16.1.1 Protocol and Amendments

Title: A Single Arm, Open-label, Long-term Efficacy and Safety Study of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune Thrombocytopenia (ITP)

Amgen Protocol Number (Romiplostim) 20101221

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I have read the attached protocol entitled A Single Arm, Open-label, Long-term Efficacy and Safety Study of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune Thrombocytopenia (ITP), dated **15 August** 2014, and agree to abide by all provisions set forth therein.

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I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Principal Investigator Date (DD Month YYYY)

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Protocol Synopsis

Title: A Single Arm, Open-label, Long-term Efficacy and Safety Study of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune Thrombocytopenia (ITP)

Study Phase: 3b

Indication: Pediatric ITP

Primary Objective:

- To describe the percentage of time that pediatric subjects with ITP have a platelet response in the first 6 months from the start of treatment with romiplostim

Secondary Objectives:

- To describe the percentage of time that pediatric subjects with ITP have a platelet response over the study duration
- To describe the percentage of time that pediatric subjects with ITP have an increase in platelet count ≥ 20 x 10^9/L above baseline over the study duration
- To describe the use of rescue ITP medications
- To describe the incidence of antibody formation
- To describe the safety of romiplostim as a long-term treatment in pediatric thrombocytopenic subjects with ITP

Exploratory Objectives:

- To describe the incidence of sustained platelet response
- To describe the incidence of splenectomy
- To describe the subject incidence of romiplostim self-administration

Hypotheses: A formal hypothesis will not be tested in this study. The percentage of time with a platelet count ≥ 50 x 10^9/L in the first 6 months of the study will be estimated.

Primary Endpoint:

- The percentage of time with a platelet count of ≥ 50 x 10^9/L starting from week 2 in the first 6 months of the treatment period without rescue medication use in the past 4 weeks

Secondary Endpoints:

- The percentage of time with a platelet count of ≥ 50 x 10^9/L starting from week 2 until the end of the treatment period without rescue medication use in the past 4 weeks
- The percentage of time with an increase in platelet count ≥ 20 x 10^9/L above baseline starting from week 2 until the end of the treatment period without rescue medication use within the past 4 weeks.
- Subject incidence of rescue ITP medications used
- The incidence of anti-romiplostim neutralizing antibodies and cross-reactive antibodies to thrombopoietin (TPO) at any time during the study
- The incidence of adverse events, including clinically significant changes in laboratory values

Exploratory Endpoints

- The subject incidence with a sustained platelet count of ≥ 50 x 10^9/L for 6 months or greater without the use of any ITP medications (concomitant, rescue, or romiplostim)
- The incidence of splenectomy during the treatment period for subjects entering the study pre-splenectomy

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- The subject incidence of romiplostim self-administration

Study Design:

This is a phase 3b single arm, open label, multicenter study describing the percentage of time pediatric subjects with ITP have a platelet response while receiving romiplostim, defined as a platelet count ≥ 50 x 10^9/L and in the absence of ITP rescue medications in the past 4 weeks. This protocol will provide open label romiplostim to thrombocytopenic pediatric subjects with ITP diagnosed for at least 6 months and who have received at least 1 prior ITP therapy (excluding romiplostim) or are ineligible for ITP therapies.

The study design consists of a 4-week screening period, up to a 3-year treatment period, an end of treatment (EOT) visit, and an end of study (EOS) visit.

Sample Size: Approximately 200 subjects

Summary of Subject Eligibility Criteria:

Eligible pediatric subjects diagnosed with ITP according to the American Society of Hematology (ASH) guidelines (Neunert et al, 2011) must have thrombocytopenia (defined as a platelet count ≤ 30 x 10^9/L) or have bleeding that is uncontrolled with conventional therapy within 4 weeks of enrollment.

For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

Amgen Investigational Product Dosage and Administration:

Investigational product will be administered as a subcutaneous injection. The starting dose of romiplostim will be 1 µg/kg based on the subject's recorded screening weight in the clinic by a qualified healthcare provider. Throughout the treatment period, subjects will return to the clinic for platelet counts and undergo dose titrations under the supervision of the treating physician. Weekly dose increases will be made in increments of 1 µg/kg, up to a maximum dose of 10 µg/kg, in an attempt to reach a target platelet count of ≥ 50 x 10^9/L. Dose adjustments will be allowed to maintain a platelet count between ≥ 50 x 10^9/L and ≤ 200 x 10^9/L. Subjects who receive their first 8 doses in clinic and achieve a platelet count ≥ 50 x 10^9/L without romiplostim dose adjustments for 4 consecutive weeks will be eligible to self-administer romiplostim or have the injection administered by a caregiver.

For detailed instructions regarding investigational product presentation, dose, administration, and dose adjustments, please see Section 6.

Control Group: The study design does not include a control arm.

Procedures:

At specified time points, subjects will undergo the following assessments: informed consent (and assent, if applicable), confirmation of ITP diagnosis, ITP and medical history, physical exam including weight and vital signs. Subjects will have complete blood counts with differentials, blood chemistry profiles, local platelet counts, and a blood or urine pregnancy test for females of child-bearing potential. Research staff will document the use of concomitant and rescue medications and all adverse events reported for the subject. Subjects will also provide blood samples for anti-TPO/romiplostim antibodies and peripheral blood smears.

For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and Table 2.

Statistical Considerations:

The primary analysis will be descriptive. No formal hypothesis will be tested. Summary statistics will be provided for the primary and secondary endpoints. Categorical data will be presented in the form of number and percentage. Continuous data will be provided with the descriptive statistics (n, mean, standard deviation, median, Q1 [25th percentile], Q3 [75th percentile], minimum, and maximum). The analysis of efficacy and safety endpoints will be based on the set of subjects receiving at least one dose of romiplostim.

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Interim analyses will be conducted to support regulatory filings, and accumulating data for this study will be summarized to provide ongoing assessments of the safety of romiplostim. These interim analyses will occur at least annually until the end of the study.

For a full description of statistical analysis methods, please refer to Section 10.

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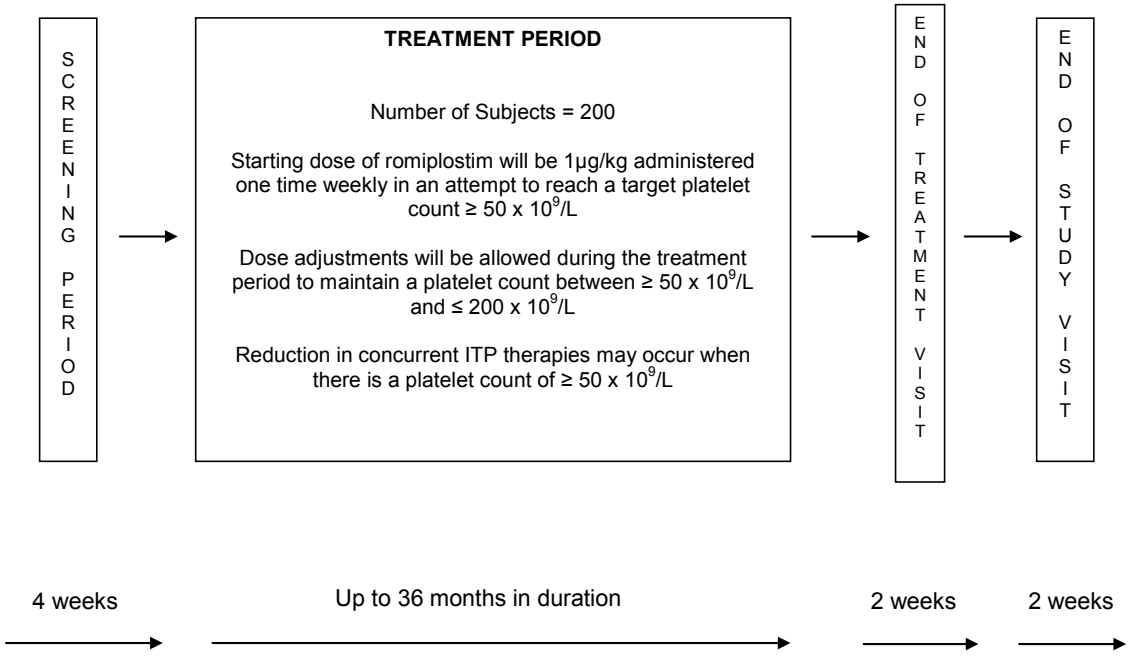
Study Design and Treatment Schema



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Study Glossary

Abbreviation or Term	Definition/Explanation
ASH	American Society of Hematology
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCSH	British Committee for Standards in Hematology
CBC	complete blood counts
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic case report form
end of study for individual subject (EOS)	defined as the last day that protocol-specified procedures are conducted for subjects who do not complete the 36 month treatment period.
end of treatment (EOT)	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
end of study (primary completion)	defined as the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary outcome
eTPO	endogenous thrombopoietin
INR	international normalized ratio
IP	investigational product
IRB/IEC	institutional review board/independent ethics committee
ITP	immune thrombocytopenia
IVIG	intravenous Immunoglobulin
IVRS	interactive voice response system: telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
source data	information from an original record or a certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies, ICH Guideline E6). Examples of source data include subject ID, randomization ID, and stratification value.
study day 1	defined as the first day that romiplostim is administered to the subject
TB	total bilirubin
TPO	thrombopoietin

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1. OBJECTIVES

1.1 Primary

The primary objective is to describe the percentage of time that pediatric subjects with immune thrombocytopenia (ITP) have a platelet response in the first 6 months from the start of treatment with romiplostim.

1.2 Secondary

The secondary objectives of the study are:

- To describe the percentage of time that pediatric subjects with ITP have a platelet response over the study duration
- To describe the percentage of time that pediatric subjects with ITP have an increase in platelet count ≥ 20 x 10^9/L above baseline over the study duration
- To describe the use of rescue ITP medications
- To describe the incidence of antibody formation
- To describe the safety of romiplostim as a long-term treatment in pediatric thrombocytopenic subjects with ITP

1.3 Exploratory

- To describe the incidence of sustained platelet responses
- To describe the incidence of splenectomy
- To describe the subject incidence of romiplostim self-administration

2. BACKGROUND AND RATIONALE

2.1 Disease

Immune thrombocytopenia is an autoimmune disorder characterized by a low circulating platelet count (thrombocytopenia) and decreased platelet production. Historically, the low circulating platelet counts were attributed to antibodies binding to platelet antigens, resulting in destruction of platelets in the reticuloendothelial system, primarily the spleen (Bottiger and Westerholm, 1972; McMillan, 1981; Kelton and Gibbons, 1982; George et al, 1995). However, a recent international consensus report suggests that a more complex disease process is present in which impaired platelet production may play an important role in the disease (Provan et al, 2010). Thrombocytopenia, as a result of ITP, places patients at risks for bruising, mucocutaneous bleeding, and, more seriously, intracranial hemorrhage.

The annual incidence of ITP among children in the United States and Europe is estimated between 19 and 64 cases/million population, with a peak incidence between

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ages 2 and 10 and affecting boys and girls equally (Terrell et al, 2010; Glanz et al, 2008; Tarantino, 2006; Zeller et al, 2000; Lilleyman, 1999).

Treatment guidelines for ITP have been published by the American Society of Hematology (ASH) ITP study group, (Neunert et al, 2011), the British Committee for Standards in Hematology and General Hematology Task Force (BCSH, 2003) and an International ITP consensus group (Provan et al, 2010). Guidelines from these groups review and provide recommendations on the diagnosis, management and treatment options for ITP subjects.

Unlike adult ITP in which the majority of cases are chronic in duration, pediatric ITP most commonly occurs in the acute form (platelet count < 150 x 10^9/L for < 6 months from diagnosis), accounting for 70% to 80% of ITP cases in children (Glanz et al, 2008). Many children with acute ITP require no treatment, and in approximately 60% to 75% of cases, the thrombocytopenia resolves within 2 to 4 months regardless of therapy (Nugent, 2006). In pediatric ITP cases, 20% to 30% are considered chronic (platelet count < 150 x 10^9/L for > 6 months from diagnosis) and may become refractory to standard treatments (Glanz et al, 2008). Chronic ITP in childhood has an estimated incidence of 0.46 per 100,000 children per year (Lilleyman, 1999; Zeller et al, 2000). Predictors for chronic ITP in children include older age (> 10 years) and an insidious presentation (Robb and Tiedeman, 1990). In addition, chronic ITP in children is associated with higher presenting platelet count (> 20 x 10^9/L), lack of mucosal bleeding at presentation, and lack of a previous acute illness (Glanz et al, 2008).

The traditional classification of chronic and acute ITP in the literature is based solely on persistence of thrombocytopenia from time of diagnosis, whereas previously mentioned, acute ITP is < 6 months and chronic ITP is > 6 months (Kuhne, 2003). However, this definition is commonly considered arbitrary (Bolton-Maggs, 2007; Buchanan and Adix, 2006; Glanz et al, 2008; Kuhne, 2006). As a result, an international working group of ITP experts recently convened and re-defined the classification. The working group now defines “newly diagnosed ITP” as 0 to 3 months from diagnosis, “persistent ITP” as lasting between 3 and 12 months from diagnosis, and “chronic ITP” as a disease duration ≥ 12 months. This classification includes patients not reaching spontaneous remission or not maintaining complete response off therapy (Rodeghiero et al, 2009). Based on these recent definitions, important determinants of disease severity and need for treatment include time since diagnosis, failure of prior ITP therapy, and bleeding symptoms.

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2.2 Treatments for ITP in Pediatric Patients

The treatment of ITP in pediatric patients is warranted to prevent clinically significant bleeding events, especially intracerebral hemorrhage. Although fatal bleeding events among children with ITP are rare and the overall incidence of intracerebral hemorrhage is between 0.2% and 1% (Cines and Blanchette, 2002), one review of 332 medical records revealed that 17% of children had major hemorrhage defined as intracranial bleeding, epistaxis requiring cautery or nasal packing, gross hematuria, or other bleeding causing a decline in hemoglobin concentration. Approximately 75% of bleeding episodes in this review occurred in children with platelet counts < 10×10^9/L (Tarantino, 2006).

The principal aim of treating children with chronic ITP is to maintain a hemostatically safe platelet count and improve quality of life, instead of trying to achieve a cure (Kalpatthi and Bussel, 2008). Clinical management of chronic ITP in children varies and does not always adhere to recommendations set forth by the ASH and the BCSH and General Hematology Task Force (Neunert et al, 2011; BCSH, 2003). The ASH guidelines incorporate both clinical and platelet count data to arrive at specific treatment recommendations; drug therapy with either intravenous immunoglobulin (IVIG) or corticosteroids is recommended for children with a platelet count (< 20×10^9/L) and minor purpura, and for children with severe life-threatening bleeding (George et al, 1996). The BCSH guidelines suggest that pronounced skin purpura and bruising may not reflect a serious risk of bleeding and recommend that only patients who experience significant mucous membrane bleeding receive treatment (Tarantino and Bolton-Maggs, 2007; Tarantino, 2006). Furthermore, the BCSH recommends that IVIG be used only for emergency treatment or for those who do not respond to corticosteroids.

In 2010, an international consensus report was published to address the investigation, diagnosis, and management of childhood ITP (Provan et al, 2010). The consensus report guidance for the diagnosis and management of ITP remains largely unchanged from the previously published BCSH and ASH guidance. Central to the committee's recommendations is the adoption of an ITP classification by duration, which is separated into 3 distinct periods: newly diagnosed ITP (0 to 3 months from diagnosis), persistent ITP (3 to 12 months from diagnosis), and chronic ITP (12 months or more from diagnosis). Once an ITP diagnosis and classification are confirmed, individual subject disease characteristics (eg, bleeding symptoms, platelet counts), psychosocial issues,

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level of activity, and lifestyles should be considered when selecting the appropriate management and treatment of the disease.

