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Background and Rationale (Part 1 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 1 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 β cells and lead to the preservation of C-peptide secretion in T1DM and to assess Diabetes-related objectives and safety of Imatinib in participants with new-onset type 1 diabetes mellitus".

ATTACHMENTS

[dngubkeaf.pdf](#)

GUIDELINES

1.1 OVERVIEW:

Type 1 diabetes mellitus (T1DM) results from the autoimmune destruction of insulinproducing β cells. Although exogenous insulin is widely available, it is not possible for affected individuals to consistently achieve euglycemia with current technology, and thus they are at risk for devastating long-term complications. This phase II study is designed to evaluate the safety and efficacy of imatinib mesylate as a novel therapy for new-onset T1DM. Imatinib is a first-in-class tyrosine kinase inhibitor that has had remarkable success as a therapy for several cancers, including

Keywords: Safety, Efficacy, Imatinib, Beta-Cell Function, New-Onset Type 1 Diabetes Mellitus

chronic myelogenous leukemia (CML). In preclinical studies, imatinib is one of only a handful of agents that has been shown in the nonobese diabetes (NOD) mouse to induce a durable remission of new-onset diabetes without continuous ongoing therapy. These findings have been extended to the clinical arena, where case reports and smaller studies have shown positive effects of imatinib in patients with autoimmune conditions and for type 2 diabetes. Although the mechanism whereby this agent functions has not been fully elucidated, the possibility that short-term therapy with imatinib can induce tolerance and lead to a durable long-term remission makes it a very attractive potential therapy for new-onset T1DM.

1.2 BACKGROUND:

T1DM is a chronic autoimmune disease in which insulin-producing β cells are completely destroyed, resulting in a lifelong dependence on exogenous insulin.²⁻⁵ Current management of T1DM is not optimal. To avoid long-term complications, affected individuals must maintain near-normal glycemic control by frequent glucose monitoring, and by taking multiple daily doses of insulin (via injection or pump) adjusted for variations in diet and exercise.⁶ Such strict glycemic control is rarely achieved with current T1DM management, and can result in recurrent severe hypoglycemia. Thus, it is not possible to fully mimic β -cell function with current therapies, and there are currently no established treatments that can prevent the autoimmune β -cell destruction before diagnosis.

After clinical presentation, affected individuals often enter a “honeymoon,” or remission, phase when they are still able to make substantial amounts of insulin.⁷⁻⁹ Nevertheless, endogenous insulin secretion continues to slowly deteriorate over the first few years of disease, eventually becoming undetectable and necessitating increasing reliance on exogenous insulin. Past studies have demonstrated that preservation of even modest endogenous insulin secretion dramatically improves metabolic control of T1DM, which, in turn, is associated with reduced morbidity and mortality.¹⁰⁻¹³ The ultimate goal of this study is to identify a means of blocking further autoimmune destruction of the β cells, retaining endogenous insulin secretion and thereby improving metabolic control. Eventually, such a therapy may also be used at an even earlier stage to prevent T1DM.

T1DM occurs in those who have an underlying genetic risk in synergy with one or more environmental exposures.²⁻⁵ Increasing evidence suggests that both adaptive and innate immunity may play a role.^{14,15} This process is mediated by the progression of a destructive T-cell infiltration of insulin-producing β cells. Both CD4+ and CD8+ T cells cooperate in the initiation of insulinitis and β -cell destruction occurs via cytokines (e.g., IFN γ , TNF α) and direct cytolytic activity.^{2-4,16-19} Development and propagation of this autoimmune destruction is not solely dependent on T cells, with potential roles ascribed to B cells, NK cells, NKT cells, dendritic cells (DCs), and

macrophages.^{3,20-24} For example, B-cell depletion in the NOD mouse has been shown to prevent and reverse diabetes,^{25,26} and in a recent clinical trial subjects with new-onset T1DM treated with rituximab, an anti-CD20 monoclonal antibody (mAb) had slower decline in β -cell loss than controls.²⁷ Thus, agents affecting more than one cell type of the immune system, or with effects on inflammation, may have greater efficacy in modulating the autoimmune response.

