event Details)	Primary	7	Expected	3	Definitely not related	participant taken to ER with complaints "upset stomach" and high glucose readings. Admitted and diagnosed with T1D and insulin therapy initiated	Active
197962	5	White	Male	11/09/2011	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Per dad's report - Subject taken to primary care provider on 09NOV2011 with symptoms of fever, cough, and nasal congestion. Primary care provider diagnosed subject with an upper respiratory tract infection. Subject was prescribed oral antibiotics and cough syrup and sent home. Symptoms resolved 13NOV2011.	Placebo
197962	6	White	Male	01/18/2012	Infection	Infection - Other (Specify in Event Details)	Primary	14	Not Expected	2	Definitely not related	Dad reports that on 18JAN2012 subject had swollen lymph nodes in neck, went to PCP 23JAN2012 and had a positive throat culture for strep. Started oral antibiotics 23JAN2012. Completely resolved 01FEB2012.	Placebo
197962	6	White	Male	09/30/2012	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Dad reports subject was diagnosed with an upper respiratory tract infection at pcp on 01OCT2012. Symptoms began 30SEP2012. Antibiotics prescribed by PCP. Symptoms resolved 04OCT2012 and	Placebo

												antibiotics were finished 10OCT2012.	
197962	7	White	Male	09/25/2013	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Puncture Wound- Subject stepped on nail that went through shoe and punctured bottom of right foot. Seen by pediatrician and given ibuprofen and prophylactic antibiotic.	Placebo
197962	10	White	Male	10/25/2016	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	13	Not Expected	2	Probably not related	Infected spider bite - seen by PCP and started on oral antibiotics x 2 wks. Quickly resolved.	Placebo
199045	9	White	Male	11/03/2014	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	On 11/3/14, participant was diagnosed with a peanut, tree nut, and sunflower seed allergy. They were prescribed an epi pen. The participant did not experience any serious problems before the diagnosis.	Placebo
199045	10	White	Male	07/13/2015	Infection	Infection - Other (Specify in Event Details)	Secondary	177	Not Expected	2	Definitely not related	On 7/13/2015, patient had pain in left ear canal and their PCP called it swimmers ear and placed the subject on ciprodex drops BID (Ciprofloxin 3 mg, with 1 mg dexamethosone). The ear did not get better, and pain persisted so his PCP changed the subject's antibiotic to bactrim 500 mg BID for 10 days. The ear pain and infection resolved by day 10. ********** On 7/13/2015, patient had pain in left ear canal and his PCP called it swimmers ear and placed him on ciprodex drops BID (Ciprofloxin 3 mg, with 1 mg dexamethosone). The ear did not get better, and pain persisted so his PCP changed his	Placebo

												antibiotic to bactrim 500 mg BID for 10 days. The ear pain and infection resolved by day 10. On Dec. 26th 2015, participant re-presented with severe pain in the right ear canal. 12/28/15 patient's parent brought him to his PCP, who lanced the legion in the ear in order to swab for culture. Patient was placed on Bactrim 500 mg BID for 10 days. Patient took Bactrim from 12/28/15 - 1/6/2016, when infection resolved. The culture came back positive for MRSA. While discussing with patient's mother she revealed two other skin infections that had not been reported previously. Filed here and in other report 2982. ********** On 7/13/2015, patient had pain in left ear canal and his PCP called it swimmers ear and placed him on ciprodex drops BID (Ciprofloxin 3 mg, with 1 mg dexamethosone). The ear did not get better, and pain persisted so his PCP changed his antibiotic to bactrim 500 mg BID for 10 days. The ear pain and infection resolved by day 10. On Dec. 26th 2015, participant re-presented with severe pain in the right ear canal. 12/28/15 patient's parent brought him to his PCP, who lanced the legion in the ear in order to swab for culture. Patient was placed on Bactrim 500 mg BID for 10 days. Patient took Bactrim from 12/28/15 - 1/6/2016, when	

												infection resolved. The culture came back positive for MRSA. While discussing with patient's mother she revealed two other skin infections that had not been reported previously. Filed here and in other report 2982.	
199045	10	White	Male	07/27/2015	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	On 7/27/15 patient discovered an infected area on the skin of the crevice of his buttocks. Patient went to the doctor and the site was swabbed and reported to be a staph infection. Started on Bactrim 500 mg BID. Site cleared completely by 8/5/15.	Placebo
199541	6	White	Female	05/10/2013	Musculoskeletal/Soft Tissue	Fracture	Primary	.	Not Expected	3	Definitely not related	On 5/10/13, participant fell at school and broke humerus in right arm. Went to ER. Underwent surgery and had 3 pins placed in humerus. Post surgery, arm was fitted with a soft cast and splint. They were admitted for 3 days due to severe swelling in the hand and arm. 5/16/13, participant is being fitted for a hard cast.	Active

199541	7	White	Female	02/25/2014	Endocrine	Thyroid function, low (hypothyroidism)	Primary	.	Not Expected	2	Definitely not related	Subject was seen by dermatologist for alopecia areata. He suspected Hashimoto't Thyroiditis in addition, and conducted lab tests.	Active
199618	11	White	Male	02/09/2016	Infection	Infection with unknown ANC	Primary	.	Not Expected	2	Probably not related	February 9th 2016 subject complained of a sore throat, no other symptoms, to mom. Subject was taken to the pediatricians on 2/11/16 where they did a rapid strep culture that was negative and mom stated that the doctor did not think subject had strep. On 2/13/16 the office called to tell mom that the culture that was sent for the strep came back positive. Started antibiotic on 2/13/16.	Placebo
199618	11	White	Male	03/07/2016	Infection	Infection with unknown ANC	Primary	12	Not Expected	2	Possibly related	Subject was at doctors for a recheck on recent strep infection. Was negative for strep and mono, but was diagnosed, per mom, "with some bacterial infection". Was started on antibiotics, mom did not remember then name of them (start 3/9th end 3/19). Symptoms were; "sore throat for over 24 hours, lots of mucus and very bad breath".	Placebo
199618	12	White	Male	01/13/2017	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Probably not related	Ottitis media with effusion, participant was placed on Antibiotic therapy for 10 days.	Placebo
200178	9	White	Female	02/14/2012	Musculoskeletal/Soft Tissue	Fracture	Primary	42	Not Expected	2	Definitely not related	9 year old participant fell and fractured left arm near wrist. Xrays performed, not displaced, casted without problem as outpatient. Discomfort managed with non narcotic analgesics.	Active

200178	10	White	Female	05/01/2012	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	4	Not Expected	1	Definitely not related	Participant had upper respiratory infection with rhinorrhea, no cough. Low grade temp x1 = 100.0 F. Event resolved in 4 days without sequelae.	Active
200178	10	White	Female	07/13/2012	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	1	Not Expected	1	Definitely not related	Participant had X1 day of non bloody vomiting and diarrhea. No fever. Possibly related to some spoiled food. Resolved spontaneously.	Active
200178	10	White	Female	09/30/2012	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	6	Not Expected	1	Definitely not related	Patient experienced mild pain in right elbow after competitive softball games on Sept. 30 and October 6. Denies swelling or limited ROM. Took 200 mg Ibuprofen with resolution of pain.	Active
200178	10	White	Female	12/07/2012	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Patient experienced a laceration to upper right knee from a fall on a rusty pipe at school . Participant taken to ER where the wonld was cleaned and 3 sutures where placed. Wound healed without complications. Sutures removed 12/17/12. Tetanus booster given on 12/10/12.	Active
200178	11	White	Female	12/26/2013	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	19	Not Expected	2	Definitely not related	Participant developed sore throat, hoarse voice, congested cough without wheezing or fever. No improvement after 2 weeks. Saw PMD, placed on Augmentin x 10 days. Symptoms improved and resolved after approx 7 days on antibiotic. Recovered without sequelae	Active
200178	12	White	Female	04/27/2014	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	10	Not Expected	2	Definitely not related	Pt. developed middle ear infection secondary to URI. Treated with Amoxicilin BID for	Active

												10 days. Symptoms resolved by end of antibiotic course	
200178	14	White	Female	05/04/2016	Musculoskeletal/Soft Tissue	Fracture	Primary	22	Not Expected	2	Definitely not related	Participant fractured middle finger of right hand playing basketball. Finger became swollen and bruised immediately. Saw orthopedic physician. Finger splinted for 3 weeks. Healed without sequelae.	Active
200258	14	White	Female	08/14/2015	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	1	Not Expected	3	Probably not related	Mother reported subject fainted before diarrhea/vomiting and fever. ER visit for IV fluids	Active
201622	7	Black/ African American	Male	02/24/2014	Pulmonary/ Upper Respiratory	Pneumonitis/pulmonary infiltrates	Primary	13	Not Expected	2	Definitely not related	Symptoms for 1 week, then diagnosed with pneumonia by X-ray in md office.	Active
202163	3	White	Male	06/29/2012	Surgery/Intra-Operative Injury	Intra-operative injury	Primary	0	Not Expected	2	Definitely not related	Outpatient biopsy surgery for diagnosis of celiac disease. Unrelated to the study.	Active
202163	5	White	Male	07/01/2014	Allergy/Immunology	Autoimmune reaction	Primary	.	Not Expected	2	Definitely not related	Diagnosed with celiac disease in the beginning of July 2014. Patient was unsure of exact date of diagnosis.	Active
205979	2	Black/ African American	Male	04/19/2012	Surgery/Intra-Operative Injury	Intra-operative Injury - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Patient had adenoidectomy and replacement of "ear tubes" - previously placed ear tubes were dislodged causing ear infections and adenoidectomy was also performed in hope if improving his inner ear problems	Placebo
206031	12	White	Male	09/22/2014	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Hand-foot-and-mouth disease with a fever of 103F with blisters around the mouth, hand and foot.	Active
206031	12	White	Male	03/21/2015	Infection	Infection with unknown ANC	Primary	12	Not Expected	2	Definitely not related	MOC reported symptoms of: stuffy nose, cough, no reports of a fever. Participant took 10	Active

												day course of amoxicillin 1 tab, TID, PO from 5/23/2015-4/2/2015	
206142	14	White	Female	12/10/2014	Pulmonary/ Upper Respiratory	Nasal cavity/paranasal sinus reactions	Primary	16	Not Expected	2	Definitely not related	Pulmonary/Upper respiratory_other: Sinusitis (unable to choose "other" for "type of event" above) Diagnosed with sinusitis at pcp, treated with methylprednisolone dosepak followed by oral antibiotic and flonase.	Placebo
206142	14	White	Female	07/17/2015	Infection	Infection with unknown ANC	Primary	3	Not Expected	2	Probably not related	vaginal candida infection 7/17/15 to 7/20/15 treated with oral diflucan 150 mg x 1 and 3 days of nystatin vaginal cream; resolved with treatment; no other symptoms suggestive of elevated glucose	Placebo
206943	7	White	Male	09/03/2013	Neurology	Cognitive disturbance	Primary	.	Not Expected	2	Definitely not related	New diagnosis of Attention Deficit Hyperactivity Disorder reported. Per mother's report, parents were notified by the school in late August 2013 that subject should be evaluated for potential ADHD. Mother reports that she had not noticed any changes in behavior at home. Subject was taken to their primary care provider on 03SEP2013 with a letter from the school. Subject was diagnosed with ADHD and stated on Concerta daily.	Active
207312	8	White	Female	12/02/2014	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	367	Not Expected	2	Definitely not related	Fever and vomiting, diagnosed as dehydration.	Placebo
207312	9	White	Female	03/10/2015	Syndromes	Flu-like syndrome	Primary	0	Not Expected	2	Definitely not related	Diagnosed as viral syndorme.	Placebo

