Randomized, Double-Blinded, Placebo-Controlled Trial of R788 for the Treatment Adult Chronic Immune Thrombocytopenic Purpura

IRB Protocol
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A. Study Purpose and Rationale

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by antibody-mediated destruction of platelets, as well ad decreased platelet production. Patients with ITP have accelerated clearance of circulating IgG-coated platelets via Fcγ receptor (FcγR)-bearing macrophages in the spleen and liver, and similar autoimmune destruction of megakaryocytes in the bone marrow, leading to different levels of thrombocytopenia and variable degrees of mucocutaneous bleeding[1-3].

Many patients exhibit responses to established therapies, including corticosteroids, IVIG, anti-D, splenectomy, and rituximab. Nonetheless, there are a significant minority of patients who retain persistently low platelet counts despite treatment. They consequently remain at risk for intracranial hemorrhage as well as other bleeding complications. There are a number of medications currently being studied for their ability to safely and stably increase the platelet count in patients with ITP, a testament to the unmet need for better treatments in these patients. For example, several novel thrombopoietic agents have each shown promise in ameliorating thrombocytopenia in some patients with ITP[5,6].

Syk is a protein tyrosine kinase that associates with the FcγR in various inflammatory cells, including macrophages, which are thought to be the cells responsible for platelet clearance in ITP. Binding of FcγRs I, IIA, and IIIA to their ligands induces activation of the receptor complex and phosphorylation of the immunoreceptor activating motifs (ITAMs) with the downstream recruitment and activation of Syk. This in turn leads to activation of various genes resulting in cytoskeletal rearrangement that then mediates phagocytosis in cells of the monocyte/macrophage lineage. Given its central role in FcγR-mediated signal transduction and propagation of the inflammatory response, Syk has been considered a reasonable target for inhibition in various autoimmune and malignant conditions, including rheumatoid arthritis and lymphoma[7,8].

R788 (R935788), a small molecule prodrug of the biologically active R406, is a potent and relatively selective, orally available inhibitor of Syk[9]. In animal models, treatment with R406/R788 has been shown to be safe[10] and effective in reducing inflammation and joint damage in immune-mediated rheumatoid arthritis[11]. We have previously demonstrated that in mice injected with an antibody to integrin αIIβ, a murine model of ITP, pretreatment with R788 was protective against the development of thrombocytopenia[12]. In addition, mice injected with an anti-red cell antibody as a model of AHA also successfully responded to treatment.

We further published the first open-label, phase II pilot study of the safety and efficacy of R788 for the treatment of chronic refractory ITP. In a small cohort of 16 adults with ITP, all of whom have failed at least 2 prior treatments, and 11 of whom underwent splenectomy, R788 was safe and effective in increasing and maintaining platelet counts. Half of the patients treated with R788 achieved platelet counts greater than 50,000 on greater than 95% of study visits. Another 25% of patients achieved a transient platelet response and sustained other clinical benefits, such as reduced need for rescue treatment with IVIg or anti-D. The mean peak platelet count in

these 12 patients was >100,000, from a baseline mean platelet count of 16. The most common treatment-related toxicity was diarrhea. Nausea, vomiting, blood pressure increase and LFT abnormalities were also noted and were mainly dose-limited.

The purpose of this study is to conduct a larger, double-blinded, placebo-controlled trial of the efficacy and safety of the Syk inhibitor R788 in adults with chronic ITP. The underlying hypothesis of this study is that blocking FcγR signaling by inhibiting Syk would ameliorate platelet destruction in patients with ITP.

B. Study Design and Statistical Analysis

Patients will be randomly assigned to either the treatment arm or placebo in a 1:1 fashion, stratified based on splenectomy status. The random allocation sequence will be generated by the Department of Medical Statistics with the blocked randomization method. Clinphone will be used to randomly assign patients into the study with the interactive voice response system. No cross-over is planned.