Regardless of which guidelines are being followed, medical management is generally preferred over splenectomy for children who have ITP between 6 and 12 months. Traditional pre-splenectomy treatment options include oral corticosteroids (including pulse oral dexamethasone), IVIG, and for children who are Rhesus-positive, intravenous (IV) anti-D (Blanchette and Price, 2003). Less commonly, immunosuppressive strategies have been used to treat chronic ITP which include cyclophosphamide, azathioprine, cyclosporine, mycophenolate mofetil, and autologous stem cell transplantation (Buchanan and Adix, 2006). While each of these therapies has been shown to result in increased platelet counts, the potential toxicity of these approaches compels physicians to weigh the likelihood of clinical efficacy against the likelihood of the occurrence of clinically relevant adverse events (Tarantino, 2006).

Recently rituximab has also been used to treat pediatric ITP. A prospective study of the use of rituximab among children with chronic refractory ITP demonstrated a 31% response rate with response defined as maintenance of a platelet count > 50 x 10^9/L for 4 consecutive weeks (Bennett et al, 2006). However, rituximab carries a significant warning regarding infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (Rituxan® [rituximab] Prescribing Information, 2012). Long-term suppression of B cells by rituximab is generally not associated with decreased immunoglobulin levels (except possibly in very young children) or serious infections (Parodi et al, 2006). Although the need for prophylactic IVIG has not been demonstrated, patients must be closely monitored. Hepatitis B virus reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients with hematologic malignancies treated with rituximab (Kalpatthi and Bussel, 2008; Rituxan® [rituximab] Prescribing Information, 2012).

Splenectomy is considered only for those children who have severe ITP. The fact that 36% of chronic pediatric ITP patients are reported to experience spontaneous remission (Reid, 1995) suggests that there could be a role for therapeutic agents that have the ability to delay splenectomy. Splenectomy is recommended in both ASH and BCSH guidelines for children with ITP lasting > 1 year with both low platelet count and bleeding symptoms, although the BCSH guidelines stress that splenectomy is warranted only with demonstrable impairment on quality of life (Kalphatthi and Bussel, 2008; Tarantino and Bolton-Maggs, 2007). In the recently published international consensus

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report, splenectomy is also cited as a surgical treatment option, but is generally deferred for as long as possible (Provan et al, 2010).

Splenectomy is successful in resolution of life threatening thrombocytopenia in 75% to 85% of pediatric patients but is associated with an increased risk of sepsis (Nugent, 2006). A recent survey revealed that only approximately one-third of respondents would recommend splenectomy as first-line therapy for a child with severe chronic refractory ITP, a decision influenced mostly by factors affecting long-term outcome, such as risk of sepsis, thromboembolic events, possible relapse, likelihood of spontaneous remission without splenectomy, and the irreversible nature of splenectomy (Neunert et al, 2008). Moreover, splenectomy may not be warranted in younger patients who are at relatively high risk for infection with encapsulated organisms (Kuhne et al, 2007; Bennett et al, 2006).

2.3 Romiplostim Background

Romiplostim is a recombinant non-glycosylated 59 kDa thrombopoietic protein produced in *Escherichia coli*. It is a fusion protein (peptibody), composed of a human immunoglobulin IgG1 Fc domain with each single chain subunit covalently linked at the C-terminus to a peptide chain containing 2 thrombopoietin (TPO) receptor binding domains. Romiplostim stimulates platelet production by a mechanism similar to that of endogenous thrombopoietin (eTPO); however, there is no amino acid sequence homology between romiplostim and eTPO. The lack of sequence homology with eTPO reduces the probability that if antibodies to romiplostim are produced they will cross react with eTPO and cause thrombocytopenia.

Romiplostim is approved for use in the adult chronic ITP setting in various regions of the world under the trade name of Nplate® (romiplostim); the specific clinical indication varies by region. The most common side effects reported include headache, aching joints, dizziness, difficulty sleeping, muscle aches, pain in extremities and abdominal pain.

For additional information on romiplostim, please refer to the most current version of the Romiplostim Investigator's Brochure.

2.4 Pediatric Clinical Data

Proof of concept for the treatment of ITP in the pediatric population has been established in Study 20060195. Protocol 20060195 was a Phase 2 randomized, double-blind, placebo-controlled, 12-week study designed to assess the safety, tolerability, and

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efficacy of romiplostim for the treatment of pediatric thrombocytopenic subjects with ITP. A total of 22 subjects (17 romiplostim; 5 placebo) between 12 months and 17 years of age were randomized in a 3:1 ratio to receive romiplostim or volume-matched placebo at a starting dose of 1 µg/kg administered weekly by subcutaneous injection. Subjects returned to the clinic weekly for platelet counts and undergo dose titrations under the supervision of the treating physician.

All 22 subjects received blinded investigational product (IP) and were evaluated for efficacy. Of the 17 subjects who received romiplostim, 15 (88%) achieved a platelet response ≥ 50 x 10^9/L for 2 consecutive weeks during the 12-week treatment period (after excluding platelet counts within 4 weeks after rescue medication use). The same 15 subjects also achieved an increase in platelet count ≥ 20 x 10^9/L above baseline for 2 consecutive weeks (after excluding platelet counts within 4 weeks of rescue medication use). None of the placebo-treated subjects achieved either endpoint.

With regards to rescue medication use, 2 of 17 subjects (11.8%) in the romiplostim group, and 2 of the 5 subjects (40.0%) in the placebo group received rescue medication support during the treatment period.

During the treatment period, adverse events were reported for the majority of subjects in each treatment group (16 of 17 subjects [94.1%] in the romiplostim group and 4 of 5 subjects [80%] in the placebo group), with most adverse events reported as mild to moderate in severity. The most frequently reported adverse events (subject incidence > 25% in either treatment group) were (romiplostim, placebo) headache (6 subjects, 35.3%; 2 subjects, 40.0%), epistaxis (6 subjects, 35.3%; 1 subject, 20.0%), cough (2 subjects, 11.8%; 2 subjects, 40.0%), vomiting (2 subjects, 11.8%; 2 subjects, 40.0%), and nasal congestion (0 subjects, 0.0%; 2 subjects, 40.0%).

Bleeding was the only event of interest observed on study. When adjusted for exposure duration, the rate of bleeding was 7.3 events per 100 subjects-weeks in the romiplostim arm and 11.9 events per 100 subject-weeks in the placebo arm. Bleeding events were mostly mild and occurred early in the treatment period when platelet counts were < 50 x 10^9/L. No bleeding adverse events were considered to be serious or treatment related.

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2.5 Bone Marrow Reticulin Evaluation in ITP

Reticulin is a normal component of the bone marrow that can be detected with reticulin (silver) stain (Thiele et al, 2005; Kuter et al, 2007). Increased reticulin (reticulin fibrosis) is associated with many benign conditions, while increased collagen fibrosis (detected by trichrome staining) is characteristic of myeloproliferative disease (Kuter et al, 2007). In a retrospective analysis of bone marrow biopsies from 40 patients with ITP, reticulin was present in approximately two-thirds of romiplostim-naïve patients (Mufti et al, 2006). Increased reticulin above normal levels may be observed with or without concomitantly increased collagen in several conditions. Increased reticulin without collagen fibrosis is associated with conditions such as hairy cell leukemia, human immunodeficiency virus infection, pulmonary arterial hypertension, and treatment with hematopoietic growth factors (Kuter et al, 2007).

Increased reticulin has been observed following treatment with recombinant human thrombopoietin (rHuTPO), interleukin-3, and interleukin-11 (Kuter, 2007; Kuter et al, 2007), and is likely a response to stimulation of megakaryocytes by thrombopoietin (TPO) (Douglas et al, 2002), or related to cytokines or other factors that are elaborated by the megakaryocytes (Castro-Malaspina et al, 1981; Yanagida et al, 1997; Schmitt et al, 2000). Bone marrow reticulin (or the presence of reticulin on study) was observed in 3.7% (10 of 271) of subjects evaluated who had received romiplostim for ITP [data on file]. Increased reticulin formation may be due to the increased number of megakaryocytes in the bone marrow as a result of romiplostim treatment, consistent with findings associated with other thrombopoietins (Kuter, 2007).

Recent evidence has shown that the amount of bone marrow reticulin detected by silver staining often exhibits no correlation to disease severity, while the presence of type 1 collagen, as detected by trichrome staining, is often associated with more severe disease, a poorer prognosis (Kuter et al, 2007), and may be associated with malignant conditions such as chronic idiopathic myelofibrosis (Tefferi, 2005).

To prospectively evaluate the incidence of both reticulin and collagen formation in the bone marrow during treatment with romiplostim, a trial in adults with ITP receiving open label romiplostim for up to 3 years is in progress (Amgen study 20080009). Three cohorts of subjects will undergo repeat bone marrow evaluation after 1, 2, or 3 years to evaluate the incidence and potential sequelae of reticulin and collagen formation in the bone marrow. To date, no development of collagen has been seen in cohorts 1 (1 year) and 2 (2 years). Increase by 2 grades in reticulin has been observed in no subjects in

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cohort 1 and 2 subjects in cohort 2. Cohort 3 evaluations are in progress. Bone marrow studies of children with ITP to evaluate reticulin and collagen formation have not previously been conducted.

2.6 Anti-romiplostim Antibody Results

To date, anti-romiplostim neutralizing antibodies have been detected in samples from 2 adult subjects with ITP. One of the subjects presented with anti-romiplostim neutralizing antibodies at the end of study (EOS) time point but tested negative for neutralizing antibodies to romiplostim on follow-up 4 months later (after discontinuation of romiplostim). The second subject had neutralizing antibodies to romiplostim at an unscheduled time point after dosing with romiplostim but tested negative for neutralizing antibodies to romiplostim at 2 follow-up time points (week 132 and EOS) after discontinuation of romiplostim. No cross-reactive binding antibodies to TPO were observed.

For a complete summary of all safety and efficacy data collected in both the adult and pediatric ITP indications for the romiplostim clinical development program, please refer to the most recent version of the Romiplostim Investigator's Brochure.

2.7 Pediatric Risk Assessment

Previously reported safety results of the earlier phase 2 study (20060195), the currently enrolling phase 3 study (20080279), and open-label long-term follow-up study (20090340) support a favorable benefit risk profile with the use of romiplostim in thrombocytopenic pediatric subjects. This study represents the fourth investigation of romiplostim in thrombocytopenic pediatric subjects with ITP.

2.8 Rationale

The treatment of ITP in pediatric patients is warranted to prevent clinically significant bleeding events, especially intracerebral hemorrhage. The management of children with ITP who either fail to respond to treatment or relapse following splenectomy is often challenging. It is recognized that multiple therapeutic options are available and can be used as a single agent or in combination. However, the sustained remission rate with monotherapy has proved disappointing, and controlled studies have not been performed. Furthermore, small studies have demonstrated the potential for improved outcomes with combination therapy, but there is no accepted standard of care (Robb and Tiedeman, 1990). Appreciating the toxicities associated with many of the available treatments and knowing the limitations of current therapies, including failure after splenectomy, the management of pediatric ITP remains medically challenging.

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Treatment with a thrombomimetic therefore represents a unique opportunity to treat this challenging disease with a novel therapy. The route of administration, schedule, starting dose, and subsequent dose adjustments of romiplostim have been well established in previous pediatric and adult ITP studies and will be used for dosing and administration in this protocol. Romiplostim will be administered initially in the clinic by a qualified health care provider as a subcutaneous injection. The starting dose of romiplostim will be 1 µg/kg/week based on the subject's recorded screening weight. Throughout the treatment period, subjects will return to the clinic to provide platelet counts and undergo dose titrations under the supervision of the treating physician. Weekly dose increases will continue in increments of 1 µg/kg up to a maximum dose of 10 µg/kg in an attempt to reach a target platelet count of ≥ 50 x 10^9/L. Dose adjustments will be allowed to maintain a platelet count between ≥ 50 x 10^9/L and ≤ 200 x 10^9/L.

2.9 Clinical Hypotheses

No formal hypothesis will be tested in this study. The percentage of time with a platelet count ≥ 50 x 10^9/L in the first 6 months of the study will be estimated.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 3b single arm, open-label, multicenter study evaluating the percentage of time pediatric subjects with ITP have a response while receiving romiplostim, defined as a platelet count ≥ 50 x 10^9/L and in the absence of ITP rescue medications in the past 4 weeks. This protocol will provide open-label romiplostim to thrombocytopenic pediatric subjects with ITP diagnosed for at least 6 months and who have received at least 1 prior ITP therapy (excluding romiplostim) or are ineligible for other ITP therapies.

The study design consists of a 4-week screening period, up to a 3-year treatment period, an end of treatment (EOT) visit, and an end of study (EOS) visit.

Subjects entering the study on medications to raise platelet counts may remain on these concomitant medications, as needed, along with romiplostim. After the initiation of romiplostim, if subjects require additional medications to raise platelet counts, or an increase in dose of existing medications, rescue ITP therapies may be initiated (see Section 6.4). If the subject's platelet count is ≥ 50 x 10^9/L, concomitant or rescue ITP therapies can be reduced or discontinued.

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Approximately 200 subjects with ITP will be enrolled and will receive weekly romiplostim until they complete the study, discontinue participation in the study for any reason, or the study ends.

The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.

3.1.1 Subjects With an Onset of Sustained Platelet Response

During the treatment period, romiplostim doses will be adjusted as outlined in Table 1. Subjects who dose reduce romiplostim such that they no longer require treatment with romiplostim, no longer require ITP medications (concomitant or rescue), and have an onset of a sustained platelet response (defined as a consecutive platelet counts $\geq 50 \times 10^9$/L) will be monitored for at least 6 months beginning with the first platelet count $\geq 50 \times 10^9$/L. Subjects whose platelet count remains $\geq 50 \times 10^9$/L in the absence of any medications for ITP for at least 6 months will then be followed every 12 weeks for the duration of the 36-month treatment period.

If during the 36-month treatment period the platelet count subsequently falls below $< 50 \times 10^9$/L, treatment with romiplostim at the initial starting dose may be resumed. Subsequent doses will be adjusted as shown in Table 1. Clinic visits will be resumed per the Schedule of Assessments (Table 2).

3.1.2 Non-responding Subjects

Subjects who have a platelet count $\leq 20 \times 10^9$/L for 4 consecutive weeks at the maximum romiplostim dose of 10 µg/kg should be discontinued from romiplostim and will be considered non-responders. If the subject is a non-responder but the investigator believes the subject has obtained clinical benefit, the investigator must contact the Amgen medical monitor for the subject to continue participation in the study.

3.2 Number of Centers

There will be approximately 50 centers located in (but not limited to) Australia, Canada, Europe, Israel, South Africa, South America, and the United States.

Sites that do not enroll any subjects within 6 months of site initiation may be closed.

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3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as "subjects." It is anticipated that approximately 200 subjects will be enrolled into this study.

Please refer to Section 10.2 for sample size considerations

3.4 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Participants

For an individual subject, the length of participation includes a 4-week screening period, up to a 36-month treatment period, an EOT visit, and an EOS visit. The maximum duration for a subject completing the study will be approximately 3 years and 2 months.

3.5.2 End of Study

Primary Completion: the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary analysis. This will occur once the last subject participating has completed the EOS visit.

4. SUBJECT ELIGIBILITY

Before any study-specific procedure is performed, the appropriate written informed consent must be obtained (see Section 11.1). In addition to written informed consent, the assent of the child also must be obtained if requested by the investigative site's respective institutional review board/independent ethics committee (IRB/IEC).

Once informed consent (and assent, if applicable) has been obtained, the site will register the subject in the interactive voice response system (IVRS) and enter limited information about screening of potential candidate (sex, age, and race), date, and outcome of the screening process (eg, enrolled into study, reason for ineligibility, or refused to participate).