207312	9	White	Female	08/01/2015	Pulmonary/ Upper Respiratory	Cough	Secondary	.	Not Expected	1	Definitely not related		Placebo
207312	9	White	Female	08/01/2015	Pulmonary/ Upper Respiratory	Cough	Primary	.	Not Expected	1	Definitely not related	Mother was suffering from pneumonia and called pediatrician when participant developed cough. MD prescribed antibiotics over the phone.	Placebo
207312	9	White	Female	01/29/2016	Infection	Infection - Other (Specify in Event Details)	Primary	8	Not Expected	2	Definitely not related	Sore throat and fever of 103.3 F; participant was taken to primary care physician who diagnosed her with right ear infection. Participant was prescribed Zithromax for 10 days. Mother also alternated Tylenol and Motrin for fever. Participant had recovered at time of study visit.	Placebo
207650	12	White & Asian	Male	09/30/2012	Musculoskeletal/Soft Tissue	Fracture	Primary	18	Not Expected	2	Definitely not related	On Sept. 30th /12, participant fell of a skateboard and landed on Right hand. Subject complained of pain, taken to the ER on Oct. 1st, 12; X-ray right arm done. On Oct. 3rd/ 12, participant was called and seen in the Fracture clinic. Participant had wrist fracture presented on the x-ray and right arm cast applied. On Oct. 18th, 12 a follow up Fracture clinic appointment- control x-ray done and as per subject's parent "everything was o.k." Right arm cast removed, no further treatment necessary.	Active
207650	14	White & Asian	Male	08/01/2014	Infection	Infection - Other (Specify in Event Details)	Primary	12	Not Expected	2	Definitely not related	Participant complaining of earache on Aug 1st while attending camp. Two days after earache started was taken to walk in clinic. Parent indicated that the participant was	Active

												diagnosed with an "ear infection". Antibiotics given Amoxicillin 500mg po X 10days. Participants activity was restricted due to the ear infection. Unable to swim.	
207650	14	White & Asian	Male	02/25/2015	Infection	Infection - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	Parent reports that on Feb 25th the participant had a fever. Temperature was not taken by a thermometer but parent stated that the participant felt warm. No flu like symptoms reported, no sore throat or cough or nasal congestion present. Parent stated that the participant felt "draggy". Participant missed one day of school and returned to school on Feb 27. Parent stated that the participant felt back to "normal" on Feb 27th in the evening.	Active
207653	11	White	Male	02/10/2014	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Positive strep throat at PCP 10FEB2014. Treated with oral antibiotics.	Placebo
207653	12	White	Male	07/15/2015	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	Subject was diagnosed with mild asthma by PCP. Well controlled, no acute attacks. Had been on inhalers prior for "environmental allergies" but had not been officially diagnosed with asthma until July 2015.	Placebo
207653	12	White	Male	08/03/2015	Infection	Infection with unknown ANC	Primary	7	Not Expected	2	Probably not related	diagnosed by pediatrician with sinus infection, received oral antibiotics, recovered	Placebo
208401	7	White	Female	03/14/2016	Infection	Infection - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	URI with fever of 104F, cough, sore throat	Placebo
208843	8	White	Male	02/14/2013	Infection	Infection with unknown ANC	Primary	11	Not Expected	2	Definitely not related	10 course of amoxicillin 1tsp TID QD PO from 2/15/2013-2/25/2013	Active

209027	13	White	Male	11/15/2013	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	10	Not Expected	1	Definitely not related	Cold	Active
209027	13	White	Male	03/02/2014	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	14	Not Expected	1	Definitely not related	cold	Active
209105	11	Unknown or Not Reported	Male	11/24/2015	Infection	Infection - Other (Specify in Event Details)	Primary	1	Expected	1	Definitely not related	General malaise as in non-specific viral illness	Active
209106	14	Unknown or Not Reported	Male	12/13/2015	Pulmonary/Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	2	Not Expected	1	Definitely not related	Mild common cold symptoms	
209452	7	White	Female	03/15/2016	Infection	Infection - Other (Specify in Event Details)	Primary	6	Not Expected	1	Definitely not related	Upper Respiratory Infection Symptoms	Active
209452	7	White	Female	03/21/2016	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	43	Not Expected	2	Definitely not related	Subject presented with right ear pain. Serous Otitis Media diagnosed and antibiotics given. This ear pain continued even after antibiotic treatment and so OTC flonase was instructed to be used for therapy which eventually event subsided.	Active
209452	7	White	Female	05/24/2016	Endocrine	Pancreatic endocrine: glucose intolerance	Primary	1	Expected	3	Definitely not related	Participant showed Glucose Intolerance at scheduled 43 month Visit. Upon completion of OGTT blood glucose was 361 ml/dl and so was admitted for new onset of Type 1 DM.	Active
210883	5	White & Asian	Male	01/01/2013	Gastrointestinal	Vomiting	Primary	1	Not Expected	2	Definitely not related	had between 3-5 episodes of vomiting on 1/1/2013 over a 24 hours period. No IV fluids required. Resolved on its own without sequelae.	Placebo
210883	7	White & Asian	Male	12/17/2014	Gastrointestinal	Vomiting	Primary	0	Not Expected	2	Definitely not related	Participant vomited 2xs in 24 hours, no meds or IVs indicated.	Placebo

210965	5	White	Female	03/10/2014	Infection	Infection with unknown ANC	Primary	.	Not Expected	2	Definitely not related	10 day Amoxicillin prescribed 9mL BID PO.	Placebo
210965	6	White	Female	06/19/2014	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	4	Not Expected	2	Definitely not related	Rash with fever 6/19-6/23/2014. Resoved spontaneously. Saw PCP and checked for strep, but results were negative. Given Motrin PRN.	Placebo
210965	6	White	Female	08/15/2014	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	2	Not Expected	2	Definitely not related	Fever lasted less than 24 hours. No IGV fluids, participant took children's ibuprofen QID PRN for two days	Placebo
210965	6	White	Female	03/17/2015	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	10	Not Expected	2	Definitely not related	Participant was given amoxicillin 800mg PO BID for 10 days	Placebo
210965	7	White	Female	04/14/2015	Gastrointestinal	Vomiting	Secondary	0	Not Expected	2	Definitely not related	Participant's mother reported participant vomiting 7 times at night with no additional symptoms within 24 hours. MOC said that participant was not taken to the hospital or given any medication.	Placebo
210965	7	White	Female	04/21/2015	Gastrointestinal	Vomiting	Primary	1	Not Expected	2	Definitely not related	Participant's mother reported participant vomiting 7 times at night with no additional symptoms within 24 hours. MOC said that participant was not taken to the hospital or given any medication. ********** Participant's mother reported participant vomiting 7 times at night with no additional symptoms within 24 hours. A slight fever of 100.3 was reported on the same date. MOC said that participant was not taken to the hospital or given any medication.	Placebo

210965	8	White	Female	06/13/2016	Musculoskeletal/Soft Tissue	Fracture	Primary	30	Not Expected	2	Definitely not related	broken ulna; subject had cast for 4 weeks	Placebo
211189	11	White	Male	06/26/2013	Allergy/Immunology	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Primary	0	Not Expected	1	Definitely not related	Since 9 months of age participant has displayed symptoms of allergies (stuffy nose, itchy eyes, sneezing) which has been treated by OTC allergy medications. Participant had formal allergy testing performed in June 2013 and specific allergens identified (egg whites, cow's milk, birch & oak trees, orchard grass, ragweed). Participant continues to take oral allergy medicine to relieve symptoms (Zyrtec).	Active
211441	5	White	Male	11/19/2013	Infection	Infection - Other (Specify in Event Details)	Primary	21	Not Expected	2	Definitely not related	Sinus infection reported by participant's mother at 3 month follow up visit. Participant began taking Amoxicillin BID for 10 days starting 11/20/13 however symptoms did not improve so participant began taking Augmentin BID for 10 days starting 12/1/13. At the conclusion of the 10 days of Augmentin BID symptoms fully resolved, 12/10/13. AE was assessed by study MD at 3 month follow up visit on 1/13/14.	Active
211441	5	White	Male	12/19/2013	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	3	Not Expected	1	Definitely not related	At 3 month follow up, participant's mother reports AE of stomach virus. The duration being 3 days over which time no medication for AE was taken. Participant's symptoms included vomiting and diarrhea, which fully resolved by the afternoon of the third day. AE was assessed by study MD.	Active

211441	5	White	Male	03/21/2014	Infection	Infection - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	Per mom, participant dx'd with Cox Sacki virius--blisters on hands and feet.	Active
211441	6	White	Male	08/26/2014	Surgery/Intra-Operative Injury	Intra-operative Injury - Other (Specify in Event Details)	Primary	14	Not Expected	2	Definitely not related	Participant had umbilical and epigastric hernia repairs performed through outpatient surgery. No hospitilization required.	Active
211441	7	White	Male	03/07/2016	Allergy/Immunology	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Primary	.	Not Expected	2	Probably not related	Seasonal allergy flare	Active
211441	8	White	Male	12/27/2016	Gastrointestinal	Vomiting	Primary	366	Not Expected	2	Probably not related	As per mom participant had stomach virus for one day no treatment required resolved in one day. Grade 2, not related per study team.	Active
211441	8	White	Male	01/28/2017	Pulmonary/Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	2	Not Expected	2	Probably not related	As per Mom participant had the flu from January 28th- 30th was given one dose of Tamiflu and symptoms resolved on January 30th. Grade 2 as per study team not related as per study team	Active
211676	15	White	Female	02/09/2015	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	3	Not Expected	1	Definitely not related	15 year old female had fever 101.0 F, body aches, cough from 09FEB2015 through 12FEB2015. Taken to health care provider and diagnosed with flu lile virus.	Active
212102	6	White	Female	05/29/2016	Ocular/Visual	Ocular surface disease	Primary	10	Not Expected	2	Definitely not related	Pt developed conjunctivitis on 5/29/16 that required topical medication for treatment	Active
212102	7	White	Female	01/26/2017	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	0	Not Expected	2	Definitely not related	Fever of 103F reported, needing tylenol to bring it down.	Active

212215	17	White	Female	06/03/2013	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Participant developed stress fractures in both tibias. Participant states she believes that the stress fractures are likely caused by her participation in volleyball. Treatment will involve physical therapy, a bone scan, and air casts or "boot" casts for immobilization, rest from playing volleyball and other sports for a period of time.	Active
212215	17	White	Female	10/10/2013	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Participant was playing volleyball and she tripped over a teammate's foot. She caught herself when she fell and twisted her right elbow. Participant sought care at Ortho On Call (outpatient care for orthopedic injuries). Participant was prescribed Hydrocodone (patient took 1 pill) and Voltarin for swelling. Participant states she is doing better and was able to play volleyball again after one week of rest.	Active
212215	18	White	Female	02/21/2014	Pain	Pain	Secondary	.	Not Expected	2	Definitely not related	Participant had 4 wisdom teeth removed on 2/21/14. Pain secondary to wisdom teeth removal. Participant was prescribed Hydrocodone (taken 2/21/14-2/23/14) and Ibuprofen 800mg (taken 2/23/14-2/27/14) for pain.	Active
212215	18	White	Female	02/21/2014	Gastrointestinal	Dental: teeth	Primary	.	Not Expected	2	Definitely not related	Participant had 4 wisdom teeth removed on 2/21/14.	Active
212215	19	White	Female	08/27/2015	Endocrine	Endocrine - Other (Specify in Event Details)	Primary	0	Not Expected	2	Probably not related	Participant experienced a presumed hypoglycemic event whwith symptoms of feeling sweaty, shaky, 'woozy' and was unable to walk back from class	Active

												at school. Participant was given apple juice and after consuming the juice, felt better.	
212260	4	White	Female	05/06/2015	Pulmonary/ Upper Respiratory	Pneumonitis/pulmonary infiltrates	Primary	4	Not Expected	2	Definitely not related	Parent reported pneumonia symptoms starting 5/6/15. Symptoms included fever, cough, fatigue. Diagnosed via auscultation, no chest x-ray. Patient prescribed amoxicillin. Symptoms resolved on 5/10/15.	Active
212260	4	White	Female	06/06/2015	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	On 6/6/15 subject's mother took subject to the emergency room for a fever of 102.5, vomiting, and nausea. Subject did not have a headache. Emergency room MD told mother subject had a virus and sent her home after evaluation. Subject took Ibuprofen and Tylenol as needed to treat symptoms. Symptoms resolved on 6/9/15.	Active
212554	4	White	Male	10/01/2013	Infection	Infection - Other (Specify in Event Details)	Primary	21	Not Expected	2	Definitely not related	Patient's mother reports he came down with a cold on October 1, but still was not well after 2.5 weeks at which point she took him to his pediatrician and he was found to have a sinus infection. He began treatment with 5-day course of azythromycin on October 18 and reports the infection responded appropriately.	Placebo
212554	4	White	Male	11/20/2013	Gastrointestinal	Vomiting	Primary	1	Not Expected	2	Definitely not related	Patient had 2-5 episodes of vomiting over 8 hour timeframe, however IV fluids were NOT required.	Placebo
212554	5	White	Male	12/30/2013	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia	Primary	1	Not Expected	2	Definitely not related	Patient received IPV, MMR and DTap immunizations and later that day developed a fever of 102.7 degrees.	Placebo