The primary outcome measure will be durable platelet count, defined as a platelet count of greater than 50,000 on at least 75% of study visits, based on previous literature and clinical significance. Platelet count will be measured at each study visit by the core laboratory. Patients who received rescue therapy within 2 weeks of study visit will be excluded from analysis for that study visit.

Secondary outcome measures include absolute mean platelet counts in the two groups, absolute mean peak platelet counts, frequency of platelet response and number of rescue treatments (IVIg, Anti-D) required during the study.

In order to achieve 80% power with a P value of 0.05 a sample size of 71 patients in each arm was calculated using the Chi-square test, assuming a minimal clinically-significant effect size of 20% and a placebo response of 10%. In order to account for attrition, a 80 subject will be recruited for each arm.

Data will be analyzed using descriptive statistics (mean, standard deviation) and a t-test to compare group differences.

C. Study Procedure

Patients will be screened on two separate occasions at least 2 weeks apart to meet inclusion criteria. Platelet count must be below 30,000 on both occasions.

Patients will be seen at 2 week intervals by a physician. A clinical exam and interview to assess for symptoms will be performed. Platelet count will be measured by the core laboratory.

The frequency of study visits is typical for patients with severe, refractory ITP. No significant pain or discomfort other than that typically associated with blood draws will be experienced by the patient.

Patients will be followed for 6 months. At the end of the 6 month period they will be offered continued routine care at the hematology clinic where they were recruited.

D. Study Drugs

R788 is an investigational study medication. Please see **Section A** for the review of safety and efficacy data. It is supplied as white to off-white plain oval tablets in two tablet strengths, 25 mg and 100 mg. Patients will self-administer 125 mg of R788 daily, based on previous dose-escalation studies of efficacy and safety.

In addition to the active agent, each tablet contained microcrystalline cellulose, sodium starch glycolate, copovidone, and magnesium stearate. The appropriate number of tablets will be dispensed at each study visit to ensure continuous dosing during the 2 week interval period between visits. Patients will return unused tablets at each study visit to be counted to monitor compliance.

E. Medical Device

Not applicable.

F. Study Questionnaires

None.

G. Study Subjects

Inclusion criteria: diagnosis of ITP, as per ASH guidelines; platelet count less than 30,000, failed at least one prior treatment; age greater than 18 years; both sploenectomized and nonsplenectomized patients.

Exclusion criteria: active malignancy, GFR less than 30, ALT more than 1.5 times the upper limit of normal.

Additionally, patients will only be included in this study if they have not received IVIg or anti-D therapy within 2 weeks of enrollment, and no other therapies within 12 weeks of enrollment.

H. Recruitment of Subjects

Patients will be recruited through the hematology clinic at CPMC and Weill Cornell, at the discretion of their primary hematologist.

I. Confidentiality of Study Data

All study data will be stored in a confidential manner. All study materials will be coded with a unique subject identifier as assigned in the study. This will not include any personal indentifiers.

J. Potential Conflict of Interest

There are no conflicts of interest.

K. Location of the Study

The study will be conducted at the hematology clinic at CPMC and Weill Cornell.

L Potential Risks

Potential risks include mental discomfort, physical discomfort from blood drawing, 50% chance that the patient may receive placebo and/or that the treatment will not work. In addition, there is a risk of an adverse reaction to the study medication, as described in **Section A**, including GI discomfort, liver function abnormalities, blood pressure increase and weight gain.

M. Potential Benefits

The main benefit of this study is sustained improvement in platelet count, which is expected in 50% of the patients. Some patients may not benefit from this study.

N. Alternative Therapies

Patients included in this study have already been tried on at least one alternative therapy.

O. Compensation of Subjects

Subjects will receive all study medications free of cost. All medical visits and laboratory tests will also be provided free of charge the all subjects. No other compensation will be provided.

P. Costs to Subjects

There will be no cost to the subjects.

Q. Minors as Research Subjects

Patients under the age of 18 will not be included in this study.

R. Radiation or Radioactive Substances

Not applicable.

S. References

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