

BACKGROUND INFORMATION

FOR

THE ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

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1. EXECUTIVE SUMMARY

KEY POINTS:

Unmet Medical Need

- Chronic immune (idiopathic) thrombocytopenic purpura (ITP) is a serious and potentially life-threatening condition due to risks such as intracranial and other serious bleeding events and the side-effects of existing therapies (George et al, 1996).
- Existing ITP treatments are often unsuccessful in long term use in a high proportion of severely affected patients because of adverse effects (eg, corticosteroids) or an intermittent mode of administration (eg, IVIG infusions) that makes them unsuitable for routine, chronic use. Morbidity in chronic ITP is attributed to the side effects of treatment (eg, life-threatening bleeding) as well as the disease itself (Portielje et al, 2001).
- For patients who have undergone splenectomy but still have low platelet counts, data are limited and treatment options are few, with outcomes often inadequate (Vesely et al, 2004; McMillan and Durette, 2004).
- Lack of satisfactory treatments has led to widespread off-label use of drugs not approved for this indication. Drugs commonly used off-label in ITP patients (eg, rituximab, cyclophosphamide, azathioprine, vinca alkaloids, danazol) have not been the subject of large, controlled studies, and are associated with significant toxicities.

Background

- The underlying pathogenesis of ITP is peripheral destruction of platelets due to antibodies directed against platelet antigens (eg, GPIIb/IIIa and/or GPIb/IX). Evidence suggests that impaired thrombopoiesis, in addition to platelet destruction, contributes to thrombocytopenia in ITP (Ballem et al, 1987; Houwerzijl et al, 2004; McMillan et al, 2004).

- Romiplostim was designed to bind to the thrombopoietin (TPO, or c-Mpl) receptor and stimulate platelet production, a novel mode of therapy compared with existing treatments for ITP, which focus on non-specific immunosuppression to reduce antibody production.
- Amgen's experience with the development of thrombopoiesis-stimulating agents, and knowledge of the risks associated with the development of TPO-specific neutralizing antibodies, stimulated our development of a novel TPO receptor agonist that is structurally unrelated to TPO itself. Indeed, romiplostim has no amino acid sequence homology to endogenous TPO (eTPO), greatly reducing the probability that antibodies to romiplostim, if produced, will bind to eTPO and cause thrombocytopenia.
- In phase 1 and 2 clinical studies, dose-dependent increases in platelet counts were observed in healthy subjects and subjects with ITP. The results supported the use of 1.0 µg/kg as the starting dose for weekly administration of romiplostim.

Efficacy

- Throughout the development of romiplostim, Amgen has worked with the FDA and sought guidance and input into pivotal study design, endpoints and an acceptable efficacy and safety database of subject numbers and duration of treatment for this orphan, chronic, disease indication.
- Romiplostim's efficacy was demonstrated in 2 well-designed, placebo-controlled, multicenter phase 3 studies developed under the FDA's Special Protocol Assessment process. The primary efficacy endpoint was the rigorously-defined measure of durable platelet response, developed to capture a stable response maintained in the absence of any other ITP medication.
- One study enrolled subjects who had not undergone splenectomy (20030212; 21 placebo, 41 romiplostim) and the other enrolled splenectomized subjects (20030105; 21 placebo, 42 romiplostim). Both study populations had inadequate platelet responses to existing ITP treatments, and the combined median platelet count was below $20 \times 10^9/L$ at study entry.

- In the 2 pivotal studies (20030105 and 20030212) combined, the primary endpoint, durable platelet response, was achieved by approximately half of all subjects who received romiplostim (41 of 83 subjects; 49.4%), compared with one of 42 subjects who received placebo (2.4%) ($p < 0.0001$). Results were significant for each study individually as well.
- Romiplostim was statistically significantly superior to placebo for all key secondary efficacy endpoints in the combined population as well as for each individual study.
- Rescue medication (mostly corticosteroids and IVIG) was required by 59.5% of subjects in the placebo group and 21.7% of subjects in the romiplostim group ($p < 0.0001$) during the treatment period (combined pivotal study population). Of 16 placebo and 23 romiplostim subjects who entered the study receiving concurrent ITP medications, 6 placebo (37.5%) and 20 romiplostim (87.0%) subjects had either reduced by $> 25\%$ or entirely discontinued those medications at study week 25.
- The ability of romiplostim to maintain platelet counts over a longer period of time was shown for subjects who completed the pivotal studies and continued into the open-label extension Study 20030213. Total exposure for subjects receiving romiplostim was up to 24 weeks in a pivotal study and up to 60 additional weeks in Study 20030213.
- Subjects originally randomized to the placebo arms of the pivotal trials showed improvements in all measures of efficacy when they received romiplostim on the extension Study 20030213, relative to their performance during their phase 3 parent study.
- Bleeding events were not captured as a prospectively-defined efficacy endpoint, but were collected as adverse events. In the combined pivotal studies, bleeding events that were \geq grade 2 (moderate) in severity occurred at a higher subject incidence among placebo subjects (34%) than subjects receiving romiplostim (16%), and post-hoc statistical comparison showed this difference to be significant ($p = 0.017$). The subset of clinically significant bleeding events (\geq grade 3) also occurred in more placebo subjects (12%) than romiplostim subjects (7%).

- Across the entire ITP clinical program, an inverse relationship between bleeding events and platelet counts was observed. All clinically significant (\geq grade 3) bleeding events occurred at platelet counts $< 20 \times 10^9/L$. All moderate (\geq grade 2) bleeding events occurred at platelet counts $< 50 \times 10^9/L$.

Safety

- A total of 204 subjects with ITP have received at least 1 dose of romiplostim; 128 subjects had at least 26 weeks of exposure, and 74 subjects had at least 52 weeks of exposure. Long term follow-up continues.
- Safety data from 125 subjects in the 2 pivotal phase 3 studies demonstrated that when compared with placebo, romiplostim was relatively well tolerated. Adverse Drug Reactions that occurred at a $\geq 5\%$ higher subject incidence in the romiplostim group than the placebo group identified in the 2 pivotal studies are shown in the table below.

Preferred Term	Romiplostim n = 84	Placebo n = 41
Arthralgia	26%	20%
Dizziness	17%	0%
Insomnia	16%	7%
Myalgia	14%	2%
Pain in extremity	13%	5%
Abdominal Pain	11%	0%
Shoulder Pain	8%	0%
Dyspepsia	7%	0%
Paraesthesia	6%	0%

Headache was the most commonly reported adverse drug reaction, occurring in 35% of patients receiving romiplostim and 32% of patients receiving placebo. Increased reticulin in the bone marrow, thrombocytosis, and recurrence of thrombocytopenia after cessation of treatment are additional adverse drug reactions observed in subjects receiving romiplostim.

- No neutralizing antibodies that cross-reacted with TPO were reported in the clinical development program. Of the 204 patients in clinical studies receiving romiplostim, one subject developed neutralizing antibodies to romiplostim; importantly, these did not cross react with endogenous TPO. Approximately 4 months later, after discontinuation of romiplostim, neutralizing antibodies were no longer detectable.

- The incidence of thrombotic / thromboembolic events observed in clinical trials was similar between romiplostim and placebo.
- There is a concern that TPO receptor agonists may stimulate the progression of hematopoietic malignancies or myelodysplastic syndrome (MDS), as the TPO receptor is predominantly expressed on the surface of cells of the hematopoietic lineage. In a single-arm, open-label study in which 20 subjects with MDS received romiplostim, 2 subjects had transient increases in blast cell counts that were inconsistent with progression to AML; one subject had an event of disease progression to AML, which is consistent with the natural course of the disease.
- In the ITP studies, hematologic malignancies were reported in 3 subjects: B-cell lymphoma (0 placebo, 1 [0.5%] romiplostim, in a subject with preexisting lymphadenopathy and several lymphoid aggregates in pretreatment bone marrow) and multiple myeloma (1 [2.2%] placebo, 1 [0.5%] romiplostim).
- In some subjects, platelet counts transiently decreased below the pretreatment baseline levels upon discontinuation of romiplostim. Romiplostim, like other thrombopoietic agents, causes increased platelet production; treatment does not alter the underlying rate of platelet destruction. Therefore, it is expected that in ITP patients platelet counts will return to baseline levels upon discontinuation of romiplostim treatment, resulting in an increased risk for bleeding, particularly if romiplostim is discontinued in the presence of anticoagulants or anti-platelet agents.
- Increased bone marrow reticulin (or the presence of reticulin on study) has been observed in 9 of 219 subjects who have received romiplostim (120-day update dataset used). This finding was not associated with reports of adverse clinical sequelae, the diagnosis of chronic idiopathic myelofibrosis (CIMF), or secondary myelofibrosis.

Overall Benefit and Risk

- Chronic ITP carries risks for life-threatening bleeding, such as intracranial and other clinically significant bleeding. Few approved treatments are available for chronic ITP, and they carry considerable safety risks (eg, chronic moderate-to-high dose

- corticosteroids), contributing to morbidity in patients with chronic ITP. New options are needed to treat thrombocytopenia in this orphan indication.
- Romiplostim was effective in increasing and maintaining platelet counts in both splenectomized and non-splenectomized populations. Romiplostim was statistically significantly superior to placebo for the rigorously defined primary endpoint of durable platelet response, as well as all secondary efficacy endpoints, in both populations, as well as in the integrated pool.
 - The increases in platelet counts in the romiplostim group were achieved while romiplostim subjects were receiving significantly less rescue medication and were reducing baseline concurrent ITP medications compared with placebo subjects.
 - Bleeding events in the 2 pivotal studies were characterized by the known inverse relationship between platelet count and bleeding. Clinically significant (grade 3 or 4) bleeding events did not occur at platelet counts of $20 \times 10^9/L$ or greater, supporting the importance of maintaining platelet count.
 - The following are considered identified risks of romiplostim:
 - Re-occurrence of thrombocytopenia after cessation of treatment
 - Increases in bone marrow reticulin
 - Potential risks of romiplostim are as follows¹:
 - Progression of existing hematopoietic malignancies or MDS
 - Thrombotic / thromboembolic complications
 - Neutralizing antibodies that cross react with eTPO.
 - Progression of increased reticulin to an irreversible bone marrow fibrotic state.
 - Potential for off-label use in indications where risk-benefit ratio has not been adequately studied.
 - Risk for medication errors due to the potency of romiplostim and the small volume administered.
 - Amgen is committed to establishing a comprehensive risk management program including cautionary instructions in the prescribing information, pharmacovigilance

¹ Modified from Amgen's current Risk Management Plan, which is being revised.

(both routine and proactive), risk management activities, and additional clinical studies. Amgen believes these actions are appropriate and adequate to minimize the potential safety risks).

- The potential risks of romiplostim therapy will be managed through a Risk minimization action plan (RiskMAP) using the following tools: prescribing information, Medication Guide, targeted education and outreach (including physician education initiatives, patient and patient advocacy group initiatives) and systems to measure and demonstrate program effectiveness.
- In conclusion, the benefit-to-risk ratio for romiplostim as demonstrated by the clinical data provides a strong basis for regulatory approval of the proposed indication. Potential safety risks can be appropriately and adequately minimized in the post-marketing setting through the proposed risk management tools.

List of Abbreviations and Terms and Definitions

Abbreviation or Term	Definition/Explanation
ADR	Adverse drug reaction. An adverse drug reaction (ADR) is defined in 21 CFR 201.57(c) (7) as an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. Adverse events were identified as ADRs if they occurred at $\geq 5\%$ higher subject incidence in the romiplostim group than the placebo group in the phase 3 ITP safety set or in the Amgen pharmacovigilance safety database. Additional events were identified based on review of the study-duration adjusted adverse events in the ITP safety set, as well as Amgen medical review of safety experience to date, expected pharmacologic activity of romiplostim, and case analysis and/or review of the clinical database for additional causality.
AMG 531	Development name for romiplostim (Nplate)
c-Mpl	The thrombopoietin receptor (c-Mpl)
CIT	Chemotherapy-induced thrombocytopenia
concurrent baseline therapy	Subjects in both arms of the pivotal studies were permitted corticosteroids, azathioprine, and/or danazol at study entry at a constant dose (no dose adjustment for 4 weeks before screening).
eTPO	Endogenous thrombopoietin
ELISA	Enzyme-linked immunosorbent assay
durable platelet response	Primary endpoint in the pivotal studies; defined as at least 6 weekly platelet responses during the last 8 weeks of treatment, in the absence of any rescue medication during the treatment period
end of study	In the pivotal studies, end of study was defined as the day the platelet counts drop to $\leq 50 \times 10^9/L$, or week 36, after having already completed the 24 week treatment period and the end of treatment visit
ITP	Immune (idiopathic) thrombocytopenic purpura
ITP-PAQ	ITP-Patient Assessment Questionnaire, an ITP-specific instrument to assess patient reported outcome
IV	Intravenous
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
overall platelet response	The mutually exclusive categories of durable platelet response plus transient platelet response
transient platelet response	At least 4 weekly platelet responses, without durable platelet response, in the absence of any rescue medication during the last 8 weeks
PRO	Patient reported outcome
rescue medication	Standard rescue medications were permitted in either arm of the pivotal studies for major bleeding or wet purpura, or if the investigator concluded that the subject was at immediate risk. Recommended rescue medications were IVIG, platelet

Abbreviation or Term	Definition/Explanation
	transfusions, and corticosteroids.
reticulin	In this document, reticulin refers to a normal component of the bone marrow that can be detected using a reticulin (silver) stain. In contrast, bone marrow fibrosis is detected by specific staining techniques (trichrome among many).
RiskMAP	Risk minimization action plan (as per FDA guidelines "Guidance for Industry - Development and Use of Risk Minimization Action Plans, March 2005," and "Guidance for Industry - Premarketing Risk Assessment, March 2005").
SC	Subcutaneous
SOC	System organ class (as classified by MedDRA)
SPA	Special Protocol Assessment by FDA
TMP	The active peptide portion of AMG 531
TPO	Thrombopoietin
weekly platelet response	A platelet count $\geq 50 \times 10^9/L$ on a weekly scheduled dose day from week 2 to week 25

2. UNMET MEDICAL NEED

2.1 Key Points

- Chronic ITP is a serious and potentially life-threatening condition due to risks such as intracranial bleeding and other clinically significant bleeding and the side-effects of existing therapies (George et al, 1996).
- Standard ITP treatments are often unsuccessful in long-term use in a high proportion of severely affected patients because their adverse effects (eg, corticosteroids) or intermittent mode of administration (eg, IVIG infusions) make them unsuitable for routine, chronic use. For patients who have undergone splenectomy but still have low platelet counts, data are limited and treatment options are few, with outcomes often inadequate (Vesely et al, 2004; McMillan and Durette, 2004).
- Lack of satisfactory treatments has led to widespread off-label use of drugs not approved for this indication. Drugs commonly used off-label in ITP patients (eg, rituximab, cyclophosphamide, azathioprine, vinca alkaloids, danazol) have not been the subject of large, controlled studies, and are associated with significant toxicities.
- An unmet medical need exists in both the pre- and post-splenectomy settings for a well-tolerated and effective chronic treatment for thrombocytopenia in patients with ITP.

Romiplostim has been developed to treat thrombocytopenia in patients with ITP, a serious disease with significant risks such as intracranial bleeding. The medical need for new therapies to treat ITP is apparent in the small number of drugs approved for this indication and the unsatisfactory risk-benefit profile of these existing agents. This assertion is reinforced by the assignment of Fast Track Status to the romiplostim program in ITP.

2.2 Chronic ITP

Chronic ITP is a serious and life-threatening condition that affects more adult women than men (approximately 2:1). The incidence of ITP in the United States (US) is estimated as 58 to 66 new cases per million population per year, or approximately

16,000 new cases per year (McMillan, 1997). In Europe, the incidence of ITP in adults is estimated as 20,863 new cases per year (Frederickson and Schmidt, 1999; Franco-Garcia et al, 1998).

Recently, studies have reported that patients with persistent severe thrombocytopenia that does not respond to therapy within the first 2 years after diagnosis have considerable morbidity due to the effects of ITP and ITP treatments (Portielje et al, 2001 and Cohen et al, 2000). In patients diagnosed with thrombocytopenia associated with ITP, age may be associated with a risk of higher morbidity and mortality, including the risk of severe bleeding over time (Andres et al 2003; Cortelazzo et al, 1991).

