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Study Procedures (Part 6 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus)

In 1 collection

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ABSTRACT

This is Part 6 of "Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-Onset Type 1 Diabetes Mellitus".

This clinical study is supported by JDRF. The aim of the collection is to determine whether imatinib will slow the progression of the autoimmune destruction of ß cells and lead to the preservation of C-peptide secretion in T1DM and to assess Diabetes-related objectives and safety of Imatinib in new-onset type 1 diabetes mellitus".

ATTACHMENTS

dngubkeaf.pdf

DOI

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PROTOCOL CITATION

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COLLECTIONS

Collection of Protocols and Guidelines for Safety and Efficacy of Imatinib for Preserving Beta-cell Function in New-onset Type 1 Diabetes Mellitus

KEYWORDS

Safety, Efficacy, Imatinib, Beta-cell function, New-Onset Type 1 Diabetes Mellitus

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Collection of Protocols and Guidelines for Safety and Efficacy of Imatinib for Preserving Beta-cell Function in New-onset Type 1 Diabetes Mellitus

GUIDELINES

6.1 INTENSIVE DIABETES MANAGEMENT

During the study, all participants will receive “intensive” management of their diabetes, and HbA1C will be assessed every 3 months to evaluate metabolic control. The goal of treatment will be to maintain the HbA1C level as close to normal as possible, without frequent occurrence of hypoglycemia. All individuals should strive for targets in accordance with current ADA recommendations, with HbA1C levels of less than 7% in adults and less than 7.5% in adolescents (age 12–17 years), and with preprandial glucose levels of 90–130 mg/dL (plasma), postprandial levels of less than 180 mg/dL, and bedtime levels of 110–150 mg/dL.[178] All participants will be expected to take a sufficient number of daily insulin injections to meet the glycemic targets. In general, the expectation is that all participants will receive at least three injections of insulin daily, including short- and long-acting insulin preparations, or will utilize continuous subcutaneous insulin infusion (CSII insulin pump). Glucose levels should be checked at least four times daily. After reviewing these records, the diabetes management team will contact the treating physician about possible adjustments in the insulin regimen, referral to a registered dietitian, or other approaches that the diabetes management team believes would improve the glucose control if necessary. Records of glucose measurements and communication with the participant will be kept as source documentation. Participants will be contacted by the diabetes educator every 2 weeks between visits to assess their diabetes. In addition, insulin use and hypoglycemic events will be captured at each visit on the appropriate CRFs. Participants will be required to record the amount of insulin they have used during the 5-day period immediately preceding each study visit. Insulin use logs will be provided to participants at each study visit and collected at the next visit. These logs will serve as the source documents.

6.2 RANDOM ASSIGNMENT, BLINDING, AND UNBLINDING

See the steps tab.

6.4 GENERAL ASSESSMENTS

- Medical history includes T1DM time of diagnosis and clinically significant diseases or medical procedures. Copies of growth velocity charts should be obtained if available
- Adverse events. Participants will be assessed for AEs
- Concomitant medications. All concomitant medications and their indications will be recorded
- Comprehensive physical examination and vital signs. Weight, temperature, blood pressure, respiration, and pulse

6.5 LABORATORY ASSESSMENTS

- Serum chemistries: Electrolytes (sodium, calcium, potassium, chloride, phosphate, total CO2), blood urea nitrogen (BUN), creatinine, and liver panel (AST, ALT, alkaline phosphate, direct and total bilirubin)
- Hematology: Complete blood cell count with differential, and platelets
- Infectious disease serology, hepatitis B (HBsAg and anti-HBcAb) and C, HIV, toxoplasmosis, VZV, EBV (IgG, IgM, EBNA), CMV (IgG, IgM)
- PPD skin test or IGRA

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- Urine hCG
- Urinalysis
- C-peptide levels (measured as part of MMTT)
- Plasma Glucose (measured as part of MMTT)
- HbA1c levels

6.6 DISEASE-SPECIFIC ASSESSMENTS

- MMTT
- Glucose (glucometer readings)
- Insulin use (U/kg body weight/day)
- Hypoglycemia events
- Serum Adiponectin levels
- Plasma Glucagon levels
- Plasma Proinsulin levels

6.7 BONE AND MINERAL METABOLISM ASSESSMENTS

Serum calcium, serum phosphate, PTH, 25-OH Vitamin D and serum bone turnover markers (serum CTX, osteocalcin). Bone turnover markers are exploratory only and are not part of the secondary endpoint safety assessment, per section 3.3.2.

