**TITLE: Pathobiology of Thrombocytopenia and Bleeding in Patients with Wiskott-Aldrich Syndrome**

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## LIST OF ABBREVIATIONS:

AE Adverse event
ALT Alanine aminotransferase (SGPT)
AST Aspartate aminotransferase (SGOT)
BUN Blood urea nitrogen
CBC Complete blood count
CIB Clinical Investigator's Brochure
COPD Chronic obstructive pulmonary disease
CRF Case report form
DSMB Data Safety Monitoring Board
FDA Food and Drug Administration
GSK Glaxo SmithKline
HIV Human immunodeficiency virus
HSCT Human Stem Cell Transplantation
IB Investigator brochure
ICH Intracranial hemorrhage
ICF Informed consent form
IPF Immature Platelet Fraction
IRB Institutional Review Board
ITP Idiopathic thrombocytopenia purpura
IVIg intravenous immunoglobulin
Mg Milligram
mL Milliliter
NSAID Non-steroidal anti-inflammatory medications
PI Principal Investigator
PT Prothrombin Time
PTT Partial thromboplastin time
RBC Red blood cell
REPEAT Repeated ExPosure to Eltrombopag in Adults with Idiopathic Thrombocytopenic purpura
RN Registered nurse
OPSS Overwhelming post-splenectomy sepsis
SAE Serious adverse event
SCF Stem cell factor
TBI Total Body Irradiation
TPO Thrombopoietin
TpoR Thrombopoietin receptor
ULN Upper limit of normal
WBC White blood cell
WAS Wiskott Aldrich Syndrome
XLT X-Linked Thrombocytopenia

# 1. INTRODUCTION

## 1.1. Background

Promacta® (Eltrombopag) received accelerated FDA approval on Nov 20, 2008 for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Formerly GlaxoSmithKline (GSK) and now Novartis is also developing eltrombopag for the treatment of aplastic anemia, MDS, and chemotherapy-induced thrombocytopenia.

Wiskott Aldrich Syndrome (WAS) is an X-linked disease characterized by immunodeficiency, eczema and thrombocytopenia; a milder form of the disease known as X-Linked Thrombocytopenia (XLT) also exists. The two forms are on a spectrum but typically patients with XLT may be relatively asymptomatic except for signs of bruising and bleeding whereas patients with full blown WAS manifest more symptoms making clinical distinction relatively easy. The estimated incidence in the US is 1 per million people (Sullivan et al. 1994 and Ochs and Rosen 2007). The thrombocytopenia in both WAS and XLT is characterized by: severe thrombocytopenia with platelet counts frequently less than 10-30,000/ul; small platelets which may be dysfunctional; and, as a result, a high rate of serious bleeding including intracranial hemorrhage. Currently patients are treated using platelet transfusion, splenectomy, and/or human stem cell transplantation (HSCT) and experimentally with gene therapy. These are effective in different ways but there appears to be a clearly increased risk of sepsis after splenectomy and morbidity and mortality with HSCT. In addition, even patients with full blown WAS who will undergo transplantation may benefit from waiting until they are 12-24 months of age instead of being transplanted at 2-6 months of age because of relentless thrombocytopenia. There is an estimated 10% risk of malignancy, e.g. development of lymphoma, but this is not usually an early phenomenon. Perhaps 1-3 of the 15 patients in the study might be at risk for lymphoma over a lifetime but it is not likely to happen during the relatively short time course of the study. If it were to happen in one patient, it would be attributed to the natural history of the disease. There would be no specific way to determine the etiology of any lymphoma that developed.

Because eltrombopag has been shown to be efficacious in substantially increasing platelet counts in a high percentage of adult and now pediatric chronic ITP patients, this study seeks to effectively treat patients who exhibit similar pathologies, as well as to evaluate the state of platelets in patients with WAS and relate it to clinical bleeding. Eltrombopag has recently been licensed for children over the age of 1 year for treatment of chronic ITP which is pertinent because the great majority of patients anticipated to be enrolled on this study are children. The study also aims to demonstrate whether eltrombopag administered daily will increase platelet production and platelet count and reduce bleeding in patients with WAS.

## 1.2. Rationale

Eltrombopag has been remarkably efficacious in substantially increasing platelet counts in a high percentage of patients with chronic ITP (low platelets). The principal investigator Dr. James Bussel has been involved in various trials using eltrombopag; a recently published article detailing the success of eltrombopag illustrates the utility of this treatment (Gerrits et al, 2015). To greatly reduce or eliminate the risk of intracranial hemorrhage (ICH) in patients with WAS would be highly meaningful, as one of the five patients that we currently follow at our institution with XLT has already had an ICH; this is in keeping with published data. Even a relatively small increase in platelet count could be sufficient to prevent ICH in these patients. The ultimate purpose of providing

thrombopoietic treatment is to prevent serious, primarily intracranial, hemorrhage. Based on its utility in other diseases such as chronic ITP, thrombopoietic therapy appears to be the most promising approach for relieving the thrombocytopenia in WAS patients.

There is a very high rate of very serious bleeding associated with WAS and XLT patients (Ochs and Thrasher, 2006) that far exceeds that seen in almost any other form of childhood thrombocytopenia, including ITP (approximately 0.5%) (Kühne et al, 2003). We are targeting a pediatric population in the hopes of controlling and managing the excessive bleeding that occurs in a high percentage of patients with Wiskott Aldrich Syndrome including X-Linked Thrombocytopenia.