Several promising studies have shown that interventions shortly after the time of T1DM diagnosis can alter the natural course of the honeymoon phase. Cyclosporine prolongs endogenous insulin secretion, and some participants experienced complete remission.^{28,29} However, long-term treatment is limited by toxicity and by the transience of the effects.³⁰⁻³² More targeted therapy with a short course of two different preparations of an anti-CD3 mAb have been promising, although not all respond, and the effects wane over time.³³⁻³⁶ Recent new onset trials with other agents have had mixed results, with some agents causing acute worsening in beta cell function (IL-2 with rapamycin, Long et al, Diabetes, in press), some showing no effect^{37,38} and some showing initial preservation but without sustained effects.^{27,39} Despite these early successes, there is ongoing concern with the durability of the response, and the safety and tolerability of the agents offered. Thus, there is currently no established, acceptable immunotherapy for new-onset T1DM to preserve endogenous insulin secretion. The limitations may stem from the need for a multi-faceted approach to interdicting the autoimmune response, using either a combination of drugs⁴⁰, or a drug that affects multiple different cell types or pathways. The drug proposed in this trial, imatinib, falls into this latter camp.

1.3 SCIENTIFIC RATIONALE

Imatinib mesylate, also known as CGP57148B, STI-571, Gleevec®, or Glivec® (Novartis), is a specific inhibitor of the Abl protein tyrosine kinases (v-Abl, Bcr-Abl, and c-Abl).⁴¹⁻⁴³ Imatinib's activity against cells bearing the Bcr-Abl translocation, created by the Philadelphia chromosome abnormality, has resulted in a unique niche for the treatment of CML.⁴⁴⁻⁴⁸ However, imatinib's activity is not limited to Abl, as it also inhibits other constitutively activated tyrosine kinases, such as platelet-derived growth factor receptor (PDGFR), c-kit (CD117), macrophage colony stimulating factor receptor (c-fms), Abl-related gene, and Lck, whereas other kinases are probably not affected.⁴⁹⁻⁵⁴ The inhibitory activity against c-kit and PDGFR has resulted in imatinib's expanded use as a therapy for gastrointestinal stromal tumors (GIST),⁵⁵ eosinophilic disorders,⁵⁶ and systemic mast cell disease.^{56,57}

In addition to its remarkable effect on malignant cells, imatinib has been shown to affect various arms of the immune system. Imatinib treatment may lead to impaired

T-cell function and decreased DC number in CML patients,⁵⁸⁻⁶⁰ although other studies have not documented such effects.⁶¹⁻⁶⁴ Similarly, while some reports suggest that imatinib enhances DC function both in human^{65,66} and mouse,⁶⁷⁻⁶⁹ other studies demonstrated that relatively high concentrations (1–5 μ M) inhibited the development and the functional capacity of human or mouse DCs,⁷⁰⁻⁷² as well as human monocytes/macrophages.⁷³⁻⁷⁵ Several investigators have now shown that imatinib has significant anti-inflammatory properties in different mouse models. Wolf et al demonstrated in a mouse model of acute hepatic inflammation that imatinib inhibits tumor necrosis factor-alpha (TNF α) production in macrophages, conferring a strong anti-inflammatory effect.⁷⁶ Dietz et al noted that delayed-type hypersensitivity was reduced in mice treated with imatinib.⁷⁷

Most recently, it has become clear that imatinib can function as an effective immunosuppressive drug. In preclinical studies, imatinib efficiently prevents disease and induces remission of mouse and rat models of autoimmune arthritis.⁷⁸⁻⁸⁰ Moreover, this drug inhibits collagen-induced arthritis effectively in mice and blocks PDGFR-mediated signaling in synovial fibroblasts obtained from rheumatoid arthritis patients.⁸¹⁻⁸³ Efficacy in rheumatoid arthritis may also result from effects on mast cells: treatment of rheumatoid synovia in vitro with imatinib inhibits c-kit and induces apoptosis of mast cells.⁸⁴ Furthermore, imatinib treatment ameliorates autoimmune nephritis in two mouse models of lupus.^{85,86} In studies of scleroderma, Soria et al reported that imatinib limits dermal fibroblast proliferation.⁸⁷ Imatinib reduces production of extracellular matrix and suppresses experimental fibrosis,⁸⁸ and prevents fibrosis in different models of systemic sclerosis.⁸⁷ Imatinib inhibits PDGF-mediated responses related to the development of intimal hyperplasia in giant cell arteritis.⁸⁹ Imatinib may also be effective in the treatment of anti-neutrophil cytoplasmic autoantibodies-associated vasculitis (ANCA), based on inhibition of T-cell activation in samples taken from affected patients.⁹⁰

