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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

Stephen.Gitelman [1], Jeffrey A. Bluestone[2]

[1]Professor of Clinical Pediatrics, Department of Pediatrics University of California, San Francisco Room S-679, Campus Box 0434, 513 Parnassus Avenue, San Francisco, CA 94143;

[2]Professor of Medicine, Pathology, Microbiology & Immunology, University of California, San Francisco, Campus Box 0540, 513 Parnassus Avenue San Francisco, CA 94143

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Gitelman UCSF

Stephen.Gitelman

ABSTRACT

This is a collection of protocols for: "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

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KEYWORDS

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

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GUIDELINES

Safety and Efficacy of Imatinib for Preserving Beta-cell Function in Newonset Type 1 Diabetes Mellitus

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August 23, 2016

IND # 117,644

Sponsored by the Juvenile Diabetes Research Foundation International (JDRF).

SAFETY AND EFFICACY OF IMATINIB FOR PRESERVING BETA-CELL FUNCTION IN NEW-ONSET TYPE 1 DIABETES MELLITUS

Version 7.0 (January 29, 2016)

IND # 117,644

Protocol Co-Chair

Jeffrey A. Bluestone, Ph.D.
Professor of Medicine, Pathology,
Microbiology & Immunology
University of California, San Francisco
Campus Box 0540
513 Parnassus Avenue
San Francisco, CA 94143
Tel: 415-514-1683 Fax: 415-564-5813
Email: jbluest@diabetes.ucsf.edu

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Protocol Co-Chair

Stephen E. Gitelman, MD
Professor of Clinical Pediatrics
Department of Pediatrics
University of California, San Francisco
Room S-679, Campus Box 0434
513 Parnassus Avenue
San Francisco, CA 94143
Tel: 415-476-3748 Fax: 415-476-8214
Email: sgitelma@peds.ucsf.edu

This clinical study is supported by JDRF and conducted by the University of California, San Francisco.

Protocol Approval

A	B
Trial ID:	Protocol Version: 8.0
	Dated: August 23, 2016
IND # 117,644	Protocol Chairs: Jeffrey Bluestone, PhD and StephenGitelman, MD
Title: Safety and Efficacy of Imatinib for Preserving ß-cell Function in New-onset Type 1Diabetes Mellitus	
I confirm that I have read the above protocol in the latest version. I understand it, and I will workaccording to the principles of good clinical practice (GCP) as described in the US Code of FederalRegulations (CFR)—45 CFR part 46 and 21 CFR parts 50, 56, and 312, and in the InternationalConference on Harmonization (ICH) document Guidance for Industry: E6 Good Clinical Practice:Consolidated Guidance dated April 1996. Further, I will conduct the study in keeping with local legaland regulatory requirements. As the principal investigator, I agree to carry out the study by the criteria written in the protocoland understand that no changes can be made to this protocol without written permission of the studysponsor. Principal Investigator (Print) Principal Investigator (Sign) Date	

Synopsis

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

IND Sponsor Stephen E. Gitelman, MD

Conducted by University of California, San Francisco

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Protocol Chairs Jeffrey Bluestone, Ph.D. and Stephen E. Gitelman, MD

Accrual Objective Total of 66 participants will be enrolled during ~78 to 104 weeks.

Study Duration Each participant will be in the study for 104 weeks.

Study Design The study will be a multicenter, two-arm, double-blind, placebo-controlled, 2:1 randomly assigned, phase II clinical trial for individuals with recent-onset T1DM. The randomly assigned participants will receive either a 6-month course of imatinib or matching placebo tablets over a period of 26 weeks. Both treatment and placebo groups will undergo identical procedures and will be followed for 104 weeks. The primary endpoint, 2-hour C-peptide AUC in response to a mixedmeal tolerance test (MMTT), will be measured at 52 weeks. Safety, diabetes control, ß-cell function, and immune function will be assessed for 104 weeks. Both groups will receive intensive diabetes management. During the follow-up phase, participants will undergo serial clinical and immunologic assessments over the 104 week study period, and possible mechanisms of imatinib action will be assessed.