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

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4.1 Inclusion Criteria

4.1.1 Diagnosis of primary ITP according to The American Society of Hematology (ASH) Guidelines (Neunert et al, 2011) at least 6 months before screening, regardless of splenectomy status

4.1.2 Age ≥ 1 year and < 18 years at the time of providing informed consent

4.1.3 Subject must be refractory to a prior ITP therapy, having relapsed after at least 1 prior ITP therapy, or be ineligible for other ITP therapies

Examples of prior therapy include but are not limited to: corticosteroids, IVIG, anti-D immunoglobulin, and platelet transfusions. Subjects who have failed a splenectomy are eligible for study participation

4.1.4 Subject has a documented platelet count ≤ 30 $x10^9$/L or is experiencing bleeding that is uncontrolled with conventional therapies

4.1.5 Subject's legally acceptable representative (or subject, if applicable) has provided informed consent before any study-specific procedure; and subject has provided assent, where required by the IRB/IEC

4.1.6 Adequate hematologic, renal, and liver function during the screening period:

- Hemoglobin > 10.0 g/dL
- Serum creatinine ≤ 1.5 times the upper limit of normal
- Total serum bilirubin ≤ 1.5 times the upper limit of normal
- AST and ALT ≤ 3.0 times the upper limit of normal

4.2 Exclusion Criteria

4.2.1 Known history of a bone marrow stem cell disorder (Any abnormal bone marrow findings other than those typical of ITP must be approved by Amgen before a subject may be enrolled in the study)

4.2.2 Prior bone marrow transplant or peripheral blood progenitor cell transplant

4.2.3 Known active or prior malignancy except non-melanoma skin cancers within the last 5 years

4.2.4 Known history of myelodysplastic syndrome

4.2.5 Known history of bleeding diathesis

4.2.6 Known history of congenital thrombocytopenia

4.2.7 Known history of hepatitis B, hepatitis C or human immunodeficiency virus

4.2.8 Known history of systemic lupus erythematosus, Evans syndrome, or autoimmune neutropenia

4.2.9 Known history of antiphospholipid antibody syndrome or known positive for lupus anticoagulant

4.2.10 Known history of disseminated intravascular coagulation, hemolytic uremic syndrome, or thrombotic thrombocytopenic purpura

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4.2.11	History of venous thromboembolism or thrombotic events
4.2.12	Previous use of romiplostim**. Previous use of** eltrombopag **within 4 weeks of enrollment.**
4.2.13	Previous use of PEG-rHuMGDF, recombinant human thrombopoietin (rHuTPO) or any other platelet producing agent
4.2.14	Rituximab (for any indication) or 6-mercaptopurine within 8 weeks of enrollment, or anticipated use at any time during the study
4.2.15	Splenectomy within 4 weeks of the screening visit
4.2.16	Alkylating agents within 8 weeks before the screening visit or anticipated use during the time of the proposed study
4.2.17	Vaccinations known to decrease platelet counts within 8 weeks before the screening visit
4.2.18	Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational agent(s)
4.2.19	Subject will have investigational procedures performed while enrolled in this clinical study
4.2.20	Female subject of child bearing potential (defined as having first menses) is not willing to use, in combination with her partner highly effective methods of birth control during treatment and for 1 month after the end of treatment
4.2.21	Subject is pregnant or breast feeding, or might become pregnant within 1 month after the end of treatment
4.2.22	Subject has known hypersensitivity to any recombinant Escherichia coli derived product (eg, Infergen®, Neupogen®, somatropin, and Actimmune®)
4.2.23	Subject has previously enrolled into this study
4.2.24	Subject will not be available for protocol-required study visits or procedures, to the best of the subject's and investigator's knowledge
4.2.25	Subject has any kind of disorder that, in the opinion of the investigator, may compromise the ability of the subject to give written informed consent and/or to comply with all required study procedures

5. SUBJECT ENROLLMENT

Before subjects may be entered into the study, Amgen requires a copy of the site's written institutional review board/independent ethics committee (IRB/IEC) approval of the protocol, informed consent form and assent form if applicable. All subjects or legally acceptable representatives must personally sign and date the consent and assent form (if applicable) before study-specific procedures are performed. Adverse events are only reported for subjects enrolled in the study. Subjects are considered enrolled once they have been entered through the IVRS and have received their first dose of IP.

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All subjects who enter into the screening period for the study (entry is defined as the point at which informed consent is signed) will receive a unique subject identification number before any study procedures are performed. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed at the time of rescreening or enrollment.

6. TREATMENT PROCEDURES

6.1 Classification of Product(s) and/or Medical Device(s)

The Amgen Investigational Product used in this study: romiplostim.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, and administration of romiplostim.

6.2 Romiplostim

Romiplostim will be manufactured and packaged by Amgen Inc. and distributed using Amgen's clinical study IP distribution procedures. Romiplostim is supplied in a 5 mL single-use vial as a sterile, white, preservative-free, lyophilized powder containing a protein concentration of 0.5 mg/mL of 10 mM histidine, 4.0% mannitol, 2.0% sucrose, 0.004% polysorbate 20, and a pH 5.0 when reconstituted with 1.2 mL of sterile water for injection.

6.2.1 Dosage, Administration, and Schedule

IP will be administered as a subcutaneous injection. The starting dose of romiplostim will be 1 µg/kg based on the subject's recorded screening weight. Initially, IP will be administered in the clinic by a qualified health care provider and subjects will return to the clinic weekly to provide blood samples for platelet counts and undergo any dose titrations under the supervision of the treating physician. Subjects who receive their first 8 doses in the clinic and achieve a stable dose of romiplostim for at least 4 weeks may be allowed to self-inject romiplostim or have the injection administered by a caregiver. Weekly dose increases will continue in increments of 1 µg/kg up to a maximum dose of 10 µg/kg in an attempt to reach a target platelet count of $\geq 50 \times 10^9$/L. Dose adjustments will be allowed to maintain a platelet count between $\geq 50 \times 10^9$/L and $\leq 200 \times 10^9$/L. Dose adjustments will be evaluated every 12 weeks due to potential body weight changes.

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If a dose of < 0.05 mL is required, dilution of romiplostim in a 1:2 ratio (a protein concentration of 0.25 mg/mL) or a 1:4 ratio (a protein concentration of 0.125 mg/mL) may be made with 0.9% saline to ensure an appropriate dispensable volume is delivered.

Subjects will be monitored for the onset of a sustained platelet response (see Section 3.1.1) and, if achieved, may dose-reduce romiplostim. If a subject no longer requires treatment with romiplostim but there is subsequently a fall in platelet counts of < 50 x 10^9/L during the 36-month treatment period, treatment with romiplostim should resume at the initial weekly dose of 1 µg/kg.

The effects of overdose of romiplostim are not known. In high-dose preclinical studies, the noted effects were related to the pharmacological action of romiplostim. In the event of an overdose, platelet counts should be monitored frequently. Please refer to Section 6.2.2 for dosage adjustments.

Specific romiplostim details, including labeling, storage, preparation, dilution, administration, etc., are provided in a separate Investigational Product Instruction Manual. Each romiplostim box number is to be recorded on each subject's Investigational Product Administration electronic case report form (eCRF).

6.2.2 Dosage Adjustments: Delays or Rules for Withholding Investigational Product

Each subject's dose will be adjusted based on platelet counts. The rules outlined in Table 1 describe how the adjustments are to be made during the study.

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Table 1. Dose Adjustment Rules

Platelet count (x 10^9/L)	Investigational Product Dose Adjustment Rule[a]
< 50[b]	Increase dose by 1 µg/kg each week (to a maximum of 10 µg/kg)
50 to 200[b]	Dose remains constant
> 200 to < 400 [b,c]	After the platelet count remains in this range for 2 consecutive weeks, dose reduce by 1 µg/kg
≥ 400 [b,c,d]	Withhold the dose and dose reduce by 1 µg/kg on the next scheduled day of dosing when platelet count falls < 200 x 10^9/L

[a] If the platelet count is elevated in response to the initiation or increase in dose of another ITP medication, then the same dose of IP should be administered when the platelet count is ≤ 200 x 10^9/L.
[b] Romiplostim may be used with other therapies for ITP (refer to Section 6.4). If the subject's platelet count is ≥ 50 x 10^9/L, other ITP therapies may be reduced or discontinued.
[c] If the current dose is 1 µg/kg and a dose reduction is required, the dose will be withheld until the platelet count falls to < 50 x 10^9/L. Once the platelet count is < 50 x 10^9/L, dosing will resume at a dose of 1 µg/kg using the dose adjustment rules above.
[d] If platelet count ≥ 400 x 10^9/L is due to rescue medications, it is at the discretion of the investigator to reduce the dose by 1 µg/kg.

In situations in which withholding a romiplostim dose results in a rapid drop in platelet count, an alternate dosing schedule may be authorized on a case-by-case basis with the approval of an Amgen medical monitor.

The subject's body weight will be reassessed every 12 weeks. Subsequent doses of romiplostim will be re-calculated using the new weight. If the volume (mL or µL) of IP will be increasing due to an increase in body weight > 2.5 kg, the unit dose (µg/kg) of IP should not be increased until a platelet count has decreased to < 50 x 10^9/L requiring an increase in dose.

All doses of romiplostim will be administered on a weekly basis. Should a subject miss a dose of romiplostim, the dose can be taken within 1 day of the scheduled date of administration. Should the subject miss a dose outside of the 1 day window, the subject will continue with the subsequent dose at the next scheduled weekly date.

Dosing will be stopped at any time during the study if neutralizing antibodies to romiplostim or to eTPO are detected.

6.2.3 Non-responders to Romiplostim

Subjects with a platelet count of < 20 x 10^9/L for 4 consecutive weeks at the maximum romiplostim dose of 10 µg/kg should be discontinued from romiplostim and will be considered non-responders. Non-responders will be discontinued from the study and undergo all EOT and EOS procedures.

If the subject is a non-responder but the investigator believes the subject has obtained clinical benefit, the investigator must contact the Amgen medical monitor for

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consideration of continued participation in the study. If subject is allowed to remain on study and receive a stable romiplostim dose for at least 4 weeks, the subject will be eligible for self- administration.

6.3 Self-administration of Romiplostim

Romiplostim will initially be administered by the investigator or qualified health care professional at clinic visits. At the investigator's discretion, subjects who have been dosed in the clinic and achieve a platelet count ≥ 50 x 10^9/L without romiplostim dose adjustments for 4 consecutive weeks will be eligible to self-administer romiplostim or have the injection administered by a caregiver.

Those subjects who self-administer their medication, as well as those who are eligible to self-administer but choose not to, will only be required to return to the site for ongoing evaluations (including platelet counts) at designated study visits (performed every 4 weeks), as long as their dose of romiplostim remains stable.

In the event of a change in dose of romiplostim (per the dose adjustment rules in Table 1), subjects will be required to return to the clinic for 2 consecutive weeks to confirm that the dose adjustment was appropriate. Subjects will need to be on a stable dose and have a platelet count ≥ 50 x 10^9/L for 2 consecutive weeks without romiplostim dose adjustments before resuming self-administration.

Before subjects begin romiplostim self-administration, it is the responsibility of the investigator to ensure that subjects or their caregivers are trained to prepare and administer the injection. Subjects and/or subject's caregivers will receive training and study tools designed to educate the subject on the proper storage, reconstitution, and self-administration of romiplostim. Once subjects or their caregivers have adequately demonstrated their ability to reliably administer the medication, subjects may be allowed to self-inject (or have the injection given by their caregiver) away from the investigational site. The completion of training on self- injection (or training to a caregiver) will be recorded in the subject's source documentation. All training will be monitored.

The site will be required to ensure that subjects are supplied with necessary materials required for self-injecting, including dispensing of the IP. All used vials of romiplostim must be returned to the clinic for drug accountability. Subject diary cards to record the dose, dosing date, and any dosing or storage errors will be provided to subjects.

While subjects are self-injecting, the IP must be provided to subjects every 4 weeks, during the regular clinic visits. Shipping of romiplostim to subjects is prohibited.

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Subjects are expected to store romiplostim in a refrigerator and to notify the site personnel if an error in storage or dosing was made.

6.4 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care, except for those listed in Section 6.6.

All prescription and non-prescription concomitant medications, used to treat conditions other than ITP, administered at the time of enrollment, ongoing after enrollment, as well as changes in such concomitant medications and any new concomitant medications taken while the subject is on study, will be recorded on the appropriate eCRF through the EOT or the EOS visit, whichever is later.

Concomitant and Rescue Therapy for ITP

Concomitant medications are allowed for subjects enrolled into the study in any situation deemed medically necessary to increase platelet counts. Medications to increase platelet counts starting before enrollment and continuing unchanged (dose and schedule) while on treatment with romiplostim will be defined as concomitant medications for ITP. Rescue medication is defined as any medication or transfusion, other than romiplostim and excluded medications, that is administered after enrollment to the subject with the intent of raising platelet counts or to prevent bleeding and includes concomitant medications for ITP in which the dose and/or schedule is increased. For the purposes of this study, the permitted rescue medications include the following:

- corticosteroids
- platelet transfusions
- IVIG
- azathioprine
- anti-D immunoglobulin
- danazol

Antifibrinolytics can be used at any time during the study and will not be considered rescue medication(s).

Inhaled and/or topical corticosteroids intended to treat non ITP conditions (eg, inhaled steroids for asthma) will not be considered concomitant medications for ITP or rescue

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medications and continuing on such medication(s) will not affect the definition of platelet response.

Rescue medication is allowed throughout the duration of the study when platelet counts are < 20 x 10^9/L and/or when a subject has bleeding or wet purpura. Rescue medication is also allowed in any situation deemed medically necessary by the treating physician to increase platelet counts to treat or prevent bleeding.

Reduction or discontinuation of concomitant or rescue medications for ITP is recommended based on investigator judgment when platelet counts are ≥ 50 x 10^9/L.

Rescue medications are not provided by Amgen.

6.5 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of any investigational or non-investigational product(s) or device(s).

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.6 Excluded Treatments During Study Period

The following medications are not permitted during this study:

- commercially available romiplostim (Nplate®)
- other thrombopoietic receptor agonists (eg, eltrombopag, also known as Promacta® or Revolade®)
- any cytotoxic agents or alkylating agents
- Mycophenolate Mofetil
- Rituximab
- rHuTPO
- interferon
- treatments for ITP other than allowed rescue medications
- any other investigational agents that are not approved for commercial use

If a subject requires administration of any of the medications listed above, Amgen should be consulted before administration of the medication when possible. In all cases, Amgen must be informed within 24 hours. Amgen may decide that the subject will be ineligible to receive additional administrations of IP, in which case, the subject should complete the EOT and EOS visits.

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6.7 Other Treatment Procedures

If treatment with romiplostim is deemed to be ineffective or intolerable, the investigator may decide to perform a splenectomy. If a splenectomy is performed, the subject will discontinue treatment with romiplostim and follow the procedures for the EOT and EOS visits.

7. STUDY PROCEDURES

All subjects and/or their legally acceptable representatives (eg, parents, legal guardian) will sign and date the informed consent form before subjects can undergo any study-specific procedures. If required by the IRB/IEC, the assent of the child also must be obtained in addition to written informed consent. Refer to the Schedule of Assessments (Table 2) for an outline of the procedures required at each visit. The visit schedule is calculated from day 1 (first administration of romiplostim). All study procedures have a window of ± 1 day. Procedures that are part of routine care and not considered study specific procedures may be used as screening procedures to determine eligibility.

Missed visits or procedures that are not completed must be reported as such in the subject's source documentation, with an explanation of why the procedures were not completed.