Cohen et al, 2000, assessed the age-adjusted bleeding risk of ITP involving persistent low platelet counts ($< 30 \times 10^9/L$), and on the long-term prognosis in such cases, from a pooled analysis of an ITP clinical series based on a systematic literature search. The authors reviewed 17 case series including 1817 patients with ITP. There were 49 cases of fatal hemorrhage over 1258 to 3023 estimated patient-years at risk. The rate before age adjustment was estimated at between 0.0162 and 0.0389 cases per patient-year. A trend towards increased risk was observed when the patients were divided by age into 3 groups (younger than 40 years, 40 to 60 years, and > 60 years) with the 5 year mortality rates ranging from 2.2% for those < 40 years to 47.8% for those > 60 years. The study also projected the risk for fatal bleeds at 0.4% for patients < 40 , 1.2% for 40 – 60, and 13% for > 60 years of age. The risk for non-fatal, major bleeding events was estimated at 3% for patients < 40 and 71% for patients > 60 years of age. Accordingly, a 30 year old woman with platelet counts $< 30 \times 10^9/L$ was projected to have a 16.3% chance of a fatal bleed and a 73% chance of having a non-fatal, major bleeding event if thrombocytopenia persisted for 20 years. The main conclusion from this study was that “ITP with persistent low platelet counts carries a grave prognosis” and “therefore an active therapeutic approach in the clinical management of affected patients should be considered.”

Together these studies suggest an increased risk for morbidity and mortality in patients who have had a long duration of platelet counts $< 30 \times 10^9/L$, which is exacerbated in patients who are of advanced age (> 60 years of age). These data support the current treatment goal of maintaining platelet counts at $> 30 \times 10^9/L$ in all patients diagnosed with ITP.

2.3 Pre-splenectomy

Most current treatments for ITP have limited chronic efficacy, and are associated with considerable side effects, and/or are difficult to administer. Thus, a significant unmet medical need exists for patients with chronic ITP.

Large differences in response rates are reported in the literature for ITP (Table 1).

Historically, there has been no general agreement on a standard definition of response in ITP, and definitions of response in the literature vary widely (Ruggeri, 2008).

According to ITP treatment guidelines, initial treatment for adults with ITP usually begins with corticosteroids. The morbidities associated with corticosteroid treatment may have a substantial impact on the health and day-to-day functioning of patients. Thus, corticosteroids are not well tolerated over time due to their side effects, and the course of treatment is often determined by tolerance to these effects.

IVIg and anti-D immunoglobulin (WinRho[®]) are approved for use in ITP (Gamunex [immune globulin intravenous (human)] prescribing information 2005; WinRho[®] [Rho (D) immune globulin (human)] prescribing information 2006; WinRho SDF summary of product characteristics 2006). Both are administered as intravenous (IV) infusions: IVIg (as a divided dose over 4 to 6 hours) is infused over 2 to 5 days, and anti-D is infused over 2 to 5 minutes. Both are short-acting and are generally used intermittently to “rapidly raise platelet counts to prevent bleeding or allow a patient with ITP to undergo surgery” (Gamunex[®] [immune globulin intravenous (human)] prescribing information, 2005) or “in clinical situations requiring an increase in platelet count to prevent excessive hemorrhage” (WinRho[®] [Rho (D) immune globulin (human)] prescribing information, 2006; WinRho SDF summary of product characteristics 2006). Anti-D immunoglobulin has been used to attempt to postpone splenectomy in recently-diagnosed patients (Cines and Bussel, 2005). In the largest series to date, 25% to 30% of previously treated patients showed responses off therapy lasting longer than 1 year (Cooper et al, 2002).

2.4 Post-splenectomy

Splenectomy is generally the next step for adults who fail to respond to corticosteroids, IVIg, or anti-D immunoglobulin or who prove intolerant to therapy (Cines and Blanchette, 2002). Splenectomy is not an option for all patients, either because they are ineligible or from personal choice. These patients continue with medical therapy. Splenectomy is

increasingly viewed as a last resort by patients and some physicians, particularly in the United States and in some European countries. In recent studies, the rate of splenectomy has been reported as approximately 20% to 25%, whereas for older cohorts described in the literature the splenectomy rate was 50% to 60% or higher (Rodeghiero and Ruggeri, 2007). Post-splenectomy, patients are left with a lifelong risk of bacterial sepsis that is not totally prevented by vaccinations (Cines and Bussel, 2005). Some data suggest that patients who have had a splenectomy may be at increased risk for developing pulmonary hypertension (Hoepfer et al, 1999).

Approximately 30% to 40% of adults who undergo splenectomy either fail to respond or relapse at a later date (Cines and Blanchette, 2002). For these patients, corticosteroids and IVIG are the only approved therapy (Deltasone[®] [prednisone] prescribing information 1995; Decadron[®] [dexamethasone] prescribing information 2004; Gamunex [immune globulin intravenous (human)] prescribing information, 2005).

With the option of splenectomy now behind them, these patients are often faced with prolonged exposure to corticosteroids, and the consequent increased risk of side effects. The following drugs have frequent off-label use in this setting: rituximab (discussed below), cyclophosphamide, azathioprine, vinca alkaloids, and danazol. However, responses to these treatments require life-long administration, and may be associated with significant risks.

Few publications are available on long-term outcomes after splenectomy failure in adults. The largest prospective study is the report by McMillan and Durette (2004) of 105 adults with chronic ITP who required additional therapy after failing splenectomy. The mean follow-up after splenectomy for this group was 142.9 months (median of 110 months). During the time following relapse all subjects required multiple third line treatments, commonly including corticosteroids, danazol, azathioprine, cyclophosphamide, high-dose cyclophosphamide, and combination chemotherapy.

While 75 (71.4%) patients attained at least a partial stable remission following additional therapy (platelets at least $30 \times 10^9/L$ for more than 2 months), these occurred slowly (mean of 68.1 months to remission; median 46 months). For 51 (48.6%) patients, remission persisted after therapy was discontinued, whereas 24 (22.9%) patients required continued treatment. For the 24 patients on continued ITP therapy, remission lasted for a mean of 50.7 months (median 48 months; range 2 to 167 months).

However, a subgroup of patients received no benefit from additional therapy. Thirty (28.6%) patients were unresponsive to all treatments they received. In this group, 1 patient developed uncontrolled bleeding after splenectomy and died despite high-dose corticosteroid therapy and platelet transfusions. Three patients who received corticosteroid therapy after splenectomy without benefit refused additional treatment. The remaining 26 patients received an average of 6.1 (median, 5; range, 3 to 10) ITP treatments without significant benefit. Of the patients studied, 16% died from the disease or treatments of ITP. Eleven patients died of bleeding, and the remaining patients experienced significant morbidity from ITP and its treatment.

Although no controlled studies have been published in this indication, rituximab is used frequently as a first-line therapy for splenectomy failures (Cines and Bussel, 2005; Cooper et al, 2004). Rigorous data supporting its use in this indication have not been generated. A review of the literature identified 19 studies (313 patients) in patients with ITP with data suitable for an analysis of efficacy, and 29 studies (306 patients) with data suitable for safety analysis (Arnold, 2007). There were no controlled studies, and no studies met all the author's criteria for study quality. Approximately half of the subjects in this analysis had had a splenectomy. In this review, treatment with rituximab was associated with a platelet count response (defined in various ways) in approximately 60% of patients with chronic ITP; responses lasted from 2 to 48 months.

In one study, 57 subjects with chronic ITP (31 splenectomized) and who had received 2 or more previous ITP treatments were treated with rituximab (Cooper et al, 2004). The overall response rate (platelets $> 50 \times 10^9/L$) was 54%, with 18 subjects achieving complete responses and 13 subjects partial responses. A retrospective study including 89 refractory ITP subjects, 49 of whom were splenectomized, demonstrated an overall response rate (platelets $> 50 \times 10^9/L$) of 55% with a median follow-up of 9 months (2 to 42 months) (Penalver et al, 2006); 41 subjects (46%) had complete responses (platelets $> 100 \times 10^9/L$) and 8 subjects (9%) achieved a partial response (platelets between 50 and $100 \times 10^9/L$).

Although a profound depletion of all peripheral blood B cell populations can be achieved by rituximab, many ITP patients do not respond and/or relapse. For example, in the Cooper study described above, 11 of the 13 subjects with partial responses relapsed at a median of 10 weeks (Cooper et al, 2004). Similarly, in the Penalver study, 37 of 49 responding subjects relapsed after 1 year (Penalver et al, 2006).

Rituximab carries a black box warning regarding infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy. In addition, hepatitis B virus reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients with hematologic malignancies treated with rituximab (Rituxan package insert, 2008).

2.5 Conclusions

Chronic ITP is a serious condition due to risks such as intracranial bleeding and other significant bleeding. Corticosteroids and immunoglobulins (IVIg and anti-D) are the only approved medical treatments for use in patients with ITP. The benefits and risks of these treatments, splenectomy, and various unapproved therapies for ITP are outlined in Table 1 (approved for use in patients with ITP) and Table 2 (not approved for use in patients with ITP).

An unmet medical need exists for all patients with chronic ITP for an effective, tolerable and safe long-term therapy to maintain platelet counts $> 50 \times 10^9/L$, regardless of splenectomy status, in light of the modest efficacy of available therapies when employed chronically, and the clinically significant adverse effects associated with their use.

Table 1. Benefits and Risks of Current Treatments – Approved for Use in ITP

Treatment/Source	Response Rate	Response Definition/Detail	Adverse Effects
Corticosteroids <i>Literature review</i> ^a	50% to 90% 10% to 30%	short-term response long-term response	Increased risk for infection, psychosis, hyperglycemia, hypertension, myopathy, weight gain, and sodium and fluid retention. ^{d,o} Bone loss is a concern after several months of use; daily doses as low as >2.5 to 5 mg have been associated with adverse skeletal effects. ^{e,f}
Corticosteroids <i>Retrospective cohort of 201 adults from a single center</i> ^b	52%	61/118 (52%) achieved platelet count $\geq 150 \times 10^9/L$ after corticosteroids as initial therapy (given for mean 2 ± 0.7 months then slow tapering); mean duration of remission 5.2 ± 1.3 months.	
Corticosteroids <i>Prospective study of 114 adults who failed splenectomy</i> ^c	19%	20/105 (19%) refractory patients achieved platelet count $\geq 30 \times 10^9/L$ for ≥ 2 months.	
Splenectomy <i>Retrospective cohort of 201 adults from a single center</i> ^b	87%	Of 55 patients who underwent splenectomy, 87% had initial response, 60% stable response.	Mortality was 1.0% (48/4955) with laparotomy and 0.2% (3/1301) with laparoscopy. Complication rates were 12.9% (318/2465) with laparotomy and 9.6% (88/921) with laparoscopic splenectomy ^g .
Splenectomy <i>Literature review</i> ^a	66%	Complete response in 1731/2623 (66%) adults with follow-up for 1 to 153 months.	
Splenectomy* <i>Clinical practice guidelines</i> ^d	67%	Approximately 67% of patients achieve and sustain a normal platelet count with no additional therapy.	Complications were twice as frequent among patients older than 65 years ⁱ . Small risk of fatal bacterial infection ^d . Long-term risk of overwhelming sepsis syndrome ^a .
Splenectomy <i>Literature review</i> ^h	60 - 70%	Approximately 30%-40% of adults either fail to respond or relapse.	

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^a Cines and Bussel, 2005; ^b Zimmer, et al, 2004; ^c McMillan and Durette, 2004; ^d George et al, 1996; ^e Reid 1997; ^f van Staa, 2006; ^g Kojouri et al, 2004; ^h Cines and Blanchette, 2002; ⁱ Portielje et al, 2001; ^j Godeau, et al, 2002; ^k Bussel et al, 1988; ^l Gamunex Prescribing Information; Telacris Biotherapeutics Inc, Research Triangle Park NC, November 2005; ^m George, et al, 2003; ⁿ Scaradavou et al, 1997; ^o Cines and McMillan, 2005; ^p WinRho® [Rho D immune globulin human] prescribing information 2006.

* As a surgical procedure, splenectomy is not “approved” but is considered part of standard of care.

Table 1. Benefits and Risks of Current Treatments – Approved for Use in ITP

Treatment/Source	Response Rate	Response Definition/Detail	Adverse Effects
IVIG <i>Prospective study of previously untreated adults with ITP^j</i>	63% 29%	Short-term: 56 patients received one 3-day treatment: day 21, platelets were >50x10 ⁹ /L in 35 (63%) and >150x 10 ⁹ /L in 21 (38%). Long-term: In 34 with no other treatment, platelets at month 12 were >50x 10 ⁹ /L in 10 (29%) and >150x 10 ⁹ /L in 9 (26%).	Postinfusion headache. Rarely, aseptic meningitis, acute renal failure, pulmonary insufficiency, thrombosis, or hemolysis ^a .
IVIG <i>Prospective study of adults with chronic ITP^k</i>	12.5%	5/40 (12.5%) patients reached >150x10 ⁹ /L with no other treatment for ≥3 months after 1-15 infusions; 11 (27.5%) others (6 splenectomized) maintained ≥20x10 ⁹ /L without any other ITP therapy	
IVIG <i>Double-blind, randomized clinical trial of Gamunex vs Gamune N^l</i>	90%	Of 97 adults and children with ITP, 90% increased platelet counts from ≤20 x 10 ⁹ /L to >50 x10 ⁹ /L within 7 days after treatment; 74% were sustained for 7 days.	

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^a Cines and Bussel, 2005; ^b Zimmer, et al, 2004; ^c McMillan and Durette, 2004; ^d George et al, 1996; ^e Reid 1997; ^f van Staa, 2006; ^g Kojouri et al, 2004; ^h Cines and Blanchette, 2002; ⁱ Portielje et al, 2001; ^j Godeau, et al, 2002; ^k Bussel et al, 1988; ^l Gamunex Prescribing Information; Telacris Biotherapeutics Inc, Research Triangle Park NC, November 2005; ^m George, et al, 2003; ⁿ Scaradavou et al, 1997; ^o Cines and McMillan, 2005;

^p WinRho[®] [Rho D immune globulin human] prescribing information 2006.

* As a surgical procedure, splenectomy is not “approved” but is considered part of standard of care.

Table 1. Benefits and Risks of Current Treatments – Approved for Use in ITP

Treatment/Source	Response Rate	Response Definition/Detail	Adverse Effects
Anti-D immunoglobulin <i>Prospective study of newly-diagnosed adults with ITPⁿ</i>	49%	16/33 (49%) achieved remission (normal platelet count without treatment for >3 months without subsequent relapse) with intermittent anti-D.	Headaches, chills, fevers, asthenia, pallor, diarrhea, nausea, vomiting, arthralgia, myalgia, dizziness, hyperkinesia, abdominal or back pain, hypotension, hypertension, increased LDH, somnolence, vasodilation, pruritus, rash, and sweating. Cases of intravascular hemolysis, clinically compromising anemia, acute renal insufficiency and disseminated intravascular coagulation have occurred ^p .
Anti-D immunoglobulin <i>Prospective study of non-splenectomized children and adults with ITP and HIV-ITPⁱ</i>	72%	189/261 (72%) had platelet increase $\geq 20 \times 10^9/L$ ("responders"), and 119 (46%) had increases $> 50 \times 10^9/L$; effect lasted >21 days in 50% of responders.	
Anti-D immunoglobulin <i>Prospective single-arm, open-label trial of non-splenectomized adults with chronic ITP^p</i>	88%	21 of 24 had an increase $\geq 20 \times 10^9/L$ during the first 2 courses of therapy	

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^a Cines and Bussel, 2005; ^b Zimmer, et al, 2004; ^c McMillan and Durette, 2004; ^d George et al, 1996; ^e Reid 1997; ^f van Staa, 2006; ^g Kojouri et al, 2004; ^h Cines and Blanchette, 2002; ⁱ Portielje et al, 2001; ^j Godeau, et al, 2002; ^k Bussel et al, 1988; ^l Gamunex Prescribing Information; Telacris Biotherapeutics Inc, Research Triangle Park NC, November 2005; ^m George, et al, 2003; ⁿ Scaradavou et al, 1997; ^o Cines and McMillan, 2005; ^p WinRho® [Rho D immune globulin human] prescribing information 2006.

* As a surgical procedure, splenectomy is not "approved" but is considered part of standard of care.