These findings have been extended to the clinical arena, where a few case reports and a phase I study show positive effects of imatinib in patients with rheumatoid arthritis.^{79,91-94} Early studies suggest that imatinib may have a role in the treatment of systemic sclerosis.⁹⁵⁻⁹⁸ Imatinib therapy improved cutaneous sclerosis and inflammatory manifestations of the disease in 3 treated subjects,^{96,97} and a specific gene signature of imatinib response has been identified.⁹⁶ Seven trials evaluating the efficacy of Imatinib in systemic sclerosis are now posted on the clinicaltrials.gov web site. Imatinib was also effective and well tolerated in a phase I study of 6 patients with active spondyloarthritis.⁹⁹ There is a case report of a patient with bullous pemphigoid, the most frequent autoimmune blistering dermatosis, with eosinophilia and a deletion consistent with hypereosinophilic syndrome, who

responded to imatinib therapy.¹⁰⁰ There is one case report of imatinib therapy inducing a long-standing remission in a patient with Crohn's disease, without significant side effects.¹⁰¹ Imatinib has also been reported to treat intractable psoriasis in a patient who was receiving this agent for GIST.¹⁰²

Although the aforementioned studies suggest efficacy, the mechanisms are unclear. In vitro studies suggest that imatinib may have direct effects on T-cell, B-cell, and antigenpresenting cell signaling and function. Imatinib can inhibit human T-cell proliferation in vitro without inducing apoptosis,^{77,103,104} and analysis of the TCR-induced signaling cascade revealed a reduced phosphorylation of ZAP-70, LAT, Lck and ERK1/2, as well as reduced levels of activated NFκB.^{77,104,105} Interestingly, Lck has been suggested as a direct target of imatinib.⁵² Studies in the mouse demonstrated that imatinib could impair memory CD8+ T-cell development but did not affect the primary response and cytotoxic activity or induce apoptosis.¹⁰⁶⁻¹⁰⁸ However, lytic function of human CD8+ T cell has recently been shown to be inhibited by imatinib.¹⁰⁹

The proposed trial represents a unique approach to the treatment of T1DM and will provide critical validation of the hypothesis that a new class of kinase inhibitors, represented by the first-in-class compound imatinib, will demonstrate a novel therapy for T1DM. The possibility that short-term therapy with imatinib can induce tolerance and lead to a durable long-term remission makes it a very attractive potential therapy for patients with new-onset T1DM. If this therapy is safe and effective, then its use can be expanded to other autoimmune disorders, and possibly to T1DM prevention.

1.4 PRECLINICAL AND CLINICAL EXPERIENCE:

1.4.1 Preclinical Studies:

1.4.1.1 Studies in the NOD Mouse:

The known mechanisms of imatinib action and observations in other autoimmune settings suggest that imatinib may have an important role in treating T1DM. Hagerkvist et al noted that imatinib prevents T1DM in the NOD mouse when administered from 9 to 35 weeks of life; it did not affect the extent of islet inflammation when given from 3 to 9 weeks of age or when treated out to 35 weeks, but the β-cell area is significantly greater in treated animals.¹¹⁰ They also examined specific effects of imatinib on the β cell. Three doses of imatinib partially protect against T1DM in streptozotocin (STZ)- injected mice. It also protects cultured islets from various apoptosis-promoting agents, including pro-inflammatory cytokines, nitric oxide, and STZ.^{110,111} Thus, imatinib appears to act on multiple levels in

diabetes, including reduction of insulin resistance and prevention of β -cell apoptosis. The authors concluded that imatinib enhances β -cell survival via a mechanism similar to ischemic preconditioning, as they found NF κ B activation, increased nitric oxide and reactive oxygen species production, and depolarization of the inner mitochondrial membrane.

1.4.1.1.1 Prevention of T1DM

Treatment of prediabetic NOD mice starting at 12 weeks of age (a stage when insulinitis is firmly established)¹¹² with imatinib orally once a day at 1.5

Figure 1. Induction of diabetes remission. Imatinib or oil treatment was initiated at the time of disease onset (blood glucose >250 mg/dL) and continued for 3 weeks. Individual glucose readings for imatinib- (A) and oil-treated mice (B) are shown. (C) The percentage of diabetic mice is shown for each group : imatinib n=28, oil n=15. From Louvet et al.¹¹²

mg/mouse for 7 weeks led to complete protection from hyperglycemia during treatment, whereas half of the control mice developed diabetes. After cessation of treatment, only ~40% of the imatinib-treated animals became progressively diabetic. The majority of the mice remained nondiabetic at more than 50 weeks of age. Treatment of mice with cyclophosphamide (CY)-induced diabetes (a more robust model with rapid onset of disease) resulted in only ~30% of imatinib-treated animals developing diabetes within 3 weeks after CY injection, in contrast to 85% of the control mice. These results confirmed that imatinib can prevent T1DM.