Any blood sample collected according to the Schedule of Assessments (Table 2) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to ensure minimized risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

If informed consent is provided by the subject, or the subject's legally authorized representative, Amgen may do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand ITP, the dose response and/or prediction of response to romiplostim, characterize antibody response, or characterize aspects of the molecule (eg, metabolites). Results from this analysis will be documented and maintained, but may not be reported as part of this study.

All subjects enrolled will have samples assayed for binding and if positive, neutralizing antibodies.

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7.1 Schedule of Assessments

The Schedule of Assessments is found in Table 2 below.

Table 2. Schedule of Assessments

Procedures	Screening	In Clinic Dosing Period[a]	Romiplostim Treatment Period (up to 36-months)[b]			End Of Treatment Visit	End of Study Visit
	- 4 Weeks	Week 1 to Week 8	Weekly	Every 4 Weeks	Every 12 Weeks		
Informed consent	X						
Confirmation of primary ITP diagnosis	X						
ITP/medical history	X						
Physical exam	X				X	X	
Vital signs	X				X	X	
Weight	X				X		
Central lab CBC with differential	X	X[c]		X[b]		X	
Central lab blood (serum) chemistry	X				X	X	
Local lab platelet counts	X	X	X[b,d]			X	X
Local lab peripheral blood smear		X[c]		X[b]		X	
Pregnancy test	X				X[f]	X[f]	
Concomitant /rescue medications	X	X	X	X	X	X	X
Adverse event reporting		X	X	X	X	X	
Serious adverse events	X	X	X	X	X	X	X
Antibody sample[e]		Day 1 (before first dose)			W12, W52 and every 24 weeks thereafter	X	
Romiplostim dosing		X	X				

ITP = immune thrombocytopenia; CBC = complete blood counts

[a] Week 1 to Week 8. All subjects will return to the clinic for weekly dosing of romiplostim, platelet counts by a local laboratory, recording of concomitant/rescue medications, and adverse event reporting.

[b] Subjects who complete 6 months of sustained platelet response (platelet count ≥ 50 x10^9/L in the absence of romiplostim or any ITP medications) will have assessments every 12 weeks for the duration of the 36-month treatment period.

[c] Central CBC with differential and local lab peripheral blood smears are to be performed every 4 weeks, including pre-dose at week 1. Screening laboratory studies may be used in lieu of the pre-treatment day 1 week 1 laboratory tests if performed within 10 days prior to the first dose. Bone marrow biopsy suggested if abnormalities detected.

[d] For subjects who establish a stable dose of romiplostim and are self-administering, have the injection administered by a caregiver, or meet this criterion but still prefer to come to the clinic for romiplostim administration, platelet counts will be monitored every 4 weeks.

[e] For subjects who test positive for antibodies, see Section 7.1.3. Antibody sampling during romiplostim treatment is only conducted if subject is receiving study drug.

[f] Local lab urine or serum pregnancy test for female subjects of child-bearing potential (defined as having first menses)

7.1.1 Routine Blood Tests

Screening and baseline blood tests for central laboratory testing must be obtained after written informed consent and assent (if applicable). Screening laboratory studies may be used in lieu of any required pre-treatment day 1 week 1 laboratory tests if performed within 10 days prior to the first dose.

Refer to the central laboratory manual for instructions on collection, preparation, storage, and shipment of blood samples. Complete blood counts (CBC) with differential and blood chemistries will be evaluated at a central laboratory and as outlined in Table 3 (List of Analytes in Laboratory Specimens).

The investigator should review locally assessed peripheral blood smears before the first dose of romiplostim and every 4-12 weeks thereafter. Additional locally-assessed blood smears may be collected more frequently as clinically indicated or at the request of Amgen. Abnormalities such as nucleated red blood cells, teardrop cells (dacrocytes), and blasts should be recorded in the eCRFs.

Should an abnormality be identified in a CBC or a peripheral blood smear at any time during the study, it is recommended that a bone marrow biopsy be performed and submitted to a central laboratory for further assessment. In addition to routine analysis, silver and trichrome stains for the assessment of reticulin and collagen, as assessed by the modified Bauermeister scale (Appendix B), will be conducted by the central laboratory. All data collected from the bone marrow biopsy will be reported to Amgen as part of the study.

Urine or blood pregnancy testing, for female subjects of child bearing potential (defined as having first menses), will be reported by the local laboratory before the first dose of romiplostim, every 12 weeks thereafter, and at the end of treatment visit. Pregnancy testing will not be analyzed or reported by the central laboratory.

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Table 3. List of Analytes in Laboratory Specimens

Blood Chemistry	Hematology	Other Labs
Blood urea nitrogen	RBC	Antibodies[a]
Creatinine	Hemoglobin	• to romiplostim
Total bilirubin (TB)	Hematocrit	• to the peptide portion of romiplostim
Alkaline phosphatase (ALP)	MCV	• cross-reacting to eTPO
Lactate dehydrogenase	MCH	Local lab blood smears[b]
AST	MCHC	Local lab urine or blood pregnancy test
ALT	RDW	(if applicable)
		Central lab optional bone marrow
	Platelets[c]	biopsy if abnormality is identified (see
	WBC	Section 7.1.1) to include silver and
	Differential	trichrome stain
	• Seg Neuts	
	• Bands/stabs	
	• Eosinophils	
	• Basophils	
	• Lymphocytes	
	• Monocytes	
	• Myeloblasts	
	• Promyelocytes	
	• Myelocytes	
	• Metamyelocytes	
	• Atypical lymphocytes	
	Calculated ANC	
	Nucleated RBC	

[a] Additional samples for antibody status may be obtained as requested by the investigator or Amgen.
[b] Locally-assessed blood smears will be performed throughout the study and as requested by the investigator or Amgen.
[c] Platelet counts are performed by local laboratory only.

7.1.2 Platelet Counts

Platelet counts will be evaluated by the investigative site's local laboratory and used to assess the need for romiplostim dose adjustments and to evaluate platelet response to therapy. Platelet counts will not be analyzed or reported by the central laboratory. The investigational site's laboratory should be used whenever possible for the assessment of platelet counts; however, in certain circumstances platelet count may be assessed at a laboratory local to the subject's residence. Throughout this study, the laboratory analyzing a subject's platelet count should be consistent.

All platelet counts required for dosing decisions will be collected and recorded on the eCRFs.

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7.1.3 Antibody Testing Procedures

Refer to the central laboratory manual for instructions on collection, preparation, storage, and shipment of antibody samples. Baseline antibody samples must be obtained on day 1 before the first administration of romiplostim.

Blood samples will be collected from all subjects for the measurement of anti-romiplostim binding antibodies. Binding antibodies will be assessed for their ability to bind to romiplostim or the peptide portion of romiplostim, and their potential (if any) to cross-react with eTPO. Samples testing positive for binding antibodies will also be tested for neutralizing antibodies by assessing their ability to neutralize romiplostim and/or eTPO in a cell-based bioassay. Binding antibodies may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. While the subject is receiving IP, blood samples will be collected for anti-romiplostim antibodies at week 12, week 52, every 24 weeks thereafter, and at the EOT visit. Only positive results for neutralizing antibodies will be provided to investigational sites; if no results are provided, sites may assume that no neutralizing antibodies to romiplostim were identified.

Subjects who test positive for neutralizing antibodies to romiplostim or to eTPO during the course of the study (or at the EOT visit) will be removed from treatment and will be asked to return for additional follow-up testing. This testing should occur every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks). More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-romiplostim antibody response, may also be asked to return for additional follow-up testing.

Should a subject fail to respond or fail to maintain a response to romiplostim, an unscheduled serum sample will be required to rule out anti-romiplostim antibodies.

7.2 Sample Storage and Destruction

Any blood sample collected according to the Schedule of Assessments (Table 2) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also

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include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by or for the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand ITP and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject and/or the subject's legally authorized representative retain the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject (or their legally authorized representative), the investigator is to provide the sponsor with the required study and subject number so that any remaining (eg, blood) samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample.

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7.3 Medical History

A complete medical history is required. The complete medical history related to ITP including prior therapies, bleeding history, and any bone marrow biopsy data will be collected at screening. For subjects referred to the research center, copies of the subject records from the referring physician should be obtained.

7.4 Concomitant Medications

In addition to routine concomitant medications for conditions other than ITP, during the course of the study, all concomitant and rescue medications administered for ITP will be recorded in the eCRF from screening until the end of treatment or end of study visit.

7.5 Screening

The screening period begins on the date that the subject (and/or the subject's legally authorized representative) signs the IRB/IEC-approved informed consent form and continues until the date of enrollment. Procedures that are part of routine care are not considered study-specific procedures. All subjects will be screened for eligibility before enrollment.

The following screening procedures must be completed within 4 weeks before the day of first dose of romiplostim:

- informed consent (and assent if required by IRB/IEC)
- confirmation of ITP diagnosis
- ITP and medical history
- physical exam as per standard of care including weight and vital signs. Physical examination findings should be recorded on the medical history or adverse event eCRF
- concomitant medications
- central lab CBC with differential and blood chemistry
- confirmation of one local lab platelet count ≤ 30 x 10^9/L and/or documentation of bleeding that was uncontrolled with conventional therapies for ITP
- local lab urine or serum pregnancy test for female subjects of child-bearing potential (defined as having first menses)
- serious adverse events that occurred after the signing of informed consent

If subjects do not successfully complete screening within 4 weeks after initial informed consent, their screen failure will be registered in the IVRS. Subjects who fail screening will be allowed to re-screen. Subjects who rescreen must repeat relevant screening procedures within the new 4-week screening window. If the subject's screening platelet count is > 30 x 10^9/L without evidence of uncontrolled bleeding with conventional

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therapies upon initial assessment the site may reassess the platelet count during the 4-week screening period without registration of screen-failure or re-consenting the subject.

7.6 Romiplostim Treatment Period (Up to a 36 Months Duration)

Subjects that meet all study entrance criteria will be enrolled using IVRS to receive romiplostim.

The following procedures will be completed during the romiplostim treatment period at the times designated in the Schedule of Assessments (Table 2):

- documentation of concomitant and rescue medications
- adverse event reporting
- central lab CBC with differential (every 4 weeks)
- central lab blood chemistry (every 12 weeks)
- local lab platelet counts.
- collection of blood samples for anti-romiplostim antibodies (first sample is collected before first dose of romiplostim, then at week 12, week 52, and every 24 weeks thereafter)
- local lab peripheral blood smear (every 4 weeks)
- physical exam with vital signs and weight (every 12 weeks)
- local lab urine or serum pregnancy test for female subjects of child-bearing potential (defined as having first menses) every 12 weeks
- romiplostim administration

Note: Administration of romiplostim should be the last procedure completed during each visit that it is required.

For the first 8 weeks of treatment, all subjects will return to the clinic for weekly administration of romiplostim. Subjects who have received their first 8 doses in the clinic and achieve a stable dose of romiplostim for at least 4 weeks may be allowed to self-inject romiplostim or have the injection administered by a caregiver. For subjects who established a stable dose of romiplostim and are self-administering, platelet counts will be monitored every 4 weeks. For complete details on self-administration, refer to Section 6.3. Subjects who stop romiplostim and all other medications for ITP (concomitant or rescue) due to the onset of a sustained platelet response will continue to be monitored per the schedule of assessments for at least 6 months from the first platelet count ≥ 50 x 10^9/L.

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If the subject has maintained a sustained platelet response, subsequent visits and procedures including the platelet counts, CBC, and peripheral blood smears will be performed every 12 weeks for the duration of the 36-month treatment period. If the subject's platelet counts fall to < 50 x 10^9/L and treatment with romiplostim is resumed, the visit schedule will revert to weekly platelet counts, and CBC with peripheral blood smear evaluations every 4 weeks. The visit assessment weeks and procedures resume counting from first dose of romiplostim after enrollment.

7.7 End of Treatment Visit (EOT)

All subjects will complete an EOT visit. For subjects who complete the 36-month treatment period and who have been off romiplostim and other medications for ITP (concomitant or rescue) for 4 weeks or more, the EOT visit will be the final study visit and will occur after the completion of the 36-month treatment period. For subjects ending the 36-month treatment period for non-response or other reasons while still receiving romiplostim, this visit will be 1 week after the last administration of romiplostim.

The following assessments will be completed at the EOT visit:

- physical exam, including vital signs
- documentation of concomitant and rescue medications
- adverse event reporting
- central lab CBC with differential and blood chemistry
- local lab platelet counts
- collection of blood samples for anti-romiplostim antibodies
- local lab peripheral blood smear
- local lab urine or serum pregnancy test for female subjects of child-bearing potential (defined as having first menses)

7.8 End of Study Visit (EOS)

Four weeks after the last dose of romiplostim for subjects who end the 36-month treatment period for non-response or other reasons while still receiving romiplostim will have an EOS visit.

The following assessments will be completed at the EOS visit:

- local lab platelet count
- serious adverse event reporting
- documentation of concomitant and rescue medications

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8. WITHDRAWAL AND REPLACEMENT OF SUBJECTS

8.1 Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving IP or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from IP and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 2) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 2) and the level of follow-up that is agreed to by the subject (eg, follow-up in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study. Subjects who withdraw early should complete an EOT and EOS visit. The data generated may potentially not be included in the subject's study data, except in the case of a possibly related serious adverse event, where data will be collected.

8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Section 12.1.

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8.2.1 Reasons for Removal From Treatment

Reasons for removal from romiplostim or observation might include the following:

- **protocol specified criteria**
- subject request (or the subject's legally authorized representative)
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, pregnancy)
- death
- lost to follow-up
- decision by Sponsor (other than subject request, safety concern, lost to follow-up)

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are as follows:

- **protocol specified criteria**
- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

8.3 Replacement of Subjects

Subjects who withdraw from the study early will not be replaced.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study, and involves an intervention such as elective cosmetic surgery or a medical procedure while on study is not considered an adverse event.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's

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legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of “requires hospitalization”, if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of “other medically important serious event”. Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

9.2 Reporting of Adverse Events

9.2.1 Reporting Procedures for Adverse Events That do not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product through the end of treatment period are reported using the applicable eCRF (eg, Adverse Event Summary CRF).

Because all subjects who enter the study will be diagnosed with ITP according to the ASH guidelines, ITP should not be reported as an adverse event during the conduct of the study.

The investigator must assign the following adverse event attributes:

- adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms)
- dates of onset and resolution (if resolved)

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- severity
- assessment of relatedness to romiplostim
- action taken

The adverse event severity grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grading scale. The severity grading scale used in this study is described in Appendix A.

The investigator must assess whether the adverse event is possibly related to the romiplostim. This relationship is indicated by a "yes" or "no" response to the question: Is there a reasonable possibility that the event may have been caused by the romiplostim?

The investigator must assess whether the adverse event is possibly related to any study-mandated activity (eg, administration of investigational product, protocol-required therapies, device(s) and/or procedure (including any screening procedure(s)). This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity (eg, administration of investigational product, protocol-required therapies, device(s)), and/or procedure?"

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

The Investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after last dose of IP (for subjects who have sustained platelet responses and never resume IP after sustained response during the trial); or the later of the EOT and EOS visits, are recorded in the subject's medical record and are submitted

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to Amgen. All serious adverse events must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable CRF.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

If the electronic data capture (EDC) system is unavailable to the site staff to report the Serious Adverse Event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the Investigator's knowledge of the event. See Appendix A for a sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSerious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available

The investigator must assess whether the serious adverse event is possibly related to any study-mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by a study activity/procedure"?

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable CRF (eg, Adverse Event Summary CRF).

If a subject is permanently withdrawn from the study because of a serious adverse event, this information must be submitted to Amgen.

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Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator should notify the appropriate IRB/IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through 1 month after the last dose of romiplostim.