Table 2. Benefits and Risks of Current Treatments – Not Approved for Use in ITP

Treatment/Source	Response Rate	Response Definition/Detail	Adverse Effects
Rituximab <i>Retrospective study including 89 multitrated refractory ITP subjects, 49 splenectomized^f</i>	55%	Platelets greater than $50 \times 10^9/L$; median follow-up of 9 months (2 to 42 months). 41 subjects (46%) had CR (platelets $>100 \times 10^9/L$) and 8 (9%) had PR (platelets $50 - 100 \times 10^9/L$).	Infusion reaction: fever, chills, headache, bronchospasm, severe B cell reduction, and potential for infection ⁱ .
Rituximab <i>Literature review^b</i>	60%	Approximately 60% of patients with ITP respond (platelets $\geq 50 \times 10^9/L$); responses last from 2 to 48 months.	
Rituximab <i>Literature review^c</i>	56%	23/41 (56%) achieved platelets $\geq 150 \times 10^9/L$ for ≥ 3 months with no other treatment.	
Rituximab <i>Prospective study of adults with chronic ITP^d</i>	20%	5/25 (20%) achieved platelets $>100 \times 10^9/L$.	
Azathioprine <i>Literature review^e</i>	20%	Approximately 20% responses.	Cytopenias, gastrointestinal symptoms, secondary malignancies ⁱ .
Azathioprine <i>Literature review^c</i>	29%	32/109 (29%) adults with ITP non-responsive to splenectomy achieved normal platelet count or $\geq 150 \times 10^9/L$ for ≥ 3 months with no other treatment.	
Danazol <i>Literature review^c</i>	1%	1/90 patients achieved platelets $\geq 150 \times 10^9/L$ for ≥ 3 months with no other treatment.	Hepatotoxicity, rash, and masculinization ⁱ .
Danazol <i>Prospective study of adults with refractory ITP or contraindications to splenectomy or corticosteroids^f</i>	67%	38/57 (67%) achieved response (platelets $\geq 50 \times 10^9/L$ for ≥ 2 months) with daily dosing; of these, 27 (46%) were in response at a median (SD) of 119 (45) months.	
Danazol <i>Prospective study of adults with ITP^g</i>	47%	7/15 (47%) receiving 50 mg daily for ≥ 6 months had platelets $>50 \times 10^9/L$ for ≥ 2 months (3 of whom had counts $>100 \times 10^9/L$ for ≥ 2 months).	
Danazol <i>Prospective study of adults who failed splenectomy^h</i>	34%	19/56 (34%) achieved platelets $\geq 30 \times 10^9/L$ for ≥ 2 months.	

^a Penalver et al, 2006; ^b Arnold, 2007; ^c Vesely, 2004; ^d Stasi, et al, 2001; ^e George, 2006; ^f Maloisel, et al, 2004; ^g Mylvaganam et al, 1989; ^h McMillan and Durette, 2004; ⁱ Cines and McMillan, 2005; ^j Cines and Blanchette, 2002.

3. BACKGROUND

3.1 Key Points

- The underlying pathogenesis of ITP is peripheral destruction of platelets due to antibodies directed against platelet antigens (eg, GPIIb/IIIa and/or GPIb/IX). Evidence suggests that impaired thrombopoiesis, in addition to platelet destruction, contributes to thrombocytopenia in ITP (Ballem et al, 1987; Houwerzijl et al, 2004; McMillan et al, 2004).
- Romiplostim was designed to bind to the TPO receptor and specifically stimulate platelet production, a novel mode of therapy compared with existing treatments for ITP, which focus on non-specific immunosuppression to reduce antibody production.
- Amgen's experience with the development of thrombopoiesis-stimulating agents, and knowledge of the risks associated with the development of TPO-specific neutralizing antibodies, stimulated our development of a novel TPO receptor agonist that is structurally unrelated to TPO itself. Indeed, romiplostim has no amino acid sequence homology to endogenous TPO (eTPO), greatly reducing the probability that antibodies to romiplostim, if produced, will bind to eTPO and cause thrombocytopenia.
- In phase 1 and 2 clinical studies, dose-dependent increases in platelet counts were observed in healthy subjects and subjects with ITP. The results supported the use of 1.0 µg/kg as the starting dose for weekly administration of romiplostim.

3.2 Product Description

Romiplostim (AMG 531) is an Fc fusion protein comprised of human immunoglobulin IgG1 Fc domains, with each single-chain subunit covalently linked at the C-terminus to a peptide chain containing 2 thrombopoietin (TPO) receptor-binding domains.

Romiplostim is produced by recombinant DNA technology in *Escherichia coli* and is purified as a dimer consisting of 2 Fc-peptide-peptide subunits. This type of engineered recombinant product is referred to as a "peptibody". The Mpl binding (peptide) domain and Fc carrier domain confer the biological activity and control persistence of the drug in the body, respectively. The molecular weight is 59 kilodaltons.

A peptibody is a novel platform, the culmination of research efforts to design a thrombopoiesis-stimulating agent with both specificity and minimal risk for the development of neutralizing anti-drug antibodies (see Section 3.3). Romiplostim has no amino acid sequence homology to endogenous thrombopoietin (eTPO); thus, anti-drug antibodies would not be expected to cross-react with eTPO. Anti-drug antibodies that developed in animal studies did not cross-react with eTPO, and thrombocytopenia was not observed in antibody-positive animals.

Romiplostim is proposed to be indicated for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP):

- who are non-splenectomized and have had an insufficient response or are intolerant to corticosteroids and/or immunoglobulins.
- who are splenectomized and have had an insufficient response to splenectomy.

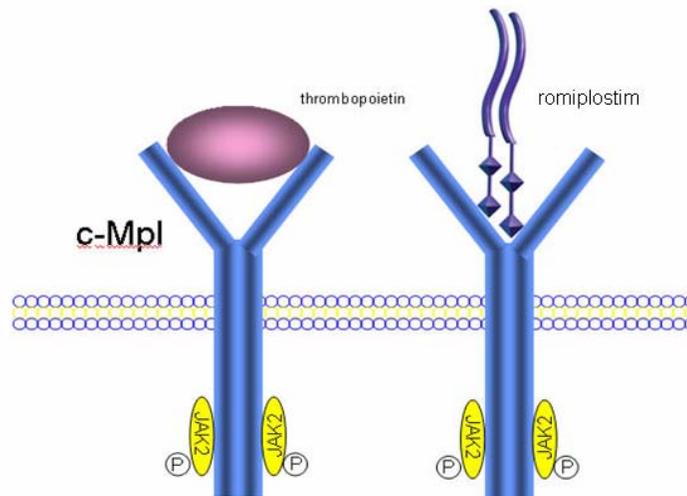
3.3 Rationale for Development of Romiplostim and Mechanism of Action

Since the cloning of the c-Mpl (TPO receptor) and its ligands in the early 1990s, a number of c-Mpl ligands have been developed in the interest of increasing platelet production in patients with bone marrow failure. The earliest clinical candidates, rHuTPO (Genentech) and pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF; Amgen) were potent stimulators of thrombopoiesis and enhanced platelet recovery when given after chemotherapy in clinical trials (Basser, 2002; Kuter, 2004). Although antibodies to TPO were observed in the initial study of rHuTPO, they were nonneutralizing and transient (Vadhan-Raj, 1997). In the case of PEG-rHuMGDF, thrombocytopenia developed in a number of healthy volunteers and cancer patients who received multiple doses of PEG-rHuMGDF in clinical trials, and it was determined that antibodies were being generated against PEG-rHuMGDF that cross-reacted with and neutralized eTPO, with adverse clinical consequences (Li et al, 2001; Crawford et al, 1998; Basser et al, 2002).

Efforts to develop c-Mpl receptor ligands thus turned toward TPO peptide and nonpeptide (small molecule) mimetics, which activate the receptor but have no amino acid sequence homology to eTPO. Romiplostim is the first TPO mimetic peptide that has no amino acid sequence homology to eTPO. Romiplostim's 2 TPO receptor-binding

domains directly stimulate platelet production through activation of the thrombopoietin receptor, c-Mpl (Figure 1).

Figure 1. Proposed Mechanism of Action of Romiplostim



Romiplostim mimics the action of endogenous thrombopoietin by interacting with the c-Mpl dimer and triggering intracellular signals.

Because of the potential clinical impact of generation of neutralizing antibodies against romiplostim and/or eTPO, a sophisticated immunogenicity assessment program was initiated to support the development of romiplostim. This is described in the discussion of immunogenicity, Section 5.9.5.

3.3.1 Biology of Thrombopoiesis and the TPO receptor

Signaling through c-Mpl stimulates all processes leading to platelet production with the exception of pro-platelet formation and platelet shedding, which is inhibited by c-Mpl ligands (Debili et al, 1995; Nichol et al, 1995; Kaushansky et al, 1994; Kuter et al, 1994). The natural ligand for c-Mpl is eTPO (Kato et al, 1995; Bartley et al, 1994; de Sauvage et al, 1994; Lok et al, 1994, Kuter et al, 1994), which is produced in the liver, with lesser amounts coming from the spleen, kidneys, and bone marrow (Chang et al, 1995; Shimada et al, 1995; de Sauvage et al, 1994; Lok et al, 1994).

Hepatic production of eTPO is thought to be a constitutive process as there is no evidence of transcriptional regulation of eTPO production in the liver or kidney of rats or mice (de Sauvage et al, 1996; Fielder et al, 1996; Chang et al, 1995; Shimada et al, 1995; Kuter et al, 1994; Kaushansky 2006).

Plasma concentrations of eTPO are thought to be modulated through receptor-mediated clearance by platelets and megakaryocytes. This mechanism is supported by the observation of an inverse relationship between platelet production rate and the amount of circulating eTPO (Chang et al, 1996; Fielder et al, 1996; Kuter, 1996; Kuter and Rosenberg, 1995; Nichol et al, 1995). This inverse relationship is best demonstrated in cases of chemotherapy-induced thrombocytopenia (Heits et al, 1997; Shimazaki et al, 1997; Hamaguchi et al, 1996; Bernstein et al, 1995; Nichol et al, 1995). However, lower-than-expected concentrations of eTPO have been reported in serum samples collected from other thrombocytopenic conditions, such as preterm infants with thrombocytopenia (Watts et al, 1999), thrombocytopenic patients with ITP (Sungaran et al, 1997; Chang et al, 1996), patients with human immunodeficiency virus (HIV)-associated ITP (Harker et al, 1998), patients with myelodysplastic syndrome (MDS) (Hellström-Lindberg et al, 1999), and patients with severe liver disease (Martin et al, 1997; Peck-Radosavljevic et al, 1997; Shimodaira et al, 1996; Usuki et al, 1996). These conditions may represent states of functional eTPO deficiency or, in the case of severe liver disease, primary eTPO deficiency. Although primary or functional eTPO deficiency is probably not the sole cause of thrombocytopenia in these settings, administration of exogenous factors that stimulate platelet production has been shown to augment platelet counts in some of these patients.

3.3.2 Pathobiology of ITP

ITP is an autoimmune disorder in which thrombocytopenia results when platelets are destroyed more rapidly than they can be produced. Auto-antibodies produced by patients with ITP have been shown to bind to megakaryocytes and platelet antigens such as GPIIb/IIIa, GPIb/IX, and GPIa/IIa, suggesting that these patients may have impaired megakaryopoiesis (McMillan et al, 2004; Houwerzijl et al, 2004). This hypothesis is further supported by observations made in autologous-platelet-survival studies using ¹¹¹indium-labeled platelets, which showed decreased or normal platelet production in approximately two-thirds of patients with ITP. This result is paradoxical in that low circulating platelet counts would ordinarily be expected to increase platelet

production (Ballem et al, 1987; Heyns et al, 1986; Stoll et al, 1985; Heyns et al, 1982). eTPO levels in plasma and serum from patients with ITP overlap with the normal range, an exception to the general association of high serum TPO with low platelet count observed in other thrombocytopenic disease states (Emmons et al, 1996; Chang et al, 1996; Nichol 1997).

Currently available treatments for ITP target modulation of the immune system, the objective being to reduce destruction of platelets. The mechanisms of action of these agents are not completely understood. The mechanism of action of corticosteroids in ITP is believed primarily to be decreased destruction of antibody-coated platelets (as well as reduced antibody production) by the spleen and bone marrow; increased marrow platelet production may play a role in some patients (Levine, 2004). Anti-D immunoglobulin is thought to act through formation of anti-Rho(D) (anti-D)-coated RBC complexes, resulting in Fc receptor blockade, thus sparing antibody-coated platelets (WinRho package insert).

A variety of explanations for IVIG's mechanism of action have been proposed including Fc receptor blockade, attenuation of complement-mediated tissue damage, neutralization of autoantibodies by antibodies to idiotype, neutralization of superantigens, modulation of cytokine production, and down-regulation of B-cell responses (Gamunex prescribing information, Ballow, 1997; Debre et al, 1993; Soubrane et al, 1993; Clarkson et al, 1986). In addition to these proposals, Ravetch and coworkers demonstrated that IVIG mediates its protective effect by its ability to induce the expression of the inhibitory Fc γ RIIB receptor on effector cells (Samuelsson et al, 2001). These results are consistent with the findings of Lazarus and coworkers that IVIG drives signaling through activating Fc γ R on dendritic cells (Siragam et al, 2006).

In contrast, romiplostim exerts its therapeutic benefit by directly stimulating platelet production through activation of the TPO receptor, c-Mpl (Figure 1).

3.4 Clinical Pharmacology

In healthy subjects, the pharmacokinetics of romiplostim was nonlinear after a single IV dose of romiplostim from 0.3 to 10.0 μ g/kg. After a single 2- μ g/kg SC dose, peak serum concentrations were observed between 24 and 36 hours postdose in healthy subjects (Study 20000109).

In the long-term extension study 20030213 (ITP subjects), the pharmacokinetics of romiplostim over the dose range of 3 to 15 µg/kg indicated that peak serum concentrations were observed at about 7 to 50 hours postdose (median, 14 hours) with half-life values ranging from 1 to 34 days (median, 3.5 days). The serum concentrations varied among subjects and did not correlate with the dose administered. The elimination of serum romiplostim is in part dependent on TPO receptors on platelets. As a result, for a given dose, subjects with high platelet counts will tend to achieve lower romiplostim serum concentrations, and vice versa. In another ITP clinical study, no accumulation in serum was observed after 6 weekly doses of romiplostim (3 µg/kg).

3.5 Dosage Regimen

Starting Dose/schedule:

Study 20000109 was the first study of romiplostim in humans (healthy subjects). Dosing was initiated at an IV dose of 10.0 µg/kg based on preclinical primate data. However, romiplostim was considerably more potent in humans than had been predicted from the preclinical studies (ie, all 4 subjects receiving IV romiplostim at 10.0 µg/kg had a 4- to 7-fold peak increase in circulating platelet counts compared with their baseline values). As a result, the doses were reduced. Dosing recommenced using SC dosing at 0.1 µg/kg, and escalated to 0.3, 1.0 and 2.0 µg/kg. The 1.0-µg/kg dose was considered the minimally active dose, defined as the dose at which 2 subjects had a 1.5-fold increase over baseline for 2 consecutive platelet counts.

Also in this study, IV and SC routes were compared and found to yield similar platelet responses. The temporal response was similar to that seen with other thrombopoietic agents (Harker et al, 2000, Vadhan-Raj, 1997).

In subjects with ITP, romiplostim was well tolerated when given as 2 doses 2 to 3 weeks apart (depending on platelet count) at doses of 0.2 to 10.0 µg/kg SC (Study 20000137 Part A). Target platelet counts (doubled from baseline and $\geq 50 \times 10^9/L$ and $\leq 450 \times 10^9/L$) were achieved in some subjects in the 3.0-, 6.0-, and 10.0-µg/kg cohorts; no subjects in the 0.2-, 0.5-, or 1.0-µg/kg cohorts achieved the target response. A dose-dependent trend was observed in the proportion of subjects with target platelet counts after the first dose. A similar trend after the second dose was difficult to evaluate; 3 subjects (1 in the 6-µg/kg cohort and 2 in the 10-µg/kg cohort) did not receive their second romiplostim dose because their platelet count exceeded the target platelet range

after the first dose. Platelet responses were highly variable, suggesting that individual dose adjustment is warranted to produce adequate platelet responses.

Study 20010218, also in subjects with ITP, was done concurrently with Study 20000137 Part A, using unit dosing. When converted to weight-based dosing Study 20010218 confirmed the findings (minimally active dose, starting dose) of Study 20000137 Part A.

For the majority of subjects platelets had fallen to below $50 \times 10^9/L$ 2 weeks after the first dose, suggesting that weekly dosing is required to achieve and maintain platelet counts in the desired therapeutic range.

In the blinded, placebo-controlled, dose-finding and safety study 20000137 Part B, mean weekly platelet counts increased in a dose-dependent manner after administration of romiplostim, although the data were highly variable. However, the proportion of subjects with platelet counts above $50 \times 10^9/L$ did not show a clear dose association (7/8 [88%], 5/8 [63%], and 1/1 [100%] in 1.0, 3.0, and 6.0 $\mu g/kg$ dose cohorts, respectively), suggesting high intersubject variability in the response to the romiplostim treatment. Some subjects in the 3.0 and 6.0 $\mu g/kg$ dose cohorts had platelet counts above $450 \times 10^9/L$. These results supported the use of 1.0 $\mu g/kg$ as the starting dose for weekly administration of romiplostim in later studies in subjects with ITP, with the inclusion of individual dose-adjustments based on platelet count.