1.4.1.1.2 Remission Induction

Many agents prevent T1DM in the NOD mouse before the development of insulinitis,^{20,113} but only a handful of agents are successful in inducing remission in overtly diabetic NOD mice. Louvet et al¹¹² found that only 1 week after initiation of treatment, imatinib reversed diabetes in more than 40% of diabetic animals (Figures 1A and 1C) and after 2 weeks the remission rate jumped to ~80% of the mice (n = 28). The effect of imatinib was most notable in mice with glucose levels that were modestly elevated at diagnosis (250–350 mg/dL) but was also effective in mice with glucose levels > 300–450 mg/dL, although less so. Mice treated with vehicle alone did not reverse diabetes (Figures 1B and 1C).

Figure 1. Induction of diabetes remission. Imatinib or oil treatment was initiated at the time of disease onset (blood glucose >250 mg/dL) and continued for 3 weeks. Individual glucose readings for imatinib- (A) and oil-treated mice (B) are shown. (C) The percentage of diabetic mice is shown for each group : imatinib n=28, oil n=15. From Louvet et al.¹¹²

1.4.1.1.3 Tolerance Induction:

With cessation of imatinib therapy at 3 weeks, all mice became hyperglycemic within 10 weeks (Figure 2A). However, by increasing treatment duration from 3 weeks to 10 weeks the majority of the mice remained euglycemic (Figure 2B).¹¹² Thirty-five weeks after initiation of therapy, ~50% of imatinib-treated animals had reversed from diabetes into a state of long-term tolerance without the need of continuous treatment.

Figure 2. Long-lasting remission of diabetic NOD mice. Imatinib treatment (gray shaded area) was initiated at the time of disease onset and continued for (A) 3 weeks (n=8) or (B) 10 weeks (n=17). From Louvet et al.¹¹²

1.4.1.1.4 Leukocyte Infiltration of the Pancreas:

Treatment of prediabetic NOD mice for variable periods of time with imatinib did not prevent insulinitis.¹¹² There were subtle differences in severe and mild insulinitis in the drug-treated versus control islets, but these findings were not statistically significant, in accord with prior studies.¹¹⁰ Similarly, pancreatic islets from long-term normoglycemic mice after cessation of imatinib treatment still harbored significant insulinitis. Thus, while preventing clinical disease, imatinib does not eliminate leukocyte infiltration of the pancreas. It should be noted that this observation is different from what has been observed for anti-T-cell agents such as Thymoglobulin and anti-CD3, which clear the islets of infiltration, suggesting a different mechanism of action.^{114,115}

1.4.1.1.5 Relevance of Tyrosine Kinase–blocking Activity:

As documented previously,¹¹⁶ imatinib can affect a series of tyrosine kinases in vitro including abl, c-kit, c-fms, and PDGFR. To pinpoint the relevant kinases in T1DM therapy, different TK-blocking agents that share targets with imatinib have been tested.¹¹² These studies suggest that the dramatic effects of imatinib in the reversal of diabetes are not due to a single drug activity but due to the combination of the anti-inflammatory effects short term, due at least in part to its PDGFR antagonism, combined with longer term effects, perhaps due to its c-abl- and c-kit-specific activities. A clinical case report (see section 1.3.2) lends further support for this proposal.¹¹⁷

1.4.1.2 Studies in Rat and Mouse Models of T2DM:

Hagerkvist et al reported that imatinib normalizes peripheral insulin resistance in rats fed a high-fat diet.¹¹⁸ Han et al extended these observations in the diabetic dyslipidemia (db/db) mouse, noting that imatinib reduces insulin resistance and induces diabetes remission.¹¹⁹ Liver steatosis and serum transaminitis are markedly reduced in treated animals. Imatinib also decreased TUNEL+ apoptotic β cells and increased BrdU+ β - cell numbers. A unifying explanation for these effects is that imatinib ameliorates endoplasmic reticulum (ER) stress: ER stress appears to play an important role in insulin resistance, and Abl kinase, an imatinib target, has been reported to play a role in this process.¹²⁰ Indeed, a variety of ER stress markers in the liver and adipose tissue were reduced by imatinib treatment of these animals. Recent findings that kinase inhibition of IRE1 α ameliorates ER stress and consequent apoptosis¹²¹ lends additional support to the potential role of imatinib in this process.

1.4.2 Clinical Studies in Patients with Diabetes:

Since approved for treatment of CML, several case reports and small case series have appeared describing patients with T2DM who have experienced significant improvement or resolution on imatinib.¹²²⁻¹²⁴ Reductions in cholesterol and triglycerides have also been described in treated patients.¹²⁵

These changes have not been ascribed to significant effects with decreased appetite or weight loss. Fitter et al¹²⁶ have further evaluated mechanisms whereby metabolic control improves for subjects with T2DM treated with imatinib. They have noted that adiponectin levels increase ~ 3-fold within 3 months of initiating imatinib, and remain elevated with on-going therapy out to 12 months. This adipokine increases glucose uptake and fatty acid oxidation in muscle, and decreases hepatic gluconeogenesis; low adiponectin levels are associated with increased insulin resistance and higher risk for T2DM.