						is defined as ANC <1.0 x 10e9/L)							
212554	5	White	Male	02/25/2014	Infection	Infection with unknown ANC	Primary	6	Not Expected	2	Definitely not related	Participant's mother reported being diagnosed with a sinus infection after having cold symptoms for over a month. Participant was prescribed a 10 day course of cefdinir and completed 6 days of antibiotic treatment.	Placebo
212554	5	White	Male	06/11/2014	Gastrointestinal	Vomiting	Primary	1	Not Expected	2	Definitely not related	Mother reports participant experienced nausea with vomiting x6 in a 24-hour period. Participant treated with sprite and rest at home. No IV fluids or TPN were required. Event has completely resolved at this time.	Placebo
212554	6	White	Male	03/05/2015	Infection	Infection with unknown ANC	Primary	.	Not Expected	2	Definitely not related	Participant was diagnosed with mononucleosis by his primary care physician.	Placebo
212554	6	White	Male	03/13/2015	Endocrine	Pancreatic endocrine: glucose intolerance	Primary	15	Expected	3	Possibly related	6Y child subject presented to the hospital after recording a blood glucose level of HIGH on meter (>600). Two weeks ago they began experiencing lethargy and irritability - dx w/ mono 8 days ago. Approximately 5 days ago they were placed on Prednisolone, which they took 3 days. Two days ago had polyuria/polydipsia at which time mother tested their blood sugar on meter and got the "HIGH" reading. Participant's primary care provider advised mother to take them to PCH for admission. While inpatient, participant was diagnosed with	Placebo

												type 1 diabetes mellitus indicating insulin therapy. Participant was discharged the next day. ********** 6Y child subject presented to the hospital after recording a blood glucose level of HIGH on meter (>600). Two weeks ago they began experiencing lethargy and irritability - dx w/ mono 8 days ago. Approximately 5 days ago they were placed on Prednisolone, which they took 3 days. Two days ago had polyuria/polydipsia at which time mother tested their blood sugar on meter and got the "HIGH" reading. Participant's primary care provider advised mother to take them to PCH for admission. While inpatient, participant was diagnosed with type 1 diabetes mellitus indicating insulin therapy. Participant was discharged the next day.	
212600	17	White	Male	07/14/2015	Pain	Pain	Primary	6	Not Expected	2	Definitely not related	Subject underwent extraction of his wisdom teeth on approximately 7/14/2015. The pain which resulted from this procedure required 5-6 tablets of Vicodin per day for relief, through approximately 7/20/2015.	Active
213274	8	Unknown or Not Reported	Female	03/21/2015	Endocrine	Endocrine - Other (Specify in Event Details)	Primary	.	Expected	2	Definitely not related	Type 1 diabetes Clinical diagnosis. Had symptoms for 1 day. Diagnosed with diabetes without ketoacidosis, but was hospitalized for 4 Days. I was	Placebo

												informed of the event 31st of March 2015.	
213313	6	White	Male	02/26/2013	Infection	Infection with unknown ANC	Primary	12	Not Expected	2	Definitely not related	Low grade fever, stuffy nose, was prescribed 200mg amoxicillin for 10 days PO TID.	Active
213955	10	White	Male	07/15/2015	Pulmonary/ Upper Respiratory	Bronchospasm, wheezing	Primary	10	Not Expected	2	Probably not related	Reported having Bronchitis with some cough and fatigue	Placebo
214401	4	White	Female	03/19/2013	Infection	Infection - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	Diagnosed viral infection - viral pink eye and viral upper respiratory infection with bronchospasm	Placebo
214401	6	White	Female	02/18/2015	Infection	Infection with unknown ANC	Primary	9	Not Expected	2	Probably not related	Had cough that did not go away until PMD prescribed 5 day Z-Pack.	Placebo
214401	6	White	Female	11/18/2015	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	7	Not Expected	2	Probably not related	Subject fell off the jungle gym and hit her head. Family took subject to ED. No tests were done as the diagnosis was a mild concussion. Resolved without any issues.	Placebo
214401	6	White	Female	11/18/2015	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	32	Not Expected	1	Definitely not related	subject fell off jungle gym and hit her head. Parent took to ER which said mild concussion. No CT scan done.	Placebo
214401	7	White	Female	08/18/2016	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	Mom called 8/19/2016 to inform site that participant had a small rash on her legs 8/18/2016, which spread to her arms, hands and feet on 8/19/2016. The rash itched and mom gave her benedryl.	Placebo
214401	8	White	Female	04/01/2017	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	OLI saw optometrist on 4/1/2017 for red, irritated, and itchy eyes. She was told her reaction was a result of her allergy to grass and pollen. She was prescribed eye drops (Pazeo 0.7%) for relief.	Placebo

214401	8	White	Female	05/01/2017	Infection	Infection - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	OLI visited local urgent care for symptoms of bladder infection. Was prescribed Keflex (500mg, 3x/day for 7 days).	Placebo
214511	7	White	Female	03/27/2014	Neurology	Mood alteration	Primary	.	Not Expected	2	Definitely not related	Participant takes Lexapro 1/2 tsp for anxiety. Started taking September 2011 before enrolled into study. ********** Participant takes Lexapro 1/2 tsp for anxiety. Started taking September 2011 before enrolled into study.	Active
214511	9	White	Female	11/04/2016	Surgery/Intra-Operative Injury	Intra-operative injury	Primary	0	Not Expected	2	Definitely not related	baby tooth extraction; IV anesthesia indicated	Active
214522	10	White	Female	03/29/2014	Musculoskeletal/Soft Tissue	Fracture	Primary	44	Not Expected	2	Definitely not related	Subject was involved in an auto accident 29Mar2014, and reported it at study visit 04Apr2014. Post accident, subject had some difficulty walking, but no pain. Transported via ambulance to ER. Diagnosed with fracture of L2. Subject kept overnight in the hospital for precautionary reasons. Did not receive any medications while in the ER or hospital. Subject was placed in a removable back brace to immobilize the back; it may be removed for showering only, and subject must be sitting. Back brace must be worn for six weeks. Followed up with PCP 2 days post accident; no changes recommended for treatment. Subject will see neurologist once an appointment is made. Will return to school as scheduled (currently on spring	Active

												break). Subject reports feeling fine, no pain.	
214675	4	White	Male	09/21/2015	Constitutional Symptoms	Insomnia	Primary	21	Not Expected	2	Probably not related	Mother reported that subject had insomnia, start 9/21/15 that stopped 10/12/15 when she administered oral insulin/placebo in the morning instead of in the evening.	Placebo
214675	4	White	Male	01/11/2016	Infection	Infection - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	Participant had flu with strep throat, treated with Amoxicillin x 10 days	Placebo
214675	5	White	Male	11/11/2016	Lymphatics	Lymphatics - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	participant had tonsillectomy and adenoidectomy on 11/11/16	Placebo
215575	5	White	Male	01/06/2014	Allergy/Immunology	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Primary	.	Not Expected	2	Definitely not related	seasonal allergies	Active
215575	7	White	Male	02/13/2016	Infection	Infection - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	Molluscum Contagiosum start 2/13/16, moderate, location bilateral inner thighs, infected. Amoxicillin and Mupirocin ointment 2% topical started 2/14/16, ongoing	Active
215575	8	White	Male	12/23/2016	Infection	Infection - Other (Specify in Event Details)	Primary	5	Not Expected	2	Probably not related	Participant reported having the flu. Tamiflu taken BID x 5 days and Advil was taken PRN.	Active
216121	9	White	Female	01/24/2015	Infection	Infection - Other (Specify in Event Details)	Primary	1	Not Expected	2	Definitely not related	Subject had mild cold, mild fever (not measured), mild cough and nasal congestion on Jan. 24, 15. Did not seek medical attention. Would have missed 1 day of school.	Active

												Symptoms resolved on Jan. 25, 15.	
216122	6	White	Female	03/05/2014	Infection	Infection - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	Subject was sick on Mar. 5th: flu symptoms and vomiting, home from school; and on Mar.6th: fever only (not measured) home from school. Childrens Advil (100 mg.) PRN given. Did not seek medical attention. Symptoms resolved on Mar. 7th, 14.	
216122	6	White	Female	03/27/2014	Infection	Infection - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	Subject was sick on Mar. 27th: vomiting, home from school early; on Mar.28th: fever only (low grade); and on Mar. 29th low grade fever only in the evening. Childrens Advil (100 mg.) PRN given. Did not seek medical attention. Symptoms resolved on Mar. 30th, 14.	
216868	14	White	Male	08/08/2014	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	.	Not Expected	1	Definitely not related	Participant reported they have developed a notable coating to hair and scalp. Coating is not oily or greasy, but has a matt appearance that can not be removed when washing.	Placebo
216868	15	White	Male	01/03/2015	Gastrointestinal	Diarrhea	Primary	31	Not Expected	2	Possibly related	Participant reported having developed diarrhoea which was ongoing for several weeks. Participant was absent from school as result. GP visits with negative test results. Participants mother reported that the GP thought it was possibly virus. No treatment given.	Placebo
216868	15	White	Male	02/06/2015	Gastrointestinal	Diarrhea	Primary	.	Not Expected	2	Probably not related	Participant has continued to have episodes of Diarrheoa, has had several visits to GP with investigations. A referral has	Placebo

												been made to gastroenterology clinic.	
216868	17	White	Male	06/19/2017	Hemorrhage/Bleeding	Hemorrhage, pulmonary/upper respiratory	Primary	1	Not Expected	2	Definitely not related	Nose bleed episodes. 19/06/2017 and 20/06/2017. PI informaed, no treatment required.	Placebo
217024	4	White	Female	06/24/2013	Pulmonary/ Upper Respiratory	Nasal cavity/paranasal sinus reactions	Primary	4	Not Expected	2	Definitely not related	Participant had a stuffy nose from June 24 to June 28, 2013.	Active
217024	4	White	Female	07/26/2013	Pulmonary/ Upper Respiratory	Nasal cavity/paranasal sinus reactions	Primary	5	Not Expected	2	Definitely not related	Participant had a stuffy nose from July 26 to July 31, 2013.	Active
217024	6	White	Female	03/09/2015	Endocrine	Pancreatic endocrine: glucose intolerance	Primary	.	Expected	3	Probably not related	Participant presented for their 24-month TN07 visit and was found to have a 2-hour BG of 229 and 232 by YSI and an HbA1c of 8.1%. The subject was seen in our clinic on 9/MAR/2015 and diagnosed with type 1 diabetes and initiated insulin treatment.	Active
217665	11	White	Female	04/01/2015	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Congestion, sneezing, sore throat, fever 99.5 F. Was taken to pediatrician where participant was diagnosed with left ear infection. Treated with Amoxicillin for 5 days.	Placebo
218080	7	White	Male	07/15/2014	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	After pt repeated presented to pediatrician for cough, runny nose and sneezing, allergy testing was ordered. Pt tested positive for shellfish, shrimp, dust mite, and cockroach allergies. Pt then referred to see Dr. Lockey, who felt that the pt was probably not allergic to shrimp and felt asthma was a more appropriate culprit. Pt was diagnosed with asthma by allergist/immunologist on	Placebo

												15JUL2014, but is still undergoing further testing.	
218080	8	White	Male	11/25/2014	Infection	Infection - Other (Specify in Event Details)	Primary	5	Not Expected	1	Definitely not related		Placebo
218374	7	White	Female	01/30/2013	Gastrointestinal	Vomiting	Primary	0	Not Expected	1	Definitely not related	Subject vomitted at school one time.	Placebo
218374	7	White	Female	02/06/2013	Neurology	Personality/behavioral	Primary	.	Not Expected	2	Definitely not related	Mom states subject has increased anxiety when going to school and has struggled with school/class time activities.	Placebo
218374	7	White	Female	02/07/2013	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	87	Not Expected	2	Definitely not related	subject C/O pain in abdominal area	Placebo
219189	13	Unknown or Not Reported	Male	09/13/2014	Infection	Infection with unknown ANC	Primary	3	Not Expected	2	Probably not related	Participant/mother states having flu like symtoms about month ago (mother not sure about exact dates, but she believes was from September 13 to September 16, 2014). Symptoms lasted for 2- 3 days, only treated it with over the counter medications (Tylenol cold) to relieve symptomatology. Patient recovered without sequelae.	Placebo
219630	15	White	Female	12/30/2012	Infection	Infection with unknown ANC	Primary	9	Not Expected	2	Definitely not related	z-pack 250mg QD, PO	Placebo
219630	15	White	Female	01/30/2013	Infection	Infection - Other (Specify in Event Details)	Secondary	16	Not Expected	2	Definitely not related	Ear/sinus infection after wisdom teeth operation. Symptoms of ear pain.	Placebo
219630	16	White	Female	11/26/2013	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	386	Not Expected	2	Definitely not related	Participant had a fever 103-104. degrees F. Partcipant took cold medicine (dayquil , mucinex, ibuprofen, and tylenol.	Placebo