Maximum Dose of Romiplostim:

The pivotal studies included a maximum dose of 15 $\mu g/kg$. In the open-label extension Study 20030213, the maximum dose was 30 $\mu g/kg$ and was reduced first to 15 $\mu g/kg$ and then to 10 $\mu g/kg$ when it became apparent that little additional clinical benefit was achieved at doses above this level, and thus the excess exposure for subjects was unnecessary. Based on results from Study 20030213, the maximum dose in all other studies was reduced to 10 $\mu g/kg$.

Dose Adjustment:

In the pivotal studies, platelet count response was defined as $\geq 50 \times 10^9/L$. To maintain subjects within the desired platelet count range, dosage adjustments during the treatment period in the pivotal studies were made according to predefined dose adjustment rules. Experience from the pivotal trials and other romiplostim clinical studies are reflected in the dosing adjustments recommended in the draft label.

3.6 Conclusions

Building on the experience and challenges of PEG-rHuMGDF, one of the earliest thrombopoiesis-stimulating agents, Amgen designed the first TPO mimetic peptide. Romiplostim was developed to mimic the action of eTPO by interacting with the c-Mpl dimer, stimulating platelet production. Romiplostim, however, lacks amino acid sequence homology to TPO, greatly reducing the probability that antibodies to romiplostim, if produced, will bind to eTPO and cause thrombocytopenia.

Amgen, in collaboration with FDA, has conducted clinical development of romiplostim for patients with ITP, an autoimmune disease in which increased platelet consumption and impaired thrombopoiesis diminish platelet count, causing life-threatening thrombocytopenia. The results of the romiplostim clinical studies demonstrate that romiplostim is able to increase megakaryopoiesis and thrombopoiesis in patients with chronic ITP. The dose adjustment of romiplostim provided a sufficient means for these patients to achieve and maintain a satisfactory platelet count to avoid the adverse outcomes of their disease.

4. EFFICACY

4.1 Key Points

- Throughout the development program of romiplostim, Amgen has worked with the FDA and sought guidance and input into pivotal study design, endpoints and an acceptable efficacy and safety database of subject numbers and duration of treatment for this chronic orphan disease indication.
- Romiplostim's efficacy was demonstrated in 2 well-designed, placebo-controlled, multicenter phase 3 studies developed under the FDA's Special Protocol Assessment (SPA) process. The primary efficacy endpoint was the rigorously defined measure of durable platelet response, developed to capture a stable response maintained in the absence of any other ITP medication.
- One study enrolled subjects who had not undergone splenectomy (20030212; 21 placebo, 41 romiplostim) and the other enrolled splenectomized subjects (20030105; 21 placebo, 42 romiplostim). Both study populations had inadequate platelet responses to existing ITP treatments, and the combined median platelet count was below $20 \times 10^9/L$ at study entry.
- In the 2 pivotal studies (20030105 and 20030212) combined, the primary endpoint, durable platelet response, was achieved by approximately half of all subjects who received romiplostim (41 of 83 subjects; 49.4%), compared with one of 42 subjects who received placebo (2.4%) ($p < 0.0001$). Results were significant for each study individually as well.
- Romiplostim was statistically significantly superior to placebo for all key secondary efficacy endpoints in the combined population as well as for each individual study.
- Rescue medication (mostly corticosteroids and IVIG) was required by 59.5% of subjects in the placebo group and 21.7% of subjects in the romiplostim group ($p < 0.0001$) during the treatment period (combined pivotal study population). Of 16 placebo and 23 romiplostim subjects who entered the study receiving concurrent ITP medications, 6 placebo (37.5%) and 20 romiplostim (87.0%) subjects had either reduced by $> 25\%$ or entirely discontinued those medications at study week 25.

- The ability of romiplostim to maintain platelet counts over a longer period of time was shown for subjects who completed the pivotal studies and continued into the open-label extension Study 20030213. Total exposure for subjects receiving romiplostim was up to 24 weeks in a pivotal study and up to 60 additional weeks in Study 20030213.
- Subjects originally randomized to the placebo arms of the pivotal trials showed improvements in all measures of efficacy when they received romiplostim on the extension Study 20030213, relative to their performance during their phase 3 parent study.
- Bleeding events were not captured as a prospectively-defined efficacy endpoint, but were collected as adverse events. In the combined pivotal studies, bleeding events that were \geq grade 2 (moderate) in severity occurred at a higher subject incidence among placebo subjects (14; 34%) than subjects receiving romiplostim (13; 16%), and post-hoc statistical comparison showed this difference to be significant ($p = 0.017$). Clinically significant bleeding events (\geq grade 3) also occurred in more placebo subjects (5; 12%) than romiplostim subjects (6; 7%).
- Across the entire ITP clinical program, an inverse relationship between bleeding events and platelet counts was observed. All clinically significant (\geq grade 3) bleeding events occurred at platelet counts $< 20 \times 10^9/L$. All moderate (\geq grade 2) bleeding events occurred at platelet counts $< 50 \times 10^9/L$.

4.2 Regulatory Interactions

Throughout the global development of romiplostim, Amgen has worked with FDA and sought guidance. The 2 pivotal studies were designed and reviewed with input from regulatory authorities through the Special Protocol Assessment (SPA).

Specific input and guidance obtained from FDA addressed:

- the acceptability of a global development program including 2 separate placebo-controlled pivotal studies in an agreed-upon number of patients with chronic ITP

- the acceptability of clinical endpoints based on platelet count measurements, which are accepted by clinically recognized treatment guidelines
- efficacy and safety databases with adequate size and treatment duration, recognizing the need for chronic therapy in this orphan disease population.

4.3 Pivotal Study Design and Methodology

The 2 studies that form the basis of the marketing application, Studies 20030105 and 20030212, were reviewed by FDA under its SPA process. These pivotal efficacy studies were placebo-controlled, randomized, double-blind, phase 3 studies in subjects with chronic ITP.

The 2 pivotal studies had a similar design but enrolled subjects (1) who were refractory to splenectomy (Study 20030105), or (2) who had not undergone splenectomy (Study 20030212). Subjects had a diagnosis of ITP according to American Society of Hematology (ASH) guidelines (George et al, 1996) and consistent with the British guidelines (Provan et al, 2003). Subjects > 60 years of age had to have a documented history of chronic ITP with bone marrow confirmation. For study entry, platelet count (mean of 3 counts taken during the screening and pre-treatment periods) was required to be $\leq 30 \times 10^9/L$, (the trigger for treatment according to the ITP guidelines [George et al, 1996; Provan et al, 2003]) with no individual count $> 35 \times 10^9/L$.

Subjects receiving ITP medications were allowed on study if these medications (corticosteroids, azathioprine, and/or danazol) were maintained at a constant dose and schedule for 4 weeks before screening. In addition, throughout the 24-week treatment period rescue medication was permitted for major bleeding or wet purpura, or if the investigator felt the subject was at immediate risk (those commonly used in the 2 pivotal studies were corticosteroids, IVIG, platelet transfusions, and anti-D immunoglobulin).

Because ITP is a chronic disease, it is expected that subjects will receive romiplostim for as long as medical treatments are required. This would likely be the case for any thrombopoietic stimulating agents. To obtain information on the long-term effects of romiplostim administration, the clinical program includes a long-term, open-label extension study, Study 20030213, in which subjects who completed a prior 24-week romiplostim treatment study and whose platelet count subsequently fell below $50 \times 10^9/L$, establishing the need for continued treatment, could receive open-label romiplostim.

Platelet boundaries in which a constant dose should be maintained were established as $50 \times 10^9/L$ to $200 \times 10^9/L$, within which range patients are generally not at increased risk for bleeding or thrombosis. The 2 pivotal studies used a starting dose of $1 \mu\text{g}/\text{kg}$, with individual dose adjustment based on platelet counts, to a maximum permitted dose of $15 \mu\text{g}/\text{kg}$, a dose/schedule based on the results of 3 previous dose-finding studies (see Section 3.5). The recommended maximum dose of romiplostim in the post-marketing setting is $10 \mu\text{g}/\text{kg}$. Dosing begins at $1 \mu\text{g}/\text{kg}$ with weekly $1\text{-}\mu\text{g}/\text{kg}$ increases. The goal of therapy is to avoid bleeding by maintaining a platelet count $\geq 50 \times 10^9/L$, withholding romiplostim dosing and assessing platelet counts weekly if platelet counts reach $\geq 400 \times 10^9/L$.

Platelet counts were monitored weekly throughout the 24-week treatment period in the pivotal studies. In the ongoing extension study, platelet counts are monitored weekly, but subjects who achieve a stable dose of romiplostim for at least 3 weeks are allowed to self-inject romiplostim, and are required to return to the site for study visits at week 4, 8, 12, 16, and every 4 weeks until the completion of the study. In the post-marketing setting, the proposed platelet monitoring approach will reflect how platelet counts were monitored in the pivotal studies and the extension study: weekly monitoring until a stable platelet count (greater than or equal to $50 \times 10^9/L$ for at least 4 weeks without dose adjustment) has been achieved, and then monthly monitoring.

Patient reported outcome (PRO) data were collected in both pivotal studies as well as Study 20030213. Each of these studies included assessments of subjects using the SF-36 questionnaire as well as the ITP-Patient Assessment Questionnaire (ITP-PAQ), an instrument that was developed and validated for adult patients with ITP in these studies (Mathias et al, 2007). The ITP-PAQ is an ITP-specific instrument, consisting of 44 items that form 10 scales. The SF-36 is a generic instrument. Ten scales from ITP-PAQ and 8 scales and 2 summary scales from SF-36 constituted PRO endpoints. PRO was assessed in the pivotal studies with the primary hypothesis testing a significant improvement from baseline to week 25 for all scales of the ITP PAQ and SF-36.

The primary efficacy analysis in the phase 3 studies was based on the full analysis set, consisting of all randomized subjects analyzed according to their randomized treatment group. The incidences of durable and overall platelet responses, proportion of subjects requiring rescue medication, and incidence of subjects achieving durable platelet response with stable dose were compared between the romiplostim and placebo groups

by using the Cochran Mantel-Haenszel test stratified by baseline concurrent ITP therapy (yes/no) and by study when data were combined. In an integrated analysis, data from the 2 pivotal phase 3 studies (20030105 and 20030212) were combined to estimate the treatment effect more precisely and to examine trends in subgroups of subjects. The 2 populations differed in their history of splenectomy, but were otherwise consistent in terms of disease population, dosing schedule of investigational product, and the evaluation period for efficacy.

4.4 Primary Endpoint

The management of ITP is dictated by platelet count and clinical symptoms, as defined in the ASH and British Guidelines (George et al, 1996; Provan et al, 2003). Treatment decisions are guided by platelet count measurements, which are objective and readily measurable. There have been few clinical trials in ITP, and historically, there has been no general agreement on a standard definition of response (Ruggeri et al, 2008).

In collaboration with the FDA, the primary endpoint for the pivotal studies was much more stringently defined to determine the efficacy of romiplostim in maintaining a stable and adequate platelet count once dosing had been optimized. The endpoint of durable platelet response (at least 6 weekly platelet responses [platelet counts $\geq 50 \times 10^9/L$] during the last 8 weeks of treatment, in the absence of rescue medication at any time during the 24-week treatment period) provides a measurement of effective treatment in a chronic setting (ie, maintenance of response).

Bleeding events were not a pre-specified endpoint in the pivotal studies, because bleeding events may be subjective in assessment and difficult to quantify, whereas platelet counts lend themselves to objective measurement. No validated scale exists for bleeding events in ITP. In clinical practice, the goal of ITP treatment is increasing platelet counts to avoid clinical sequelae related to thrombocytopenia such as bruising and bleeding (George et al, 1996; Provan et al, 2003). A platelet count of $\leq 30 \times 10^9/L$ is the recommended threshold for consideration of initiation of treatment recommended by both of these groups. Investigators who felt subjects were at risk of immediate bleeding would most likely administer rescue medication rather than wait to reach a bleeding endpoint. Rescue medications were permitted in both arms of the pivotal studies for major bleeding or wet purpura, or if the investigator felt the subject was at immediate risk, and the data from the pivotal study showed that the placebo subjects used more

rescue medications. Therefore, any assessment of romiplostim's effect with respect to bleeding events would be confounded by this intervention.

Data presented in the following sections are from the marketing application, except where indicated. A 120-day safety update will be submitted on 22 February 2008 and those data will be included at the 12 March 2008 ODAC meeting.

4.5 Study Population

Demographic characteristics were well balanced between the romiplostim and placebo groups within both pivotal studies, and were representative of a heterogeneous population of patients with chronic ITP. The 62 subjects in the non-splenectomized group (Study 20030212) were a median of 52.0 years old (range: 21 to 88 years) with a higher proportion of women (69.4%) than men (30.6%). For the 63 splenectomized subjects (Study 20030105), the median age was 52.0 years (range: 26 to 88 years) and again there were more women (60.3%) than men (39.7%).

Subjects in both pivotal studies varied considerably in the duration of their ITP at the time they entered the study. Non-splenectomized subjects had a median of 2.1 years since diagnosis (range 0.1, 31.6 years) and splenectomized subjects a median of 8.0 years (range 0.6, 44.8 years). Consistent with protocol requirements, all subjects had received at least one previous treatment for ITP. Most of the non-splenectomized subjects (53/62; 85%) had received from 1 to 4 previous treatments, but the splenectomized subjects were very extensively treated, with 51/63 (81%) having received from 5 to 10 previous treatments including splenectomy.

ITP treatment history is summarized in Table 3. Approximately 95% of subjects in both studies had received corticosteroids and 80% had received IVIG; 29% of non-splenectomized subjects and 71% of splenectomized subjects had received rituximab. Despite these treatments, platelet counts at study entry were still well below $30 \times 10^9/L$, indicating a seriously ill population in both studies: for non-splenectomized subjects, median platelet count at baseline was $19.3 \times 10^9/L$ (range 2 to $31 \times 10^9/L$), and for splenectomized subjects, median platelet count at baseline was $14.0 \times 10^9/L$ (range 2 to $29 \times 10^9/L$).

Table 3. ITP Treatment History (Phase 3 ITP Safety Set)

	Placebo (N = 41)	Romiplostim (N = 84)	Total (N = 125)
Number of Subjects with Prior ITP Treatment - n (%)			
Corticosteroids	38 (92.7)	80 (95.2)	118 (94.4)
Immunoglobins	37 (90.2)	71 (84.5)	108 (86.4)
Anti-D immunoglobulin (WinRho)	15 (36.6)	39 (46.4)	54 (43.2)
IVIG	34 (82.9)	66 (78.6)	100 (80.0)
Chemotherapy	12 (29.3)	21 (25.0)	33 (26.4)
Vincristine/vinblastine	10 (24.4)	17 (20.2)	27 (21.6)
Cyclophosphamide	6 (14.6)	12 (14.3)	18 (14.4)
Azathioprine	11 (26.8)	19 (22.6)	30 (24.0)
Danazol	21 (51.2)	27 (32.1)	48 (38.4)
Rituximab	20 (48.8)	43 (51.2)	63 (50.4)
Other	16 (39.0)	32 (38.1)	48 (38.4)
Number of Splenectomy Subjects - n (%)	21 (51.2)	42 (50.0)	63 (50.4)

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The phase 3 ITP safety set consists of all subjects who received investigational product in either phase 3 study, 20030105 or 20030212.

Percentages are based on number of subjects treated. If a subject received at least one dose of romiplostim, then the subject was counted in the romiplostim group; otherwise the subject was counted in the placebo group.

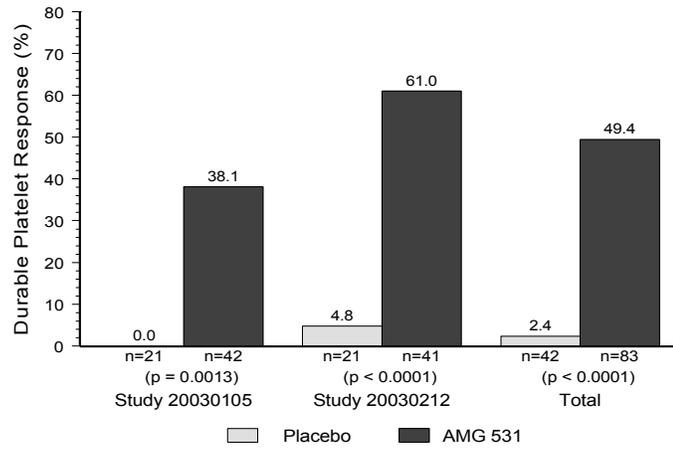
^aITP treatments include: corticosteroids, anti-D immunoglobulin, IVIG, vincristine/vinblastine, danazol, cyclophosphamide, azathioprine, rituximab, other, and splenectomy status (Yes).