In a case report of another tyrosine kinase inhibitor, a 64-year-old man with metastatic renal cell carcinoma was started on sunitinib 8 months after the diagnosis of diabetes.¹¹⁷ He was presumed to have T1DM, based on strongly positive GAD antibody titers. After ~15 weeks on sunitinib, the insulin dose was decreased, until he discontinued insulin altogether at ~45 weeks on sunitinib. Sunitinib was discontinued at about that same time, but glycemic control has remained near normal over the ensuing 30 weeks, with persisting elevation of GAD antibody titers. His weight remained stable over the treatment period.

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

1.5.1 Risks

1.5.1.1 Overview

There is an extensive safety experience in patients treated with imatinib for CML and GIST (see larger clinical trials in Refs. ^{45,47,55,127-131} and the package insert at http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf). Overall, imatinib has been well tolerated in clinical trials. Adverse events (AE) are typically mild to moderate (grades 1 to 2) and manageable without dosage reduction or permanent discontinuation of therapy. The most common side effects include gastrointestinal reactions (nausea, vomiting, and diarrhea), edema, muscle cramps, and rash. Hematological toxicities (thrombocytopenia, neutropenia, and anemia) are dosedependent and reversible, and noted much more frequently in CML than in GIST, suggesting they relate in large part to the underlying disease. Specific issues are discussed in more detail below. These side effects tend to be more noticeable in older and sicker patients who are on higher doses of imatinib. Many of these adverse events may improve spontaneously while continuing therapy at the same

dose. It is difficult to extrapolate fully from the past safety and tolerability experiences in cancer to a diabetes setting, in which our study participants will be younger, will be carefully selected so as not to have concurrent or chronic medical problems, and will be on lower doses of the drug and for a shorter duration. Our expectation, however, is that the therapy will be even better tolerated than in other settings in which it has been traditionally used (B. Druker, Oregon Health Sciences University, personal communication). The published and unpublished experience has been that imatinib is generally better tolerated in younger patients, including children.¹³²⁻¹³⁵ No AEs unique to children have been reported, with the possible exception of transient, reversible effects on growth rate (as detailed in section 1.5.1.11).

1.5.1.2 Gastrointestinal Reactions

Nausea constitutes the most common side effect of therapy. It has been noted in up to 40%–60% of subjects with CML or GIST, and it is usually mild, grade 1, and dose related. Nausea occurs much more commonly when the drug is taken on an empty stomach, and can be avoided when taken with food. Ingestion with food has not been shown to affect pharmacokinetic parameters. Diarrhea is also experienced by some patients, possibly from imatinib blockade of c-kit, and is often dose related.

1.5.1.3 Edema

Edema is present in about half of patients on imatinib. It is usually superficial, mild to moderate in nature, and does not require specific therapy. It usually manifests as periorbital edema and is most noticeable first thing in the morning. Edema in the lower extremities is noted much less frequently. More marked issues with fluid retention, such as pulmonary edema or ascites, occur rarely, and have typically been limited to those with more advanced stages of CML. This issue generally occurs at higher doses, and in elderly patients, and has been less common in children.

1.5.1.4 Cutaneous Reactions

Cutaneous reactions have been reported in ~30% of patients during imatinib treatment. The rashes are often pruritic, and most commonly erythematous, maculopapular lesions on the forearms and trunk, and sometimes also involve the face. The rashes are usually mild (grades 1–2) and self-limited. About 3% are higher grade, and again are usually associated with higher doses of therapy. Severe exfoliative rashes have been noted in 1 in 500 treated subjects, and they usually occur early in the course of treatment. Imatinib treatment has been associated on rare occasions with induction of vitiligo-like lesions, which may be related to blockade of c-kit in melanocytes.^{136,137} This finding appears to increase with dose and duration of treatment, and is reversible with dose reduction or discontinuation. Paradoxically, a patient with vitiligo has been described who had repigmentation of

his lesions while on imatinib treatment for GIST.¹³⁸

1.5.1.5 Muscle Cramps, Bone Pain, Arthralgias

Arthralgias affect 25%–50% of treated patients. As with other issues, this is usually mild to moderate, and manageable without reduction of the drug dose. Cramps usually occur in the hands, feet, calves and thighs, and tend not to change over time in terms of location, frequency, and intensity. Ionized calcium and magnesium levels are normal. Bone pain and arthralgias are reported typically early in the course of therapy and usually subside after several months.