The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). The Pregnancy Surveillance Program (PSP) will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case to Amgen as specified below.

In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 1 month after the end of the dose of romiplostim.

Any lactation case should be reported to Amgen's global Lactation Surveillance Program (LSP) within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix D).

10. STATISTICAL CONSIDERATIONS

The statistical analysis of this open-label study will be descriptive in nature only. No hypothesis testing is planned. Categorical data will be presented in the form of number and percentage. Continuous data will be provided with the descriptive statistics

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(n, mean, standard deviation, median, Q1 [25th percentile], Q3 [75th percentile], minimum, and maximum).

10.1 Study Endpoints, Subsets, and Covariates

10.1.1 Study Endpoints

Primary Endpoint:

- The percentage of time with a platelet count of ≥ 50 x 10^9/L starting from week 2 in the first 6 months of the treatment period without rescue medication use within the past 4 weeks

Secondary Endpoints:

- The percentage of time with a platelet count of ≥ 50 x 10^9/L starting from week 2 until the end of the treatment period without rescue medication use within the past 4 weeks
- The percentage of time with an increase in platelet count ≥ 20 x 10^9/L above baseline starting from week 2 until the end of the treatment period without rescue medication use in the past 4 weeks.
- Subject incidence of rescue ITP medications used
- The incidence of anti-romiplostim neutralizing antibodies and cross reactive antibodies to TPO at any time during the study
- The incidence of adverse events, including clinically significant changes in laboratory values

Exploratory Endpoints:

- The subject incidence with a sustained platelet count of ≥ 50 x 10^9/L for 6 months or greater without the use of any ITP medications (concomitant, rescue, or romiplostim)
- The incidence of splenectomy during the treatment period for subjects entering the study pre-splenectomy
- The subject incidence of romiplostim self-administration

10.1.2 Analysis Sets

10.1.2.1 Full Analysis Set

The full analysis set will consist of all enrolled subjects. Analyses for demographics and baseline characteristics will use this analysis set.

10.1.2.2 Safety Analysis Set

The safety analysis set will consist of all subjects who receive at least 1 dose of romiplostim. The analyses of all safety endpoints will be based on the safety analysis set.

10.1.2.3 Efficacy Analysis Set

The efficacy analysis set will consist of all subjects who received at least 1 dose of romiplostim. The analyses of all efficacy endpoints will be based on the efficacy analysis set.

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10.1.2.4 Per Protocol Analysis Set

The per protocol analysis set will consist of all subjects who received at least 1 dose of IP and met all eligibility criteria. A sensitivity analysis using the per protocol set will be conducted for the primary efficacy endpoint.

10.2 Sample Size Considerations

The sample size for this study is governed by the number of pediatric ITP subjects who meet the eligibility requirements during enrollment period. It is estimated that approximately 200 subjects will enroll into this study. The percentage of time achieving platelet response in the first 6 months of treatment period for ITP subjects with romiplostim (both adults and pediatric) is estimated at 74%. The standard deviation of percentage of time is estimated between 30% and 36% based on previous Nplate data. Given the sample size of 200 subjects, the half width of the 95% confidence interval (CI) for the percentage of time achieving platelet response is estimated to be between 4% and 5%.

10.3 Planned Analyses

The analysis will be descriptive in nature. No formal hypothesis is to be tested.

10.3.1 Interim Analyses

Interim analyses will be conducted to support regulatory filings, and accumulated data for this study will be summarized to provide ongoing assessments of the safety of romiplostim. These interim analyses will occur at least annually until the end of the study.

10.3.2 Analysis of Key Study Endpoints

10.3.2.1 Efficacy Endpoints

The primary endpoint for this study is the percentage of time with platelet response starting from week 2 in the first 6 months of the treatment period. Platelet response is defined as platelet count ≥ 50 $x10^9$/L at a scheduled protocol visit. Platelet counts within 4 weeks of a rescue ITP medication will not be deemed as platelet response. The 95% CI will be calculated for the estimated percentage of time.

Summary statistics of platelet counts and responses will be provided at weeks 1 to 8 and then every 4 weeks.

The percentage of time with platelet response starting from week 2 until the EOT period will be summarized with 95% CI.

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Missing platelet counts at weeks 12 and 16, and every 4 weeks thereafter will be imputed by using the mean of the 2 closest non-missing platelet counts within ±1 week before study discontinuation. If still missing after imputation, platelet counts will be considered as non-response.

The proportion of subjects with splenectomy during the study will be summarized for the subjects who entered this study without splenectomy.

10.3.2.2 Safety Endpoints

The exposure-adjusted incidence rates as well as subject incidence rates of adverse events will be summarized by system organ class and by preferred term according to the MedDRA dictionary. Exposure-adjusted rate is defined as total number of events divided by time of duration when subjects were under observation. The summary includes all treatment-emergent adverse events recorded from the start of IP on this study, or any worsening of conditions present at baseline before dosing in this study. This summary for adverse events will be performed for the following categories

- all adverse events
- romiplostim-related adverse events
- serious adverse events
- adverse events leading to withdrawal from the study
- adverse events of interest (hemorrhage events, etc.)

In addition, incidence and exposure-adjusted rates of adverse events by period may also be explored.

Subject listings for all adverse events, serious adverse events, and adverse events leading to withdrawal from the study will be provided.

The incidence and percentage of subjects who develop anti-romiplostim antibodies (binding and if positive, neutralizing) at any time will be tabulated.

Summary statistics will be provided for blood chemistry and CBC at each time point. Shift tables between the worst post-baseline and baseline values will be provided (based on the National Cancer Institute CTCAE, version 3.0).

10.3.3 Primary Analysis

The objective for the primary analysis will be to summarize the data with the respect to the primary and secondary endpoints for the trial. The primary analysis will occur after the last subject has completed all investigational treatment and observations on this protocol. The primary analysis will serve as the final analysis for the trial.

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10.3.4 Additional Analyses

10.3.4.1 Subject Accountability

The number of subjects who enrolled into the study, received at least 1 dose of IP, completed the IP, completed the study and prematurely withdrew, and the reason for premature withdrawal, will be summarized.

10.3.4.2 Demographic and Baseline Characteristics

Demographics and selected current study baseline characteristics will be summarized using descriptive statistics and listed for the following:

- age, sex, and race
- height, weight
- medical history
- ITP history
- baseline hematology
- baseline physical examination
- baseline vital signs

10.3.4.3 Investigational Product Administration

Summary statistics will be provided for cumulative dose (by µg and µg/kg) and average weekly dose (by µg/week and µg/kg/week). Exposure summary by baseline splenectomy status (yes/no) and concurrent ITP therapy status will also be provided. Weekly summary for weight-based dose will also be provided.

A listing of IP administration, including weight-based dose and reason for ending IP will be provided.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template will be communicated by letter from the Amgen Clinical Study Manager to the investigator. The written informed consent documents should be prepared in the language(s) of the potential subject population.

If the subject is ≥ age 7 but has not attained the legal age for consent for treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will take place, the investigator is responsible for

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obtaining written assent from the subject. For specific local information, consult the country-specific requirements of the applicable countries.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent and assent (if applicable) from the subject and/or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any IP is administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The investigator is also responsible for asking the subject or his/her legally acceptable representative if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study. If the subject or his/her legally acceptable representative agrees to such notification, the investigator shall inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator should document such in the subject's medical record.

The acquisition of informed consent and, if applicable, assent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent/assent form should be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form and assent form, if applicable, should be retained in accordance with institutional policy, and a copy of the signed consent form/assent form should be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form/assent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form/assent form to attest that informed consent was freely given and understood.

11.2 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for

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written approval. A copy of the written approval of the protocol and informed consent and if applicable the assent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IRB/IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator will be responsible for obtaining annual IRB/IEC/head of medical institution approval and renewal throughout the duration of the study. Copies of the investigator's reports and the IRB/IEC/head of the medical institution's continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen:

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRFs or other documents submitted to Amgen, subjects should be identified by a subject identification number only, with a complete and accurate date of birth on the demographics CRF.
- For Serious Adverse Events reported to Amgen, subjects should be identified by their initials, date of birth, and a subject identification number, initials for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not for submission to Amgen (eg, signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with Federal regulations/ICH GCP Guidelines it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records, including personal information, without violating the confidentiality of the subject.

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11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The Coordinating investigator, identified by Amgen, will be one or more of the following:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an Investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the investigator must be obtained. The IRB/IEC/head of the medical institution must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB/IEC/ head of the medical institution to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The investigator should notify the IRB/IEC head of the medical institution in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product, and by what mechanism, after termination of the study and before it is available commercially.

12.2 Study Documentation and Archive

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

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In this study, the IVRS captures the following data points and these are considered source data: subject identification number, the date of the screening, the date of enrollment, date of first dose and the date and reason for early withdraw or study completion.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities. Elements should include:

- subject files containing completed CRF, informed consent forms, and subject identification list
- study files containing the protocol with all amendments, investigator's brochure, copies of prestudy documentation, and all correspondence to and from the IRB/IEC and Amgen
- proof of receipt/delivery sheet, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement (if applicable), and all drug-related correspondence

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Amgen representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen Clinical Monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or

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designees). Inspection of site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs must be maintained and readily available.
- Updates to electronic CRFs will be automatically documented through the software's "audit trail."
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review will be performed on subject data received at Amgen. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be created in the EDC system database for site resolution and closed by Amgen reviewer.
- The principal investigator signs only the Investigator Verification Form for this electronic data capture study. This signature will indicate that the principal investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study-specific Self-evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit—week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the study and at study closeout.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 2), the investigator can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

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12.5 Language

eCRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language. Consult the country-specific requirements for language requirements.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several principal investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship—the criteria described below should be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The Clinical Study Agreement among the institution, principal investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

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12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document. Depending on the study agreement and consent form, subjects may be compensated for reasonable expenses not associated with study related injuries (eg, travel costs).

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14. APPENDICES

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Appendix A. Additional Safety Assessment Information

Adverse Event Toxicity Grading Scale

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 is available at the following link: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Serious Adverse Event Completion Instructions

Completion Instructions - Electronic Adverse Event Contingency Report Form (for use for Studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Definitions:

- **Adverse Event - Any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment.**
- **Serious Adverse Event – An adverse event that meets serious criteria**
- **Suspected Adverse Reaction (SAR) – An adverse event that is suspected to be related to an Amgen product in an observational study.**
- **Serious Suspected Adverse Reaction – An SAR that meets serious criteria**

What types of events to report on this form:

Type of Event	Clinical Trials
Adverse Event that is *not serious*	No
Serious Adverse Event (regardless of relationship)	Yes

Type of Event	Observational Studies
Suspected Adverse Reaction (SAR)	Yes
Serious Suspected Adverse Reaction	Yes
Serious Adverse Events that are not suspected to be related	ONLY if instructed by protocol or by local Amgen office or CRA

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the adverse event term for the previous report as well as the start date for the initial event.

3. **Adverse Event**

   Provide the date the Investigator became aware of this Information

   Adverse Event Diagnosis or Syndrome* –

   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

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Date Started* – Enter date the adverse event first started rather than the date of diagnosis or hospitalization. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**

Date Ended – Enter date the adverse event ended. For serious events, this is not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

Is event serious?* – Indicate Yes or No. This is a mandatory field.

Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:

- Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

Relationship to IP/drug under study* – The Investigator must determine and enter the relationship of the event to the IP/drug under study at the time the event is initially reported. ***For observational studies, remember that SARs are, by definition, related to the drug under study.*** **This is a mandatory field.**

Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field for serious events.**

- Resolved – End date is known
- Not resolved / Unknown – End date is unknown
- Fatal – Event led to death

If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP/drug under study or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**
   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP/Drug Under Study Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event

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7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

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AMGEN Study 20101221 Romiplostim	Electronic Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by Amgen prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day _____ Month _____ Year _____

3. ADVERSE EVENT

Provide the date the investigator became aware of this information: Day____ Month____ Year____

Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP/drug under study	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the Event may have been caused by IP/drug under study or an Amgen device used to administer the IP/drug under study?				Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
						Romiplostim		<Device>			
						No ✓	Yes ✓	No ✓	Yes ✓		
				☐Yes ☐No							
				☐Yes ☐No							
				☐Yes ☐No							

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required/prolonged hospitalization; 04 Persistent or significant disability /incapacity; 05 Congenital anomaly / birth defect; 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

Site Number	Subject ID Number

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

AMGEN Study 20101221 Romiplostim	Electronic Adverse Event Contingency Report Form For Restricted Use

IP/Drug/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
<<IP/Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Test Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

FORM-056006 *Version 6.0 Effective Date 07 JUL 2014*

Page 2 of 3

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AMGEN Study 20101221 Romiplostim	Electronic Adverse Event Contingency Report Form For Restricted Use

Signature of Investigator or Designee - _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

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Appendix B. Modified Bauermeister Scale

Grade	Quantification of bone marrow reticulin and collagen
0	No reticulin fibres demonstrable
1	Occasional fine individual fibres and foci of a fine fibre network
2	Fine fibre network throughout most of the section; no coarse fibres
3	Diffuse fibre network with scattered thick coarse fibres but no mature collagen (negative to trichrome staining)
4	Diffuse, often course fibre network with areas of collagenization (positive trichrome staining)

(Bauermeister, 1971; Bain et al, 2001)

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Appendix C. Pregnancy Notification Worksheet

AMGEN Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm___/ dd___/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm___/dd___/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm___/dd___/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm___/ dd___/ yyyy____ ☐ Unknown

Estimated date of delivery mm___/ dd___/ yyyy____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm___/ dd___/ yyyy____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm___/ dd___/ yyyy____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Appendix D. Lactation Notification Worksheet

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

Study Design: ☐ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm____/ dd____/ yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2. Page 1 of 1

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Amendment # 1

Protocol Title: A Single Arm, Open-label, Long-term Efficacy and Safety Study of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune Thrombocytopenia (ITP)

Amgen Protocol Number 20101221

EudraCT number 2011-005019-96

Amendment Date: **15 July 2014**

Rationale:

As a result of regulatory reviews, additional routine monitoring has been added to the protocol. This amendment includes the following changes:

- To update the inclusion criteria to include hematologic, renal, and liver criteria
- To add pregnancy monitoring as applicable every 12 weeks and at the end of treatment visit

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Description of Changes:

Section: Header of the Document and Investigator's Agreement

Replace: 15 January 2014

With: **15 July 2014**

Section: Title Page,

Add: **Amendment 1: 15 July 2014**

Section 4.1.6: Inclusion Criteria

Add:

Adequate hematologic, renal, and liver function during the screening period:

- **Hemoglobin > 10.0 g/dL**
- **Serum creatinine ≤ 1.5 times the upper limit of normal**
- **Total serum bilirubin ≤ 1.5 times the upper limit of normal**
- **AST and ALT ≤ 3.0 times the upper limit of normal**

Section 7.1, Table 2 Schedule of Assessments

Add:

X[f] under Pregnancy test after Every 12 weeks and End of Treatment Visit

Add footnote f:

[f] **local lab urine or serum pregnancy test for female subjects of child-bearing potential (defined as having first menses)**

Section 7.1.1 Routine Blood Tests, Paragraph 5

Add:

Urine or blood pregnancy testing, for female subjects of child bearing potential (defined as having first menses), will be reported by the local laboratory before the first dose of romiplostim**, every 12 weeks thereafter, and at the end of treatment visit.** Pregnancy testing will not be analyzed or reported by the central laboratory.