219630	17	White	Female	03/22/2015	Neurology	Myelitis	Primary	.	Not Expected	3	Probably not related	subject was admitted on 3/22/2015 for weakness and numbness (all 4 extremities), incontinence and diplopia. The brain MRI shows numerous demyelinating lesions (brain, spinal cord, right optic nerve). Subject started on high doses of steroids (Solumedrol 1000mg daily) x 5 days on the day of admission with a plan of switching to prednisone after that. Labs from LP are still pending, but the current most likely diagnosis is MS or NMO. They have been monitoring blood sugars, which have stayed in the 100s.	Placebo
220081	4	White	Male	06/13/2014	Infection	Infection - Other (Specify in Event Details)	Primary	17	Not Expected	2	Definitely not related	Subject was diagnosed with Lyme Disease. Received Amoxicillin for treatment.	Active
220081	5	White	Male	07/14/2015	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	1	Not Expected	2	Probably not related	Generalized rash - flat pink, on neck and chest.	Active
220081	5	White	Male	08/15/2015	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	Head cold	Active
220089	7	White	Male	05/08/2013	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	10	Not Expected	2	Probably not related		Placebo
220089	7	White	Male	05/21/2013	Pain	Pain	Primary	1	Not Expected	2	Probably not related	Child had Headache while at disney park. Mom tok child back to hotel for rest and medication (tylenol 10ml given, advil 12.5 ml given with relief)	Placebo
220089	7	White	Male	09/28/2013	Allergy/Immunology	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Primary	3	Not Expected	2	Probably not related	On Sept 28/13 Child woke up with seasonal allergy symptoms of nasal stuffiness and runny nose. This is usual for child at this time of year. Aerius 5ml od started on Sept 28/13 and	Placebo

												symptoms relieved by Oct 1/13. Aerius continues until season is over.	
220473	7	White	Male	06/10/2015	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	30	Not Expected	2	Definitely not related	Participant in TN07 had a tonsillectomy in on June 10, 2015 and was discharged the same day without any complications. ********** Participant in TN07 had a tonsillectomy in on June 10, 2015 and was discharged the same day without any complications. 1/28/16: Received medical records from outside hospital. Participant had a tonsillectomy with adenoidectomy on July 10, 2015. It was an outpatient procedure at Memorial Hospital, with no complications.	Placebo
221040	6	White	Male	02/09/2014	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	7	Not Expected	2	Definitely not related	ear infection. seven days of amoxicillin PO. 2/10/2014-2/16/2014	Active
221718	7	White	Male	07/15/2014	Endocrine	Pancreatic endocrine: glucose intolerance	Primary	5	Expected	3	Definitely not related	Hospitalization for new onset of diabetes	Placebo
223717	13	White	Male	09/18/2015	Sexual/Reproductive Function	Sexual/Reproductive Function - Other (Specify in Event Details)	Secondary	5	Not Expected	3	Definitely not related	Testicular torsion ********** Hydatid torsion	Placebo
223717	13	White	Male	09/19/2015	Gastrointestinal	Nausea	Primary	21	Not Expected	2	Possibly related	Nausea and vomiting commenced on 19 Sept 2015, three days after study drug commenced on 16 Sep15. Not eating -28 September and 3 October, so did not have study capsules on that day.	Placebo
223717	13	White	Male	12/03/2015	Dermatology/Skin	Urticaria (hives, welts, wheals)	Primary	14	Not Expected	3	Probably not related	Intermittent itchy rash - face, chest, anus. Impression mild viral cause or allergy related.	Placebo

												On antihistamines for seasonal allergic rhinitis at the time.	
224296	15	White	Male	02/17/2015	Musculoskeletal/Soft Tissue	Fracture	Secondary	64	Not Expected	2	Definitely not related	On 3 month Interim phone contact, when asked if any changes to health since last scheduled visit, client mentioned that they had fractured the left thumb during a ski trip on March break holiday. Client was seen at clinic at ski hill, then ER and a half slab splint placed on his thumb. A follow up with plastic surgery was scheduled six days later at which time a thumb spica cast was put on for one week. patient states it has healed well and no discomfort is remaining.	Active
224296	15	White	Male	03/11/2015	Gastrointestinal	Nausea	Secondary	0	Expected	1	Possibly related	The study participant came in for his six month OGTT. After the test was complete, he felt nauseated for 5-6 hours after. He did not vomit. He did not take any medication nor did it affect his daily routine. It resolved spontaneously.	Active
224296	16	White	Male	04/11/2016	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	17	Not Expected	2	Definitely not related	Participant reported not feeling well (earache and cough). Participant went to see a physician at a clinic and was diagnosed with pneumonia and a sinus infection. Participant was given oral antibiotics for 10 days. The participant missed approximately one week of school during the illness/recovery phase. The participant is now recovered and completing all normal activities of daily living. **********	Active

												Participant reported not feeling well (earache and cough). Participant went to see a physician at a clinic and was diagnosed with pneumonia. Participant was given oral antibiotics for 10 days. The participant missed approximately one week of school during the illness/recovery phase. The participant is now recovered and completing all normal activities of daily living.	
224296	16	White	Male	04/11/2016	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	17	Not Expected	2	Definitely not related	PARTICIPANT REPORTED NOT FEELING WELL (EARACHE AND COUGH); WAS SEEN BY A DOCTOR AND DIAGNOSED WITH A SINUS INFECTION. PARTICIPANT WAS GIVEN ORAL ANTIBIOTICS X 10 DAYS AND MISSED ONE WEEK OF SCHOOL DURING THE ILLNESS/RECOVERY PHASE. THE PARTICIPANT FULLY RECOVERED.	Active
224296	17	White	Male	02/03/2017	Neurology	Neurology - Other (Specify in Event Details)	Primary	8	Not Expected	2	Definitely not related	Head injury resulting in a concussion Participant was swimming and swam head first into the wall of the pool. Did not loose consciouness. Could remember where they lived but did not know how to get there. This confusion lasted from the time of the event at 1945, until they went to bed for the day at 2300. They did not seek medical care and symptoms of confusion had resolved the following day. The participant stayed off of work and home	Active

												from school until February 11, 2017.	
227373	4	White	Male	09/02/2013	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	1	Not Expected	2	Definitely not related	Runny nose - Rhinorrhea	Active
227916	12	Unknown or Not Reported	Male	07/15/2013	Pain	Pain	Primary	0	Not Expected	1	Definitely not related	Headache, slight fever (possible, not measured), ache in body one day. The day after well again.	Active
227916	12	Unknown or Not Reported	Male	11/07/2013	Gastrointestinal	Constipation	Primary	0	Not Expected	1	Definitely not related	Constipation and stomache ache during one day. Went to the emergency unit, had medication for the constipation and was thereafter well.	Active
229387	8	Unknown or Not Reported	Male	03/13/2015	Endocrine	Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Secondary	.	Not Expected	3	Definitely not related	Elevated T4 of 20.7 (5.6-14.9), T3 uptake 41% (nml 22-35), FT4 8.5 (1.4-3.8). Noted to have goiter. Dx with hyperthyroidism. Started on Methimazole 5 mg oral tablet twice a day. ********** Elevated T4 of 20.7 (5.6-14.9), T3 uptake 41% (nml 22-35), FT4 8.5 (1.4-3.8). Noted to have goiter. Dx with hyperthyroidism. Started on Methimazole 5 mg oral tablet twice a day. Pt hospitalized for one night for a thyroidectomy on 8/19/16 for diagnosis of Graves Disease diagnosed on 3/13/2015. Despite taking Methimazole, it was determined that surgery was recommended. Tolerated surgery well, suture line healed well, procedure well tolerated without complications.	Placebo

												Participant is no longer taking Methimazole and is now on Synthroid 50mcg po once a day. Surgical procedure resolved 9/17/16, event is unexpected and not related as per study team. Hormone replacement therapy ongoing. ********** Elevated T4 of 20.7 (5.6-14.9), T3 uptake 41% (nml 22-35), FT4 8.5 (1.4-3.8). Noted to have goiter. Dx with hyperthyroidism. Started on Methimazole 5 mg oral tablet twice a day. Pt hospitalized for one night for a thyroidectomy on 8/19/16 for diagnosis of Graves Disease diagnosed on 3/13/2015. Despite taking Methimazole, it was determined that surgery was recommended. Tolerated surgery well, suture line healed well, procedure well tolerated without complications. Participant is no longer taking Methimazole and is now on Synthroid 50mcg po once a day. Surgical procedure resolved 9/17/16, event is unexpected and not related as per study team. Hormone replacement therapy ongoing. error in charting, correction: surgical procedure resolved on 8/19/16	
229552	6	White	Male	12/27/2015	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	strep throat with sore throat, nausea, and fever 102F; prescribed amoxicillin for 10 days BID by PCP	Active
229552	6	White	Male	01/14/2016	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	strep throat with sore throat, nausea and fever 102F,	Active

												prescribed amoxicillin for 10 days BID by PCP	
229729	15	White	Female	02/07/2015	Infection	Infection - Other (Specify in Event Details)	Primary	11	Not Expected	2	Definitely not related	Diagnosed with Strep Throat at PCP office. Treated with oral antibiotic, started on 09FEB2015.	Active
229729	16	White	Female	07/18/2016	Infection	Infection - Other (Specify in Event Details)	Primary	11	Not Expected	2	Probably not related	Seen by PCP on 20JUL2016 for sinus infection, oral antibiotic prescribed x 10 days.	Active
229729	17	White	Female	02/14/2017	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Seen by PCP on 14FEB2017 for symptoms of upper respiratory tract infection, tested positive for influenza. Prescribed Tamiflu. Symptoms fully resolved prior to stopping Tamiflu on 18FEB2017.	Active
230382	13	White	Female	12/01/2014	Hemorrhage/Bleeding	Hemorrhage, GU	Primary	.	Not Expected	2	Definitely not related	Menorrhagia first reported to site at Month 36 Visit, after subject started on oral contraceptives as therapy (on 12Jun2016). Subject was uncertain of start date, but estimated it had been present for approximately a year. Sub-investigator who examined subject today found a reference in participant binder to heavy flow with subject's first period (01Dec2014), so she designated that as the start date.	Active
230382	14	White	Female	08/23/2015	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	10	Not Expected	3	Definitely not related	Subject began to experience foot pain on 8/23/2015. When this did not resolve, subject saw an MD, and x-ray revealed a one-inch piece of an embroidery-type needle was embedded in subject's foot. Outpatient surgery was scheduled and the needle removed without difficulty. There were no signs of	Active

												infection, and subject returned to school the next day.	
230382	15	White	Female	04/15/2016	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	At Month 36 Visit on 22Jul2016, subject reported episode of strep throat, which was treated with amoxicillin.	Active
230382	15	White	Female	06/24/2016	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	Subject was found to have a dark mole with irregular borders on the left upper chest/shoulder area, so removal was recommended. Pathology revealed it was a benign nevus.	Active
233459	9	White	Female	09/06/2016	Endocrine	Adrenal insufficiency	Primary	3	Not Expected	3	Definitely not related	Patient admitted to hospital with a one week history of abdominal pain, weakness, dizziness and vomiting, investigations performed, which identified cortisol level at 06:00hrs, 28nmol/L (low) and ACTH at 06:00hrs, 3300 ng/L (high). Treatment plan implemented - oral hydrocortisone 3 times per day and oral fludrocotisone 2 times per day. Participant discharged from hospital on 9 September 2016. Patient for review in endocrinology clinic in approximately 2 weeks from date of discharge.	Active
233839	7	Unknown or Not Reported	Male	10/09/2015	Pulmonary/ Upper Respiratory	Edema, larynx	Primary	2	Not Expected	2	Definitely not related	He had Croup diagnosed on 10/9/15 with low grade fever, hoarse voice and cough. Put on Prednisolone 100mg for three days.	Placebo
234791	9	White	Female	01/27/2016	Musculoskeletal/Soft Tissue	Fracture	Primary	42	Not Expected	2	Definitely not related	Participant was skiing with school and fell twice. First time walking near lodge and slipped and landed on outstreched Right arm. Second time	Active

												participant was skiing and tried to stop in process and fell again on right arm.	
235033	4	White	Male	02/11/2014	Infection	Infection - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	Subject was not feeling well on Feb. 11th. and Feb.12th; as per participants parent had a mild cold with low- grade fever (not measured) and runny nose. Childrens Tylenol PRN given. Missed 2 days of kindergarten - Feb. 11th and Feb. 12th. / 14. Symptoms resolved on Feb. 13th. / 14.	Placebo
235033	5	White	Male	02/10/2015	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	On Feb. 10, 15 subject was sick with vomiting X4, diarrhea X4, and fever (not measured). Given Children's Tylenol PRN and Gravol kids PRN. On Feb. 11 was feeling better; missed 2 days of school Feb. 10 and 11. Symptoms resolved on Feb. 12, 15.	Placebo
235033	5	White	Male	07/08/2015	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	Subject was sick, had fever 38.3 C on Jul. 8th, 15. Childrens Advil PRN given. On Jul. 9th, 15 had low grade fever, no meds given. Symptoms resolved on Jul. 10th, 15. As per subjects parent: symptoms interfered with subjects regular ADLs and would have missed two days of school.	Placebo
235033	6	White	Male	05/11/2016	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	1	Not Expected	2	Definitely not related	Subject had low grade fever (not measured) on May 11th, 16; no other symptoms present, did not seek medical attention. Children's Tylenol PRN X 1 given. Missed one day from school. Back to normal on May 12th, 16.	Placebo