1.5.1.6 Hepatotoxicity

Liver toxicity, if an issue, usually emerges during the first few months of therapy, but can be a late finding. Frequent monitoring of liver function is suggested during therapy. Grade 1 elevations in transaminases occur in up to 10% of treated patients and often normalize while continuing on therapy. Grade 3 events have been reported in 2%–5% of subjects in GIST and CML trials, but these events may be confounded by a variety of other factors, including leukemic liver infiltration. For grade 3 events in oncology settings, therapy is temporarily interrupted. Imatinib is permanently discontinued for grade 3 events that recur with drug re-challenge.

1.5.1.7 Myelosuppression

The development of myelosuppression is much more common in CML than GIST, and may relate to the underlying effects of the cancer on the bone marrow. In the phase II study of imatinib for GIST, anemia (9% of subjects, 2% grades 3 or 4), neutropenia (7% of subjects, 5% grade 3 or 4), and leukopenia (5% of subjects, 1% grades 3 or 4) were the most commonly reported findings; grades 3 or 4 thrombocytopenia was noted in <1%. Complete blood counts with differential will be monitored at the same time points as liver function tests. For myelosuppression of grade 3 or higher severity in oncology settings, therapy is temporarily interrupted, and permanently discontinued for grade 3 events that recur with drug re-challenge.

1.5.1.8 Cardiac Toxicity

Prior concern was raised that imatinib may induce cardiac dysfunction, based on a report of 10 subjects with left ventricular dysfunction and congestive heart failure.¹³⁹ The ejection fraction for these subjects dropped significantly during the course of imatinib therapy, but the authors did not report the size of the underlying cohort from which these cases were derived, nor did they report baseline cardiac function, or other physiological risk factors that might be associated with cardiac dysfunction. A subsequent retrospective review of a large database of 942 GIST patients treated with 400–800 mg of imatinib for a median of 24 months revealed

only 2 patients (0.2%) who may have had a cardiotoxic effect from this drug.¹⁴⁰ Atallah et al reported that 0.6% of 1276 patients (median age 70) treated with imatinib developed congestive heart failure, and half of these continued therapy.¹⁴¹ The cases typically occurred in elderly patients with preexisting cardiac conditions. A recent study in knockout mice revealed that PDGFR- β signaling is required for the cardiac response to pressure overload-induced stress.¹⁴² This provides a mechanistic basis for the observation that cardiac toxicity induced by PDGFR inhibitors, such as imatinib, is generally observed only in patients with preexisting cardiac conditions. Druker (personal communication) has not noted any cardiac issues in treatment of over 1000 patients with imatinib, with the exception of 2 patients over age 65 who developed congestive heart failure; thus, aside from a careful past medical history he does not suggest routine cardiac studies for subjects on imatinib. The relatively short course of proposed treatment and younger, otherwise healthy population would suggest that this will not be an issue in this trial. Subjects enrolled in this trial will have careful baseline history and physical examination to ensure no preexisting cardiac problems.

1.5.1.9 Infectious Disease

Imatinib has been well tolerated, and patients receiving chronic therapy do not appear to be abnormally susceptible to viral infections or opportunistic infections.^{45,47,55,127,128,131} Further reassurance comes from evaluation in a mouse model in which imatinib selectively impaired expansion of memory cytotoxic T cells but the expansion of naïve cytotoxic T-cells (CTLs) in response to viral infection in vitro and in vivo was not impaired.¹⁰⁷

1.5.1.10 Reproductive Toxicity

Despite the growing clinical experience with imatinib in CML and GIST, there is still only limited data on the effects of imatinib on fertility and/or pregnancy. Animal studies have shown that this drug is teratogenic in rats but not rabbits (Gleevec IB). Spermatogenesis is impaired in rats, dogs, and monkeys. Female rats receiving imatinib doses of 45 mg/kg, which approximates the usual clinical dose of 400 mg/day, experience significant post-implantation loss, including increased fetal resorption, stillbirth, and early pup mortality. It does not appear to cause chromosome damage. Exposure to doses of 100 mg/kg (approximating a clinical dose of 800 mg/day) during organogenesis results in teratogenic effects, with exencephaly or encephalocele, and absent or reduced frontal and parietal bones. Based on these studies, it has been classified as a class D drug. However, there have been a series of case reports and small series reporting normal outcomes following pregnancies.¹⁴³⁻¹⁵¹ The largest compilation of clinical experience is from a retrospective chart review of 180 women exposed to drug during pregnancy; outcome data were available for 125.¹⁵⁰ Of these, 50% delivered normal children and 28% had elective terminations (3 following the identification of abnormalities).