4.6 Primary Endpoint – Durable Platelet Response

The subject incidence of durable platelet response was the primary endpoint in the pivotal studies and the integrated analysis of efficacy. This was defined as at least 6 weekly platelet responses during the last 8 weeks of treatment in the absence of rescue medication at any time during the treatment period. A weekly platelet response was defined as a platelet count of $\geq 50 \times 10^9/L$ on the weekly scheduled dose day from week 2 (first assessment of response) to week 25 (response assessment, last dose), in the absence of any rescue medication during the previous 8 weeks.

Results for the primary endpoint of durable platelet response are shown in Figure 2 and Table 4 for each pivotal study and for the integrated data. A statistically significant effect was seen for romiplostim relative to placebo whether or not subjects had undergone splenectomy. Among both pivotal studies only 1 placebo subject achieved a durable platelet response (this subject was receiving danazol 200 mg, 4 times a day throughout the study as concurrent ITP therapy, but no rescue medication).

Figure 2. Subject Incidence of Durable Platelet Response - Studies 20030105 and 20030212 Combined



Durable platelet response was defined as weekly platelet count $\geq 50 \times 10^9/L$ for 6 or more times during weeks 18-25 in the absence of rescue medication any time during the treatment period.
For individual studies, p-value is from Cochran-Mantel-Haenszel controlling for baseline concurrent ITP therapy;
For total, p-value is from Cochran-Mantel-Haenszel controlling for splenectomy status and baseline concurrent ITP therapy.

**Table 4. Subject Incidence of Durable Platelet Response
Baseline Concurrent ITP Therapy Status Based on Randomization Strata (Phase 3 Study Subjects)**

Incidence of Durable Platelet Response	Study 20030105		Study 20030212		Total	
	Placebo (N = 21)	Romiplostim (N = 42)	Placebo (N = 21)	Romiplostim (N = 41)	Placebo (N = 42)	Romiplostim (N = 83)
Overall						
Incidence rate	0/21 (0.0%)	16/42 (38.1%)	1/21 (4.8%)	25/41 (61.0%)	1/42 (2.4%)	41/83 (49.4%)
95% exact binomial CI	(0.0%, 16.1%)	(23.6%, 54.4%)	(0.1%, 23.8%)	(44.5%, 75.8%)	(0.1%, 12.6%)	(38.2%, 60.6%)
By Baseline Concurrent ITP Therapy						
Yes	0/7 (0.0%)	5/14 (35.7%)	1/8 (12.5%)	8/16 (50.0%)	1/15 (6.7%)	13/30 (43.3%)
No	0/14 (0.0%)	11/28 (39.3%)	0/13 (0.0%)	17/25 (68.0%)	0/27 (0.0%)	28/53 (52.8%)
Incidence rate of (Romiplostim - Placebo)	38.1%		56.2%		47.0%	
95% normal approximation CI	(23.4%, 52.8%)		(38.7%, 73.7%)		(35.3%, 58.7%)	
Mantel-Haenszel common odds ratio of (Romiplostim /Placebo)	-		24.447		40.447	
95% confidence interval	(-, -)		(3.336, 179.181)		(5.231, 312.753)	
Treatment group comparison p-value ^a	0.0013		< 0.0001		< 0.0001	

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Durable platelet response was defined as weekly platelet count $\geq 50 \times 10^9/L$ for 6 or more times during Weeks 18 - 25 in the absence of rescue medication any time during the treatment period.

^a For individual studies, p-value is from Cochran-Mantel-Haenszel controlling for baseline concurrent ITP therapy; For total, p-value is from Cochran-Mantel-Haenszel controlling for splenectomy status and baseline concurrent ITP therapy.

4.7 Additional Platelet Endpoints

Additional platelet endpoints evaluated in the pivotal studies are shown in Table 5. Additional platelet endpoints were chosen on the basis of clinical relevance. A platelet count of $\geq 50 \times 10^9/L$ is considered a protective level (Cines and Blanchette, 2002); a count of $30 \times 10^9/L$ is considered the trigger for treatment according to the ITP guidelines [George et al, 1996; Provan et al, 2003]. Since subjects in the pivotal studies entered with a platelet count of $30 \times 10^9/L$ or below, an increase of $\geq 20 \times 10^9/L$ would bring them to a level at which bleeding would usually be unlikely.

As described in Section 2.2, data suggest an increased risk for morbidity and mortality with increased duration spent at a platelet count $< 30 \times 10^9/L$; thus, measures of duration (eg, weeks with platelet response) were also incorporated into the platelet endpoints in the pivotal studies.

Romiplostim was statistically significantly superior to placebo for all key secondary efficacy endpoints in the combined population (20030105 and 20030212) as well as for each individual study.

Table 5. Additional Platelet Endpoints (Phase 3 Study Subjects)

	Study 20030212		Study 20030105		Total	
	Placebo	Romi- plostim	Placebo	Romi- plostim	Placebo	Romi- plostim
Endpoint	(N = 21)	(N = 41)	(N = 21)	(N = 42)	(N = 42)	(N = 83)
Subject Incidence of Overall Platelet Response^a	3 (14.3%)	36 (87.8%)	0 (0.0%)	33 (78.6%)	3 (7.1%)	69 (83.1%)
Treatment group comparison p-value ^b	< 0.0001		< 0.0001		< 0.0001	
Mean (SD) Number of Weeks with Platelet Response	1.3 (3.5)	15.2 (7.5)	0.2 (0.5)	12.3 (7.9)	0.8 (2.5)	13.8 (7.8)
Treatment group comparison p-value (analysis of variance ^c)	< 0.0001		< 0.0001		< 0.0001	
Subject Incidence of Durable Platelet Response with Stable Dose	0/21 (0.0%)	21/41 (51.2%)	0/21 (0.0%)	13/42 (31.0%)	0/42 (0.0%)	34/83 (41.0%)
Treatment group comparison p-value ^b	< 0.0001		0.0046		< 0.0001	
Subject Incidence of Platelet Count $\geq 20 \times 10^9/L$ Increase from Baseline	7/21 (33.3%)	38/41 (92.7%)	5/21 (23.8%)	37/42 (88.1%)	12/42 (28.6%)	75/83 (90.4%)
Treatment group comparison p-value ^b	< 0.0001		< 0.0001		< 0.0001	
Mean (SD) Number of Weeks with Platelet Counts Increase $\geq 20 \times 10^9/L$ from Baseline	1.8 (3.8)	16.9 (7.4)	0.5 (1.0)	14.5 (7.9)	1.1 (2.8)	15.7 (7.7)
Treatment Group Comparison p-value (analysis of variance ^c)	< 0.0001		< 0.0001		< 0.0001	

^aDurable platelet response plus transient platelet response. Transient platelet response was defined as at least 4 weekly platelet responses, without durable platelet response.

^bFor individual studies, p-value is from Cochran-Mantel-Haenszel controlling for baseline concurrent ITP therapy; for total, p-value is from Cochran-Mantel-Haenszel controlling for splenectomy status and baseline concurrent ITP therapy.

^cFor individual studies, p-value is from main effects (treatment and concurrent ITP therapy) model after testing for non-significant interaction (p-value ≥ 0.10); for total, p-value is from ANOVA model (treatment, splenectomy status and baseline concurrent ITP therapy).

Change From Baseline in Platelet Counts

From median baseline platelet counts of $17.7 \times 10^9/L$ (placebo) and $15.7 \times 10^9/L$ (romiplostim) in the combined analysis of the 2 pivotal studies, platelet counts increased after one dose in the romiplostim group to $35.5 \times 10^9/L$ at the next measurement the following week, at which time they were $18.0 \times 10^9/L$ in the placebo group. After 3 doses

of romiplostim (measured week 4), the median platelet count was above $50 \times 10^9/L$ in both pivotal studies.

A post-hoc analysis of the number of weeks with a platelet count within a specified range (< 10 , $10 - 20$, $20 - 30$, $30 - 50$, and $\geq 50 \times 10^9/L$) was done for subjects in both treatment groups. Subjects receiving placebo (not censored for rescue medications) spent more time with lower platelet counts and less time with higher platelet counts, while the reverse was true for subjects receiving romiplostim. For example, placebo subjects had platelet counts below $10 \times 10^9/L$ for 212/952 weeks (22.3%) while for subjects receiving romiplostim the value was 126/2056 (6.1%) weeks. Placebo subjects had platelet counts $\geq 50 \times 10^9/L$ for 130 (13.7%) weeks; for subjects receiving romiplostim the value was 1278 (62.2%) weeks.

4.8 Proportion of Subjects Requiring Rescue Medications

An overall reduction of 37.8% in the proportion of subjects who received rescue medication was observed for romiplostim-treated subjects in the combined analysis: 59.5% of subjects in the placebo group and 21.7% of subjects in the romiplostim group ($p < 0.0001$) required rescue medication during the treatment period. The treatment effect was more pronounced in the non-splenectomized population (Study 20030212): 61.9% of subjects in the placebo group and 17.1% in the romiplostim group received rescue medication ($p = 0.0004$), but was significant for splenectomized subjects (Study 20030105) as well: 57.1% placebo, 26.2% romiplostim ($p = 0.0179$).

The types of rescue medications used by subjects in the pivotal studies are summarized in Table 6. Corticosteroids and IVIG were the most commonly used rescue medications in both studies, and approximately twice the proportion of placebo subjects received these medications as did romiplostim subjects (Table 6). As described in Table 1, corticosteroids and IVIG carry risks for potentially serious adverse effects, and the benefits of being able to reduce or eliminate their use are considerable.

Table 6. Rescue Medication Use in Studies 20030105 and 20030212

	Non-splenectomized 20030212		Splenectomized 20030105	
	Placebo (n=21)	Romiplostim (n=41)	Placebo (n=21)	Romiplostim (n=42)
Subjects receiving rescue medications – n (%)	13 (61.9)	7 (17.1)	12 (57.1)	11 (26.2)
Corticosteroids	6 (28.6)	7 (17.1)	8 (38.1)	7 (16.7)
IVIg	7 (33.3)	4 (9.8)	11 (52.4)	7 (16.7)
Anti-D Immunoglobulin	4 (19.0)	2 (4.9)	0 (0.0)	0 (0.0)
Platelet Transfusions	2 (9.5)	0 (0.0)	4 (19.0)	5 (11.9)
Cyclosporin	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)
Rituximab	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Azathioprine	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)

4.9 Proportion of Subjects Able to Reduce or Discontinue Concurrent ITP Therapies

In the integrated analysis of the 2 pivotal studies, 16 of 42 (38%) subjects in the placebo group and 23 of 83 (28%) subjects in the romiplostim group were receiving concurrent ITP therapies at baseline. All 16 (100%) of the placebo subjects were receiving a single concurrent treatment, while 18 (78.3%) of the romiplostim subjects were receiving 1 concurrent ITP treatment and 5 (21.7%) were receiving 2 concurrent treatments. At the week-25 timepoint, 3 placebo subjects (18.8%) had a > 25% reduction and 3 (18.8%) had discontinued all concurrent ITP treatment; while 8 romiplostim subjects (34.8%) had a > 25% reduction and 12 (52.5%) had discontinued all concurrent ITP therapies. While the reduction of concurrent ITP therapies (especially prednisone) was a prominent feature of both pivotal studies, it was more obvious in the post-splenectomy population. In Study 20030105, 12 romiplostim subjects began the study receiving concurrent ITP medication. All 12 subjects were receiving prednisone, and 2 were receiving azathioprine and 2 were receiving danazol in addition to the prednisone. By week 25, prednisone had been reduced or discontinued in all 12 subjects, and azathioprine and danazol were discontinued in all cases.

4.10 Time to Platelet Count $\leq 50 \times 10^9/L$ After Treatment Discontinuation

Subjects were considered to have completed the pivotal study when their platelet counts dropped to $\leq 50 \times 10^9/L$ after completing romiplostim treatment at week 25, or by week 36, whichever came first. At that point they became eligible to screen for enrollment in

the open-label extension Study 20030213. Platelet counts generally decreased fairly rapidly after discontinuation of treatment with romiplostim; the median for 43 subjects in the romiplostim group to reach $\leq 50 \times 10^9/L$ was 2.0 weeks (with platelet counts being measured weekly).

Seven subjects in the pivotal studies (5 non-splenectomized and 2 splenectomized) were able to discontinue romiplostim during the treatment period and had a platelet count above $50 \times 10^9/L$ at week 25, the final week of the treatment period, and then maintained platelet counts above $50 \times 10^9/L$ until week 36, the end of study, without additional romiplostim treatment or other ITP treatment. Platelet counts between weeks 25 and 36 for these 7 subjects were well above $50 \times 10^9/L$, generally above $100 \times 10^9/L$. None of these subjects entered the extension Study 20030213, and thus subsequent information about them is unavailable.

Spontaneous remissions occur in ITP, although rarely. Definitions of “remission” in the ITP literature vary widely; for example, in a study of repeated infusions of IVIG given as intended long-term treatment, remission was defined as a platelet count $> 150 \times 10^9/L$ requiring no treatment for at least 3 months (Bussel et al, 1988). In a study of treatments for splenectomy failures (McMillan and Durette, 2004), stable remission was considered a “normal” platelet count for more than 2 months.

4.11 Change From Baseline at Each Scheduled Visit for PRO Instruments

In splenectomized subjects (Study 20030105), several subscales of the ITP-PAQ indicated a significant positive effect of romiplostim on measures of PRO as shown by the mean change from week 1 to week 25. Exploratory analyses (not adjusted for .multiplicities) yielded the following results: the subscale Physical Health - Symptoms showed a difference in means for romiplostim – placebo of 10.55 ($p = 0.0205$), indicating that subjects receiving romiplostim perceived an improvement in their physical symptoms. The Physical Health - Bother² subscale was also significantly improved

² Physical Health – Bother (PHB):

(q13) Q17 – feel physically unattractive due to bruising, wounds, etc.?

(q14) Q29 – to what extent has ITP affected your physical health?

(q15) Q29a – how bothered have you been by ITP on your physical health?

relative to placebo ($p = 0.0091$), as were Social Quality of Life ($p = 0.0172$) and Women's Reproductive Health ($p = 0.0272$).

For nonsplenectomized subjects (Study 20030212), compared to the placebo group, subjects in the romiplostim group reported greater improvement from week 1 to 25 on nine out of 10 ITP-PAQ scales, with the exception of the Work Quality of Life scale. The Physical Health - Activity scale was the only scale that showed a statistically significant difference in mean change for romiplostim vs placebo ($p = 0.0164$). Subjects in the romiplostim group also reported higher Patient Global Assessment scores at the conclusion of the study as compared to subjects in the placebo group.

4.12 Extension Study (Study 20030213)

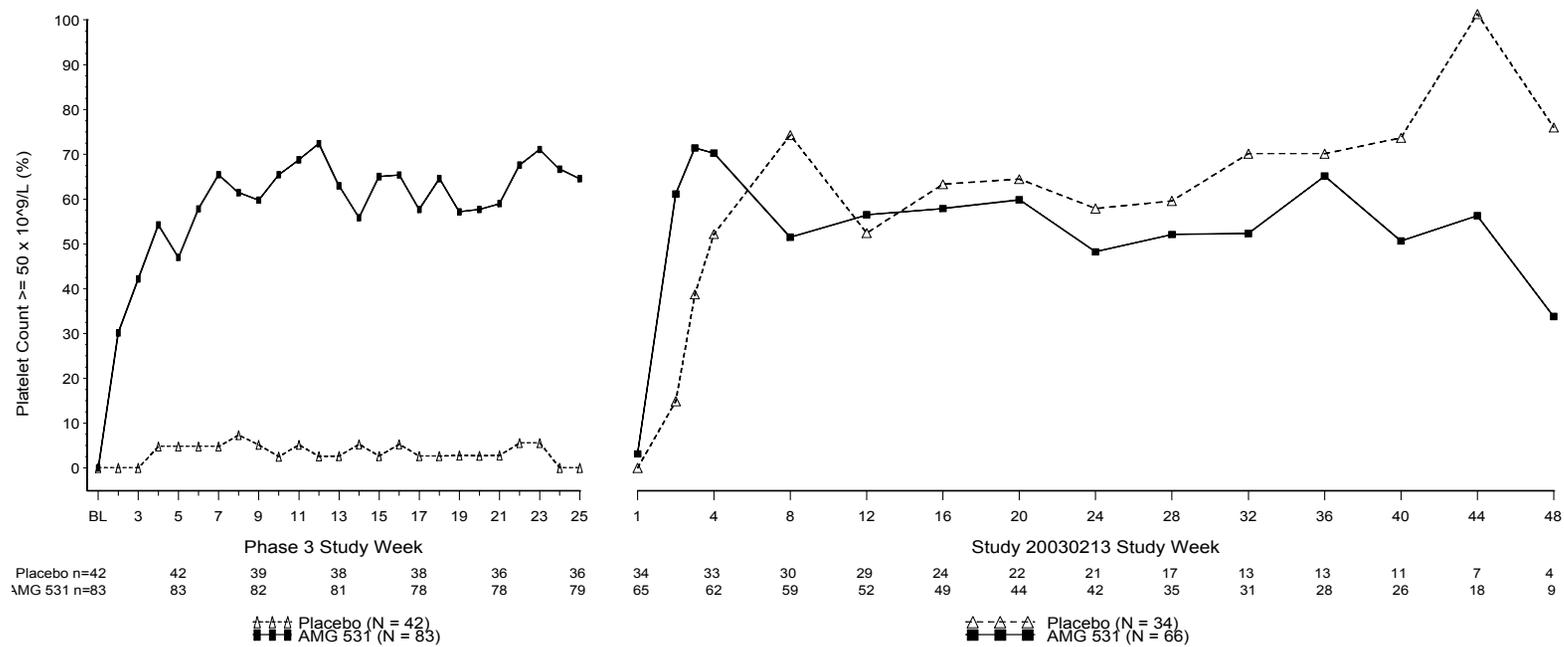
After 24 weeks of treatment, subjects were considered to have completed the pivotal studies when their platelet counts dropped to $\leq 50 \times 10^9/L$, or week 36, whichever came first. Subjects whose platelet counts dropped to $\leq 50 \times 10^9/L$ were then eligible to enroll in the open-label extension Study 20030213. Subjects who had previously received placebo entered Study 20030213 at an initial weekly dose of $1 \mu\text{g}/\text{kg}$, whereas subjects who had previously received romiplostim started at the same weekly dose as in their previous study.