Preliminary analysis of 5 patients enrolled in this study along with 3 additional WAS/XLT patients (Gerrits et al, 2015) show that 5 of 8 WAS/XLT patients (3 XLT and 2 WAS) who were on eltrombopag treatment of at least 1 month (1 adult and 4 children) were platelet responders, as evidenced by achieving at least one platelet count $\geq 50 \times 10^9$/L and double the baseline count. Six of 8 patients had reduced bleeding symptoms. Four eltrombopag-treated patients had platelet counts $\geq 20 \times 10^9$/L above baseline counts and 4 patients reached counts $\geq 100 \times 10^9$/L.

# 2. OBJECTIVE(S)

## 2.1. Primary Objective

- To describe the pathophysiology of thrombocytopenia and bleeding in patients with Wiskott-Aldrich Syndrome (WAS) especially those with XLT (since they will be more stable and available for study) and determine their response to thrombopoietic agents *in vitro* and *in vivo*.

## 2.2. Secondary Objective

- This study aims to explore the functional state of circulating platelets in patients with WAS and to relate it to clinical bleeding. Furthermore to demonstrate whether a thrombopoietic agent, eltrombopag, administered daily will increase platelet production and platelet count, and reduce bleeding in patients with WAS.

# 3. INVESTIGATIONAL PLAN

## 3.1. Study Design

Fifteen patients (approximately 80% children) with WAS/ XLT will be enrolled and undergo baseline screening including not only blood drawing but also history of illness in the past, while ten additional WAS and XLT otherwise ineligible or unwilling patients who will not undergo study treatment and ten control subjects will undergo a one-time blood draw. The pediatric control and non-treatment WAS/XLT subjects will be pediatric patients who are having their blood drawn for reasons not related to an acute illness and will provide a limited amount of additional blood. The pediatric control and non-treatment WAS/XLT subjects will have their blood drawn at Cornell after giving consent. They will not be asked for more than 5-10 ml of blood per year of age up to a maximum of 30 ml total in one draw. Blood drawn will be studied for stem cells and

megakaryocytopoiesis, Immature Platelet Fraction (IPF), and platelet function (see table). These subjects will have their blood drawn for another purpose e.g. pre-op clearance for surgery and therefore it will be a small amount of extra blood posing a minimal risk to the subject. Subsequently, treatment patients will start on 2 mg/kg of eltrombopag and be seen every two weeks in the first month, and monthly for the first year. Although Promacta is commercially available in 25 mg and 50 mg tablets, it is also available for clinical studies in 12.5 mg tablets which will be provided by Novartis for this study. In this study, the starting dose will be based upon weight; patients over 50 kg will start at 50 mg daily unless they are of East Asian origin in which case they will use 25 mg as their initial dose. The dose of eltrombopag will be titrated for each subject based on their platelet response (see table 1). Overall, in this study, doses between 12.5mg every other day and 75mg once daily are anticipated to be required to maintain platelet counts between 50 and 400Gi/L. However, as explained in the provided dosing guidelines, the dose of eltrombopag will be reduced whenever the platelet count exceeds 200Gi/L in order to prevent it from reaching 400Gi/L. The goal is to have a platelet count in a safe hemostatic range, albeit not necessarily a normal platelet count.

Eltrombopag starting doses for children < 50kg will be scaled by body weight and the starting dose will be approximately 2 mg/kg once daily unless they are of East Asian origin in which case they will use approximately 1 mg/kg as their initial dose. This starting dose is based on the findings of GlaxoSmithKline's PETIT2 study: Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial.

This dosing schedule is based on those used in GlaxoSmithKline's 'PETIT' study: Eltrombopag in Pediatric patients with Thrombocytopenia from ITP.

For young children unable to swallow a tablet, eltrombopag powder for oral suspension (Eltrombopag PfOS) will be used. Each sachet contains eltrombopag equivalent to 20mg per gm of powder. Please see Appendix 3 for details and dose adjustment guidelines for subjects receiving the suspension formulation. Repeat assessment with the same testing will be performed at week 4. Dose adjustment will be based on the monthly monitoring of the platelet count.

The IPF will be measured at each visit with the CBC. Platelet count data will be collected throughout the study and used as part of the assessment of efficacy. Platelet count data will be collected as part of the CBC monthly during the first year of administration of study drug and at any dose change (eltrombopag or concomitant medication). If a subject continues on a stable dose during any stage of the study for greater than 4 weeks, a CBC (including platelet count) with differential will be performed no less frequently than every 4 weeks. Further information regarding reduction in use of concomitant medications for thrombocytopenia, use of rescue therapy, incidence and severity of bleeding and other symptoms associated with thrombocytopenia and infections will also be collected and summarized.

Platelet function will be assessed by whole blood flow cytometry as described by and in collaboration with Dr. Michelson (see appendix for attached abstracts).

Treatment will be initiated at Cornell.Patients will be seen either at Cornell or by a their local doctor 1-3 months thereafter. A recently developed bleeding score, designed to incorporate the four leading bleeding scores, will be administered on study visits to semi-quantitatively assess bleeding.[14] The Page bleeding score is completed using the information from this questionnaire. The hypothesis is that patients with Wiskott-Aldrich Syndrome will have more bleeding at given platelet counts than will patients with ITP. Furthermore the degree of bleeding will correlate not only with the platelet count but with the degree of platelet dysfunction. Platelet size will be explored also. We anticipate the platelet function and bleeding scores will improve with the institution of Promacta therapy if the

platelet counts increase. Even if some of these changes in bleeding are small, the overall direction will help to clarify the effect of treatment on these scores.

There is no placebo; thus, patients will be compared to themselves descriptively before and after treatment through complete physical examinations, complete blood draws, urinalysis, and platelet studies.