235033	6	White	Male	05/22/2016	Gastrointestinal	Diarrhea	Primary	2	Not Expected	2	Definitely not related	Subject was sick on May 22nd and 23rd., 16. Had diarrhea X 5, no meds given, did not seek medical attention, back to normal on May 24th., 16. Would have missed one day of school May 23rd. 16 (stat holiday).	Placebo
235303	5	White	Male	04/21/2015	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	5	Not Expected	2	Probably not related	On April 21, 2015 participant was taken to the Emergency Room for coughing, wheezing and shortness of breath. As per parent's description participant was treated with two breathing treatments (aerosol) and was discharged on the same day with a possible diagnosis of Asthma vs Allergies , but not confirmed. No previous history of Asthma before this visit. Also, the following meds were prescribed : -Prednisolone 6.7 ml 15 mg/5ml for 5 days - Ventolin(albuterol) HFA 90 mcg inhaler 4 puffs every 4 hours for 2 days. Parent states he is doing well with no symptoms as April 26, 2015.	Placebo

235303	5	White	Male	04/27/2015	Endocrine	Endocrine - Other (Specify in Event Details)	Primary	.	Expected	2	Probably not related	Description: On April 27, 2015 at dinner time, participant was complaining of increased thirst. Parent decided to check their blood glucose (finger stick) since the subject was taking prednisolone for the past 5 days(for asthma like symptoms - see previous adverse event) and knew that prednisolone could elevate blood glucose values. The Finger stick blood glucose result was 369 mg/dL; therefore participant was taken to the emergency room where they were worked up for possible diagnosis of Type 1 diabetes. As per phone conversation with doctors at the hospital and parent, participant was admitted to the hospital with two Blood glucose results of 369 mg/dl and 415 mg/dl, a hemoglobin A1C of 6 % and no ketones. Participant was started on 6 units of Lantus and some Novolog at the time of the admission (4/27/15). Participant's father states the subject has not received any short acting insulin on 4/28/15 since they have been dealing with 3 - 4 hypoglycemics events during the day, they were only given Lantus 3 units at bedtime on 4/28/15. As per phone conversation today 4/29/15 , participant's father reports that the subject will be discharged today from the hospital, and was adviced to give them 1 unit of Lantus at	Placebo

												bedtime. The endocrinologist told the parent that he believes that prednisolone played a role in increasing the blood glucose, but given the fact that the subject has history of positive autoantibodies, they feel the subject is developing type 1 diabetes. They also ordered auto antibodies but will take two weeks to get their results back.	
236322	12	White	Male	04/15/2017	Pulmonary/ Upper Respiratory	FEV(1)	Primary	0	Not Expected	1	Definitely not related	Fever, most probably viral aetiology	Placebo
236509	4	White	Male	12/20/2014	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Participant's pediatrician diagnosed him with croup. He was treated with a single "steroid pill" in office "to help open up his lungs to help him breathe."	Placebo
236509	5	White	Male	11/23/2015	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Subject started symptoms of upper respiratory infection on 11/16/15, took ibuprofen and children's cough syrup. On 11/23 parent took subject to doctor and subject diagnosed with strep pharyngitis. Subject took amoxicillin from 11/23/15 to 12/2/15 and strep pharyngitis was resolved on 12/2/15.	Placebo
236554	17	White	Male	03/04/2015	Gastrointestinal	Vomiting	Primary	2	Not Expected	2	Definitely not related	Vomiting illness for 3 days. Vomiting up to 5 times a day in 24hours. Oral rehydration at home. Recovered completly. Other members of the family had the same illness at the	Placebo

												same time. Study drug missed for 3 days 04.03.15-06.03.15.	
236554	17	White	Male	03/25/2015	Dermatology/Skin	Rash: acne/acneiform	Primary	.	Not Expected	2	Definitely not related	Pre existing problem - acne on back and shoulders. This has however been with no reslove for may years. Therefore participant attended GP. Given new medication by GP - Lymecycline 408 mg daily dose. Currently ongoing. Medications CRF updated.	Placebo
236744	3	White	Male	10/01/2013	Lymphatics	Lymphatics - Other (Specify in Event Details)	Primary	14	Not Expected	2	Definitely not related	Adenoid enlargement	Active
236744	6	White	Male	11/15/2015	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	30	Not Expected	2	Probably not related	Headaches, unknown cause	Active
237034	3	White	Female	04/02/2014	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	2	Not Expected	2	Definitely not related	Subject had intense ear pain and fever (no drainage). Diagnosed with middle ear infection. Started amoxicillin 2/2/14 and completed medication course on 2/12/14. Pain and fever subsided on 2/4/14. ********** Subject had intense ear pain and fever (no drainage). Diagnosed with middle ear infection. Started amoxicillin 4/2/14 and completed medication course on 4/12/14. Pain and fever subsided on 4/4/14.	Placebo
237034	4	White	Female	01/16/2015	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	3	Not Expected	2	Definitely not related	Subject started with intense left ear pain and low grade fever (no drainage) on January 16. Diagnosed with left middle ear infection 1/17/15 and took	Placebo

												amoxicillin 1/17-1/27/15. Pain and fever subsided on 1/19/15.	
237034	4	White	Female	03/30/2015	Infection	Infection - Other (Specify in Event Details)	Primary	1	Not Expected	2	Definitely not related	Subject started with sore throat and fever. Diagnosed with strep throat.	Placebo
237435	4	White	Female	10/13/2013	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	11	Not Expected	2	Definitely not related	Rash on back	Placebo
237435	4	White	Female	10/23/2013	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	13	Not Expected	2	Definitely not related	Pityriasis rosea on trunk Used con med Econazole	Placebo
237435	4	White	Female	11/15/2013	Infection	Infection - Other (Specify in Event Details)	Primary	19	Not Expected	2	Definitely not related	Sinus Infection ********** Upper Respiratory Infection	Placebo
237435	4	White	Female	12/03/2013	Infection	Infection - Other (Specify in Event Details)	Primary	8	Not Expected	2	Definitely not related	Sinus infection	Placebo
237435	4	White	Female	12/13/2013	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Upper respiratory infection	Placebo
237435	4	White	Female	12/18/2013	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Bilateral otitis media	Placebo
237435	4	White	Female	12/29/2013	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Sinus infection	Placebo
237435	4	White	Female	01/08/2014	Infection	Infection - Other (Specify in Event Details)	Primary	22	Not Expected	2	Definitely not related	Sinus infection	Placebo
237435	4	White	Female	01/14/2014	Pulmonary/ Upper Respiratory	Cough	Primary	3	Not Expected	1	Definitely related		Placebo
237435	4	White	Female	01/15/2014	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	15	Not Expected	2	Definitely not related	Unilateral, parent does not recall which ear was involved	Placebo
237435	4	White	Female	03/06/2014	Auditory/Ear	Otitis, middle ear (non-infectious)	Primary	17	Not Expected	2	Definitely not related	Right ear	Placebo
237435	4	White	Female	03/11/2014	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other	Primary	3	Not Expected	2	Definitely not related	Viral Upper Respiratory Infection	Placebo

						(Specify in Event Details)							
237435	4	White	Female	04/03/2014	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	viral upper respiratory infection	Placebo
237435	4	White	Female	08/25/2014	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Viral Upper respiratory infection	Placebo
237435	5	White	Female	11/03/2014	Infection	Infection - Other (Specify in Event Details)	Primary	48	Not Expected	2	Definitely not related	Ringworm	Placebo
237435	5	White	Female	11/10/2014	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	30	Not Expected	2	Definitely not related	Intermittent stomach aches	Placebo
237435	5	White	Female	12/08/2014	Infection	Infection - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	Viral Upper respiratory infection	Placebo
237435	5	White	Female	12/21/2014	Infection	Infection - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	Viral Upper Respiratory Infection	Placebo
237435	5	White	Female	01/17/2015	Infection	Infection - Other (Specify in Event Details)	Primary	16	Not Expected	2	Definitely not related	Viral Upper Respiratory Infection	Placebo
237435	5	White	Female	01/18/2015	Infection	Infection - Other (Specify in Event Details)	Primary	36	Not Expected	2	Definitely not related	Ringworm right leg	Placebo
237435	5	White	Female	03/01/2015	Infection	Infection - Other (Specify in Event Details)	Primary	17	Not Expected	2	Definitely not related	Ringworm left neck	Placebo
237435	5	White	Female	03/31/2015	Infection	Infection - Other (Specify in Event Details)	Primary	12	Not Expected	2	Definitely not related	Viral Upper Respiratory Infection	Placebo
237435	5	White	Female	05/07/2015	Infection	Infection - Other (Specify in Event Details)	Primary	15	Not Expected	2	Definitely not related	Cold Virus	Placebo
237435	5	White	Female	05/25/2015	Pulmonary/ Upper Respiratory	Cough	Primary	14	Not Expected	2	Definitely not related	Coughing presumed to be from post-nasal drip, did not require narcotics, but required a course of prednisone.	Placebo

237435	5	White	Female	06/02/2015	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	Itchy rash bilateral arms and legs	Placebo
237435	5	White	Female	08/13/2015	Infection	Infection - Other (Specify in Event Details)	Primary	12	Not Expected	2	Definitely not related	Viral cold	Placebo
237435	6	White	Female	09/26/2015	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Cold virus	Placebo
237435	6	White	Female	10/14/2015	Infection	Infection - Other (Specify in Event Details)	Primary	89	Not Expected	2	Definitely not related	Oral Canker Sores	Placebo
237435	6	White	Female	12/12/2015	Infection	Infection - Other (Specify in Event Details)	Primary	12	Not Expected	2	Definitely not related	head and chest cold	Placebo
237435	6	White	Female	01/14/2016	Infection	Infection - Other (Specify in Event Details)	Primary	18	Not Expected	2	Definitely not related	Head and Chest Cold	Placebo
237435	6	White	Female	02/09/2016	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Conjunctivitis left eye	Placebo
237435	6	White	Female	03/01/2016	Infection	Infection - Other (Specify in Event Details)	Primary	14	Not Expected	2	Definitely not related	Chest cold	Placebo
237435	6	White	Female	03/15/2016	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Sinusitis	Placebo
237435	6	White	Female	03/29/2016	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	19	Not Expected	2	Definitely not related	laceration to forehead	Placebo
237435	6	White	Female	04/17/2016	Infection	Infection - Other (Specify in Event Details)	Primary	34	Not Expected	2	Definitely not related	Upper respiratory infection	Placebo
237435	7	White	Female	11/01/2016	Pulmonary/Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	21	Not Expected	2	Definitely not related	Cold virus	Placebo
237435	7	White	Female	11/12/2016	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	Eczema	Placebo