Of the 125 subjects randomized into the 2 pivotal studies, 115 completed the studies, and 100 of these 115 subjects enrolled in Study 20030213. A total of 34 subjects received placebo in a pivotal study and romiplostim in the extension study, and 66 received romiplostim in both studies. Total exposure for subjects receiving romiplostim was up to 24 weeks in a pivotal study and up to 60 weeks in Study 20030213 for a maximum exposure of 84 weeks as of the data cutoff for the extension study.

In the pivotal studies, 30.1% of romiplostim subjects achieved platelet counts above $50 \times 10^9/L$ by week 2, and 54.2% by week 4, with approximately 50% to 70% of subjects maintaining platelet counts $\geq 50 \times 10^9/L$ thereafter. The response was similarly rapid in the extension study, with 44.3% of subjects reaching platelet counts $\geq 50 \times 10^9/L$ at week 2 and 63.2% at week 4. As shown in Figure 3, the proportion of subjects achieving a platelet response ($> 50 \times 10^9/L$) in the extension study was similar to that observed in the phase 3 studies.

Median platelet count was relatively unchanged in the placebo groups during both pivotal studies; in contrast, the romiplostim treatment groups in both pivotal studies showed a rapid initial increase. Former placebo subjects who went on to receive romiplostim in the extension study showed a pattern of platelet count increases similar to that of romiplostim -treated subjects in the pivotal studies. Both subjects who had previously received placebo and those who had previously received romiplostim had a median platelet count above $50 \times 10^9/L$ by week 4 of the extension study. Between weeks 12 and 36 of Study 20030213, median platelet counts were generally similar for subjects who had previously received placebo or romiplostim in the phase 3 studies (range: 95 to $128 \times 10^9/L$ and 81 to $106 \times 10^9/L$, respectively).

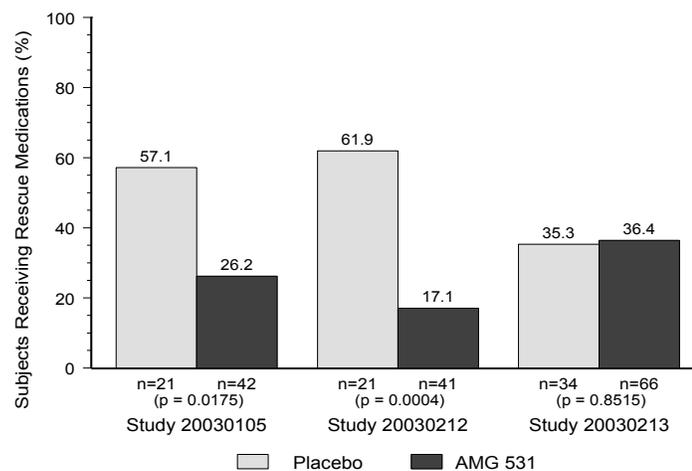
**Figure 3. Subject Incidence of Platelet Response (Weekly Platelet Counts $\geq 50 \times 10^9/L$) -
Left Panel: 20030105 and 20030212 (Romiplostim vs Placebo); Right Panel: 20030213 (All Subjects Received Romiplostim)**



Missing platelet counts in study 20030213 on Week 8, 12, 16, etc. were imputed using the average of the neighboring values within ± 1 weeks. Subject is not considered as having a weekly incidence within 8 weeks after receiving any rescue medications. All subjects received AMG 531 in Study 20030213 but were listed under their randomized treatment in a previous phase 3 study.

The subject incidence of rescue medication use on Study 20030213 was similar for subjects who had previously received placebo (35.3%) and for those who had previously received romiplostim (36.4%) during the parent pivotal studies (Figure 4). Approximately 30% of subjects received rescue medication during weeks 1 – 12 and weeks 12 – 24 in Study 20030213; the proportion decreased during later 12-week intervals. As would be expected for a study of longer duration, the subject incidence of rescue medication use was higher in the extension study than for romiplostim subjects in the pivotal studies (Figure 4). However, for the previous placebo subjects, regardless of splenectomy status, the proportion of subjects receiving rescue medication was lower during Study 20030213 than during the parent pivotal study.

Figure 4. Proportion of Subjects who Received Rescue Medications During Treatment Period: Studies 20030105 and 20030212 (Placebo, Romiplostim); Study 20030213 (Prior Placebo, Prior Romiplostim – All Subjects Received Romiplostim on Study)



Rescue medication was defined as any medication that was administered for the intended purpose of raising platelet count. All subjects received AMG 531 in Study 20030213 but were listed under their randomized treatment in a previous phase 3 study. For individual studies, p-value is from Cochran-Mantel-Haenszel controlling for baseline concurrent ITP therapy; For total, p-value is from Cochran-Mantel-Haenszel controlling for splenectomy status and baseline concurrent ITP therapy.

4.13 Bleeding Events

As explained previously, bleeding events were not prespecified efficacy endpoints because they are subjective in nature, no validated scale exists for bleeding events in ITP, and their assessment is likely to be confounded by rescue medication given when

the platelet count reaches levels at which intervention is recommended by treatment guidelines ($30 \times 10^9/L$).

Because bleeding events are an obvious outcome of the efficacy endpoint (platelet counts), bleeding events have been assessed as post-hoc analyses of adverse events collected on the adverse event case report forms. Bleeding events (including grade 3 or higher [“clinically significant”] events) were identified from the clinical database before unblinding of the pivotal studies, and included any adverse event considered by the sponsor as a bleeding event regardless of system organ class.

The following trends were apparent:

- *In the pivotal studies, overall incidences of bleeding events were similar for the placebo and romiplostim groups; however, a greater proportion of bleeding events were moderate or severe in placebo subjects.*

Overall, bleeding events of any severity occurred at similar subject incidences in the placebo and romiplostim groups. In the phase 3 ITP safety set, bleeding events occurred in 25 (61.0%) placebo subjects and 48 (57.1%) romiplostim subjects. In the ITP safety set, the subject incidences were 29 (63.0%) (placebo) and 128 (62.7%) (romiplostim). Study duration-adjusted values also showed little difference for subject incidence of overall bleeding events between placebo and romiplostim for any of the safety sets.

A higher percentage of placebo subjects had a bleeding event with a maximum severity of moderate (22%) or severe (9.8%) in intensity compared with the romiplostim subjects; 8.3% moderate or 4.8% severe.

- *Bleeding events that were \geq grade 2 in severity occurred in more placebo subjects than romiplostim subjects.*

In the combined pivotal studies, bleeding events that were \geq grade 2 (moderate) in severity occurred at a higher subject incidence among placebo subjects (14; 34%) than subjects receiving romiplostim (13; 16%), and post-hoc statistical comparison showed this difference to be significant ($p = 0.017$). Clinically significant bleeding events (\geq grade 3) also occurred in more placebo subjects (5; 12%) than romiplostim subjects (6; 7%).

- *An inverse relationship between platelet count and bleeding events was the driving factor for most trends observed in the clinical studies.*

A post-hoc analysis was done assessing the association between clinically significant bleeding events and platelet count, using the lowest platelet count within 7 days before or after the event start date. The number of weeks with a platelet count within a specified range (< 10, 10 – 20, 20 – 30, 30 – 50, and $\geq 50 \times 10^9/L$) was calculated for subjects in both treatment groups. This analysis revealed that:

- all clinically significant bleeding events occurred at platelet counts < $20 \times 10^9/L$, while most occurred at platelet counts < $10 \times 10^9/L$ (60% placebo vs 90% romiplostim) supporting the importance of maintaining platelet count.
- the post-hoc analysis of grade 2 or higher bleeding events showed that only 1 bleeding event occurred in a romiplostim subject at a platelet count between 30 and $50 \times 10^9/L$; all other grade 2 or higher bleeding events occurred at platelet counts < $20 \times 10^9/L$.

5. SAFETY

5.1 Key Points

- A total of 204 subjects with ITP have received at least 1 dose of romiplostim; 128 subjects had at least 26 weeks of exposure, and 74 subjects had at least 52 weeks of exposure. Long term follow-up continues.
- Safety data from 125 subjects in the 2 pivotal phase 3 studies demonstrated that when compared with placebo, romiplostim was relatively well tolerated. Adverse Drug Reactions that occurred at $\geq 5\%$ higher subject incidence in the romiplostim group than the placebo group identified in the 2 pivotal studies are shown in the table below.

Preferred Term	Romiplostim n = 84	Placebo n = 41
Arthralgia	26%	20%
Dizziness	17%	0%
Insomnia	16%	7%
Myalgia	14%	2%
Pain in extremity	13%	5%
Abdominal Pain	11%	0%
Shoulder Pain	8%	0%
Dyspepsia	7%	0%
Paraesthesia	6%	0%

Increased reticulin in the bone marrow, thrombocytosis, and recurrence of thrombocytopenia after cessation of treatment are additional adverse drug reactions observed in subjects receiving romiplostim. Headache was the most commonly reported adverse drug reaction, occurring in 35% of patients receiving romiplostim and 32% of patients receiving placebo.

- No neutralizing antibodies that cross-reacted with TPO were reported in the clinical development program. Of the 204 patients in clinical studies receiving romiplostim, one subject developed neutralizing antibodies to romiplostim; importantly, these did not cross react with endogenous TPO. Approximately 4 months later, after discontinuation of romiplostim therapy, neutralizing antibodies to romiplostim were no longer detectable.
- The incidence of thrombotic / thromboembolic events observed in clinical trials was similar between romiplostim and placebo groups.

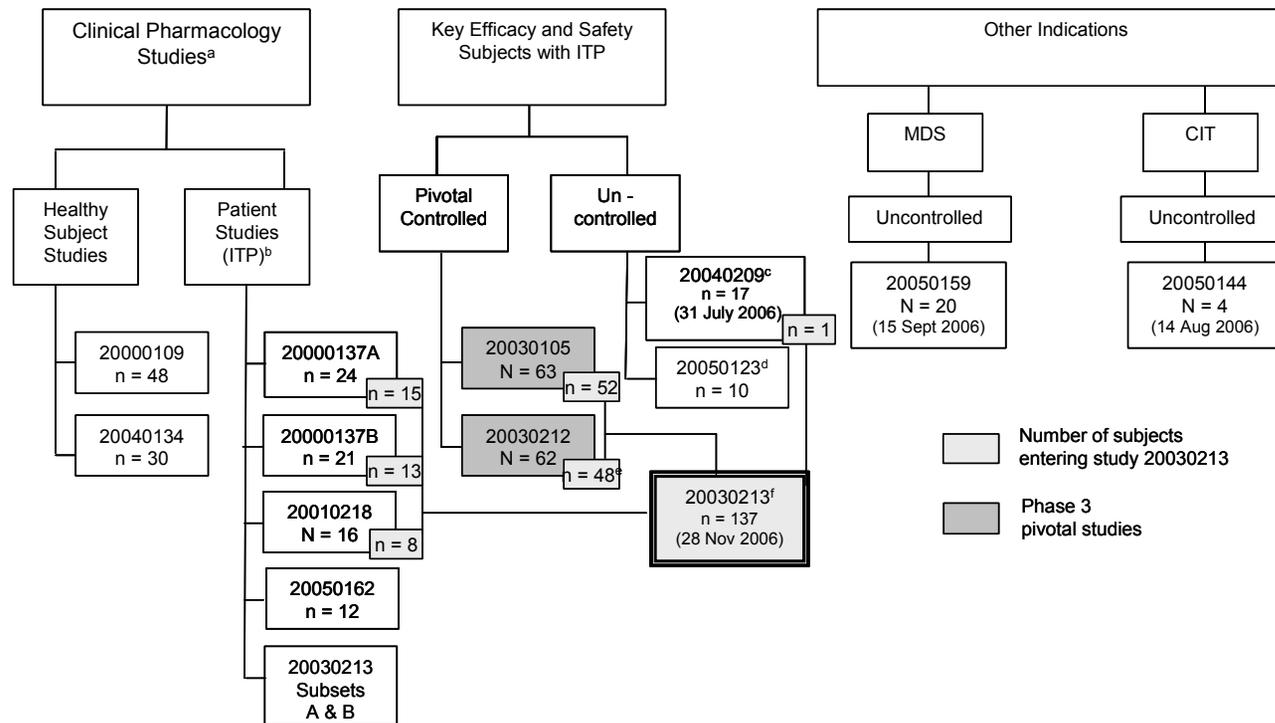
- A potential risk exists that TPO receptor agonists may stimulate the progression of hematopoietic malignancies or MDS, as the TPO receptor is expressed on the surface of cells of the hematopoietic lineage. In a single-arm, open-label study in which 20 subjects with MDS received romiplostim, 2 subjects had transient increases in blast cell counts that were inconsistent with progression to AML; one subject had an event of disease progression to AML, which is consistent with the natural course of the disease. In the ITP studies, hematologic malignancies were reported in 3 subjects: B-cell lymphoma (0 placebo, 1 [0.5%] romiplostim, in a subject with preexisting lymphadenopathy and several lymphoid aggregates in the bone marrow) and multiple myeloma (1 [2.2%] placebo, 1 [0.5%] romiplostim).
- In 4 subjects, platelet count transiently decreased below the pretreatment baseline levels upon discontinuation of romiplostim. Romiplostim, like other thrombopoietic agents, causes increased platelet production, and treatment does not alter the underlying rate of platelet destruction. Therefore, it is expected that in ITP patients platelet counts will return to baseline levels upon discontinuation of treatment, resulting in an increased risk for bleeding, particularly if romiplostim is discontinued in the presence of anticoagulants or anti-platelet agents.
- At the time of the 120-day update, increased bone marrow reticulin (or presence of reticulin on study) has been observed in 9/219 ITP subjects who received romiplostim. This finding was not associated with adverse clinical sequelae. No cases of chronic idiopathic myelofibrosis (CIMF) or secondary myelofibrosis have been observed.

5.2 Methodology

5.2.1 Safety Datasets

Safety data in this marketing application are from 13 clinical studies including clinical pharmacology, pharmacokinetics, safety, efficacy, and quality of life in subjects with ITP, MDS, or CIT (Figure 5).

Figure 5. Overview of Romiplostim Clinical Studies in the Marketing Application



Number of subjects entering study 20030213
Phase 3 pivotal studies

CIT = chemotherapy-induced thrombocytopenia; ITP = immune (idiopathic) thrombocytopenic purpura; MDS = myelodysplastic syndrome

Note: Studies are organized by primary location in the submission. Shaded = pivotal trial (ITP); double border = supportive efficacy data (ITP). Dates in parentheses are data cutoff dates for this application.

^a No biopharmaceutics studies were done. No studies of intrinsic or extrinsic factors were done.

^b Studies 20000137B, 20010218, and 20050162 could have been classified under either clinical pharmacology or efficacy and safety studies. These studies are included in the Clinical Summary of Pharmacology.

^c Individual treatment study for subjects not qualifying for other studies.