Dr. Bussel has an appointment at Memorial Sloan Kettering, so a patient initiated at Cornell can be followed with appropriate testing at the MSKCC site. In addition, a patient who comes to the Cornell site to provide consent and initiate treatment may be followed at another site for local Laboratory Testing.

Urinalysis, Admission Panel (including liver tests), CBC with Platelet and Differential, PT/PTT, PFA, Fibrinogen, D-Dimers, Platelet Function Analysis, Immature Platelet Fraction (Platelet Reticulocyte Count), and Single Platelet Flow Cytometry will be assessed.

# 4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

## 4.1. Number of Subjects:

25 WAS/XLT Patients (10 of whom will have a blood draw only) + 10 Normal Control Patients = 35 Total Patients

## 4.2. Inclusion Criteria:

In order to be eligible for study entry, subjects must comply with the following:

• Males or females from 3 months to 80 years old

• Signed written informed consent obtained prior to study entry

• Clinical diagnosis of WAS or XLT

• Platelet levels less than 75 x $10^9$/L

• Adequate renal and hepatic function (creatinine and bilirubin less than or equal to 1.5 x ULN, AST and ALT less than or equal to 2.5 x ULN)

### 4.3. Exclusion Criteria:

Any patient is ineligible for study entry if he/she:

- Over the age of 80
- Pregnant or lactating women
- Fertile men who are not practicing or who are unwilling to practice birth control while enrolled in the study or until at least 6 months after treatment

- Aspirin, aspirin-containing compounds, salicylates, non-steroidal anti-inflammatory medications (NSAIDS), clopidogrel or ticlopidine, warfarin or other vitamin K antagonists, unfractionated or low molecular heparin within 7 days of first treatment

- Red blood cell transfusion in the past four weeks

- Elevated (> 1.5 x ULN) prothrombin time (PT) or partial thromboplastin time (PTT)

- New York Heart Classification III or IV heart disease. Other severe cardiovascular or cardiopulmonary disease, including COPD.

- Known HIV infection, hepatitis B or C infection

- Any infection requiring antibiotic treatment within 3 days

- Other concurrent medical or psychiatric conditions that, in the Investigator's opinion, may be likely to confound study interpretation or prevent completion of study procedures and follow-up examinations.

- Prior malignancy with less than a 5-year disease-free interval, excluding nonmelanoma skin cancers and carcinoma in situ of the cervix

Eligibility criteria for controls:

a) Within 5 years of the age of the enrolled patient

b) No overt hematologic diagnosis

c) Male

## 4.4. Withdrawal Criteria:

1. Treatment with eltrombopag should be discontinued because of abnormal liver tests if any of the following 4 conditions apply:

- ALT levels $\geq$ 3 times upper limit of normal (ULN) and bilirubin levels > 1.5 times (> 35 % conjugated bilirubin) ULN,

- (2) ALT levels $\geq$ 3 times ULN and appearance or worsening of hepatitis symptoms or rash,

- (3) ALT levels remain $\geq$ 3 times ULN for $\geq$ 4 weeks, or
- (4) ALT levels are $\geq$ 5 times ULN.
- If a subject has an adverse experience that would, in the investigator's judgment, make continued participation in the study an unacceptable risk
- Note: If the subject's ALT and bilirubin levels decrease so that both are < 1.5 times ULN, the

investigator may decide to restart the medication and monitor on a weekly basis.

- Study medications will be discontinued in the event of any thrombosis

If subject's platelet count goes above 200,000, the dose of study medication will be reduced.

As indicated on page 5, perhaps 2-3 of the 15 patients in the study might be at risk over a lifetime for a malignancy such as lymphoma, but it is not very likely to happen during the relatively short time course of the study. If 1 patient develops another type of malignancy or 2 patients develop a Non-Hodgkin Lymphoma during the course of the study, the study will be stopped. Prior to the study being restarted (if this is the desire of the investigators), there will be a formal request to re-open the study submitted to the FDA with a letter of support from Novartis.

#### 4.4.1. Study Stopping Rules

1. Two malignancies of any type or 1 malignancy that is not leukemia or lymphoma

2. No platelet increase to > 30,000 in 8 consecutive patients

3. Transaminitis to > 5x ULN in more than 50% of the patients

4. If 33% of patients (with a minimum of 6 patients in the study) achieve the individual withdrawal criteria for liver events, the study will be stopped and reviewed with Novartis and the FDA.

#### 4.4.2. Patient Stopping Rules

1. Malignancy

2. Transaminase and bilirubin rules

3. Worsening cataracts

4. No increase in the platelet count despite dose increases to > 1.5 mg/kg body weight

# 5. STUDY TREATMENTS

## 5.1. Treatment Assignment

| | | | |
|---|---|---|---|
| **1) Review of subject's medical history** | **2) A routine physical examination, including collection of subject's height, weight, temperature, blood pressure, and pulse rate, and a review of all medicines** | **3) The study doctor will assess subject's bruising and bleeding by physical examination and by asking questions. He/she will do this by using the Page ITP Bleeding Score.**<br><br>**4) At Screening, about 10-20 mL of blood will be drawn to conduct laboratory tests.** | **5) The starting dose will be based upon weight; patients over 50 kg will start at 50mg daily unless they are of East Asian origin in which case they will use 25 mg as their initial dose. The dose of eltrombopag will be titrated for each subject based on their platelet response. Eltrombopag starting doses for children <50 kg will be scaled by body weight and the starting** |

| | | | |
|---|---|---|---|
| | **that a subject is taking.** | | **dose will be approximately 2mg/kg once daily.** |

**Note: See schedule of events on page 25**

## 5.2. Product Accountability

The pharmacy will track use of the medication. Patients will return their bottles of medication every 4 weeks.