Twelve infants had abnormalities identified, 3 with a similar complex of malformations. There did not appear to be a higher rate of spontaneous abortion. Thus, although most fetuses exposed to imatinib appear to be unaffected, there is a risk for potential malformation. In light of these findings, investigators need to ensure that all participants avoid pregnancy.

1.5.1.11 Bone and Mineral Metabolism

One small sub-study has noted hypophosphatemia with increased PTH, low normal serum calcium, and increased urinary phosphorous in patients treated with imatinib.¹⁵² The authors postulate that this is an effect mediated by PDGFR inhibition. Further studies in vivo and in vitro suggest that short-term therapy with imatinib (on the order of 3-6 months) causes an uncoupling of bone turnover, with activation of bone formation via promotion of osteoblast differentiation, and inhibition of resorption by inhibition of osteoclastogenesis and promotion of osteoclast apoptosis.¹⁵³

A recent study in rats indicated that imatinib treatment (4–12 weeks duration) resulted in narrowing or premature closure of the growth plate in the proximal tibia, although the animals were not assessed for a follow-up period after drug was withdrawn.¹⁵⁴ Three recently published case studies report decelerated growth in juvenile CML patients undergoing imatinib therapy.¹⁵⁵⁻¹⁵⁷ Notably, one of the patients progressed through puberty and reached appropriate final adult height for family while being treated continuously with imatinib¹⁵⁶; another patient experienced growth acceleration following discontinuation of imatinib¹⁵⁵, but final height was not reported¹⁵⁵

In the initial reports from the pediatric CML trials with imatinib, no growth or bone metabolism issues were reported.^{132-135,158} Following the case reports noted above, Japanese investigators performed a retrospective analysis of 48 children with CML treated with imatinib as a first line therapy for a median of 34 months¹⁵⁹. They noted that growth rate decreased in pre-pubertal children (defined as girls < age 9 years, boys < 11 years), with a median decrease after 1 year of ~0.5 in height standard deviation score (Ht-SDS) for chronological age, and further progressive decrement with on-going therapy. However, the growth rate improved during puberty, and children who initiated therapy at a pubertal age appeared to have little or no impact on growth rate. These growth issues may be confounded by a variety of issues associated with a chronic illness such as CML, which in and of itself may impact growth rate, and one should note that decreased growth rate is associated with alternate therapies for CML, such as bone marrow transplantation¹⁶⁰.

1.5.1.12 Drug Interactions

Imatinib is metabolized by the CYP3A4/5 cytochrome P450 enzyme system. Drugs that induce or inhibit this P450 will affect imatinib levels, and should be used with caution, and if possible avoided, during the course of imatinib therapy. Major CYP3A4/5 inducers may decrease imatinib levels; these include carbamazepine, dexamethasone, phenytoin, phenobarbital, progesterone, rifampin, and St. John's wort. Major CYP3A4/5 inhibitors, which will serve to increase imatinib levels, include cimetidine, erythromycin, fluoxetine, ketoconazole, ritonavir, itraconazole, verapamil, and grapefruit juice. Participants who require chronic therapy with any of these agents will be excluded from participation.

1.5.1.13 Malignancies

On-going pharmaco-vigilance data is being collected to assess risk for malignancy following imatinib exposure (see data on file, Gleevec IND 55,666). An integrated review of safety data from imatinib oncology clinical trials suggests that there may be an increased frequency of genito-urinary malignancies. However, the effect is not statistically significant, and it is limited to those subjects treated for > 2 years. Thus, we will exclude any subjects with prior malignancy, and will carefully monitor genitourinary risk throughout the study with serial urinalyses and prostate specific antigen (for male participants) When rats are treated with imatinib for 2 years, they had a shortened lifespan, and higher risk for developing cancers in the kidneys, bladder, urethra, clitoris, small intestine, parathyroid glands, adrenal glands, and stomach. The relevance of these findings to humans is not known.