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Section 7.6 Romiplostim Treatment Period (Up to a 36 Months Duration)

Add:

- **local lab urine or serum pregnancy test for female subjects of child-bearing potential (defined as having first menses) every 12 weeks**

Section 7.7 End of Treatment Visit (EOT)

Add:

- **local lab urine or serum pregnancy test for female subjects of child-bearing potential (defined as having first menses) every 12 weeks**

Amendment # 2

Protocol Title: A Single Arm, Open-label, Long-term Efficacy and Safety Study of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune Thrombocytopenia (ITP)

Amgen Protocol Number 20101221

EudraCT number 2011-005019-96

Amendment Date: **15 August 2014**

Rationale:

As a result of regulatory reviews and study template updates, this amendment includes the following changes:

- Modification of the exclusion criteria to allow prior use of eltrombopag
- Correction in the dosing modification Table 1 Dose Adjustment rules
- Removal of reticulocytes from the laboratory specimens
- Addition of "protocol specified criteria" to Sections 8.2.1, Reasons for Removal from Treatment and 8.2.2, Reasons for Removal from Study
- Update of the Appendix A, SAE Completion Instructions for faxed forms

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Description of Changes:

Section: Header of the Document and Investigator's Agreement

Replace: 15 July 2014

With: **15 August 2014**

Section: Title Page,

Add: **Amendment 2: 15 August 2014**

Section 4.2.12: Exclusion Criteria

Replace:

Previous use of romiplostim or eltrombopag

With:

Previous use of romiplostim**. Previous use of** eltrombopag **within 4 weeks of enrollment.**

Section 6.2.2: Table 1 Dose Adjustment Rules

Replace:

Table 1. Dose Adjustment Rules

Platelet count (x 10^9/L)	**Investigational Product Dose Adjustment Rule[a]**
< 50[b]	Increase dose by 1 µg/kg each week (to a maximum of 10 µg/kg)
50 to 200[b]	Dose remains constant
> 200 to < 400 [b,c]	After the platelet count remains in this range for 2 consecutive weeks, dose reduce by 1 µg/kg on the next scheduled dosing day
≥ 400 [b,c,d]	Withhold the dose and dose reduce by 1 µg/kg on the next scheduled day of dosing when platelet count falls < 200 x 10^9/L

[a] If the platelet count is elevated in response to the initiation or increase in dose of another ITP medication, then the same dose of IP should be administered when the platelet count is ≤ 200 x 10^9/L.
[b] Romiplostim may be used with other therapies for ITP (refer to Section 6.4). If the subject's platelet count is ≥ 50 x 10^9/L, other ITP therapies may be reduced or discontinued.
[c] If the current dose is 1 µg/kg and a dose reduction is required, the dose will be withheld until the platelet count falls to < 50 x 10^9/L. Once the platelet count is < 50 x 10^9/L, dosing will resume at a dose of 1 µg/kg using the dose adjustment rules above.
[d] If platelet count ≥ 400 x 10^9/L is due to rescue medications, it is at the discretion of the investigator to reduce the dose by 1 µg/kg.

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With :

Table 1. Dose Adjustment Rules

Platelet count (x 10^9/L)	Investigational Product Dose Adjustment Rule[a]
< 50[b]	Increase dose by 1 µg/kg each week (to a maximum of 10 µg/kg)
50 to 200[b]	Dose remains constant
> 200 to < 400 [b,c]	After the platelet count remains in this range for 2 consecutive weeks, dose reduce by 1 µg/kg
≥ 400 [b,c,d]	Withhold the dose and dose reduce by 1 µg/kg on the next scheduled day of dosing when platelet count falls < 200 x 10^9/L

[a] If the platelet count is elevated in response to the initiation or increase in dose of another ITP medication, then the same dose of IP should be administered when the platelet count is ≤ 200 x 10^9/L.
[b] Romiplostim may be used with other therapies for ITP (refer to Section 6.4). If the subject's platelet count is ≥ 50 x 10^9/L, other ITP therapies may be reduced or discontinued.
[c] If the current dose is 1 µg/kg and a dose reduction is required, the dose will be withheld until the platelet count falls to < 50 x 10^9/L. Once the platelet count is < 50 x 10^9/L, dosing will resume at a dose of 1 µg/kg using the dose adjustment rules above.
[d] If platelet count ≥ 400 x 10^9/L is due to rescue medications, it is at the discretion of the investigator to reduce the dose by 1 µg/kg.

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Section 7.1.1: Table 3 List of Analytes in Laboratory Specimens

Remove Reticulocytes from Hematology

Replace:

Table 3. List of Analytes in Laboratory Specimens

Blood Chemistry	Hematology	Other Labs
Blood urea nitrogen	RBC	Antibodies[a]
Creatinine	Hemoglobin	• to romiplostim
Total bilirubin (TB)	Hematocrit	• to the peptide portion of romiplostim
Alkaline phosphatase (ALP)	MCV	• cross-reacting to eTPO
Lactate dehydrogenase	MCH	Local lab blood smears[b]
AST	MCHC	Local lab urine or blood pregnancy test
ALT	RDW	(if applicable)
	Reticulocytes	Central lab optional bone marrow
	Platelets[c]	biopsy if abnormality is identified (see
	WBC	Section 7.1.1) to include silver and
	Differential	trichrome stain
	• Seg Neuts	
	• Bands/stabs	
	• Eosinophils	
	• Basophils	
	• Lymphocytes	
	• Monocytes	
	• Myeloblasts	
	• Promyelocytes	
	• Myelocytes	
	• Metamyelocytes	
	• Atypical lymphocytes	
	Calculated ANC	
	Nucleated RBC	

[a] Additional samples for antibody status may be obtained as requested by the investigator or Amgen.
[b] Locally-assessed blood smears will be performed throughout the study and as requested by the investigator or Amgen.
[c] Platelet counts are performed by local laboratory only.

With:

Table 3. List of Analytes in Laboratory Specimens

Blood Chemistry	Hematology	Other Labs
Blood urea nitrogen	RBC	Antibodies[a]
Creatinine	Hemoglobin	• to romiplostim
Total bilirubin (TB)	Hematocrit	• to the peptide portion of romiplostim
Alkaline phosphatase (ALP)	MCV	• cross-reacting to eTPO
Lactate dehydrogenase	MCH	Local lab blood smears[b]
AST	MCHC	Local lab urine or blood pregnancy test
ALT	RDW	(if applicable)
	Platelets[c]	Central lab optional bone marrow
	WBC	biopsy if abnormality is identified (see
	Differential	Section 7.1.1) to include silver and
	Seg Neuts	trichrome stain
	• Bands/stabs	
	• Eosinophils	
	• Basophils	
	• Lymphocytes	
	• Monocytes	
	• Myeloblasts	
	• Promyelocytes	
	• Myelocytes	
	• Metamyelocytes	
	• Atypical lymphocytes	
	• Calculated ANC	
	Nucleated RBC	

[a] Additional samples for antibody status may be obtained as requested by the investigator or Amgen.
[b] Locally-assessed blood smears will be performed throughout the study and as requested by the investigator or Amgen.
[c] Platelet counts are performed by local laboratory only.

Section 8.2.1: Reasons for Removal from Treatment

Add:

Reasons for removal from romiplostim or observation might include the following:

- **protocol specified criteria**
- subject request (or the subject's legally authorized representative)
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, requirement for alternative therapy, pregnancy)
- death
- lost to follow-up

Section 8.2.2: Reasons for Removal from Study

Add:

Reasons for removal of a subject from the study are as follows:

- **protocol specified criteria**
- decision by sponsor
- withdrawal of consent from study
- death
- lost to follow-up

Appendix A: Additional Safety Assessment Information

Replace:

Serious Adverse Event Completion Instructions

Completion Instructions - Electronic Adverse Event Contingency Report Form (for use for Studies using Electronic Data Capture [EDC])

The following minimum fields must be completed prior to faxing the form:
1) Site Number; 2) Subject ID Number; Initials; 3) Serious Adverse Event Diagnosis; Serious Criteria Code; Start Date of Event; 10) Signature
Ensure both pages are faxed with each submission

Note: Only events that meet serious criteria should be reported on this form.

Submit a Serious Adverse Event Report (SAER) form within 24 hours of the Investigator's knowledge of the event.

Data on the AE Summary CRF must agree with data submitted on the SAER form in the following areas: adverse event term(s), serious criteria and relationship of product to event.

Only include information that is relevant (pertinent) to the event(s) included on this SAER (eg, concomitant medications, medical history, laboratory and diagnostic tests)

Header Information

New / Follow-up – Indicate if this is a new adverse event, or a follow-up of a pre-reported event.

Follow-up – Send a Follow-up report if additional data adds to or changes the clinical interpretation of the event. Some examples are:
➢ The initial reported event has changed and additional serious criteria have been met (such as if event outcome is now fatal).
➢ Signs and symptoms were reported at the time of the initial report and a final diagnosis has now been made.
➢ A change in relationship of a study procedure or activity has occurred from the initial report.
➢ A significant change has occurred in the start date of the event or start date of a suspect concomitant medication.
➢ Additional concomitant medications and/or diagnostics have been identified that may contribute to or explain the event.
When sending a follow-up report, either:
➢ On a photocopy of the prior report, add the additional information, re-sign and date, then fax in the follow-up form – or –
➢ Complete a new form with the new information. If the serious adverse event terms have not changed, please write, in section 3 the following: "No changes in serious adverse event terms from previous

SAER form", then fax in the follow-up form.

- If a new serious adverse event term is to be added to the terms previously reported, add this new term to a photocopy of the initial form.
- If an earlier reported adverse event is being replaced by a new diagnosis or event term, on a photocopy of the initial report, strike through the term to be deleted, sign and date the deletion and add the updated event term.

1. Site Information

Site Number – Enter your assigned site number for this study

Investigator, Country, Reporter, Phone No., and Fax No. – Enter information requested

2. Subject Information

Subject ID Number – Enter the entire number assigned to the subject

Initials – Enter the subject's initials in accordance with local laws. If middle initial is unknown or does not exist, please enter a "hyphen" (eg, ESB, E-B)

Date of Birth, Sex, and Race – Enter the subject's demographic information

3. Serious Adverse Event

Provide the date the Investigator became aware of this Serious Adverse Event Information

Serious Adverse Event Diagnosis or Syndrome –

- If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
- If a diagnosis is not known, the relevant signs/symptoms meeting serious criteria should be entered.
- If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available. Do not enter "Death", as this is an outcome, not an event.

Date Started – Enter date the adverse event first started; not when the event met serious criteria, when a diagnosis was made or when the subject was hospitalized.

Date Ended – Enter date the adverse event ended, not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

Serious Criteria Code – Enter reason why the reported event has met serious criteria:

- Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other significant medical hazard" may be the appropriate serious criteria.

Relationship to IP* – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**
Relationship to Amgen device – The Investigator must determine and enter the relationship of the event to the Amgen device at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field.**

Outcome of Event – Enter the code for the outcome of the event at the time the form is completed.

- Resolved – End date is known
- Resolving / Not resolved – End date is unknown
- Fatal – Event led to death

If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to concomitant administration – only diagnostic tests or activities mandated by the protocol.

4. Hospitalization

If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study, which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt. However, if the subject is retained in the study unit and becomes an in-patient due to an AE, the event would be reportable as an SAE.

5. Investigational Product

Investigational Product – If applicable, indicate whether the Investigational Product is blinded or open-label

Initial Start Date – Enter date the product was first administered, regardless of dose.

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Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.

Action Taken with Product – Enter the status of the product administration.

Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event

6. Relevant Concomitant Medications

Indicate if there are any relevant medications, including protocol-specified diluents and challenge agents.

Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other relevant medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

Co-suspect – Indicate if the medication is suspect for the event

Continuing – Indicate if the subject is still taking the medication

Event Treatment – Indicate if the medication was used to treat the event

7. Relevant Medical History

Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

8. Relevant Laboratory Tests

Indicate if there are any relevant laboratory values.

For each test type, enter the test name, units, date the test was run and the results.

9. Other Relevant Tests

Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results and units (if applicable).

10. Case Description

Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6).

Footer

Signature, Title and Date – The Investigator or designee must sign the form and provide their title and date. Designee must be identified on the Delegation of Authority form.

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AMGEN 20101221	Clinical Trial Serious Adverse Event Report Phase 1-4 *Notify Amgen Within 24 Hours of knowledge of the event*	☐New ☐Follow-up

SELECT OR TYPE IN A FAX#

1. SITE INFORMATION

Site Number	Investigator	Country	Date of Report (Day Month Year)

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Initials	Date of Birth (Day Month Year)	Sex	Race
			☐F ☐M	

3. SERIOUS ADVERSE EVENT - *Information in this section must also be entered on the Serious Adverse Event Summary CRF*

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day Month Year

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the event may have been caused by IP? If yes see section 10 No✓	Yes✓	Relationship Is there a reasonable possibility that the event may have been caused by an Amgen device? No ✓	Yes ✓	If Yes, what device?	Outcome of Event 01 Resolved 02 Resolving 03 Not resolved 04 Fatal	Check only if event is related to study procedure eg, biopsy

Serious Criteria: 01 Fatal; 02 Immediately life-threatening; 03 Required hospitalization; 04 Prolonged hospitalization; 05 Persistent or significant disability /incapacity; 06 Congenital anomaly / birth defect; 07 Other significant medical hazard

4. HOSPITALIZATION

	Date Admitted (Day Month Year)	Date Discharged (Day Month Year)
Was subject hospitalized? ☐No ☐Yes, If yes, please complete date(s):		

5. INVESTIGATIONAL PRODUCT (IP)

	Initial Start Date Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld
Romiplostim ☐Blinded ☐✓Open Label						

6. RELEVANT CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Relevant Medications? ☐ No ☐ Yes, If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

FORM-015482 v7.0 Effective date: 01-APR-2013 Page 1 of 2 *SAER Created: 17Jan2014*

AMGEN 20101221	Clinical Trial Serious Adverse Event Report Phase 1-4 *Notify Amgen Within 24 Hours of knowledge of the event*	☐New ☐Follow-up

Site Number	Subject ID Number

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Test										
Date (Day Month Year)	Unit									

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee	Title	Date

FORM-015482 v7.0 Effective date: 01-APR-2013 Page 2 of 2 *SAER Created: 17Jan2014*

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With:

Serious Adverse Event Completion Instructions

Completion Instructions - Electronic Adverse Event Contingency Report Form (for use for Studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Definitions:

- **Adverse Event - Any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment.**
- **Serious Adverse Event – An adverse event that meets serious criteria**
- **Suspected Adverse Reaction (SAR) – An adverse event that is suspected to be related to an Amgen product in an observational study.**
- **Serious Suspected Adverse Reaction – An SAR that meets serious criteria**

What types of events to report on this form:

Type of Event	Clinical Trials
Adverse Event that is *not serious*	**No**
Serious Adverse Event (regardless of relationship)	**Yes**

Type of Event	Observational Studies
Suspected Adverse Reaction (SAR)	**Yes**
Serious Suspected Adverse Reaction	**Yes**
Serious Adverse Events that are not suspected to be related	**ONLY if instructed by protocol or by local Amgen office or CRA**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the adverse event term for the previous report as well as the start date for the initial event.

3. **Adverse Event**

   Provide the date the Investigator became aware of this Information

   Adverse Event Diagnosis or Syndrome* –

   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started rather than the date of diagnosis or hospitalization. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended. For serious events, this is not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

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If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

Is event serious?* – Indicate Yes or No. This is a mandatory field.

Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:

- Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

Relationship to IP/drug under study* – The Investigator must determine and enter the relationship of the event to the IP/drug under study at the time the event is initially reported. ***For observational studies, remember that SARs are, by definition, related to the drug under study.*** **This is a mandatory field.**

Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field for serious events.**

- Resolved – End date is known
- Not resolved / Unknown – End date is unknown
- Fatal – Event led to death

If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP/drug under study or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**
   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

5. **IP/Drug Under Study Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.
6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.

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For each test type, enter the test name, units, date the test was run and the results.