## 5.3. Treatment Compliance

This will be assessed by discussion with the patient and with pill counts in the returned bottles. Furthermore we would carefully review the diet and, in particular, try to ensure that the pills are taken correctly ie on a very empty stomach.

## 5.4. Concomitant Medications and Non-Drug Therapies

Concomitant ITP medications will be tracked. None can be used in the first 4 weeks of the study. Patients receiving them will be taken off study. The same is true for non-drug therapies of ITP.

### 5.4.1. Permitted Medications and Non-Drug Therapies

Stable doses of oral corticosteroids are allowed. No other "ITP" therapy is allowed in the study except for 3-4 weekly IVIG at doses of 300-500 mg/kg. Medication doses cannot be changed during the first 4 weeks of therapy.

### 5.4.2. Prohibited Medications and Non-Drug Therapies

All other ITP therapies, whether drug or non-drug, are prohibited during the first 4 weeks of therapy. Splenectomy is allowed at any time during the study however, if effective, it will end the study participation (treatment) for that subject.

## 5.5. Treatment after the End of the Study

All ITP therapies including thrombopoietic agents can be used after the end of study.

## 5.6. Treatment of Investigational Product Overdose

Platelet counts will be followed carefully and treatment held for approximately one week if there is a significant drug overdose. Calcium-containing products could be used in the very unlikely event of a substantial overdose to inactivate the PROMACTA. Aspirin can also be given as needed.

## 5.7. Treatment Plan

| | Adults and children > 30 kg | Children < 30 kg | Frequency |
|---|---|---|---|
| **Urinalysis** | 10 mL | 5 mL | One Time (at screen) |
| **Admission Panel (includes ALT, AST, bilirubin)** | 2 mL | 2 mL | Every two weeks for the first month; monthly for year 1; every 2 months for year 3; every three months for years 3 - 6 |
| **CBC with Platelet and Differential and Immature Platelet Fraction (IPF)** | 2 mL | 2 mL | Every two weeks for the first month; monthly for year 1; every 2 months for year 3; every three months for years 3 - 6 |
| **PT/PTT, D-Dimers, Fibrinogen** | 5 mL | 2.5 mL | One time (at screen) |
| **PFA** | 5 mL | 2.5 mL | One time (at month 2) |
| **Single Platelet Flow Cytometry** | 10 mL | 2 mL | 3 times (at screen, at month 1-3 and at year 1-2) |

NOTE: see schedule of events on page 25

| | | | |
|---|---|---|---|
| **Control subject blood draw** | 30 mL | 10-20 mL | One time |
| **WAS Non-treatment subject blood draw** | 30mL | 10-20mL | One time |

# 6. STUDY ASSESSMENTS AND PROCEDURES

## 6.1. Critical Baseline Assessments

**Complete Blood Counts (CBCs)**

CBCs, including platelet counts and peripheral blood smears, will be monitored prior to initiation, throughout, and following discontinuation of therapy with PROMACTA. Prior to the initiation of PROMACTA, the peripheral blood differential will be examined to establish the extent of red and white blood cell abnormalities. CBCs, including platelet counts and peripheral blood smears, will be obtained weekly during the dose adjustment phase of therapy with PROMACTA and then monthly following establishment of a stable dose of PROMACTA. CBCs, including platelet counts will be obtained weekly to biweekly for at least 4 weeks following discontinuation of PROMACTA.

**Liver tests**

Serum liver tests (ALT, AST, and bilirubin) will be monitored prior to initiation of PROMACTA, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. If bilirubin is elevated, fractionation will be performed. If abnormal levels are detected, the tests will be repeated within 3 to 5 days. If the abnormalities are confirmed, serum liver tests will be monitored weekly until the abnormality(ies) resolve, stabilize, or return to baseline levels. PROMACTA will be discontinued based on the stopping rules outlined in section 6.3.1

## 6.2. Efficacy

Collection of platelet counts on week 1 (pre-dose), week 2, monthly during year 1, every two months during year 2, and every 3 months during years 3-6, along with platelet function studies. Bleeding symptoms will be monitored by bleeding score assessments.

## 6.3. Safety

This protocol is investigator initiated. The Principal Investigator is responsible for the study and will monitor the safety of the patients on the protocol.

The following safety will be reviewed by the Principal Investigator:

- Physical Exam
- Vital Signs
- Laboratory results (blood count, liver function tests, reticulocyte count, urine tests)
- SAE and AE events
- Bone marrow aspirations/biopsies (if relevant)

Adverse Events (AEs) will be graded according to Common Terminology Criteria for Adverse Events v4.03(CTCAE)The PI will determine the relationship of AEs to the test procedure/device/agent as not related, possibly related, probably related or definitely related, using standard criteria for clinical trials. Interim assessment of AEs will be conducted semi-annually by the data safety monitoring board.

Note: All serious adverse events will be followed until resolution of the events or definitive conclusion.

**Hepatotoxicity**

Administration of eltrombopag may cause hepatotoxicity. In the controlled clinical ITP studies, serum liver test abnormalities (predominantly Grade 2 or less in severity) were reported in 10% and 8% of the PROMACTA and placebo groups, respectively. Two patients (1%) treated with PROMACTA and two patients in the placebo group (3%) discontinued treatment due to hepatobiliary laboratory abnormalities. Seven of the patients treated with PROMACTA in the controlled studies with hepatobiliary laboratory abnormalities were re-exposed to PROMACTA in the extension study. Six of these patients again experienced liver test abnormalities (predominantly Grade 1) resulting in discontinuation of PROMACTA in one patient. In the extension study, one additional patient had PROMACTA discontinued due to liver test abnormalities ($\leq$ Grade 3).