237435	7	White	Female	11/29/2016	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	6	Not Expected	2	Probably not related	Cough related to sinus drainage	Placebo
237435	7	White	Female	01/05/2017	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	0	Not Expected	2	Probably not related	cough due to drainage	Placebo
237435	7	White	Female	01/21/2017	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	4	Not Expected	2	Probably not related	cough	Placebo
237435	7	White	Female	01/21/2017	Neurology	Neurology - Other (Specify in Event Details)	Primary	0	Not Expected	2	Probably not related	Headache	Placebo
237435	7	White	Female	03/03/2017	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	0	Not Expected	2	Probably not related	Sore throat	Placebo
237435	7	White	Female	03/05/2017	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	0	Not Expected	2	Probably not related	Rash on right arm and bilateral legs	Placebo
237435	7	White	Female	03/05/2017	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	2	Not Expected	2	Probably not related	Cold virus	Placebo
237435	7	White	Female	04/17/2017	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	1	Not Expected	2	Probably not related	Cough with sinus drainage	Placebo
237435	7	White	Female	04/24/2017	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	8	Not Expected	2	Probably not related	Cold virus with cough and sore throat	Placebo
237435	7	White	Female	05/28/2017	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	6	Not Expected	2	Probably not related	Cold virus with cough	Placebo
238533	15	White	Male	09/01/2013	Infection	Infection - Other (Specify in Event Details)	Primary	32	Not Expected	2	Definitely not related	Participant's mother reports Left Great toe nail infection that started 9/1/13. Participant began taking clindamycin 300	Active

												mg BID starting 9/19/13, however due to the medication being ineffective the participant stopped the clindamycin 9/24/13 and began taking Levofloxacin 500 mg QD starting 9/25/13 until 10/3/13. Participant also took Tylenol with codeine PRN for pain.	
238533	15	White	Male	09/10/2013	Pain	Pain - Other (Specify in Event Details)	Primary	8	Not Expected	2	Definitely not related	Participant's mother reports study subject was experiencing Left ear pain beginning 9/10/13, for which participant took pseudoephedrine hydrochloride 120 mg QD from 9/15/13-9/18/13.	Active
238533	15	White	Male	10/03/2013	Pulmonary/ Upper Respiratory	Cough	Primary	25	Not Expected	2	Definitely not related	Participant's mother reports study subject had a cough from 10/3/13 until 10/28/13. The cough was initially treated with over the counter medication, Triaminic 2 teaspons QD on 10/1/13 and Delsym 10 mL QD on 10/2/13. Participant then began taking prednisone QD from 10/3/13 to 10/7/13, however as cough persisted participant began taking Dymista as per allergist's reccomendation.	Active
238533	15	White	Male	12/17/2013	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	Sinus infection-Treated with Augmentin 500mg BID x 7 days.	Active
238533	15	White	Male	01/13/2014	Pulmonary/ Upper Respiratory	Cough	Primary	2	Not Expected	1	Definitely not related	Cough x 2 days. Treated with Dimetapp.	Active
238533	15	White	Male	01/30/2014	Pain	Pain - Other (Specify in Event Details)	Primary	1	Not Expected	2	Probably not related	Participant has a history of headaches however on 30/JAN/2014 the participant experienced an exacebation and was diagnosed outpatient with	Active

												migrane. The participant was given and began taking migravent as needed for the migrane.	
238533	15	White	Male	03/03/2014	Infection	Infection - Other (Specify in Event Details)	Primary	6	Not Expected	2	Definitely not related	Influenza treated with Tamiflu x 5 days.	Active
238533	15	White	Male	03/10/2014	Infection	Infection - Other (Specify in Event Details)	Primary	63	Not Expected	2	Definitely not related	Norovirus. Diarrhea and vomiting x 3 days.	Active
238533	16	White	Male	05/10/2014	Infection	Infection - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	Participant's mother reports that the study participant has had multiple episodes of vomitting and diarrhea as a result of a norovirus infection. The participant did not take any medication for their symptoms.	Active
238533	16	White	Male	11/01/2014	Neurology	Neurology - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Participant reports being diagnosed with social anxiety disorder by PMD on 11/1/14. Participant is being treated with lexapro and following up with PMD.	Active
238533	16	White	Male	01/20/2015	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Participant reports a sinus infection for which their PMD prescribed cefdinir 300 mg.	Active
238533	16	White	Male	03/04/2015	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	12	Not Expected	2	Definitely not related	Participant reports sinus infection which was initially treated with Amoxicillin for 3 days, however per PMD participant switched to Augmentin for the duration of treatment.	Active
238533	16	White	Male	04/08/2015	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	Neck spasms. Grade 2, Not related as per study team. Started on 4/8/2015. Resolved in 1 day. Treated with Diazepam 2mg BID for 1 day.	Active
238533	16	White	Male	04/08/2015	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other	Primary	0	Not Expected	2	Definitely not related	Participant reported Neck spasms for which he took Diazepam 2mg BID for 1 day.	Active

						(Specify in Event Details)						Grade 2, not related per study team. started on 4/8/2015 and stopped on 4/8/2015.	
238533	17	White	Male	07/23/2015	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Participant reported an upper respiratory viral infection. Grade 2. Not related per study team. Started on 7/23/2015 and stopped on 7/28/2015. Treated with zpack QD for 5 days and pro-air inhaler 90 mcg as needed.	Active
238533	17	White	Male	02/01/2016	Infection	Infection - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	R foot with ingrown toenail infection, grade 2, not related per study team, oral antibx started 2/1/16, topical cream started 4/21/16, ongoing	Active
238533	18	White	Male	08/11/2016	Gastrointestinal	Dental: teeth	Primary	0	Not Expected	2	Definitely not related	Wisdom teeth extraction, Amoxicillin prescribed	Active
238533	18	White	Male	08/13/2016	Infection	Infection - Other (Specify in Event Details)	Primary	11	Not Expected	2	Definitely not related	Ingrown toenail extraction for infection to bilateral great toes, grade 2, Amoxicillin prescribed.	Active
238841	8	White	Male	04/25/2016	Infection	Infection - Other (Specify in Event Details)	Primary	6	Not Expected	2	Definitely not related	URI with otitis media; symptoms included congestion, fever 102F, ear drum rupture; treated with amoxicillin for 7 days	Placebo
239046	20	White	Female	11/25/2016	Dermatology/Skin	Nail changes	Primary	3	Not Expected	2	Definitely not related	Participant attended her general practitioner on the 25/11/2016 to have her ingrown L big toe nail surgically treated under local anaesthesia. No antibiotics or other medications administered during this procedure. Dressing insitu.	Placebo
239945	8	White	Male	08/21/2014	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Sinusitis	Placebo
239945	8	White	Male	10/03/2014	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Definitely not related	Sinusitis	Placebo

239945	9	White	Male	11/20/2014	Infection	Infection - Other (Specify in Event Details)	Primary	6	Not Expected	2	Definitely not related	Bronchitis	Placebo
239945	9	White	Male	09/01/2015	Infection	Infection - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Combined sinus infection and tonsillitis	Placebo
241237	10	White	Female	04/08/2014	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	Seasonal allergies	Placebo
241237	10	White	Female	08/07/2014	Musculoskeletal/Soft Tissue	Extremity-upper (function)	Primary	.	Not Expected	1	Definitely not related	The subject got pushed and fell, putting out their hand to break the fall. The subject badly bruised their right thumb.	Placebo
241237	10	White	Female	10/29/2014	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Strep throat	Placebo
241843	10	White	Female	11/03/2014	Neurology	Neurology - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	11/3/14 participant walked into a wall at school resulting in a cut "barely" under eyebrow and a mild concussion. Went to ER that day and was prescribed Ondansetron HCl 4mg as needed for nausea. Participant has taken 3 doses and on the day of reporting (11/5/14) was doing better.	Active
241843	13	White	Female	04/12/2017	Gastrointestinal	Vomiting	Primary	2	Not Expected	2	Definitely not related	Mother reports participant woke up with a head ache and nausea this morning 4/12/17. Progressed to vomiting. Took to physician who prescribed Zofran dissolving tablets q8hrs prn N&V. At home is staying hydrated with sips of Gatorade after taking Zofran.	Active
242383	6	White	Male	10/17/2014	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	97	Not Expected	2	Definitely not related	Tip of right middle finger almost cut off by garden shears at level of mid-nail. Taken to ER where hand surgeon stitched tip back on. Bone broken, nail damaged, finger placed in splint. On 10	Active

												day course of antibiotic, follow-up with MD planned.	
242383	7	White	Male	11/25/2015	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	30	Not Expected	2	Definitely not related	Scabies. Entire family had scabies, symptoms started 11/25/15, saw MD on 11/27/15. Needed to apply Permethrin cream q10 days if needed. Applied 3x before scabies went away.	Active
242507	3	White	Female	12/29/2013	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	low grade fever, two episodes of diarrhea, decreased appetite, but able to take study medication during this time	Placebo
242507	3	White	Female	01/20/2014	Renal/Genitourinary	Renal/Genitourinary - Other (Specify in Event Details)	Primary	11	Not Expected	2	Definitely not related	urinary tract infection, treated with antibiotic for 10 days	Placebo
242507	3	White	Female	01/20/2014	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	5	Not Expected	3	Definitely not related	had viral illness with temperature spike to 105 degrees with some diarrhea. Flu screen at PCP office negative. Received Tamiflu anyway. Recovered completely.	Placebo
242507	4	White	Female	10/17/2014	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	2	Not Expected	1	Definitely not related	Had fever up to 101 degrees on 10/17-10/19/14 following well child vaccinations. Given Tylenol 6.8ml QID for 8 doses. Resolved spontaneously	Placebo
242507	4	White	Female	10/22/2014	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	7	Not Expected	2	Definitely not related	had nasal congestion for 8 days, treated with Allegra 5 ml QHS. Resolved spontaneously	Placebo
242507	4	White	Female	11/14/2014	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	6	Not Expected	2	Definitely not related	Had congestion related to "hayfever/allergies". No fever. Gave Zyrtec.	Placebo
242507	4	White	Female	07/06/2015	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	headache, took Ibuprofen for two days	Placebo

242507	4	White	Female	07/07/2015	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	strep pharyngitis, no fever, started on antibiotic	Placebo
242507	4	White	Female	07/07/2015	Auditory/Ear	Auditory/Ear - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	acute right otitis media	Placebo
242507	5	White	Female	12/22/2015	Constitutional Symptoms	Constitutional Symptoms - Other (Specify in Event Details)	Primary	2	Not Expected	2	Definitely not related	viral illness with fever up to 102 degrees, strep screen negative. Treated with Motrin, no antibiotics	Placebo
242507	6	White	Female	02/11/2017	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	4	Not Expected	2	Definitely not related	viral illness with fever up to 103F, worked up by PCP, negative for flu, strep, etc.	Placebo
242554	4	White	Male	03/20/2014	Gastrointestinal	Vomiting	Primary	5	Not Expected	2	Definitely not related		Active
243339	8	White	Male	08/24/2014	Pulmonary/Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	38	Not Expected	2	Definitely not related	Has history of snoring. Had difficulty breathing through nose on 8/24/14. Went to MD on 8/25/14, had swollen sinuses. Off Oral Insulin and singulair until allergy testing scheduled for 9/8/14	Placebo
243339	8	White	Male	12/07/2014	Gastrointestinal	Gastrointestinal - Other (Specify in Event Details)	Primary	3	Not Expected	2	Definitely not related	Gastroenteritis. Had nausea, vomiting and diarrhea 12/7-12/10/14. No reported fever. Other family members also ill. Used Phenergan liquid prn. Did not report a fever.	Placebo
243339	8	White	Male	01/16/2015	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	flu symptoms with fever 102.6 degrees and diarrhea, tested positive for flu, did not take Tamiflu. Resolved spontaneously	Placebo
243339	8	White	Male	02/24/2015	Pulmonary/Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	allergic rhinitis, has increased congestion, sneezing, no cough, no fever	Placebo