^d Ancillary study evaluating long-term effects of romiplostim on bone marrow; open to subjects in Studies 20030105, 20030212, and 20030213.

^e One subject was enrolled in study 20030213, but received no investigational product.

^f Open-label extension study enrolling subjects from any previous ITP study in the US/EU.

Table 7 shows the safety pools used in the integrated analysis of safety. The primary safety pool consisted of all subjects who received at least 1 dose of investigational product in the 2 pivotal studies 20030105 and 20030212 ("Phase 3 ITP Safety Set"). As a secondary analysis of safety, these 2 studies were combined with other studies in subjects with ITP ("ITP Safety Set"), consisting of all subjects who received investigational product in an ITP study.

The healthy volunteer safety set consists of all subjects who received investigational product in the 2 healthy subject studies (20000109 or 20040134). The MDS safety set consists of all subjects who received investigational product in an MDS study (20050159) by the date of the data cutoff (September 15, 2006) for this filing. The CIT safety set consists of all subjects who received investigational product in a chemotherapy-induced thrombocytopenia (CIT) study, 20050144 (data cutoff by August 14, 2006). The romiplostim safety set (n = 317) consists of all subjects in the ITP safety set, the MDS safety set, the CIT safety set, and the healthy volunteer safety set.

The phase 3 ITP long-term safety set consists of all subjects who were randomized and received investigational product in the 2 phase 3 ITP studies (20030105 and 20030212), with exposure and safety data up to the filing snapshot date from the extension study (20030213).

Table 7. Safety Analysis Sets

	Received Placebo Only n	Received Placebo and romiplostim ^a n	Received romiplostim Only n	Total n	Subjects From Studies
Phase 3 ITP safety set	41	1	83	125	20030105, 20030212
Phase 3 ITP long-term safety set	8	34	83	125	20030105, 20030212 20030213
ITP safety set	11	35	169	215	20030105, 20030212 20030213 20000137A, 20000137B 20010218, 20040209 20050123, 20050162
MDS safety set	0	0	20	20	20050159
CIT safety set	0	0	4	4	20050144
Healthy volunteer safety set	22	0	56	78	20000109, 20040134
Romiplostim safety set	33	35	249	317	20030105, 20030212 20030213 20000137A, 20000137B 20010218, 20040209 20050123, 20050162 20050159, 20050144 20000109, 20040134

^a Subjects who started on placebo and later received romiplostim in the open label extension study 20030213. One 20030212 subject randomized to placebo inadvertently received three doses of romiplostim.

5.2.2 Risk Management

In designing the romiplostim risk management plan, Amgen followed guidance in the European Medicines Agency (EMA) (Committee for Medicinal Products for Human Use [CHMP] guideline on risk management systems for medicinal products for human use, London, 14 November 2005). A risk management system is defined in this guideline as “a set of pharmacovigilance activities and interventions designed to identify, characterize, prevent or minimize risks relating to medicinal products, including the assessment of the effectiveness of those interventions”. Additional guidance was taken from the FDA Guidances including Premarketing Risk Assessment and The Development and Use of Risk Minimization Action Plans.

The risk management program for romiplostim is based on the assessment of risk reviewed in this section and will also include a risk minimization action plan (RiskMAP) designed to assure appropriate use in the ITP patient population studied. Guidance followed in developing the RiskMAP included the FDA guidelines “Guidance for Industry - Development and Use of Risk Minimization Action Plans (March 2005)” and “Guidance for Industry - Premarketing Risk Assessment, March 2005”.

5.3 Demographics

Demographics and baseline characteristics for the subjects in the pivotal studies are described in Section 4.5. For the larger ITP safety set (n = 215), the median age was 51 years (range: 1 to 88 years); 41 (19.1%) subjects were at least 65 years of age and 19 (8.8%) subjects were at least 75 years of age. Overall, there were 66% women and 78.1% whites (Caucasians). Baseline platelet counts were low, with an overall median of $14.7 \times 10^9/L$.

Currently, there are no (or limited) data on special populations, including pediatric subjects, subjects with hepatic impairment, subjects with renal impairment, and data on non-Caucasians.

5.4 Duration of Exposure

In the pivotal studies, exposure was higher for splenectomized subjects (Study 20030105) compared with non-splenectomized subjects (Study 20030212) (median average weekly dose 8.8 $\mu\text{g}/\text{kg}$ [placebo] and 2.9 $\mu\text{g}/\text{kg}$ [romiplostim] in Study 20030105, and 6.9 $\mu\text{g}/\text{kg}$ [placebo] and 1.9 $\mu\text{g}/\text{kg}$ [romiplostim] in Study 20030212).

In the ITP safety set (n = 215), 204 subjects received at least 1 dose of romiplostim and 11 subjects received only placebo. A total of 34 subjects received placebo initially and then received romiplostim in the open-label extension study (20030213). The number of subjects exposed to romiplostim, including the number who had long-term exposure, supports the indication (Table 8).

Table 8. Number of Subjects Exposed to Romiplostim by Treatment Duration (ITP Safety Set)

Duration of Overall Exposure	Romiplostim N =204 n (%)
1 wk to < 26 wks	76 (37.3)
≥ 26 wks to < 52 wks	54 (26.5)
≥ 52 wks	74 (36.3)

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The ITP safety set consists of all subjects who received investigational product in an ITP study (20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050123, or 20050162).

Duration of overall exposure (weeks) = (last dose date - first dose date + 7) / 7. If a subject is enrolled in multiple studies, this is the sum of treatment durations of individual studies.

A total of 117 romiplostim -treated subjects in the 125 subject phase 3 ITP long-term safety set who completed the phase 3 studies and continued into the extension study had a maximum of 83.9 weeks of exposure to romiplostim.

5.4.1 Discontinuations from Study and Investigational Product

In the 2 pivotal studies, 25 subjects prematurely discontinued investigational product; 20 (48.8%) placebo subjects and 5 (6.0%) romiplostim subjects. The most common reasons for discontinuing investigational product were subject request (7 [17.1%] placebo, 1 [1.2%] romiplostim), other (7 [17.1%] placebo, 0 [0%] romiplostim), and adverse event (1 [2.4%] placebo, 4 [4.8%] romiplostim).

Reasons for discontinuation from study (subjects could discontinue investigational product but remain on study) were: adverse event (1 [2.4%] placebo, 3 [3.6%] romiplostim), consent withdrawn (2 [4.9%] placebo, 1 [1.2%] romiplostim), death (2 [4.9%] placebo, 0 romiplostim), and pregnancy (1 [2.4%] placebo, 0 romiplostim).

5.5 Common Adverse Events

In the phase 3 ITP safety set (n = 125), the most frequently reported adverse events were headache (31.7% placebo, 34.5% romiplostim), fatigue (29.3% placebo, 33.3% romiplostim), and epistaxis (24.4% placebo, 32.1% romiplostim). Adverse events occurring at greater than a 10% higher incidence in the romiplostim group were dizziness (0% placebo, 16.7% romiplostim), myalgia (2.4% placebo, 14.3% romiplostim), and abdominal pain (0% placebo, 10.7% romiplostim).

A temporal pattern of occurrence was observed for the following treatment-related constitutional symptoms: arthralgia, fatigue, headache, and myalgia. The incidence of these events generally decreased over the course of the study.

An adverse drug reaction (ADR) is defined in 21 CFR 201.57(c) (7) as an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. Adverse events were identified as ADRs if they occurred at $\geq 5\%$ higher subject incidence in the romiplostim group than the placebo group in the phase 3 ITP safety set or in the Amgen pharmacovigilance safety database. Additional events were identified based on review of the study-duration adjusted adverse events in the ITP safety set, as well as Amgen medical review of safety experience to date, expected pharmacologic activity of romiplostim, and case analysis and/or review of the clinical database for additional causality. The following events were identified as ADRs:

	Placebo (N=41)	Romiplostim (N=84)
Arthralgia	20%	26%
Dizziness	0%	17%
Insomnia	7%	16%
Myalgia	2%	14%
Pain in Extremity	5%	13%
Abdominal Pain	0%	11%
Shoulder Pain	0%	8%
Dyspepsia	0%	7%
Paraesthesia	0%	6%

Headache was the most commonly reported adverse reaction that did not occur at $\geq 5\%$ higher patient incidence in romiplostim versus placebo, occurring in 35% of patients receiving romiplostim and 32% of patients receiving placebo. Increased reticulins in the bone marrow, thrombocytosis, and recurrence of thrombocytopenia after cessation of treatment are additional adverse drug reactions experienced by subjects receiving romiplostim.

The event of epistaxis was not included as an ADR even though it met the criterion of a $\geq 5\%$ difference between romiplostim and placebo subjects in the phase 3 ITP safety set. Amgen medical reviewers believe the evidence is not sufficient to suggest a causal relationship between epistaxis and romiplostim at this time, because epistaxis is likely

attributable to the disease of ITP itself; moreover, analysis of additional, larger safety sets failed to show an increased incidence in the romiplostim arm.

Exposure-adjusted Adverse Event Rates

The mean (SD) duration of exposure was 18.57 [6.82] and 22.83 [4.12] weeks for placebo and romiplostim, respectively for the phase 3 ITP safety set. Study duration was calculated as the end of study date minus the first dose date whereas the investigational product exposure duration would be calculated as the last dose date minus the first dose date plus 7 days. The phase 3 study design, with the opportunity to rollover to active treatment after week 24, encouraged a subject to stay in the study for the entire 24 weeks, even if the subject discontinued investigational product early. Across the 2 phase 3 studies, this occurred more often in the placebo group where 20 (48.8%) subjects discontinued investigational product, but only 6 (14.6%) discontinued the study. Because clinical measurements, including adverse events, were collected for the entire study duration, whether or not a subject was being dosed with investigational product, it is appropriate to use the study duration to calculate the adverse event rates over time.

In the ITP safety set, the highest study duration-adjusted event rates (events/100 patient-years) for all adverse events were lower for subjects who received romiplostim compared with subjects who received placebo. The most common adverse events in both treatment groups (placebo, romiplostim) were headache (161.6, 144.8), contusion (136.4, 106.2), epistaxis (90.9, 72.9), and fatigue (101.0, 63.8).

5.6 Serious Adverse Events

In the phase 3 ITP safety set there were 8 (19.5%) serious adverse events in placebo subjects and 14 (16.7%) in romiplostim subjects. There were multiple reports for each of the following serious adverse events: gastrointestinal hemorrhage (2 romiplostim subjects); intracranial hemorrhage (1 subject each for placebo and romiplostim); pneumonia (2 placebo subjects); and platelet count decreased (2 placebo subjects and 1 romiplostim subject); all other serious adverse events were reported once.

Sixty-two subjects reported at least 1 serious adverse event in the ITP safety set (cutoff date: 28 November 2006); 10 (21.7%) placebo subjects and 52 (25.5%) romiplostim subjects. In the ITP safety set, the study duration-adjusted incidence of serious adverse

events (event rate per 100 subject-years) was 121.2 for placebo subjects and 76.1 for romiplostim subjects.

In the ITP safety set, serious adverse events with the highest study duration-adjusted incidence in romiplostim subjects were thrombocytopenia (0 placebo, 16 [8.6 per 100 subject years] romiplostim), platelet count decreased (8 [40.4 per 100 subject years] placebo, 4 [2.1 per 100 subject years] romiplostim), and bone marrow disorder (0 placebo, 4 [2.1 per 100 subject years] romiplostim).

Twenty-eight of the serious adverse events, which occurred in 18 subjects (all romiplostim-treated; 15 splenectomized), were considered treatment-related.

5.7 Deaths

Included in the clinical database for this marketing application are data for 8 subjects who died during clinical studies in ITP; 3 (6.5%) placebo subjects and 5 (2.5%) romiplostim subjects. None of the deaths were considered treatment-related by the investigator. The causes of death were:

- primary atypical pneumonia (placebo) (following hospitalization for intracranial hemorrhage), (Study 20030105);
- pulmonary embolism (placebo), (Study 20030105);
- cerebral hemorrhage (placebo), (Study 20030105);
- intracranial hemorrhage (romiplostim) (2 weeks after starting aspirin therapy and discontinuing romiplostim), (Study 20030212);
- pneumococcal pneumonia (romiplostim; splenectomized subject), (Study 20030213);
- cardiac arrest (romiplostim), (Study 20030213);
- hepatic failure and renal failure in a subject with pre-existing malignant hepatic neoplasm (romiplostim), (Study 20030213);
- acute respiratory distress syndrome (romiplostim), (Study 20040209).

Based on 19.8 patient-years of exposure in subjects who received placebo and 186.5 patient-years of exposure in subjects who received romiplostim in the ITP safety set, the study duration-adjusted event rate for fatal adverse events was 15.2/100 patient-years of exposure and 2.7/100 patient-years of exposure for subjects who received placebo and romiplostim, respectively.

5.8 Injection Site Events

Injection site events are a known and expected result of SC injections. Injection site event terms were identified from the list of adverse events after database unblinding. The percentage of subjects reporting injection site events was similar for placebo (10 [21.7%]) and romiplostim (34 [16.7%]) subjects. Injection site bruising was the most common injection site event reported in both treatment groups (4 [8.7%] placebo and 18 [8.8%] romiplostim). The study duration-adjusted injection site event rate was not higher in romiplostim subjects than placebo subjects. No injection site events were serious and only 1 was severe (severe burning at the site lasting 3 days in a subject on Study 20030213).

5.9 Other Significant Adverse Events and Issues of Concern

Several additional categories of adverse events or issues of concern were explored because they represent potential safety concerns, or because of the potential association with the mechanism of action of romiplostim, or because they were requested by regulatory authorities. These are discussed below.

5.9.1 Malignancies and Progression of Malignancies

Background

Stimulation of the c-Mpl (TPO) receptor results in thrombopoietic progenitor cell expansion, differentiation, and platelet production (Kaushansky and Drachman, 2002). The c-Mpl receptor is expressed on the surface of cells of the hematopoietic lineage; there is no confirmed expression of the c-Mpl receptor on solid tumors (Graf et al, 1996; Columbyova et al 1995). In vitro studies have shown high concentrations of thrombopoietin (20 to 200 ng/mL) can stimulate certain subsets of myeloid blast cells (Corazza et al, 2006; Fontenay-Roupie et al, 1998). The TPO concentrations in these studies exceed the concentrations of romiplostim expected in the clinical studies (generally, circulating levels of romiplostim administered SC in the clinical studies have not been measurable, despite the limit of detection of the assay being approximately 18 pg/mL). Therefore, there exists a potential risk that c-Mpl receptor stimulation may accelerate the growth of pre-existing hematopoietic malignancies.

Clinical Data

At the request of the FDA (May 2007), an additional adverse event of interest, neoplasia, was specified. Neoplasia events were identified using the MedDRA version 9.0 system organ class (SOC) of “neoplasms benign, malignant and unspecified (includes cysts and polyps)”. For all ITP safety sets, the percentage of subjects with reported neoplasms was not higher in the romiplostim group than the placebo group (Table 9).

Table 9. Summary of Neoplasm Adverse Events in ITP Studies (Primary MedDRA Terms)

Phase 3 ITP Safety Set	Marketing Application	
	Placebo	Romiplostim
Total number of subjects reporting neoplasm events, n (%)	5/41 (12.2%)	2/84 (2.4%)
Study duration adjusted number of neoplasm events (events/100 subject-years on study)	32.3	4.7
P3 Long-term ITP Safety Set		
Total number of subjects reporting neoplasm events, n (%)	5/42 (11.9%)	4/117 (3.4%)
Duration adjusted number of neoplasm events (events/100 subject-years on study)	31.7	4.1
ITP Safety Set		
Total number of subjects reporting neoplasm events, n (%)	5 (10.9%)	12 (5.9%)
Duration adjusted number of neoplasm events (events/100 subject-years on study)	30.3	8.6

Hematologic malignancies were reported in 3 subjects: B-cell lymphoma (0 placebo, 1 [0.5%] romiplostim, in a subject with preexisting lymphadenopathy and several lymphoid aggregates in a pretreatment bone marrow) and multiple myeloma (1 [2.2%] placebo, 1 [0.5%] romiplostim).

Six other events were considered non-hematologic malignancies, and the remainder were benign. The non-hematologic malignancies included colon cancer (romiplostim), malignant hepatic neoplasm (romiplostim), malignant melanoma (romiplostim), metastases to the liver (placebo), and basal cell carcinoma (romiplostim). The benign events included benign ovarian tumor (placebo), fibroma (placebo), hemangioma of the liver (romiplostim), melanocytic nevus (romiplostim), and uterine leiomyoma (placebo).