Serum ALT, AST, and bilirubin will be measured prior to initiation of PROMACTA, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. If bilirubin is elevated, perform fractionation. Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until the abnormality(ies) resolve, stabilize, or return to baseline levels. Discontinue PROMACTA if ALT levels increase to
$\geq$ 3X the upper limit of normal (ULN) and are:

- Progressive, or
- Persistent for $\geq$ 4 weeks, or
- Accompanied by increased direct bilirubin, or
- Accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.

**Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis**

Eltrombopag is a thrombopoietin (TPO) receptor agonist and TPO-receptor agonists may increase the risk for the development or progression of reticulin fiber deposition within the bone marrow.

In the ITP extension study, seven patients had reticulin fiber deposition reported in bone marrow biopsies, including two patients who also had collagen fiber deposition. The fiber deposition was not clearly associated with cytopenias and did not necessitate discontinuation of eltrombopag. However, clinical studies have not yet excluded a risk of bone marrow fibrosis with cytopenias and discontinuation of eltrombopag.

Prior to initiation of eltrombopag, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, examine peripheral blood smears and CBCs monthly for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with eltrombopag and consider a bone marrow biopsy, including staining for fibrosis.

**Worsened Thrombocytopenia After Cessation of Eltrombopag**

Discontinuation of eltrombopag may result in thrombocytopenia of greater severity than was present prior to therapy with eltrombopag although this is only seen in a minority of patients who stop the drug. This worsened thrombocytopenia may increase the patient's risk of bleeding, particularly if

eltrombopag is discontinued while the patient is on anticoagulants or antiplatelet agents. In the controlled ITP clinical studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 10% and 6% of the eltrombopag and placebo groups, respectively. Serious hemorrhagic events requiring the use of supportive ITP medications occurred in 3 severely thrombocytopenic patients within one month following the discontinuation of eltrombopag; none were reported among the placebo group.

Following discontinuation of eltrombopag, obtain weekly CBCs, including platelet counts for at least 4 weeks and consider alternative treatments for worsening thrombocytopenia, according to current treatment guidelines

**History of Thromboembolic Events**
Thrombotic events can occur at any platelet count. Thrombotic/thromboembolic complications may result from excessive increases in platelet counts. Excessive doses of eltrombopag or medication errors that result in excessive doses of eltrombopag may increase platelet counts to a level that produces thrombotic/thromboembolic complications. In the controlled ITP clinical studies, one thrombotic/thromboembolic complication was reported within the groups that received eltrombopag and none within the placebo groups. Seven patients experienced thrombotic/thromboembolic complications in the ITP extension study.

Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, etc.).

**Malignancies and Progression of Malignancies**

Stimulation of the TPO receptor on the surface of hematopoietic cells by eltrombopag may increase the risk for hematologic malignancies. In the controlled ITP clinical studies, patients were treated with eltrombopag for a maximum of 6 weeks and during this period no hematologic malignancies were reported. One hematologic malignancy (non-Hodgkin's lymphoma) was reported in the ITP extension study.

**Cataracts**

Cataracts were observed in toxicology studies of eltrombopag in rodents (see Non-clinical Information). The clinical relevance of this finding continues to be evaluated in all ongoing NOVARTIS sponsored clinical studies. To date, there is however, no evidence that eltrombopag increases the incidence nor progression of cataracts in patients who have received eltrombopag. In the controlled ITP clinical studies, cataracts developed or worsened in five (5%) patients who received 50 mg eltrombopag daily and two (3%) placebo-group patients. In the ITP extension study, cataracts developed or worsened in 4% of patients who underwent ocular examination prior to therapy with eltrombopag. A significant proportion of patients in the ITP clinical studies were also exposed to chronic corticosteroid administration.

**6.3.1. Liver chemistry stopping and follow-up criteria**

**Increased Liver Chemistries**

Eltrombopag administration may cause hepatotoxicity. In the ITP controlled clinical studies, one patient experienced Grade 4 (NCI Common Terminology Criteria for Adverse Events [NCI CTCAE] toxicity scale) elevations in serum liver test values during therapy with eltrombopag, worsening of

underlying cardiopulmonary disease, and death. No patients in the placebo group experienced Grade 4 liver test abnormalities. Overall, serum liver test abnormalities (predominantly Grade 2 or less in severity) were reported in 10% and 8% of the eltrombopag and placebo groups, respectively. In the controlled studies, two patients (1%) treated with eltrombopag and two patients in the placebo group (3%) discontinued treatment due to hepatobiliary laboratory abnormalities. Seven of the patients treated with eltrombopag in the controlled studies with hepatobiliary laboratory abnormalities were re-exposed to eltrombopag in the ITP extension study. Six of these patients again experienced liver test abnormalities (predominantly Grade 1) resulting in discontinuation of PROMACTA in one patient. In the ITP extension study, one additional patient had eltrombopag discontinued due to liver test abnormalities (all $\leq$ Grade 3).

Serum ALT, AST, and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. If bilirubin is elevated, perform fractionation. Evaluate abnormal serum liver tests with repeat testing within 3 to 5 days. If the abnormalities are confirmed, monitor serum liver tests weekly until the abnormality(ies) resolve, stabilize, or return to baseline levels.

Once more than six patients are enrolled in the study: The study will be stopped if 33% of the patients develop any of the following labelled hepatotoxicity monitoring criteria for drug cessation.