Initial enrollment will be for subjects ages 18-45, with the goal to lower the age down to 12 upon acceptable safety review and prospect of benefit for this initial older cohort. When the first 10 enrollees have completed their week 26 assessment, the safety data will be reviewed by a subcommittee that includes the protocol chairs, the medical monitor, the clinical trial physician, and the DSMB. If the review concludes that significant safety concerns have been identified, then no further enrollment will occur pending further data review and evaluation by the DSMB. If the DSMB decides that the study may proceed then the FDA will be notified of study progress and determine if further age restriction is necessary, or if enrollment may be opened for subjects down to age 12. After the first 21 subjects have completed 6 months, a further safety review will occur for the DSMB. Additionally, an interim efficacy assessment will occur for the DSMB and FDA. The FDA will again be apprised of study progress, with further consideration for lowering the age of enrollees to 12, if this has not occurred earlier. If and when the age is lowered, an identical review procedure will be followed when the first 10 pediatric participants (ages 12-17) have completed their week 26 assessment. If the review is satisfactory, then enrollment will continue for subjects ages 12-45 until the study is fully enrolled. Adult participants will receive a single 400 mg tablet of imatinib or the corresponding placebo tablet daily for the first 6 months. Pediatric patients will receive 260 mg/m2/day or 400 mg/day (whichever is smaller) of active drug or placebo.

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

Secondary Endpoints:

Efficacy:

- MMTT-stimulated peak and 4 hour C-peptide AUC at weeks 52 and 104
- MMTT-stimulated 2 hour C-peptide AUC at week 104.
- MMTT-stimulated 2-hour C-peptide AUC assessed longitudinally at weeks -4, 13, 26, 52, 78, and 104.
- Insulin use in units per kilogram body weight per day at weeks 52 and 104.
- Major hypoglycemic events, as defined in section 8.2.1, occurring from randomization at weeks 0, 52 and 104.
- HbA1c levels at weeks 52 and 104

Safety:

- The rate of the following AEs in participants receiving imatinib or placebo:

1. Myelosuppression.
2. Gastrointestinal disorders.
3. Infections.
4. Hepatotoxicity.
5. Cardiac toxicity and edema.
6. Cutaneous reactions.
7. Muscle cramps, bone pain, arthralgias.
8. Fluid retention or peripheral edema.
9. Bone metabolism and growth abnormalities (not including bone turnover markers).

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10.Frequency and severity of all AEs in participants receiving imatinib or placebo.

Mechanistic:

Immunological assessments described in section 7 will be compared with clinical outcomes to determine whether there is evidence of immune tolerance to diabetes-associated autoantigens.

Metabolic:

- Proportion of patients who are exogenous insulin-free (for at least 3 months) with an HbA1C ≤ 6.5% at weeks 52 and 104 in each treatment arm.
- Proportion of subjects who achieve a persistent reduction (for at least 3 months) in insulin dose to < 0.5 units/kg at weeks 52 and 104 in each treatment arm.
- Effects on insulin resistance as derived from data on MMTT, and change in adiponectin, proinsulin levels (and proinsulin/c-peptide ratio), and glucagon levels

Inclusion Criteria

- Males and females age 12–45 years of age who meet the ADA standard T1DM criteria1. Positive for at least one islet cell autoantibody.
- Diagnosis of T1DM within 100 days of Visit 0.
- Peak stimulated C-peptide level >0.2 pmol/mL following an MMTT at screening.
- Participants of childbearing age who are sexually active must agree to effective contraception. For females, these contraceptive measures must be maintained throughout the study; for males these measures must be followed for a minimum of 3 months after discontinuation of imatinib therapy.

Exclusion Criteria

- Prior history of any significant cardiac disease such as congestive heart failure, myocardial infarction, arrhythmia, or structural defects or suspicion thereof.
- Leukopenia (<3,000 leukocytes/μL), neutropenia (<1,500 neutrophils/μL), or thrombocytopenia (<125,000 platelets/μL).
- Low Hemoglobin (baseline hemoglobin below lower limit of normal)
- Prior history of anaphylaxis, angioedema or serious cutaneous drug reactions
- Any sign of significant chronic active infection (e.g., hepatitis, tuberculosis, EBV, CMV, or toxoplasmosis), or screening laboratory evidence consistent with a significant chronic active infection (such as positive for HIV, PPD/IGRA, or HBSAg). Significant acute infections must be resolved before treatment may commence, e.g., acute respiratory tract, urinary tract, or gastrointestinal tract infections.
- Anticipated ongoing use of diabetes medications other than insulin that affect glucose homeostasis, such as metformin, sulfonylureas, thiazolidinediones, glucagon-like peptide 1 (GLP-1) mimetics, dipeptidyl peptidase IV (DPPIV) inhibitors, or amylin.
- Prior or current treatment that is known to cause a significant, ongoing change in the course of T1DM or immunologic status, including high-dose inhaled, extensive topical or systemic glucocorticoids.
- Evidence of liver dysfunction, with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 times the upper limit of normal persistent for 1 week or greater.
- Evidence of renal insufficiency as indicated by serum creatinine > 1.2 times the upper limit of normal and confirmed in a repeat test at least one week apart. Evidence of clinically significant metabolic bone disease (except adequately treated rickets).
- Females who are pregnant at the time of screening or unwilling to defer pregnancy during the 24-month study period.
- Prior treatment with imatinib or related tyrosine kinase inhibitor.
- Unable to avoid medications that affect CYP3A4: either inducers that may decrease imatinib levels, or inhibitors that may increase drug concentrations. (Refer to section 1.5.1.12 for a complete list of inducers and inhibitors.)
- Height standard deviation score ≥2 standard deviations below mean (participants of growing-age potential).
- Any sign of QT prolongation on Visit -1 noted on ECG (> 450 ms in males and > 470 ms in females).
- Known coagulation disorders or use of anticoagulants.
- Current and anticipated on-going treatment with drugs that may increase or decrease imatinib plasma