1.5.2 Potential Risks and Benefits of Trial Participation for Children

Imatinib has been used to treat Ph+ CML in children as young as age 3, and is FDA approved for this indication.^{132,134,135} Smaller trials have also been conducted in children with Ph positive acute lymphoblastic leukemia and some brain tumors^{133,161,162}. Doses of 260-340 mg/m² of imatinib in the pediatric population achieved a similar area under the curve (AUC) to the 400-mg dosing in adults; thus, we plan to employ such dosing in younger or smaller participants enrolled in this trial, offering whichever is the smaller of these two doses to pediatric participants. The safety profile was similar to that in adults, except that there were fewer reports of musculoskeletal pain and peripheral edema. As described in section 1.5.1.11, there is a potential concern about the effects of imatinib on growth, based on preclinical data several case reports, and a retrospective study of pre-pubertal Japanese children with CML (defined as girls < 9 and boys < 11 years of age)¹⁵⁹. With these initial observations in mind, we will limit enrollment to ages 12 and older for this trial. At age 12, girls have completed on average 92% of their growth, and boys 83% of their final adult height¹⁶³, thus limiting potential effects of drug on final height. Furthermore, as opposed to the studies referenced above in cancer, subjects

in this trial will only have a brief 6-month exposure period on study drug, at a modest dose, and thus will not have the long term continuous exposure that has been associated with progressive slowing in growth rate for pre-pubertal children. As detailed in section 5.2.9, effects on growth rate will be carefully assessed in subjects with significant remaining growth potential at study entry, and all subjects will have frequent monitoring of bone metabolism and bone turnover markers. One of the study stopping rules relates to impact of imatinib on growth rate (Section 3.7).

As one of the most common chronic childhood diseases, T1DM is a particular burden to children and their families. While T1DM can occur into adulthood, the worldwide incidence of T1DM is increasing rapidly in children younger than 15 years, as recently documented by the WHO Diamond Project.¹⁶⁴ During the period 1995–1999, the global annual increase in childhood T1DM was 3.4% but was as high as 5.3% in North America.¹⁶⁴ In Europe, the EURODIAB study group has found the greatest rate of increase in the 0–4 years age group and is predicting a doubling in the number of new cases in children younger than 5 years in the next decade.¹⁶⁵ Overall, prevalence of T1DM in children under age 15 in Europe is predicted to rise from 94,000 in 2005 to 160,000 in 2020.¹⁶⁵ In contrast, the incidence of T1DM in young adults over age 15 is not increasing.¹⁶⁵ For these reasons, there is considerable interest in identifying safe and effective interventions that can modify the course of T1DM in pediatric populations. Successful initial preservation of β -cell function in pediatric populations has recently been reported for several treatment modalities.^{27,33–36,39}

Evaluation of new interventions for T1DM in adults may not be informative about their success in children. It is known that the rate of β -cell decline is different in children versus adults (Greenbaum et al, Diabetes)¹⁷⁸, and therefore lack of efficacy of a treatment in adults is not necessarily predictive of efficacy in children.^{27,36} There are currently no approved interventions for new-onset T1DM. In contrast to many interventions currently being studied in the pediatric population, imatinib is approved for use in children and has an extensive clinical safety record. Imatinib is also unique among agents being studied for new-onset T1DM in that it is an oral drug, which has special relevance in the pediatric age group.

1.5.3 Potential Benefits

In this study, all participants will receive intensive diabetes management aimed at achieving near-normal metabolic control per the standard American Diabetes Association (ADA) guidelines.¹ Although intensive diabetes management is recommended for all patients with T1DM, it is not always available to all subjects in the community. The Diabetes Control and Complications Trial (DCCT) research

group documented that improved metabolic control lowers the risk for long-term complications.⁶ The means to achieve this improved control in the DCCT has become the idealized standard of care, with clinical management and education provided by a diabetes specialty team. It should be noted that such care may not necessarily be available to those outside the study, and those who are not seen by a diabetes specialty team may have worse outcomes over time.¹⁶⁶

Improved metabolic control early in the course of T1DM will have a long-standing effect on lowering the risk for long-term complications for many years to follow; i.e., there appears to be a “metabolic memory” that influences later risk. This effect has been documented in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, the long-term follow-up of the DCCT cohort.^{6,12,167-170} Although the conventional group (with less stringent metabolic control) and the intensive group (with near-normal metabolic control) have had comparable HbA1C levels since the end of the formal DCCT study, the intensive group continues to have significantly lower risk for complications 10 years later.

An additional benefit that may be realized by all participants is that maintaining nearnormal glycemic control through intensive diabetes management may, in and of itself, lead to the preservation of β -cell function.^{10,11,13,171} The benefits of endogenous insulin secretion, even if one needs to continue exogenous insulin therapy, have been demonstrated in a number of studies, including the DCCT, where those subjects with residual C-peptide had improved metabolic control, with lower risk for severe hypoglycemia and less likelihood of microvascular complications. Finally, the treatment group may have significant benefits from participation even if imatinib therapy has only modest effects on the preservation of endogenous insulin secretion, which is what was noted in the new-onset T1DM studies with anti-CD3 mAb therapy.^{34,172}

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