Treatment with eltrombopag should be discontinued because of abnormal liver tests if any of the following 4 conditions apply:

- ALT levels $\geq$ 3 times upper limit of normal (ULN) and bilirubin levels $\geq$ 1.5 times (> 35 % conjugated bilirubin) ULN,
- (2) ALT levels $\geq$ 3 times ULN and appearance or worsening of hepatitis symptoms or rash,
- (3) ALT levels remain $\geq$ 3 times ULN for > 4 weeks, or
- (4) ALT levels are $\geq$ 5 times ULN.
- If a subject has an adverse experience that would, in the investigator's judgment, make continued participation in the study an unacceptable risk
- Note: If the subject's ALT and bilirubin levels decrease so that both are $\leq$ 1.5 times ULN, the investigator may decide to restart the medication and monitor on a weekly basis.

Exercise caution when administering PROMACTA to patients with hepatic disease. Use a lower starting dose (0.3-0.4 mg/kg) of PROMACTA in patients with moderate to severe hepatic disease and monitor closely.

**6.4. Adverse Events**

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

**6.4.1. Definition of an AE**

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Significant or unexpected worsening or exacerbation of the condition/indication under study.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events that do not meet the definition of an AE include:
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

**6.4.2. Definition of a SAE**

A serious adverse event (SAE) is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. All Grade 4 laboratory abnormalities assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0 Common Terminology Criteria for Adverse Events (v 3.0)] except Grade 4 thrombocytopenia.

h. Ocular events of clinical concern.

Note: All serious adverse events will be followed until resolution of the events or definitive conclusion.

**6.4.3. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs**

During the assessment period, thrombocytopenia that results in administration of rescue treatment does not qualify as an AE or SAE. Also during this assessment period, hospital admissions that are attributable to such treatment failures or related therapy also do not qualify as AEs or SAEs. Hemorrhagic complications of thrombocytopenia not otherwise meeting regulatory serious criteria will be reported as AEs.

**6.4.4. Pregnancy**

Pregnancy will not be allowed on study. Contraception must be used for all patients of child-bearing potential.

**6.4.5. Time Period and Frequency of Detecting AEs and SAEs**

Subjects will be given an adverse event sheet to complete at every study visit. This will help us to track any adverse events that have occurred and any medications that the subject has taken between visits. Subjects are instructed to notify the PI with any adverse events that he/she experiences.

**6.4.6. Prompt Reporting of Serious Adverse Events and Other Events to NOVARTIS**

Adverse events will be reported to the Investigational Review Board (IRB) as they occur and any

serious events will be reported to NOVARTIS within 24 hours of learning of the event if they occur. CTC criterion version 3.0 will be used as a guideline for reporting adverse events.

Any serious adverse events which occur during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

**All serious adverse events must be reported by facsimile or email within 24 hours to Novartis.**

**US CPO DS&E Fax #: 877-778-9739**The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to NOVARTIS within 24 hours.

SAEs brought to the attention of the investigator at any time after cessation of eltrombopag and considered by the investigator to be related or possibly related to eltrombopag must be reported to NOVARTIS if and when they occur. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is discharged.

#### 6.4.6.1. Regulatory reporting requirements for SAEs

The PI and/or data coordinator will be reporting unexpected serious adverse events promptly to the IRB and to NOVARTIS within 24 hours of learning of the event.

### 6.4.7. Other Safety Outcomes

Liver function tests, marrow reticulin, thromboembolism and other AE's will be tracked and reported.

### 6.4.8 Data Safety Monitoring Board

Weill Cornell Medical College requires that all research approved by the WCMC IRB include an appropriate plan for the monitoring of data to ensure the safety of human subjects. Research supported by Federal agencies will be monitored according to all regulations and guidelines of the relevant Federal agency.

The WCMC Data and Safety Monitoring Board (DSMB) will review the IRB approved protocol, informed consent documents, and data and safety monitoring plan. During the course of the study, the DSMB will review the cumulative study data semi-annually to evaluate safety, efficacy, study conduct, and scientific validity and integrity of the trial. The WCMC DSMB may also convene as needed if stopping criteria are met or other safety issues arise that the Principal Investigator and/or IRB would like the WCMC DSMB to address. The study PI will submit all written DSMB recommendations to the IRB upon receipt.

# 7. DATA MANAGEMENT

Case Report Form (CRFs) (see attached) will be filled out by the study coordinator using the raw data generated by study visits.

# 8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

## 8.1. Hypotheses

The primary objective is to describe the pathophysiology of thrombocytopenia and bleeding in patients with Wiskott-Aldrich Syndrome (WAS) and determine the response to thrombopoietic agents *in vitro* and *in vivo*.

SPECIFIC AIMS:

1. To explore stem cell function in patients with WAS

2. To evaluate the functional state of circulating platelets in patients with WAS and relate it to clinical bleeding

3. To demonstrate whether a thrombopoietic agent, eltrombopag, administered daily will enhance stem cell function, increase platelet production and platelet count, and reduce bleeding in patients with WAS

## 8.2. Study Design Considerations

Limited therapies exist to treat thrombocytopenia in WAS/XLT. IV gammaglobulin and corticosteroids, mainstays in ITP, are ineffective in WAS/XLT. Platelet transfusions only last for hours. The two treatments that affect the platelets in a more lasting manner are splenectomy and human stem cell transplantation (HSCT). Splenectomy successfully increases the platelet count in most patients but is associated with an increased risk of overwhelming post splenectomy sepsis (OPSS) due to the primary immune dysfunction seen in WAS/XLT. Human Stem Cell Transplantation (HSCT) is effective but has significant morbidity and mortality. Furthermore it is ideally postponed until after 24 months of age to allow TBI, which is too long to wait for affected infants with severe thrombocytopenia in view of the high risk of ICH. It is clearly necessary to establish improved therapy for thrombocytopenia in these children.