6.8 GROWTH RATE ASSESSMENTS FOR GROWING-AGE PARTICIPANTS (AS DEFINED IN SECTION 5.2.9)

- Plain radiograph of left hand to determine bone age using the FELS atlas (Assessing the skeletal maturity of the hand-wrist).[179]
- Height measured by Stadiometer.
- Secondary sexual characteristics.
- Arm span.
- Biochemical assessments. IGF-1, IGF-BP3, LH, FSH, estradiol (females), testosterone (males), TSH, and tissue transglutaminase.

REFERENCES

178. Greenbaum CJ, Beam CA, Coulware D, Gitelman SE, Gottlieb PA, Herold KC, Lachin JM, McGee P, Palmer JP, Pescovitz MD, Krause-Steinrauf H, Skyler JS, Sosenko JM, Type 1 Diabetes TrialNet Study Group. Fall in C-peptide Over First Two Years from Diagnosis: Evidence of At Least Two Distinct Phases from Composite TrialNet Data. Diabetes. 2012; 61: 2066-2073.
179. Roche AF, Chumlea WC, Thissen D. Assessing the Skeletal Maturity of the Hand-Wrist: FELS Method. Springfield, Ill: Charles. C Thomas; 1988.

Random Assignment

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

Blinding

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

Unblinding

3 Unblinding before the study is completed will occur only if a participant's well-being is threatened and the investigator believes unblinding is necessary to protect the participant.

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4 Before treatment assignment for an individual participant is unblinded, the investigator must confer with the study sponsor and the medical monitor. The site investigator will notify the protocol chairs of the unblinding event, and the medical monitor will notify the study management team (SMT).

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

6 Sponsor approval is required for unblinding the treatment of an individual participant or subgroups of participants for unplanned interim analyses to support DSMB reviews and final analysis.

Visit Windows

7 Scheduled Visits

All scheduled study visits in Appendix 1 must occur within the time limits specified below. Visits that occur outside of the specified windows will be considered protocol deviations.

- **Visit -1** **Up to** 2-4 weeks before visit 0
- **Visit 0** No window
- **Visit 1** (± 3 days)
- **Visits 2-7** (± 7 days)
- **Visits 8-11** (± 14 days)

Appendix 1. Schedule of Events

Week	-3 to -4	0	2	4	9	13	17	22	26	39	52	78	104
Visit	-1	0	1	2	3	4	5	6	7	8	9	10	11
GENERAL ASSESSMENTS													
Informed consent	X												
Eligibility criteria	X												
Medical history	X												
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[1]	X	X		X	X	X			X		X	X	X
Secondary sexual characteristics[2]		X									(X)		(X)
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Monitoring (if applicable)	X	X		X	X	X	X	X	X		X	X	X
ECG	X		X										
LABORATORY ASSESSMENTS													
Serum chemistries and liver panel[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Autoantibodies	X												
Hematology[4]	X	X	X	X	X	X	X	X	X	X	X	X	X
Infectious disease serology[5]	X												
PPD skin test or IGRA	X												
Urine hCG	X	X		X	X	X	X	X	X		X	X	X
Urinalysis	X								X		X		X
Prostate Specific Antigen (males only)		X							X		X		X
C-peptide levels (tested from MMTT)[6]	X					X			X		X	X	X

[1] Excluding genitalia unless clinically indicated

[2] The Tanner stages will be assessed at the baseline visit for every participant under 18 years of age. After the baseline visit, Tanner stages will be assessed annually on all participants who are < stage 3. If the Tanner stage is ≥3 at the baseline visit or any subsequent visit, Tanner stages will not need to be assessed at any future visit.