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concentrations (CYP3A4 family inhibitors or inducers) or drugs that may have their plasma concentration altered by imatinib (drugs metabolized by CYP3A4/5 and CYP2D6).

- Any condition that, in the investigator's opinion, may compromise study participation or may confound the interpretation of the study results.

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LIST OF APPENDICES

Citation: Stephen.Gitelman , Jeffrey A. Bluestone (06/11/2021). Collection of Protocols and Guidelines for Safety and Efficacy of Imatinib for Preserving Beta-cell Function in New-onset Type 1 Diabetes Mellitus. https://dx.doi.org/10.17504/protocols.io.bvfqn3mw

LIST OF FIGURES

ABBREVIATIONS

A	B
ADA	American Diabetes Association
AE	Adverse event
ALT	Alanine aminotransferase
ANCA	Anti-neutrophil cytoplasmic autoantibodies-associated vasculitis
AST	Aspartate aminotransferase
ATG	Antithymocyte globulin
ATP	Adenotriphosphate
AUC	Area under the curve
CBC	Complete blood count
CFR	Code of Federal Regulations
CML	Chronic myeloid leukemia
CMV	Cytomegalovirus
CRF	Case report form
CRO	Contract research organization
CTL	Cytotoxic T cell
CY	Cyclophosphamide
DB/DB	Diabetic dyslipidemia
DC	Dendritic cell
DCCT	Diabetes Control and Complications Trial
DPT-1	Diabetes Prevention Trial of Type I Diabetes
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr virus
EDIC	Epidemiology of Diabetes Interventions and Complications Study
FDA	US Food and Drug Administration
GAD	Glutamate decarboxylase
GCP	Good clinical practice
GIST	Gastrointestinal stromal tumors
HbA1C	Hemoglobin A1C
HBSAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IFNγ	Interferon gamma
IGRA	Interferon Gamma Release Assay
IRB	Institutional Review Board

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ITN	Immune Tolerance Network
LFTs	Liver function tests
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MMTT	Mixed-meal tolerance test
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NFkB	Nuclear factor kappa B
NK	Natural killer cell
NKT	Natural killer T cell
NOD	Nonobese diabetic
PCR	Polymerase chain reaction
PDGFR	Platelet-derived growth factor receptor
PPD	Purified protein derivative test
PTH	Parathyroid hormone
IGRP	Islet-specific glucose-6-phosphatase catalytic subunit related protein
SAE	Serious adverse event
SAP	Statistical analysis plan
STZ	Streptozotocin
T1DM	Type 1 diabetes mellitus
TCR	T cell receptor
TK	Tyrosine blocking
TNFα	Tumor necrosis factor alpha
Tregs	Regulatory T cells
TUNEL +	TdT-mediated dLJTP-biotin nick-end-labeling positive cells
WHO	World Health Organization

PUBLICATION POLICY

The JDRF policy on publication of study results will apply to this study.

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Appendix 1. Schedule of Events:

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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
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.

[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.

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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
Plasma Glucose (tested from MMTT)[7]	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[8]	X					X			X		X	X	X
Plasma-Proinsulin[8]	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.

ABSTRACT

This is a collection of protocols for: "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

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FILES

Background and Rationale (Part 1 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus)
Version 1
by Stephen.Gitelman

Objectives (Part 2 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus)
Version 1
by Stephen.Gitelman

Study Design (Part 3 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus)
Version 1
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Eligibility (Part 4 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus)
Version 1
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Study Medications (Part 5 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus)
Version 1
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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)
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Mechanistic Assays (Part 7 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus)
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Adverse Events (Part 8 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus)
Version 1
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Statistical Considerations and Analysis Plan (Part 9 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus)
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Access to Source Data/Documents (Part 10 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus)
Version 1

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by Stephen.Gitelman

Quality Control and Quality Assurance (Part 11 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus)
Version 1
by Stephen.Gitelman

Ethical Considerations and Compliance with Good Clinical Practice (Part 12 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus)
Version 1
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Schedule of Events (Appendix 1 of "Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus")
Version 1
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Procedures for Performing the Mixed-Meal Tolerance Test (Appendix 2 of "Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus")
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