### 8.2.1. Sample Size Assumptions

Zero responders among 15 subjects would suggest that the true proportion responding (i.e. what would be observed if an inordinate number of subjects were studied) is unlikely to exceed 20%.

### 8.2.2. Sample Size Sensitivity

Zero responders among 15 subjects would suggest that the true proportion responding (i.e., what would be observed if an inordinate number of subjects were studied) is unlikely to exceed 20%.

## 8.3. Data Analysis Considerations

Data from all subjects who receive eltrombopag will be summarized. Results will be summarized by visit. All displays should include the number of subjects with available data at that visit.

Study endpoints include bleeding score, platelet count, platelet function, megakaryopoiesis and platelet formation.

### 8.3.1. Key Elements of Analysis Plan

Complex statistical analyses would not be appropriate for an exploratory study. Study endpoints will be summarized by visit using descriptive statistics (mean, median, standard deviation, range) or frequency counts, (as appropriate).

#### 8.3.1.1. Efficacy Analyses

Primary endpoint will be increasing platelet counts in WAS/XLT patients to above 50,000/ul. The generalizability of the data will depend upon including both WAS and XLT patients but no specific distribution of patients within these 2 groups is pre-specified. The proportion of patients showing this increase will be summarized with 95% confidence intervals. The proportion of patients maintaining this increase will be summarized for time points of interest.

Correlations will be evaluated graphically. In addition, Spearman rank correlation coefficients may be used to evaluate the association of platelet count and bleeding score, at each visit.

Any within-subject analyses may be based on Wilcoxon signed rank tests.

Secondary endpoints will involve reduction of bleeding in treated patients within 12 weeks, and to specifically examine the reduction in bleeding in those with platelet counts > 100,000/ul and also > 50,000/ul.

We anticipate that platelet function will improve as the platelet count increases but not normalize.

Therefore efficacy will depend on platelet counts, immature platelet fraction, platelet function by flow cytometry, and the bleeding score. Since the dose required may vary from patient to patient and may only be changed every 2 weeks, a platelet count > 50,000/ul at any time within the first 12 weeks will be considered a response. Similarly, secondary endpoints involving reduction in bleeding and improvement in platelet function will also be explored within a 4 to 12 week window for assessment.

Toxicity will depend upon adverse events, abnormal liver tests, and other abnormal findings.

#### 8.3.1.2. Safety Analyses

Descriptive statistics will be used to summarize the extent of exposure to eltrombopag.

The number (%) of subjects with Adverse Events and Serious Adverse Events will be reported.

Laboratory parameters will be summarized by visit using descriptive statistics.

# 9. STUDY CONDUCT CONSIDERATIONS

## 9.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Subjects will be given the consent to review prior to requesting their signature so that sufficient time is provided for the subject to consider the study. Risks and benefits will be explained in their entirety to patients. If necessary, an interpreter will be obtained to assist the patient. Any questions that the patient has will be answered prior to signing consent.

The study will be conducted in accordance with International Conference on Harmonization Guidelines for Good Clinical Practice, and the Declaration of Helsinki.

## 9.2. Quality Control (Study Monitoring)

None needed for investigator-initiated pilot study.

## 9.3. Quality Assurance

Pharmacy and clinical records.

## 9.4. Records Retention

7 years.

# 10. APPENDICES

# 1. SCHEDULE OF EVENTS ON THE LAST PAGE OF THE PROTOCOL (PAGE 25).

# 2. WEEKLY DOSE ADJUSTMENT FOR PLATELET COUNTS:

| PLATELET COUNT | DOSE ADJUSTMENT |
|---|---|
| >200 Gi/L | dose reduced by at least 5% |
| 50 to 200 Gi/L | Maintain current dose |
| <50 Gi/L and/or Significant Bleeding | Increase daily dose by at least 5% up to 75mg daily |

# 3. ELTROMBOPAG POWDER FOR ORAL SUSPENSION

Eltrombopag powder for oral suspension (Eltrombopag PfOS) is a reddish-brown to yellow powder contained inside an elongated sachet. Each sachet will contain eltrombopag olamine equivalent to 20 mg of eltrombopag per gram of powder.

## 3.1. Packaging and Labelling

Eltrombopag PfOS sachets will be packaged in a carton. Each carton pack will hold 35 sachets along with a plastic reconstitution container and a syringe-adapt cap. The pack will also contain an extra syringe-adapt cap as a spare. The contents of the label will be in accordance with all applicable regulatory requirements.

## 3.2. Preparation

The powder for oral suspension (PfOS) is presented as a reddish brown to yellow powder, which when reconstituted with water forms a reddish-brown suspension. The sachet should not be opened until ready for use. Add 9.5 mL of water drawn using a 10cc syringe into the provided plastic container. Cut open the sachet and add the entire content of the sachet into the container containing water. The container is capped and shaken for 10-20 seconds. The resulting suspension contains 2 mg/mL of eltrombopag dose. The prescribed volume (dose) is drawn through the syringe port on the cap with a syringe. Upon dosing, the rest of the remaining suspension in the container is discarded. The container and the syringe are rinsed with water and dried.

A fresh dose is prepared everyday just prior to the dosing and no storage of the reconstituted suspension is allowed.

## 3.3. Handling and Storage

Investigational product must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer investigational product. All investigational products must be stored in a secure area with access limited to the investigator and authorized site staff and under physical conditions that are consistent with investigational product-specific requirements. Eltrombopag PfOS will be stored according to the requirements listed on the label.