[3] To include sodium, calcium, potassium, chloride, phosphate, total CO_2, BUN, creatinine, AST, ALT, alkaline phosphate, direct and total bilirubin.

[4] Performed locally; to include CBC with differential and platelets.

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[5] Hepatitis B and C, HIV, toxoplasmosis, VZV, EBV, and CMV serology. CMV/EBV PCR testing may be obtained (centrally) or locally, if necessary to confirm active infection.

[6] 4-hour MMTT at Visits -1, 9, 11 and 2-hour MMTT at Visits 4, 7, and 10.

Week	-3 to -4	0	2	4	9	13	17	22	26	39	52	78	104
Visit	-1	0	1	2	3	4	5	6	7	8	9	10	11
Plasma Glucose (tested from MMTT)[4]	X					X			X		X	X	X
HbA_{1c} levels	X					X			X	X	X	X	X
STUDY DRUG ADMINISTRATION													
Study drug administration		X	X	X	X	X	X	X					
Study drug compliance			X	X	X	X	X	X	X				
DISEASE SPECIFIC ASSESSMENTS													
Glucose (Glucometer Reading)		X	X	X	X	X	X	X	X	X	X	X	X
Insulin use		X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycemia assessment		X	X	X	X	X	X	X	X	X	X	X	X
Serum-Adiponectin[7]		X		X					X		X		X
Plasma-Glucagon[6]	X					X			X		X	X	X
Plasma-Proinsulin[6]	X					X			X		X	X	X
BONE AND MINERAL METABOLISM													
Serum Calcium[8]		X		X		X			X		X		
Serum Phosphate[7]		X		X		X			X		X		
PTH		X		X		X			X		X		
25-OH Vitamin D		X									X		
Serum CTX[9]		X				X			X		X		
Osteocalcin[8]		X				X			X		X		
GROWTH RATE ASSESSMENTS[10]													
Plain Radiograph of Left Hand		X									X[11]		X[10]
Height by Stadiometer[12]	X	X	X	X	X	X	X	X	X	X	X	X	X
Arm span		X							X		X		X

[7] Samples will be archived for potential future testing.

[8] Tested as part of serum chemistry panel.

[9] Samples will be archived and tested if clinically indicated.

[10] To be performed on growing-age participants per Section 5.2.9.

[11] Bone age will be assessed annually until epiphyses are near complete closure (98% of mature height at bone age of 15 yrs 9 months for boys, 14 yrs for girls).

[12] Subjects will need to be measured with a wall mounted stadiometer to insure accurate height measurements.

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Week	-3 to -4	0	2	4	9	13	17	22	26	39	52	78	104
Visit	-1	0	1	2	3	4	5	6	7	8	9	10	11
IGF-1, IGF-BP3, LH, FSH, Estradiol (females), Testosterone (males)[13]		X							X		X		X
Total IgA		X[14]											
TSH and T4		X[13]									X[15]		X[14]
Tissue transglutaminase (IgA)[16]		X[13]									X[14]		X[14]
MECHANISTIC ASSAYS													
Serum-Autoantibody Analysis		X		X		X			X		X		X
PBMC-Flow Cytometry Panel Staining		X		X		X			X		X		X
PBMC-Cell Based Assays		X		X		X			X		X		X
PBMC-Genomics, Proteomics		X		X		X			X		X		X
PBMC- FOXP3 Methylation Assay		X		X		X			X		X		X
Whole Blood-Gene Expression Profiling		X		X		X			X		X		X
Whole Blood DNA-HLA Genotypes		X				X					X		
Plasma-Archive		X		X		X			X		X		X
Serum- Beta Cell Death Assay		X	X	X	X				X		X		X
Serum-Cytokines		X	X	X	X				X		X		

[13] Samples will be archived and tested if clinically indicated.

[14] Tested at Baseline only if not tested by referring physician within 3 months prior to Baseline.

[15] Samples will be collected at Visits 9 and 11 only if clinically indicated in growing age participants. If required, testing will be performed real-time.

[16] Performed locally.

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