243339	8	White	Male	03/02/2015	Infection	Infection - Other (Specify in Event Details)	Primary	11	Not Expected	2	Definitely not related	strep pharyngitis	Placebo
243339	8	White	Male	03/09/2015	Allergy/Immunology	Allergic reaction/hypersensitivity (including drug fever)	Primary	19	Not Expected	2	Definitely not related	had increasing rash while on Cefidinir for strep pharyngitis, was seen by PCP on 3/10/15 who thought of possible scarlet fever due to strep, went to ER 3/11/15 for worsening of rash, was treated with prednisone for 2 weeks, and received a different antibiotic one time injection	Placebo
243472	3	White	Female	03/19/2014	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	1	Not Expected	1	Definitely not related	Radial head dislocation with a typical mechanism of injury: child was rotated in air by pulling from the arms when the head of the radius in elbow slipped out from its capsule. It was manually replaced under paracetamol and naproxen medication. The child recovered without any complications.	Placebo
244386	13	White	Female	06/23/2016	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	Participant had plantar verruca (plantar's warts) removed from bilateral feet on 6/23/16 via excision/cauterization.	Active
244386	13	White	Female	08/24/2016	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	13	Not Expected	2	Definitely not related	Subject noticed "a bump" on her upper left thigh on 8/24/16 and went to local urgent care on 8/26/16 because of increased irritation. Keflex was administered (oral) and given to subject to continue at home for several days. On 8/27/16, participant presented to the emergency department complaining of increased skin irritation in addition to noticeable increase in the size of the rash on left thigh. Participant was diagnosed with	Active

												moderate cellulitis. Subject was instructed to discontinue Keflex and was started on Clindamycin. Irritation resolved within a few days after antibiotic treatment began. Records were requested from the treating facility and AE information was updated as applicable.	
247044	10	White	Female	04/27/2015	Endocrine	Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Primary	.	Not Expected	2	Probably not related	At scheduled OGTT weight loss of 2 kg, thyroid gland enlarged, thyroid blood work done--TSH suppressed <0.01 IU/L, Free T4 31 pmol/L, and thyroid peroxidase antibodies >1000 IU/L. Diagnosis of Graves Disease. Started on medication Tapazole	Placebo
248060	9	White	Female	01/09/2017	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	Participant had a cold starting January 9th - January 30th. Parent reports that child had fever some of those days (parent cannot recall what days exactly), and child was given OTC medications. Parent states that cold stopped around the end of the month but some symptoms are still showing randomly (sometimes cough).	Active
248060	9	White	Female	02/14/2017	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	14	Not Expected	2	Probably not related	Parent took participant to the doctor for a cold and stuffy nose symptoms. Doctor prescribed asthma inhaler as needed.	Active
254077	11	White	Male	11/11/2014	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	11	Not Expected	2	Definitely not related	Subject had viral upper respiratory infection	Placebo
254077	13	White	Male	11/10/2016	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Upper respiratory infection	Placebo

263065	7	White	Male	02/01/2016	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	2	Not Expected	1	Definitely not related	Sprained toe when slipped on wet floor	Active
263065	8	White	Male	10/13/2016	Dermatology/Skin	Dermatology/Skin - Other (Specify in Event Details)	Primary	7	Not Expected	1	Definitely not related	Skin grazes on both arms secondary to fall from scooter on 13 Oct 2016	Active
264860	8	White	Male	10/27/2014	Neurology	Neurology - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Concentration impairment. The participant was having difficulty with school and homework and on 10/27/14 the participant was diagnosed with Attention Deficit Disorder and was prescribed Dextroamp-ampheter.	Placebo
264860	8	White	Male	11/05/2014	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Participant was tested for strep throat as a precautionary measure as other members in the household were ill. Participant denied sore throat. Culture came back positive. Prescribed Amoxicillin 400 mg PO BID x 10 days. During next visit to pediatrician will discuss possibility of being a carrier.	Placebo
264860	10	White	Male	02/08/2017	Infection	Infection - Other (Specify in Event Details)	Primary	19	Not Expected	2	Definitely not related	On 2/8/17 participant stated coughing, bouts of which persisted for the next week and were treated with OTC cough medicine (Delsym 5mg BID prn coughing). On 2/14/17 participant was taken to pediatrician and diagnosed with bronchitis and put on antibiotics:(Azithromycin, in a 5 day "Z pack" 200 mg/5 ml). Mother of participant says the symptoms have lessened in the last day. The rest of the family have all experienced the same condition in the last week, as well. **********	Placebo

												On 2/8/17 participant stated coughing, bouts of which persisted for the next week and were treated with OTC cough medicine (Delsym 5mg BID prn coughing). On 2/14/17 participant was taken to pediatrician and diagnosed with bronchitis and put on antibiotics:(Azithromycin, in a 5 day "Z pack" 200 mg/5 ml). Mother of participant says the symptoms have lessened in the last day. The rest of the family have all experienced the same condition in the last week, as well. Wednesday, February 22,2107 participant's mom said still was coughing and re-scheduled OGTT for 4/2/17. Spoke to Mother of participant on 3/27/17 and she said the cough resolved by 2/27/17.	
271858	4	White	Male	04/28/2015	Infection	Infection with unknown ANC	Primary	10	Not Expected	2	Definitely not related	Participant had ear infection from 4/28-5/8/15, received amoxicillin for 10 days for otitis media. Symptoms resolved on 5/8/15. Provider exam at visit on 5/29/15 noted external ear canal clear, no redness, no exudates, no pain with palpation of tragus.	Placebo
277201	4	White	Female	02/18/2015	Lymphatics	Lymphatics - Other (Specify in Event Details)	Primary	13	Not Expected	2	Definitely not related	Subject had scheduled same day surgery (tonsillectomy and adenoidectomy) on Feb. 18th, 15 under general anesthesia. Morphine was given prior to the surgery. Wake up from the surgery well. From Feb. 18th to Feb. 26th subject took Childrens Tylenol q.4 hrs. to control the pain. On Feb. 26th subjects pain	Placebo

												became too great and was taken to the ER. Morphine was prescribed. Took Morphine PRN from Feb. 27th to Mar. 2nd, 15. Missed 1.5 weeks of school. Symptoms resolved on Mar. 3rd, 15.	
277201	4	White	Female	04/14/2015	Gastrointestinal	Vomiting	Primary	1	Not Expected	2	Definitely not related	On April 14th.15 subject vomited X 2. Took Children's Gravol PRN (one dose). Missed one day from school. Symptoms resolved on April 15th, 15.	Placebo
277201	6	White	Female	04/04/2017	Infection	Infection - Other (Specify in Event Details)	Primary	16	Not Expected	2	Probably not related	Subject was sick with sore throat, stuffy-runny nose and cough, started on Apr. 4th, 17. No fever, no MD attention needed. Missed two days of school: Apr. 10th. and 12th. PRN Children's Advil taken. Symptoms resolved on Apr. 20th, 17.	Placebo
277365	12	White	Male	09/01/2015	Pain	Pain - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	Hit during football game on 9/1/15. Evaluated by trainers at time. C/o headache and seen by MD on 9/3/15. Possible concussion. Took ibuprofen 400mg twice a day from 9/1/15 to 9/3/15. Cleared for football on 9/11/15.	Placebo
277980	6	White	Female	12/01/2014	Infection	Infection - Other (Specify in Event Details)	Primary	6	Not Expected	2	Probably not related	otitis media	Active
277980	6	White	Female	01/26/2015	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	2	Probably not related	UTI	Active
282701	36	White	Female	10/12/2015	Constitutional Symptoms	Weight loss	Primary	.	Not Expected	3	Definitely not related	Started new diet in June for weight loss. Diet is supervised by MD. Has lost 21% of body weight since start of study in March 2015. Weight at screening was 96.5kg. Current weight is 76.2kg.	Placebo

282701	36	White	Female	04/21/2016	Surgery/Intra-Operative Injury	Intra-operative Injury - Other (Specify in Event Details)	Secondary	11	Not Expected	2	Definitely not related	Subject lost a substantial amount of weight. Due to the weight loss, there was a significant amount of excess skin in the abdominal area. The subject underwent an abdominoplasty to remove the excess skin.	Placebo
286704	13	White	Female	06/10/2015	Pulmonary/ Upper Respiratory	Cough	Primary	30	Not Expected	2	Definitely not related	Upper Respiratoy Infection started 2 days ago. Grade 2, ongoing, not related as per study team. Fever and productive cough.	Placebo
286966	10	White & Asian	Male	04/29/2017	Infection	Infection with unknown ANC	Primary	10	Not Expected	2	Definitely not related	strep throat diagnosed by PCP; symptoms included sore throat and headache without fever; prescribed Amoxicillin PO BID for 10 days	Active
287122	12	White	Female	07/23/2015	Metabolic/Laboratory	Glucose, serum-high (hyperglycemia)	Primary	.	Expected	2	Definitely not related	During a regular study visit a pathologic OGTT value (2h: 200 mg/dL) was found.	Placebo
287768	7	White	Male	03/22/2016	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	skin boil infected with MRSA, subject had boil lanced at doctor's office, prescribed PO Bactrim for 10 days	Active
287768	7	White	Male	06/22/2016	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Definitely not related	infected mosquito bite (cellulitis) with localized swelling/inflammation; no fever; took Keflex for 10 days	Active
288057	20	White	Male	10/26/2015	Musculoskeletal/Soft Tissue	Fracture	Primary	310	Not Expected	3	Definitely not related	Subject fractured ankle and dislocated tibia and fibula while ice skating on 10/26/15. They had surgery the next day on 10/27. A rod and 9 screws were placed in lateral aspect of left tibia/fibula. They were discharged from the hospital on 10/28/15 with pain medications and stool softener. Follow up appointment on 11/9/15 showed adequate healing. As of 12/17 participant continues to	Active

												wear boot and ambulate with the assistance of a scooter.	
288057	21	White	Male	03/09/2017	Endocrine	Thyroid function, low (hypothyroidism)	Primary	.	Not Expected	2	Probably not related	Subject experienced increased headaches and body aches over a 2-week period, so sought medical evaluation. Mononucleosis was ruled out, but testing revealed a new diagnosis of hypothyroidism. Treatment with 50 mcg levothroxine was initiated. Headaches and body aches resolved at time of diagnosis (both were grade 1, per sub-Investigator).	Active
288465	13	Black/ African American	Female	01/21/2016	Infection	Infection - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Facial acne	Active
288477	6	White	Female	04/14/2015	Gastrointestinal	Vomiting	Primary	1	Not Expected	2	Definitely not related	Participant reported vomiting multiple times (10) in a 24-hour period of time. Participant's mother treated with rest and oral fluids (IV fluids were not indicated) and vomiting resolved the next day.	Active
289753	7	White	Male	06/17/2015	Pulmonary/ Upper Respiratory	Cough	Primary	7	Not Expected	1	Definitely not related	cough with fever noted at in-person visit, referred to pediatrician for evaluation	Placebo
290560	13	White	Female	03/01/2016	Allergy/Immunology	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Primary	.	Not Expected	2	Probably not related	Seasonal allergy flare, started 3/1/16, Advair prescribed, ongoing	Active

290560	13	White	Female	06/15/2016	Dermatology/Skin	Urticaria (hives, welts, wheals)	Primary	65	Not Expected	3	Probably not related	Participant reported episodes of hives and was seen and treated for chronic idiopathic urticaria with Prednisone 50mg po x5 days from June 15-19th, again on July 17th x2 days and again on August 15th - 19th x5days each time the hives resolved. Participant also reports taking Benadryl 25 mg po q6-8 hrs as needed prior to each flare last use was prior to August 15th flare up.	Active
290560	14	White	Female	03/16/2017	Pain	Pain	Primary	0	Not Expected	2	Definitely not related	Headache, grade 2, start 3/16/17, not related per study team, Tylenol 500 mg x1 taken with relief.	Active
292670	5	White	Female	03/19/2016	Musculoskeletal/Soft Tissue	Fracture	Primary	58	Not Expected	2	Definitely not related	Participant 's mother reported today that on Saturday evening, March 19, 2016, participant fell and injured left arm. Taken to urgent care center and xray revealed fracture. Advised to take Motrin and Tylenol for pain and to go to pediatric orthopedist on Monday, March 21, 2016 for casting. Went to pediatric orthopedic physician today, March 21, 2016 and cast applied. Advised to use Motrin and Tylenol prn for pain.	Active
292670	5	White	Female	05/10/2016	Infection	Infection - Other (Specify in Event Details)	Primary	16	Not Expected	2	Definitely not related	Mother of participant sent email on 5/16/16 that participant had flu for the past 6 days and decision was made to re-schedule visit planned for next Monday 5/23/2016. Called Mother of participant today 5/18/16 for details and she reported on Tuesday May10, 2016 participant ran a fever. The next day she took child to	Active

												pediatrician who said she had "flu" and prescribed Tamiflu. Participant took only two doses, one on 5/11/16 in the pm and one the next morning 5/12/16 and then refused to take more as it "tasted bad". Mother has been giving child ibuprofen 7.5 ml alternating with acetaminophen 7.5 ml P.R.N. fever since 5/10/16. On Monday, May 16, 2016, she took child back to physician who put child on Amoxicillin 5 ml BID since fevers between 100-103 degrees were still present. First dose given May 16, 2016 in pm and will continue for 10 days. Mother also put child on Culturelle once a day prophylactically to prevent antibiotic side effect of diarrhea. There have been no signs of diarrhea. Fever is still persistent and mother will email with further updates as they occur.	
292855	7	White	Male	08/11/2016	Auditory/Ear	Auditory/Ear - Other (Specify in Event Details)	Primary	0	Not Expected	2	Definitely not related	outpatient surgery for graft to left eardrum	Active
292855	8	White	Male	03/21/2017	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	5	Not Expected	2	Definitely not related	Pharyngitis that was diagnosed as Influenza B at Dr office.	Active
295400	6	White	Male	09/30/2015	Surgery/Intra-Operative Injury	Intra-operative Injury - Other (Specify in Event Details)	Primary	12	Not Expected	3	Definitely not related	Tonsillectomy	Placebo
296701	13	White	Male	09/13/2016	Musculoskeletal/Soft Tissue	Fracture	Primary	56	Not Expected	2	Definitely not related	fracture of ulna and radius requiring cast for 8 weeks and analgesia. no further follow up required. resolved.	Active