## 3.4. Dose Adjustment Guidelines for subjects receiving the suspension formulation

The dose of eltrombopag will be increased or decreased according to platelet counts as outlined above; these modifications will initially be in strength intervals of 30% (rounded up), but intermediate dosing levels may be used if the platelet response warrants it. The dose will be documented in the CRF.

### Table 1: Dose Adjustment Guidelines – Suspension formulation

| Weight (kg) | Initial dose (mg) | Initial dose (mL) | Adjust dose by (mg) | Adjust dose by (mL)[1] |
|---|---|---|---|---|
| 8 | 16 | 8 | 5 | 2.5[1] |
| 9 | 18 | 9 | 6 | 3[1] |
| 10 | 20 | 10 | 6 | 3 |
| 11 | 22 | 11 | 7 | 3.5 |
| 12 | 24 | 12 | 8 | 4 |
| 13 | 26 | 13 | 8 | 4 |
| 14 | 28 | 14 | 9 | 4.5[1] |
| 15 | 30 | 15 | 9 | 4.5[1] |
| 16 | 32 | 16 | 10 | 5 |
| 17 | 34 | 17 | 11 | 5.5 |
| 18 | 36 | 18 | 11 | 5.5 |
| 19 | 38 | 19 | 12 | 6 |
| 20 | 40 | 20 | 12 | 6 |
| 21 | 42 | 21 | 13 | 6.5 |
| 22 | 44 | 22 | 14 | 7[1] |
| 23 | 46 | 23 | 14 | 7[1] |
| 24 | 48 | 24 | 15 | 7.5[1] |
| 25 | 50 | 25 | 15 | 7.5[1] |

1. For calculated doses of 18mg – 24 mg, patient should receive 20 mg dose (one sachet). For doses of 38 mg to 44 mg, the patient should receive 40 mg dose (two sachets). For doses of 58 mg to 65 mg the patient should receive 60 mg dose (three sachets).

References

Bussel J, Provan D, Shamsi T, Cheng G, Psaila B, Kovaleva L, et al. (2009). Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. The Lancet, 373, 9664:641-648.

Bussel, J, Cheng G, Saleh M, Psaila B, Kovaleva L, Meddeb B, et al. (2007). Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. N Engl J Med, 357, 22:2237-2247.

Gerrits A, Leven E, Frelinger III A, Brigstocke S, Berny-Lang M, Mitchell W, Revel-Vilk S, Tamary H, Carmichael S, Barnard M, Michelson A, Bussel J. (2015). Effects of eltrombopag on platelet count and platelet activation in Wiskott-Aldrich syndrome/X-linked thrombocytopenia. Blood, 126, 11:1367-1378.

Kühne T, Buchanan G, Zimmerman S, Michaels L, Kohan R, et al. A prospective comparative study of 2540 infants and children with newly diagnosed idiopathic thrombocytopenic purpura (ITP) from the intercontinental childhood ITP study group. The Journal of Pediatrics, 143, 5:605-608.

Mutchinson J, Dusheiko G, Shiffman M, Rodriguez-Torres M, Sigal S, Bourliere M, et al. (2007). Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. N Engl J Med, 357, 22:2227-36.

Ochs H, Thrasher A. The Wiskott-Aldrich syndrome. (2006). Journal of Allergy and Clinical Immunology, 117, 4:725-738.

Ochs HD, Rosen FS. The Wiskott-Aldrich syndrome. In: Ochs HD, Smith CIE, Puck JM, eds. Primary Immune Deficiency Disease: A Molecular and Genetic approach. New York, NY: Oxford University Press, 2007:454-469.

Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA. A multiinstitutional survey of the Wiskott-Aldrich syndrome. J Pediatr. 1994, 125:876-885.

## SCHEDULE OF EVENTS
## "Pathobiology of Thrombocytopenia and Bleeding in Patients with Wiskott-Aldrich Syndrome." Protocol #: 0801009600

| | Screening | Day 1/Baseline | Week 2 | Week 4 | Months[4] 2 – 12 | Months[5] 14 - 24 | Months[6] 27 - 72 |
|---|---|---|---|---|---|---|---|
| Evaluation and Management | | | | | | | |
| Informed Consent | x | | | | | | |
| Bleeding Score[1] | x | x | x | x | x | x | x |
| Standard of Care | | | | | | | |
| Physical Examination | x | x | x | x | x | x | x |
| Urinalysis | x | | | | | | |
| Admission Panel (Includes liver tests such as ALT, AST, bilirubin) | x | x | x | x | x | x | x |
| CBC with Platelet and Diff | x | x | x | x | x | x | x |
| Diagnostic Tests for Platelet Function | | | | | | | |
| PT/PTT | x | | | | | | |
| D-Dimers | x | | | | | | |
| Fibrinogen | x | | | | | | |
| PFA[2] | | | | | x | | |
| Immature Platelet Fraction (Platelet Reticulocyte Count)[3] | x | x | x | x | x | x | x |
| Single Platelet Flow Cytometry[7] | x | | | x | x[8] | | |

1. The Page bleeding score will be administered at each visit in order to semi-quantitatively assess bleeding
2. PFA (Platelet function Analysis) will be assessed once for WAS/XLT patients and control patients at month 2, provided platelet count is >50 k
3. IPF will be obtained with each Cornell in-clinic CBC where possible
4. Subjects will have their blood drawn monthly and be seen every 3 months during the first year
5. Subjects will have their blood drawn every 2 months and be seen every 4 months in the second year
6. Subjects will have their blood drawn every 3 months and be seen every 6 months in the 3rd – 6th years
7. Single Platelet Flow Cytometry tests will be performed by Dr. Alan Michelson at screening, once between months 1-3, and once after 1-2 years on study.