9. Other Relevant Tests

Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. Case Description

Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

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AMGEN Study 20101221 Romiplostim	Electronic Adverse Event Contingency Report Form For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

<<For completion by Amgen prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day _____ Month _____ Year _____

3. ADVERSE EVENT

Provide the date the investigator became aware of this information: Day____ Month___ Year_____

Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP/drug under study	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship: Is there a reasonable possibility that the Event may have been caused by IP/drug under study or an Amgen device used to administer the IP/drug under study? Romiplostim No / Yes; <Device> No / Yes	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy
				☐Yes ☐No				
				☐Yes ☐No				
				☐Yes ☐No				

Serious Criteria:			
	01 Fatal	03 Required/prolonged hospitalization	06 Congenital anomaly / birth defect
	02 Immediately life-threatening	04 Persistent or significant disability /incapacity	08 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

Site Number	Subject ID Number

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

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Study 20101221
Romiplostim

Electronic Adverse Event Contingency Report Form

For Restricted Use

IP/Drug/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event: Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
<<IP/Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<<IP/Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

Site Number	Subject ID Number

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

FORM-056006 Version 6.0 Effective Date 07 JUL 2014

Page 2 of 3

AMGEN Study 20101221 Romiplostim	Electronic Adverse Event Contingency Report Form For Restricted Use

Signature of Investigator or Designee - _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

Protocol Supplement for the European Union (EU), Switzerland, and Turkey

Title: A Single Arm, Open-label, Long-term Efficacy and Safety Study of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune Thrombocytopenia (ITP)

Amgen Protocol Number (Romiplostim) 20101221

Supplement version # 1:	15 April 2014
Supplement version #2:	**15 July 2014**

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1. Explanation of Country-specific Changes to the Protocol

This supplement to the protocol provides language for European Union (EU)-specific regulatory requirements and other procedures to follow in the execution of the global study in the EU, Switzerland, and Turkey. These changes are being made to fulfill the binding elements of the Pediatric Investigation Plan and include the addition of mandatory bone marrow biopsies and aspirates for evaluation of collagen, reticulin and cytogenetics at baseline and after Year 1 and Year 2 (in separate cohorts) to assess the long term safety of romiplostim in pediatric patients with immune thrombocytopenia purpura (ITP).

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Summary of Text Changes to Protocol for the EU, Switzerland, and Turkey

Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Protocol Synopsis Primary Objective	• To describe the percentage of time that pediatric subjects with ITP have a platelet response in the first 6 months from the start of treatment with romiplostim	• To describe the percentage of time that pediatric subjects with ITP have a platelet response in the first 6 months from the start of treatment with romiplostim • **To evaluate incidence of changes in bone marrow findings at Year 1 and Year 2 after initial exposure to romiplostim**

Page 1 of 23

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Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Protocol Synopsis Secondary Objectives	• To describe the percentage of time that pediatric subjects with ITP have a platelet response over the study duration • To describe the percentage of time that pediatric subjects with ITP have an increase in platelet count ≥ 20 x 10^9/L above baseline over the study duration • To describe the use of rescue ITP medications • To describe the incidence of antibody formation • To describe the safety of romiplostim as a long-term treatment in pediatric thrombocytopenic subjects with ITP	• To describe the percentage of time that pediatric subjects with ITP have a platelet response over the study duration • To describe the percentage of time that pediatric subjects with ITP have an increase in platelet count ≥ 20 x 10^9/L above baseline over the study duration • To describe the use of rescue ITP medications • To describe the incidence of antibody formation • To describe the safety of romiplostim as a long-term treatment in pediatric thrombocytopenic subjects with ITP • **To evaluate the incidence of increased reticulin as evidenced by silver staining at Year 1 or Year 2, after exposure to romiplostim**

Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Protocol Synopsis Primary Endpoint	• The percentage of time with a platelet count of ≥ 50 x 10^9/L starting from week 2 in the first 6 months of the treatment period without rescue medication use in the past 4 weeks	• The percentage of time with a platelet count of ≥ 50 x 10^9/L starting from week 2 in the first 6 months of the treatment period without rescue medication use in the past 4 weeks • **Evaluation of bone marrow changes after Year 1 and Year 2 for the following:** - **Incidence of collagen as evidenced by trichrome staining (using the modified Bauermeister grading scale) after romiplostim exposure** - **Incidence of bone marrow reticulin increases in severity ≥ 2 grades (ie, grade 0 to 2-4, 1 to 3-4, 2 to 4), compared to baseline, or an increase to grade 3 or grade 4 as evidenced by reticulin silver staining using the modified Bauermeister grading scale after romiplostim exposure** - **Incidence of bone marrow abnormalities (eg, myelodysplastic syndrome, monosomy 7) as evidenced by cytogenetics and fluorescence in situ hybridization**

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Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Protocol Synopsis Secondary Endpoints	• The percentage of time with a platelet count of ≥ 50 x 10^9/L starting from week 2 until the end of the treatment period without rescue medication use within the past 4 weeks • The percentage of time with an increase in platelet count ≥ 20 x 10^9/L above baseline starting from week 2 until the end of the treatment period without rescue medication use in the past 4 weeks. • Subject incidence of rescue ITP medications used • The incidence of anti-romiplostim neutralizing antibodies and cross-reactive antibodies to thrombopoietin (TPO) at any time during the study • The incidence of adverse events, including clinically significant changes in laboratory values	• The percentage of time with a platelet count of ≥ 50 x 10^9/L starting from week 2 until the end of the treatment period without rescue medication use within the past 4 weeks • The percentage of time with an increase in platelet count ≥ 20 x 10^9/L above baseline starting from week 2 until the end of the treatment period without rescue medication use in the past 4 weeks. • Subject incidence of rescue ITP medications used • The incidence of anti-romiplostim neutralizing antibodies and cross-reactive antibodies to TPO at any time during the study • The incidence of adverse events, including clinically significant changes in laboratory values • **The incidence of increased reticulin as evidenced by silver staining at Year 1 or Year 2, after exposure to romiplostim**

Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Protocol Synopsis Sample Size	Approximately 200 subjects	Approximately 200 subjects **for the study overall**; **at least 60 of the 200 will be enrolled on this protocol supplement**
Protocol Synopsis Procedures	At specified time points, subjects will undergo the following assessments: collection of informed consent (and assent, if applicable), confirmation of primary ITP diagnosis, ITP and medical history, and physical exam including weight and vital signs. Subjects will have complete blood counts with differentials, blood chemistry profiles, local platelet counts, and a blood or urine pregnancy test for females of child-bearing potential. Research staff will document the use of concomitant and rescue medications and all adverse events reported for the subject. Subjects will also provide blood samples for anti-TPO/romiplostim antibodies and peripheral blood smears.	At specified time points, subjects will undergo the following assessments: collection of informed consent (and assent, if applicable), confirmation of primary ITP diagnosis, ITP and medical history, physical exam including weight and vital signs, **and baseline bone marrow biopsy and aspirate**. Subjects will have complete blood counts with differentials, blood chemistry profiles, local platelet counts, and a blood or urine pregnancy test for females of child-bearing potential. Research staff will document the use of concomitant and rescue medications and all adverse events reported for the subject. **A repeat bone marrow biopsy and aspirate will be performed after Year 1 or Year 2, based on the cohort assignment.** Subjects will also provide blood samples for anti-TPO/romiplostim antibodies and peripheral blood smears.

Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Protocol Synopsis Add after second paragraph of Statistical Considerations	Not applicable	**The analyses of bone marrow collagen as evidenced by trichrome staining, bone marrow reticulin increases using the modified Bauermeister grading scale, and cytogenetic abnormalities in the bone marrow after Year 1 and Year 2 will be descriptive. The proportion of subjects developing collagen, increase in reticulin, and any cytogenetic abnormalities in the bone marrow and the corresponding 95% exact confidence interval will be provided by treatment cohort. Logistical regression may be used to investigate the association of bone marrow abnormality and potential predictive factors.**

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Table 1. Summary of Changes

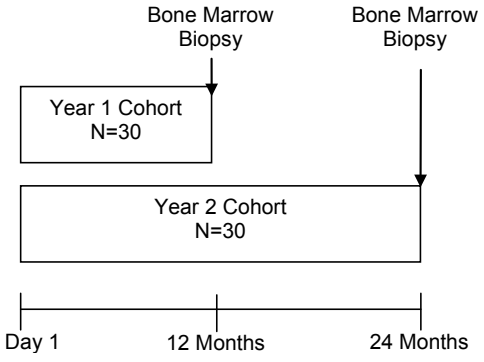
Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Study Design and Treatment Schema Add to Treatment Period Box	**Treatment Period** Number of Subjects = 200 Starting dose of romiplostim will be 1µg/kg administered one time weekly in an attempt to reach a target platelet count ≥ 50 x 10^9/L Dose adjustments will be allowed during the treatment period to maintain a platelet count between ≥ 50 x 10^9/L and ≤ 200 x 10^9/L Reduction in concurrent ITP therapies may occur when there is a platelet count of ≥ 50 x 10^9/L	**Screening/ Enrollment** For the subjects in the bone marrow subset only, a bone marrow biopsy within 1 year prior to planned first dose of romiplostim or consent to a pre-treatment bone marrow biopsy and aspirate within 3 weeks prior to planned first dose of romiplostim. Sequential enrollment to Year 1 or Year 2 bone biopsy cohort. → **Treatment Period** Number of Subjects = 200 Starting dose of romiplostim will be 1µg/kg administered one time weekly in an attempt to reach a target platelet count ≥ 50 x 10^9/L Dose adjustments will be allowed during the treatment period to maintain a platelet count between ≥ 50 x 10^9/L and ≤ 200 x 10^9/L Reduction in concurrent ITP therapies may occur when there is a platelet count of ≥ 50 x 10^9/L **Mandatory bone marrow biopsy and aspirates will be performed in at least 60 subjects at screening and after Year 1 or Year 2 in separate cohorts as follows:** 

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Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Section 1.1 Primary Objectives	The primary objective is to describe the percentage of time that pediatric subjects with immune thrombocytopenia (ITP) have a platelet response in the first 6 months from the start of treatment with romiplostim.	The primary objective**(s) are as follows:** • to describe the percentage of time that pediatric subjects with immune thrombocytopenia (ITP) have a platelet response in the first 6 months from the start of treatment with romiplostim • **to evaluate incidence of changes in bone marrow findings at Year 1 and Year 2 after initial exposure to romiplostim**

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Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Section 1.2 Secondary Objectives	The secondary objectives of the study are: • To describe the percentage of time that pediatric subjects with ITP have a platelet response over the study duration • To describe the percentage of time that pediatric subjects with ITP have an increase in platelet count ≥ 20 x 10^9/L above baseline over the study duration • To describe the use of rescue ITP medications • To describe the incidence of antibody formation • To describe the safety of romiplostim as a long-term treatment in pediatric thrombocytopenic subjects with ITP	The secondary objectives of the study are: • The percentage of time with a platelet count of ≥ 50 x 10^9/L starting from week 2 until the end of the treatment period without rescue medication use within the past 4 weeks • The percentage of time with an increase in platelet count ≥ 20 x 10^9/L above baseline starting from week 2 until the end of the treatment period without rescue medication use in the past 4 weeks. • Subject incidence of rescue ITP medications used • The incidence of anti-romiplostim neutralizing antibodies and cross-reactive antibodies to TPO at any time during the study • The incidence of adverse events, including clinically significant changes in laboratory values • **The incidence of increased reticulin as evidenced by silver staining at Year 1 or Year 2, after exposure to romiplostim**

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Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Section 3.1 Study Design Add new paragraph 2	This is a phase 3b single arm, open-label, multicenter study evaluating the percentage of time pediatric subjects with ITP have a response while receiving romiplostim, defined as a platelet count ≥ 50 x 10^9/L and in the absence of ITP rescue medications in the past 4 weeks. This protocol will provide open-label romiplostim to thrombocytopenic pediatric subjects with ITP diagnosed for at least 6 months and who have received at least 1 prior ITP therapy (excluding romiplostim) or are ineligible for other ITP therapies.	This is a phase 3b single arm, open-label, multicenter study evaluating the percentage of time pediatric subjects with ITP have a response while receiving romiplostim, defined as a platelet count ≥ 50 x 10^9/L and in the absence of ITP rescue medications in the past 4 weeks. This protocol will provide open-label romiplostim to thrombocytopenic pediatric subjects with ITP diagnosed for at least 6 months and who have received at least 1 prior ITP therapy (excluding romiplostim) or are ineligible for other ITP therapies. The study design consists of a 4-week screening period, up to a 3-year treatment period, an end of treatment (EOT) visit, and an end of study (EOS) visit. **A subset of at least 60 subjects will be enrolled sequentially into the following cohorts:** • **Bone marrow biopsy and aspirate at baseline and Year 1** • **Bone marrow biopsy and aspirate at baseline and Year 2** **All subjects in these 2 cohorts will receive romiplostim for 3 years, unless withdrawn from the study early. They will complete an End of Treatment (EOT) visit at the conclusion of their treatment period and will then return an End of Study (EOS) visit.**
Section 3.2 Number of Centers	There will be approximately 50 centers located in (but not limited to) Australia, Canada, Europe, Israel, South Africa, South America, and the United States.	There will be approximately 50 centers located in (but not limited to) Australia, Canada, Europe, Israel, South Africa, South America, and the United States. **Approximately 35 centers from the EU, Switzerland, and Turkey will participate in this supplement.**

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Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Section 3.3 Number of Subjects	Participants in this clinical investigation shall be referred to as "subjects." It is anticipated that approximately 200 subjects will be enrolled into this study.	Participants in this clinical investigation shall be referred to as "subjects." It is anticipated that approximately 200 subjects will be enrolled into this study. **Of the 200 subjects, at least 30 subjects will be enrolled into each of 2 cohorts, which are identified by bone marrow biopsy time points (Year 1 or Year 2).**
Section 4.1 Inclusion Criteria	Not applicable	Inclusion criteria 4.1.**7** • **Subject must agree to a scheduled bone marrow biopsy and aspirate at Year 1 or Year 2 following romiplostim treatment and any unscheduled biopsies if clinically indicated**
Section 4.1 Inclusion Criteria	Not applicable	Inclusion criteria 4.1.**8** • **A reticulin grade of 0, 1, 2, or 3 according to the modified Bauermeister grading scale, as assessed by central laboratory from a bone marrow biopsy performed within 1 year prior to planned first dose of romiplostim or consent to a pre-treatment bone marrow biopsy and aspirate prior to planned first dose of romiplostim**
Section 5 Subject Enrollment Add Cohorts subsection	Not applicable	**Cohorts** **This protocol supplement will recruit 2 cohorts based on subject allocation for their on-study bone marrow biopsy at Year 1 or Year 2.** **Cohorts will be confirmed through the IVRS after the subject meets all eligibility criteria (including central laboratory bone marrow biopsy and aspirate review). Once the first cohort has completed enrollment, the second cohort will begin enrolling. At least 30 subjects will be sequentially enrolled into the two cohorts.**

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Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Section 7.1, Add new Table 2b	Not applicable Renumber Table 2, as Table 2a	**Table 2b. Bone Marrow Assessments**

Procedures	Screening	Treatment Phase (up to 36 months)		End of Treatment	End of Study Visit
		Year 1	Year 2		
Bone Marrow Biopsy, Cohort 1[a]	X	X		X[b]	X[c]
Bone Marrow Biopsy, Cohort 2[a]	X		X	X[b]	X[c]

a Bone Marrow Biopsy: A baseline bone marrow biopsy and aspirate is required to determine eligibility; this can be either a bone marrow biopsy within 1 year prior to planned first dose of romiplostim (with available bone marrow tissue block or a minimum of 5 unstained, evaluable histological slides to send to a central laboratory) or a pre-treatment bone marrow biopsy and aspirate within 3 weeks prior to planned first dose of romiplostim. Central laboratory evaluation is required prior to the first dose of romiplostim. A further bone marrow biopsy and aspirate is required at Year 1 or Year 2, depending on the cohort in which the subject is enrolled (as designated by IVRS). Additional bone marrow biopsies and aspirates may be performed if clinically indicated at the discretion of the investigator and/or Amgen.

b End of Treatment (EOT): Subjects who are non-responders and withdraw from the study will require a bone marrow biopsy and aspirate at the EOT visit. A bone marrow biopsy and aspirate should be obtained for discontinued subjects who have not yet had a cohort-defined bone marrow biopsy performed.

c End of Study (EOS): EOS will be delayed for subjects who are withdrawn from the study due to the presence of collagen, or subjects who have a change to grade 3 reticulin, per central laboratory evaluation of a bone marrow biopsy. These subjects will complete an EOS visit 12 weeks after discontinuation of romiplostim and will require a repeat bone marrow biopsy.

Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Add new section 7.1.4 Bone Marrow Biopsy	Not applicable	**Bone Marrow Biopsy** **For the protocol supplement, a baseline bone marrow biopsy and aspirate is required to determine eligibility; central laboratory evaluation is required prior to first dose of romiplostim. A baseline bone marrow biopsy can be either a bone marrow biopsy within 1 year prior to the planned first dose of romiplostim (with available bone marrow tissue block or a minimum of 5 unstained, evaluable histological slides to send to a central laboratory) or a pre-treatment bone marrow biopsy and aspirate within 3 weeks prior to planned first dose of romiplostim.** **A repeat bone marrow biopsy and aspirate is required at Year 1 or Year 2 (± 4 week window) depending on the cohort assignment. A bone marrow biopsy and aspirate should be obtained for discontinued subjects who have not yet had a cohort-defined bone marrow biopsy performed.** **Should collagen be detected in any subjects during the course of the study, study drug will be discontinued and the subject will undergo an EOT visit. A repeat bone marrow biopsy will be required 12 weeks later at the EOS visit (+ 2 week window) for subjects who are withdrawn from the study due to the presence of collagen.** **Subjects who have a change to grade 3 reticulin, per central laboratory evaluation of a bone marrow biopsy, will undergo a repeat bone marrow biopsy 12 weeks after their last dose of romiplostim at the EOS visit (+ 2 week window).** **Subjects who are considered non-responders and will be discontinued from the study will require a bone marrow biopsy and aspirate sample to be taken at the EOT visit (+ 2 week window). A repeat bone marrow biopsy will also be required 12 weeks later at EOS visit (+ 2 week window) for non-responders who have a change to grade 3 reticulin or collagen, per central laboratory evaluation of a bone marrow biopsy.** **Bone marrow biopsies and aspirates where applicable, will be sent to a central laboratory for reticulin and collagen staining and analysis. Refer to Central Laboratory Manual for instructions on collection, preparation, storage, and shipment of samples. The modified Bauermeister Scale (Bauermeister, 1971) will be used for this study. Subjects with a reticulin grade of 0, 1, 2, or 3 will be eligible for this study.**

Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Add new section 7.1.4 Bone Marrow Biopsy (continued)	Not applicable	**Additional bone marrow biopsies and aspirates may be performed, if clinically indicated, at the discretion of the investigator and/or Amgen. At any time an unscheduled bone marrow biopsy and aspirate are performed on study, available bone marrow tissue block (paraffin embedded) or unstained histological slides will be submitted to the central laboratory for evaluation. Some examples of when a clinically indicated bone marrow biopsy and aspirate might be performed include abnormalities seen on a peripheral blood smear (eg, evidence of blast cells) or a CTCAE grade ≥ 2 shift in either anemia or neutropenia.**
Section 7.1.1 Routine Blood Tests, Table 3, List of Analytes in Laboratory Specimens, under Other Labs	Central lab optional bone marrow biopsy if abnormality is identified (see Section 7.1.1) to include silver and trichrome stain	**Bone marrow biopsy and aspirate** • **Megakaryocyte count** • **Reticulin/collagen grade (Bauermeister score)** • **Trichrome staining** • **Silver staining** • **Cytogenetics and fluorescence in situ hybridization(FISH)**
Section 7.5 Screening	Not applicable	**Add** • **bone marrow biopsy and aspirate (central laboratory evaluation is required prior to first administration of romiplostim)**

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Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Section 7.6 Add subsection under Romiplostim Treatment Period (Up to a 36 Months Duration)	The following procedures will be completed during the romiplostim treatment period at the times designated in the Schedule of Assessments (Table 2): • documentation of concomitant and rescue medications • adverse event reporting • central lab CBC with differential (every 4 weeks) • central lab blood chemistry (every 12 weeks) • local lab platelet counts. • collection of blood samples for anti-romiplostim antibodies (first sample is collected before first dose of romiplostim, then at week 12, week 52, and every 24 weeks thereafter) • local lab peripheral blood smear (every 4 weeks) • physical exam with vital signs and weight (every 12 weeks) • romiplostim administration	The following procedures will be completed during the romiplostim treatment period at the times designated in the Schedule of Assessments (Table 2): • documentation of concomitant and rescue medications • adverse event reporting • central lab CBC with differential (every 4 weeks) • central lab blood chemistry (every 12 weeks) • local lab platelet counts • collection of blood samples for anti-romiplostim antibodies (first sample is collected before first dose of romiplostim, then at week 12, week 52, and every 24 weeks thereafter) • local lab peripheral blood smear (every 4 weeks) • physical exam with vital signs and weight (every 12 weeks) • **local lab urine or serum pregnancy test for female subjects of child-bearing potential (defined as having first menses) every 12 weeks** • romiplostim administration **Additional Procedures Required for Cohort 1 or Cohort 2** • **Bone marrow biopsy and aspirate (one scheduled biopsy, dependent on cohort)**

Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Section 7.7 End of Treatment Visit (EOT)	All subjects will complete an EOT visit. For subjects who complete the 36-month treatment period and who have been off romiplostim and other medications for ITP (concomitant or rescue) for 4 weeks or more, the EOT visit will be the final study visit and will occur after the completion of the 36-month treatment period. For subjects ending the 36-month treatment period for non-response or other reasons while still receiving romiplostim, this visit will be 1 week after the last administration of romiplostim.	All subjects will complete an EOT visit. For subjects who complete the 36-month treatment period and who have been off romiplostim and other medications for ITP (concomitant or rescue) for 4 weeks or more, the EOT visit will be the final study visit and will occur after the completion of the 36-month treatment period. For subjects ending the 36-month treatment period for non-response or other reasons while still receiving romiplostim, this visit will be 1 week after the last administration of romiplostim. **In addition, a bone marrow biopsy and aspirate should be obtained for discontinued subjects who have not yet had a cohort-defined bone marrow biopsy performed.**

Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Section 7.8 End of Study Visit	Four weeks after the last dose of romiplostim for subjects who end the 36-month treatment period for non-response or other reasons while still receiving romiplostim will have an EOS visit. The following assessments will be completed at the EOS visit: • local lab platelet count • serious adverse event reporting • documentation of concomitant and rescue medications	Four weeks after the last dose of romiplostim for subjects who end the 36-month treatment period for non-response or other reasons while still receiving romiplostim will have an EOS visit. The following assessments will be completed at the EOS visit: • local lab platelet count • serious adverse event reporting • documentation of concomitant and rescue medications • **Bone marrow biopsy and aspirate (only for subjects with collagen or a change to grade 3 or 4 reticulin)**

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Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Section 10.1.1 Study Endpoints Primary Endpoint	• The percentage of time with a platelet count of ≥ 50 x 10^9/L starting from week 2 in the first 6 months of the treatment period without rescue medication use within the past 4 weeks	• The percentage of time with a platelet count of ≥ 50 x 10^9/L starting from week 2 in the first 6 months of the treatment period without rescue medication use within the past 4 weeks • **Evaluation of bone marrow changes after Year 1 or Year 2 for the following:** - **Incidence of collagen as evidenced by trichrome staining (using the modified Bauermeister grading scale) after romiplostim exposure** - **Incidence of bone marrow reticulin increases in severity ≥ 2 grades (ie, grade 0 to 2-4, 1 to 3-4, 2 to 4), compared to baseline, or an increase to grade 3 or grade 4 as evidenced by reticulin silver staining using the modified Bauermeister grading scale after romiplostim exposure** - **Incidence of bone marrow abnormalities (eg, myelodysplastic syndrome, monosomy 7) as evidenced by cytogenetics and fluorescence in situ hybridization**

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Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Section 10.1.1 Study Endpoints Secondary Endpoint	• The percentage of time with a platelet count of ≥ 50 x 10^9/L starting from week 2 until the end of the treatment period without rescue medication use within the past 4 weeks • The percentage of time with an increase in platelet count ≥ 20 x 10^9/L above baseline starting from week 2 until the end of the treatment period without rescue medication use in the past 4 weeks • Subject incidence of rescue ITP medications used • The incidence of anti-romiplostim neutralizing antibodies and cross reactive antibodies to TPO at any time during the study • The incidence of adverse events, including clinically significant changes in laboratory values	• The percentage of time with a platelet count of ≥ 50 x 10^9/L starting from week 2 until the end of the treatment period without rescue medication use within the past 4 weeks • The percentage of time with an increase in platelet count ≥ 20 x 10^9/L above baseline starting from week 2 until the end of the treatment period without rescue medication use in the past 4 weeks. • Subject incidence of rescue ITP medications used • The incidence of anti-romiplostim neutralizing antibodies and cross reactive antibodies to TPO at any time during the study • The incidence of adverse events, including clinically significant changes in laboratory values • **The incidence of increased reticulin as evidenced by silver staining at Year 1 or Year 2, after exposure to romiplostim**

Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Section 10.2 Sample Size Considerations	Not applicable	**A sample size of at least 60 subjects was selected for subjects undergoing bone marrow evaluations. The sample size was chosen to provide an assessment/estimation of the development of bone marrow abnormalities (eg, collagen as evidenced by trichrome staining) at Year 1 or Year 2 after romiplostim exposure using the modified Bauermeister grading scale.** **With 30 subjects in each cohort, the number of evaluable bone marrow results in each cohort is expected to be between 20 and 25. The assumption of 20 to 25 evaluable subjects is based on the approximate 30% rate of repeat inevaluable or missing bone marrow samples observed in the current Amgen adult ITP bone marrow study with romiplostim (Study 20080009). The 95% exact confidence intervals for outcomes of bone marrow abnormalities when there are 20 and 25 evaluable bone marrow results are described in Table 4.** **No historical data are available regarding the change in bone marrow morphology in this patient population. Clinical data from adult ITP subjects receiving romiplostim demonstrated that increases in bone marrow reticulin (or the presence of reticulin on study) were observed in 3.7% (10 of 271 of subjects: romiplostim 120-day safety update dataset used). However the potential incidence rate could be higher or lower given that bone marrow assessments were not systematically performed on all subjects during clinical studies.**

Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Section 10.2 Sample Size Considerations (continued)		**Table 4. 95% Exact Confidence Intervals for the Incidence Rate of a Bone Marrow Abnormality**

Number of Subjects with Evaluable Bone Marrow = 20

Number of Subjects With a Bone Marrow Abnormality	Incidence Rate	95% CI Lower Bound	95% CI Upper Bound
0	0.0%	0.0%	16.8%
1	5.0%	0.1%	24.9%
2	10.0%	1.2%	31.7%
3	15.0%	3.2%	37.9%
4	20.0%	5.7%	43.7%
5	25.0%	8.7%	49.1%

Number of Subjects with Evaluable Bone Marrow = 25

Number of Subjects With a Bone Marrow Abnormality	Incidence Rate	95% CI Lower Bound	95% CI Upper Bound
0	0.0%	0.0%	13.7%
1	4.0%	0.1%	20.4%
2	8.0%	1.0%	26.0%
3	12.0%	2.5%	31.2%
4	16.0%	4.5%	36.1%
5	20.0%	6.8%	40.7%

Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Section 10.3.1 Interim Analyses	Interim analyses will be conducted to support regulatory filings, and accumulated data for this study will be summarized to provide ongoing assessments of the safety of romiplostim. These interim analyses will occur at least annually until the end of the study.	Interim analyses will be conducted to support regulatory filings, and accumulated data for this study will be summarized to provide ongoing assessments of the safety of romiplostim. These interim analyses will occur at least annually until the end of the study. **A Bone Marrow Panel comprised of experts in the treatment of ITP and interpreting bone marrow pathology will convene approximately one time per cohort when all bone marrow biopsy samples have been evaluated for each respective cohort. The Bone Marrow Panel will independently review the central lab bone marrow results and report those results to Amgen once each respective cohort has completed. The bone marrow panel is not chartered to make recommendations to study conduct.** **A report will be generated including details of study compliance, the number of samples submitted and bone marrow biopsy results. Additional data may be summarized at intervals throughout the duration of the study. These data may be provided for regulatory or publication activities**.

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Table 1. Summary of Changes

Protocol Section	Text in Protocol	Text For the EU, Switzerland, and Turkey
Section 10.3.4 Additional Analysis, Add section 10.3.4.4 Bone Marrow Analysis	Not applicable	**Section 10.3.4.4 Bone Marrow Analysis** **The number and percentage of subjects who develop collagen as evidenced by trichrome staining at Year 1 or Year 2, will be summarized by study cohort, splenectomy status at baseline, years since diagnosis (≤ 3 vs > 3 years), age at enrollment (≥ 1 year to < 6 years; 6 years to <12 years; 12 years to < 18 years) and maximum doses and drug exposures if appropriate. In addition, logistic regression may be used to investigate the association of bone marrow abnormality and potential predictive factors.** **The number and percentage of subjects with collagen as evidenced by trichrome staining 12 weeks after romiplostim discontinuation among subjects who developed collagen will be summarized.** **The number and percentage of subjects with bone marrow reticulin increases by ≥ 2 severity grades or any increase to grade 4 (ie, grade 0 to 2-4, 1 to 3-4, 2 to 4), or change to grade 3 to 4 over baseline as evidenced by reticulin silver staining at Year 1 or Year 2, post romiplostim exposure using the modified Bauermeister grading scale will be summarized.** **The number and percentage of subjects with improvement of reticulin to a grade of ≤ 2 for subjects who developed grade 3 reticulin after initial exposure to romiplostim as measured by the modified Bauermeister grading scale will be summarized.**

Supplement Version #2

Protocol Supplement for the European Union (EU), Switzerland, and Turkey

Protocol Title: A Single Arm, Open-label, Long-term Efficacy and Safety Study of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune Thrombocytopenia (ITP)

Amgen Protocol Number 20101221

EudraCT number 2011-005019-96

Amendment Date: **15 July 2014**

Rationale:

As a result of regulatory reviews, modifications have been made to the numbering and content of the supplement inclusion criteria

AMGEN®

Description of Changes:

Section: Header of the Document

Replace: 15 April 2014

With: **15 July 2014**

Section: Title Page,

Add: **Supplement Version #2: 15 July 2014**

Page 13, Section 4.1: Inclusion Criteria

Renumber inclusion criteria 4.1.6 with 4.1.7

Page 13, Section 4.1: Inclusion Criteria

Renumber inclusion criteria 4.1.7 with 4.1.8

Replace:

Baseline bone marrow reticulin grade of 0, 1, 2, or 3 according to the modified Bauermeister grading scale, as assessed by central laboratory

With:

A reticulin grade of 0, 1, 2, or 3 according to the modified Bauermeister grading scale, as assessed by central laboratory from a bone marrow biopsy performed within 1 year prior to planned first dose of romiplostim or consent to a pre-treatment bone marrow biopsy and aspirate prior to planned first dose of romiplostim

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