296734	8	White	Female	03/22/2016	Pulmonary/ Upper Respiratory	Cough	Primary	3	Not Expected	2	Probably not related	Patient had very bad cough, visit to the doctor and prescribed medication	Active
296734	9	White	Female	10/04/2016	Musculoskeletal/Soft Tissue	Musculoskeletal/Soft Tissue - Other (Specify in Event Details)	Primary	31	Not Expected	2	Definitely not related	Patient fell down while practicing gymnastics. Orthopedic doctor said that patient should stay off gymnastics practice for a month, to wear a sling for 1 week. No medications prescribed or taken. Incident has resolved.	Active
297115	6	White	Female	05/01/2016	Infection	Infection with unknown ANC	Primary	11	Not Expected	2	Possibly related	Subject c/o sore throat and had a fever on 5/1, diagnosed on 5/2 with strep throat and started Amoxicillin.	Placebo
297115	6	White	Female	06/01/2016	Pulmonary/ Upper Respiratory	Pneumonitis/pulmonary infiltrates	Primary	19	Not Expected	2	Possibly related	Mom stated at the visit on 6/9/16 that subject has had a intermittent cough and that she had some post-nasal drip. During visits examination Dr. Becker reported "slight cough, rales LLL, no fever " graded as 1. No complaint of any pain or shortness of breath.	Placebo
297940	5	White	Female	09/01/2015	Infection	Infection - Other (Specify in Event Details)	Primary	10	Not Expected	2	Probably not related	Sinus infection diagnosed at PCP 01SEP2015 and treated with oral antibiotics x 10 days. Symptoms were completely resolved at end of antibiotic treatment.	Placebo
297940	6	White	Female	10/10/2016	Infection	Infection - Other (Specify in Event Details)	Primary	14	Not Expected	2	Probably not related	Seen outpatient by PCP and diagnosed with a sinus infection. Given oral antibiotics for 10 days and resolved completely.	Placebo
298188	10	White	Female	10/22/2015	Infection	Infection - Other (Specify in Event Details)	Primary	7	Not Expected	2	Probably not related	Patient was diagnosed with strep throat and anitbiotics were prescribed for 7 days.	Placebo
298188	12	White	Female	01/02/2017	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other	Primary	2	Not Expected	2	Probably not related	Participant had a cold with fever. Needed medication to reduce fever.	Placebo

						(Specify in Event Details)							
298188	12	White	Female	01/09/2017	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	2	Not Expected	2	Probably not related	Patient had a cold/ cough/ fever	Placebo
298188	12	White	Female	01/21/2017	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	3	Not Expected	2	Probably not related	Patient had a cold/ cough and fever around 103. Taken to urgent care but given only meds to control fever.	Placebo
299910	7	White	Male	12/26/2015	Gastrointestinal	Vomiting	Primary	3	Not Expected	2	Definitely not related	Subject was in Mexico for Christmas break and got food poisoning. Went to ER in Mexico where received IV fluids and prescribed antibiotics for three days.	Active
299910	7	White	Male	09/09/2016	Dermatology/Skin	Rash/desquamation	Primary	11	Not Expected	2	Definitely not related	Impetigo rash around nose and cheeks	Active
300122	6	White	Male	02/23/2016	Pulmonary/ Upper Respiratory	Cough	Primary	20	Not Expected	2	Definitely not related	cold, congestion, hay fever/allergies	Active
300134	9	White	Male	02/15/2016	Pulmonary/ Upper Respiratory	Cough	Primary	1	Not Expected	2	Probably not related	allergies/cold/congestion	
300134	9	White	Male	04/01/2016	Pulmonary/ Upper Respiratory	Cough	Primary	10	Not Expected	2	Definitely not related	Allergies /cold/congestion	
300134	9	White	Male	04/12/2016	Pulmonary/ Upper Respiratory	Cough	Primary	6	Not Expected	2	Definitely not related	itchy eyes, allergy symptoms, swelling of throat	
300134	9	White	Male	10/01/2016	Pulmonary/ Upper Respiratory	Cough	Primary	5	Not Expected	2	Probably not related	cough/sore throat	
300134	10	White	Male	01/16/2017	Pulmonary/ Upper Respiratory	Cough	Primary	4	Not Expected	2	Probably not related	Sore throat and cough	
300134	10	White	Male	04/18/2017	Pulmonary/ Upper Respiratory	Cough	Primary	2	Not Expected	1	Probably not related	allergy and cold symptoms	

300592	11	White	Female	08/22/2016	Allergy/Immunology	Allergy/Immunology - Other (Specify in Event Details)	Primary	.	Not Expected	2	Probably not related	Seasonal allergies and eye itchiness started at age 5 (2010). Mother reports that the eye itchiness has intensified with each season (early Spring to mid June) but some seasons are worse than others. Participant saw that brothers tolerated allergy shots and experienced improvement so she decided to start them herself.	Active
302121	8	White	Male	07/18/2015	Infection	Infection - Other (Specify in Event Details)	Primary	3	Not Expected	1	Definitely not related	sore throat d/t URI	Active
302121	8	White	Male	07/18/2015	Infection	Infection - Other (Specify in Event Details)	Primary	3	Not Expected	1	Definitely not related	Fever detected at home d/t URI	Active
302121	9	White	Male	12/09/2015	Infection	Infection - Other (Specify in Event Details)	Primary	.	Not Expected	1	Definitely not related	Upper Respiratory Infection	Active
302121	9	White	Male	09/17/2016	Pulmonary/ Upper Respiratory	Cough	Primary	.	Not Expected	1	Definitely not related	Subject developed a cough approximately 17/Sep/2016	Active
302121	9	White	Male	10/03/2016	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	.	Not Expected	2	Definitely not related	Subject developed pneumonia after a 2 week cough	Active
304068	6	White	Male	05/25/2016	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	2	Not Expected	1	Definitely not related	subject mother reports low grade fever associated suspected acute viral illness. other symptoms include cough and vomiting.	Placebo
304068	7	White	Male	03/23/2017	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	1	Not Expected	1	Probably not related	Subject's mother reports subject having a low grade fever lasting approximately 2 days that the subject stayed home from school for.	Placebo

314740	19	Multiple Selections Made	Female	12/01/2015	Blood/Bone Marrow	Blood/Bone Marrow - Other (Specify in Event Details)	Primary	.	Not Expected	2	Possibly related	Participant reported "Anemia" and has been taking Iron supplement 65mg QD.	Active
316640	13	White	Male	11/06/2016	Neurology	Dizziness	Primary	5	Not Expected	3	Probably not related	On November 6th, 2016 participant was playing basketball was knocked to the floor. He received a blow to his right eye and hit his head on the floor. Participant was dizzy, had a headache and blurry vision. He has no memory of the event. Concussion was diagnosed by neurosurgeon present at the game and concussion protocol was implemented. Child on bed rest and in darkened room with gradual increase of activity. On Nov 9th attempted return to school but dizziness with nausea occurred for 1/2 hour and activities decreased again but by November 11th all symptoms resolved. Ibuprofen 200 mg given as needed from Nov 6th to Nov 9th.	Active
334300	15	White	Male	01/18/2016	Pain	Pain	Primary	.	Not Expected	2	Definitely not related	Subject started having migraines almost every day. Went to Primary care provider and prescribed medications (Cyproheptadine and Sumatripan). On 02/16/2016 skip school because of migraine. Subject is feeling better with medications. Has previous history of migraines.	Placebo
350068	3	White	Male	01/20/2016	Infection	Infection - Other (Specify in Event Details)	Primary	9	Not Expected	2	Definitely not related	Hand, Foot and Mouth Disease; rash on feet, low grade fever	Placebo

352763	16	White	Male	04/11/2017	Musculoskeletal/Soft Tissue	Joint-function	Primary	.	Not Expected	1	Definitely not related	Surgery because of loss of range of motion	Placebo
354180	15	White	Female	12/17/2016	Pain	Pain	Primary	28	Not Expected	2	Definitely not related	Pain in hips and knees	Active
500340	3	White	Female	10/01/2011	Infection	Infection - Other (Specify in Event Details)	Primary	4	Not Expected	1	Definitely not related	Subject appeared to have hand/food /mouth disease as reported by mom. Had lesions in mouth and 1 lesion on an extremity. Tactile temp reported by mom. Fever resolved after 24 hours. Lesions resolved after 4 days. Known exposure in preschool setting. Didn't see PMD. Event noted by participant's mom.	Placebo
500340	3	White	Female	12/25/2011	Pulmonary/ Upper Respiratory	Pulmonary/Upper Respiratory - Other (Specify in Event Details)	Primary	11	Not Expected	1	Definitely not related	Participant had URI with mild unproductive dry cough 12/25/11. No fever. No interference with ADL. Resolved 1/5/12.	Placebo
500340	3	White	Female	03/01/2012	Infection	Infection - Other (Specify in Event Details)	Primary	7	Not Expected	1	Definitely not related	Participant diagnosed with anal strep infection. Treated with Cephalexin x7 days. Resolved without complications.	Placebo
500340	4	White	Female	11/14/2012	Pulmonary/ Upper Respiratory	Cough	Primary	7	Not Expected	1	Definitely not related	Participant developed runny nose and croupy cough with fever 11/14-11/18, fever resolved on 11/18, but still coughing, had chest x ray on 11/19- results were negative. Cough resolved on 11/21.	Placebo
506633	12	White	Male	04/24/2013	Constitutional Symptoms	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Primary	5	Not Expected	2	Definitely not related	Past febrile illness reported at 39 month phone visit. Symptoms completely resolved. Tmax was 103.0F. Subject was not taken to the doctor, parent treated with over the counter meds.	Placebo

515635	13	White	Male	07/08/2016	Allergy/Immunology	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Primary	8	Not Expected	2	Definitely not related	Had nasal and sinus congestion as a result of seasonal Allergies and exposure to outdoors. Went to camp out in the woods.	Active
517728	3	White	Female	01/18/2013	Ocular/Visual	Ocular/Visual - Other (Specify in Event Details)	Primary	.	Not Expected	3	Definitely not related	SURGERY to relieve chronic styes, bilateral.	Placebo
700195	14	White	Male	04/11/2014	Musculoskeletal/Soft Tissue	Fracture	Primary	.	Not Expected	2	Definitely not related	Injured right thumb while playing water polo. Taken to pediatrician, x-ray done, showed right thumb fracture. Right thumb brace applied. Will follow up with orthopedics on 17APR2014.	Active
700195	14	White	Male	07/06/2014	Musculoskeletal/Soft Tissue	Fracture	Primary	.	Not Expected	2	Definitely not related	Left foot fracture. Taken to orthopedic doctor, x-ray showed fracture. Immobilized with orthopedic boot. On crutches now.	Active
700195	17	White	Male	12/29/2016	Surgery/Intra-Operative Injury	Intra-operative injury	Primary	0	Not Expected	1	Definitely not related	Extraction of wisdom teeth.	Active
702445	7	White	Male	01/19/2017	Surgery/Intra-Operative Injury	Intra-operative Injury - Other (Specify in Event Details)	Primary	0	Not Expected	1	Definitely not related	Teeth crowding.	Placebo
703145	9	White	Male	11/07/2016	Auditory/Ear	Auditory/Ear - Other (Specify in Event Details)	Primary	10	Not Expected	2	Probably not related	Ottitis Media with effusion. Treated with Abx for 10 days. 11/07/2016-11/17/2016	Active