In a single-arm, open-label study in MDS in which 20 subjects received romiplostim, 2 subjects had transient increases in blast cell counts that were inconsistent with

progression to AML; one subject had an event of disease progression to AML, which is consistent with the natural course of the disease.

Plans for managing the potential risks for progression of existing hematopoietic malignancies or MDS are discussed in Section 6.

5.9.2 Re-occurrence of Thrombocytopenia After Cessation of Treatment

Romiplostim, like other thrombopoietic agents, causes increased platelet production; the treatment does not alter the underlying rate of platelet destruction. Therefore, it is expected that, in the presence of a chronic thrombocytopenic condition like ITP, platelet count will return to the baseline level upon discontinuation of treatment. The ITP phase 3 studies were not designed to characterize the magnitude and/or frequency of thrombocytopenia because subjects were allowed to continue directly into the open-label extension study after platelet counts fell to $50 \times 10^9/L$. (As described in Section 4.10, the median for 43 subjects receiving romiplostim to reach $\leq 50 \times 10^9/L$ after discontinuation of treatment was 2.0 weeks).

Four subjects with ITP in completed phase 1 and phase 2 studies (total $n = 57$ subjects receiving romiplostim in these studies) experienced decreases in platelet count below the pretreatment baseline levels; however, the events were transient (ie, resolved 1 to 14 days after onset) and minimal treatment was required. In these 4 cases, subjects had experienced an increase in platelet count after the initial treatment with romiplostim. It is considered that increases in platelet and megakaryocyte mass may deplete circulating eTPO, which is binding to TPO receptors on these cells (Bussel et al, 2006; Kuter and Rosenberg, 1995).

The reduction in other ITP therapies that may occur in the presence of a robust response to romiplostim could be expected to enhance the risk of thrombocytopenia upon the sudden discontinuation of romiplostim.

Bleeding Events Upon Discontinuation of Romiplostim in the Presence of an Anticoagulant and/or Anti-platelet Therapy

While participating in Study 20030212, one romiplostim subject had a fatal intracranial hemorrhage upon discontinuation of romiplostim following initiation of antiplatelet therapy for a cerebrovascular thrombosis. This subject was hospitalized for ischemic cerebrovascular accident 3 days after the last (21st) injection of romiplostim at $3 \mu\text{g}/\text{kg}$.

Platelet count on the day of the event was $107 \times 10^9/L$. Treatment included administration of antiplatelet and antihypertensive medications (acetylsalicylic acid [324 mg QD for 10 days] for stroke prevention and furosemide [40 mg, one time only] for congestive heart failure, which was ongoing since 1995). Approximately 9 days later the subject was transferred to the intensive care unit for serious intracranial hemorrhage; platelet count was $5 \times 10^9/L$. The subject died the following day, with the cause of death attributed to the cerebrovascular accident and intracranial bleed.

Plans for managing the identified risk of re-occurrence of thrombocytopenia after cessation of treatment are discussed in Section 6.

5.9.3 Increased Bone Marrow Reticulin

Background

Reticulin is a normal component of the bone marrow that can be detected using a reticulin (silver) stain. Increased reticulin staining is associated with many benign conditions. In contrast, bone marrow fibrosis is detected by specific staining techniques that detect collagen (trichrome, among many). Recent evidence has shown that the amount of bone marrow reticulin 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 and a poorer prognosis (Kuter et al, 2007), and may be associated with malignant conditions such as chronic idiopathic myelofibrosis (CIMF) (Tefferi, 2005).

Increased reticulin has been observed upon treatment with rhuTPO, IL-3, and IL-11 (Kuter 2007). TPO is a potent stimulator of megakaryocytic differentiation, maturation, and proliferation. In preclinical and clinical studies of TPO administration, reversible reticulin accumulation in the bone marrow has been reported in the literature and described in textbooks on bone marrow pathology (Kuter 2007; Yanagida et al, 1997; Douglas et al, 2002; Bain et al, 2001). In a retrospective analysis of bone marrow from 40 patients with ITP, reticulin was present in approximately two-thirds of patients who had not previously been exposed to any thrombopoiesis-stimulating agent (Mufti et al, 2006). Increased reticulin may be due to the increased number of megakaryocytes in the bone marrow of ITP patients as a result of romiplostim, consistent with findings associated with other TPOs (Kuter 2007). There is a potential risk that, with prolonged

exposure to romiplostim, increased reticulin will lead to clinical sequelae (in a worst-case scenario, bone marrow fibrosis with cytopenia).

Clinical Data

All events of “bone marrow abnormality” were assessed. These events were defined as any adverse events of increased reticulin (as indicated by various terms), whether serious or not, that was either absent or not assessed at baseline and emergent on study, or present at baseline and increased on study. These events were identified by careful inspection of the clinical database before unblinding of the pivotal studies.

Various terms have been used to describe this observation in the preclinical and clinical bone marrow reports (including “myelofibrosis”, “bone marrow abnormal”, “reticulin fibrosis”, and “fibrosis”); but, because of the tendency for romiplostim-induced changes to be reversible upon discontinuation of romiplostim treatment, and the lack of accompanying cytogenetic and flow cytometric abnormalities (when tested), the Applicant is referring to this observation as increased reticulin. However, the terms used here accurately reflect the data reported on the original case report forms.

Routine bone marrow assessments are not part of the standard care of ITP patients. They may be done in cases where the patient is not responding, is over 60 years of age, has atypical features, or if splenectomy is being considered (Cines and Bussel, 2005; George et al, 1996). Routine bone marrow assessments were not part of the pivotal phase 3 study designs, but were encouraged at the discretion of the treating physician. A bone marrow biopsy was recommended if abnormalities in the peripheral blood smear (eg, nucleated red blood cells) and /or loss of response or hyporesponse to increasing doses of romiplostim was observed.

Because this issue is of particular interest, an updated dataset is used here to present data on cases of increased reticulin. Data are included from the 120-day Safety Update. The overall subject incidence of bone marrow abnormality events for romiplostim-treated subjects was 4.1% (9 of 219 subjects) in the updated marketing application ITP safety set (120-day analysis). Most of these subjects had ITP of at least several years duration and most had undergone splenectomy. As would be expected for splenectomized patients, most had nucleated red blood cells on peripheral blood smears. There were no cytopenias associated with this finding. In most cases the bone marrow biopsies were triggered by changes in peripheral blood smear morphology (eg, tear drop and nucleated

red blood cells); some were triggered by changes in physical findings (eg, splenomegaly, increased vaginal bleeding). Most had received high doses of romiplostim. In most cases, findings were of reticulin (positive for silver stain), not collagen (trichrome stain). In 1 case, localized collagen was detected, which the investigator considered inconsistent with chronic idiopathic myelofibrosis (CIMF); in another case collagen was detected in a patient with a pretreatment del 20q on cytogenetics analysis. One of the 9 subjects is included due to a report of “bone marrow abnormality” and was subsequently found to have aplastic anemia; there was no mention of reticulin or collagen on the bone marrow reports for this subject.

Follow-up results were available in 5 cases: of these, 2 were shown to have improved reticulin in bone marrow, and 3 were shown to have stable reticulin in bone marrow upon discontinuation of romiplostim. None of the 5 follow-up cases was shown to have an increase in reticulin. Six subjects had immunophenotyping; 4 had normal results. When performed (3 cases), cytogenetics were normal in 2 cases.

Bone marrow biopsies were evaluated in Study 20050123. In this study, subjects participating in the romiplostim ITP pivotal studies were asked to consent to bone marrow biopsies (10 subjects enrolled) at baseline and after receiving treatment after either 3, 6, or 9 months in the open-label extension study (20030213). Of the 10 subjects evaluated, an increase in reticulin staining (rated mild) in a follow-up bone marrow sample was observed in 1 subject after 15 once-weekly doses of romiplostim (or a cumulative dose of 5110 µg) who was negative at baseline. Additionally, 1 subject who had no baseline sample was reported to have mild reticulin staining in the follow-up bone marrow sample (after 10 once-weekly doses of romiplostim or cumulative romiplostim exposure of 1860 µg) and 1 subject was reported to have mild reticulin at baseline, but had no follow-up reticulin assessment.

Amgen has developed a comprehensive program to manage the identified risk of increased bone marrow reticulin, which includes post-marketing studies to further define the concern. These plans are discussed in Section 6.

5.9.4 Thrombotic/Thromboembolic Complications

Background/Clinical Data

Romiplostim exerts its biological effect through the thrombopoietin receptor; therefore, romiplostim treatment is expected to increase platelet counts, which poses a theoretical risk for thrombotic / thromboembolic complications, especially if platelet levels exceed $450 \times 10^9/L$.

Thrombotic/thromboembolic events observed during the romiplostim clinical program were identified from the clinical database before unblinding of the pivotal studies. In the 3 safety sets, the duration adjusted and unadjusted incidence rates for thrombotic / thromboembolic events were similar for subjects receiving placebo and those receiving romiplostim (Table 10). The majority of cases were clinically confounded; subjects experiencing such events were found to have known risk factors such as a history of thrombotic events, presence of antiphospholipid antibodies or the factor V Leiden mutation.

In the 3 safety sets, the duration adjusted and unadjusted incidence rates for thrombotic/thromboembolic events were similar for subjects receiving placebo and those receiving romiplostim (Table 10).

Table 10. Thrombotic/thromboembolic Adverse Event Rates in the Romiplostim Clinical Program

	Marketing Application	
	Placebo	Romiplostim
Phase 3 ITP Safety Set		
Subject incidence	1/41 (2.4%)	2/84 (2.4%)
Study duration adjusted incidence (events per 100 subject-years)	5.4	4.7
Phase 3 ITP Long-term Safety Set		
Subject incidence	1/42 (2.4%)	4/117 (3.4%)
Study duration adjusted incidence (events per 100 subject-years)	5.3	6.2
ITP Safety Set		
Subject incidence	2/46 (4.3%)	9/204 (4.4%)
Study duration adjusted incidence (events per 100 subject-years)	10.1	7.0

Platelet aggregation (%) and change in platelet aggregation (%) from day -1 were examined on day 2, day 15, and at the end of study using collagen and adenosine diphosphate (ADP) as stimulants in a phase 1 double-blind, placebo-controlled study (Study 20040134) in healthy adult Japanese males. There was no detectable

enhancement or reduction of the aggregatory response of platelets after administration of romiplostim or placebo, suggesting that healthy subjects receiving romiplostim produce normally functioning platelets compared to their baseline platelets and platelets in placebo-treated healthy subjects.

Plans for managing the potential risk of thrombotic / thromboembolic complications are discussed in Section 6.

5.9.5 Neutralizing Antibodies That Cross React With eTPO

Key Points Related to Immunogenicity:

Following the administration of romiplostim to subjects with ITP in the 8 clinical studies included in the marketing application:

- One subject was positive for neutralizing antibodies against romiplostim at the end-of-study timepoint only, and was negative for neutralizing antibodies in the follow-up sample taken 4 months later. In the end-of-study sample from this subject, binding antibodies directed at romiplostim were not cross-reactive with TPO.
- No neutralizing antibodies to TPO were detected throughout the program in either subjects or animals dosed with romiplostim.
- The immunogenicity program was designed to identify an early signal of an immune response using the Biacore-based screening assay which provides a sensitive mechanism for detecting both low-affinity and high-affinity antibodies to both TPO and romiplostim.
- The ITP patient population was associated with a high background incidence of endogenous anti-TPO binding antibodies (6.9%). One subject in the group who had pre-existing antibodies to TPO (6.9%) was positive at only baseline for neutralizing antibodies; these antibodies did not cross react with romiplostim. An incidence of 4.4% of anti-TPO antibodies was observed post-romiplostim administration, suggesting that what was detected was likely a normal variation and not a “traditional” drug-induced event.
- Only one subject in the 20030213 study developed binding antibodies to both romiplostim and TPO following dosing with romiplostim.

- When considering the number of subjects with pre-existing antibodies and their natural development during the study, it is likely that seroconversion in the romiplostim treated subjects was due to the natural etiology of ITP and unlikely to have been influenced by exposure to the drug.

Background

A loss of response or hyporesponse to romiplostim within the recommended dosing range may indicate development of neutralizing antibodies against romiplostim, or increased bone marrow reticulin. The prescribing information instructs that a search for causative factors should be undertaken in the case of loss of response. Increased bone marrow reticulin is discussed in Section 5.9.3.

The peptide portion of romiplostim has no amino acid sequence homology to eTPO. This lack of sequence homology reduces the probability that antibodies to romiplostim, if produced, will bind to eTPO and cause thrombocytopenia. Some mice, rats, rhesus monkeys and Cynomolgus monkeys treated with romiplostim developed anti-romiplostim antibodies. No neutralizing anti-TPO antibodies were observed in any of these animals following treatment with romiplostim. These animals did not develop thrombocytopenia or other clinical sequelae. Although no evidence from animal studies indicates that romiplostim administration results in the development of thrombocytopenia-causing antibodies, the possibility of such an outcome in humans cannot be excluded. Therefore, antibody assessments were included in all clinical protocols in which romiplostim was administered.

An immunogenicity assessment program was initiated to support the development of romiplostim. The immunogenicity of romiplostim has been evaluated using 2 assays. One is a biosensor immunoassay to detect binding antibodies specific for romiplostim, the biologically active peptide portion of romiplostim, or TPO. This sensitive and specific immunoassay (or binding antibody assay) testing platform allowed detection of all classes of immunoglobulins capable of binding to the drug, and is the preferred method to detect low affinity antibodies (Swanson et al, 2004; Lofgren et al, 2007). The second is a cell-based bioassay that tests for the neutralization of romiplostim or TPO activity on cell growth. A positive result in the neutralizing biological assay indicates a potentially clinically relevant finding: a concern for reduced efficacy in the case of neutralizing antibodies against romiplostim, and a concern for clinical sequelae in the case of

neutralizing antibodies against TPO (cross-reactive immunogenicity resulting in thrombocytopenia).

Clinical Data

Using the neutralizing bioassay and immunoassay (binding antibody assay), subject samples were monitored for development of antibodies to romiplostim and TPO in all clinical studies, including long-term sampling in the open-label extension Study 20030213, in which samples for antibody assays were taken at screening, week 1, week 12, every 24 weeks thereafter (ie, weeks 36, 60, etc), and at the end of study.

Healthy subjects from 2 studies and subjects with ITP from 8 studies were evaluated for the development of antibodies to romiplostim or TPO. Seventy-eight healthy subjects (22 placebo and 56 romiplostim) were tested, and 215 subjects from 8 ITP clinical studies were tested (204 received romiplostim at some point, while 11 received only placebo). The results for both healthy subjects and subjects with ITP are shown in Table 11. Table 11 shows the incidence of subjects with pre dose positive antibodies to TPO and romiplostim; the incidence of subjects who developed antibodies to TPO and romiplostim (but were pre dose negative); and finally, those subjects who were pre dose positive but developed an increase in the amount of antibodies detected to either TPO or romiplostim. It should be noted that each group of subjects was independent and did not overlap. In the romiplostim dosed group, only one subject was found who developed antibodies to both romiplostim and TPO.

Table 11. Total Incidence of Binding Antibodies to Romiplostim and TPO in Subjects Receiving Romiplostim and Placebo

	Binding Antibodies in Placebo Subjects			Binding Antibodies in Romiplostim Subjects					
	Total Subjects	Subjects with Antibodies to Romiplostim (% incidence)	Subjects with Antibodies to TPO (% incidence)	Total Subjects	Pre-existing Antibody	Total Subjects with a Developing Antibody Response (% incidence)	Pre-existing Antibody		Total Subjects with a Developing Antibody Response (% incidence)
							Romiplostim	TPO	
Healthy Subject Studies	22	0 (0.0%)	1 (4.5%)	56	2 (3.6%)	1 (1.8%)	3 (5.4%)	1 (1.8%)	
ITP Subject Studies	45	4 (2 pre +) (8.9%)	6 (5 pre +) (13.3%)	204	17 (8.3%)	17 ^{a*} (2 pre +) (8.3%)	14 (6.9%)	9 ^a (2 pre +) (4.4%)	

Developing = after the first dose

Pre + are subjects who were pre-existing positive but developed an antibody response above the cut point post dose

^a 1 subject positive for antibodies to both romiplostim and TPO

* 1subject in this group had neutralizing antibodies to romiplostim

One positive neutralizing antibody result has been detected during the romiplostim clinical program in a splenectomized subject participating in the open-label extension Study 20030213. At week 60 this subject had positive anti-romiplostim binding antibody, and negative anti-TPO and anti-romiplostim neutralizing antibody results. The subject discontinued study at week 79 due to withdrawn consent; the blood sample obtained at this time was positive for anti-romiplostim binding and neutralizing antibodies (negative for anti-TPO binding antibodies). A follow-up blood sample obtained approximately 4 months after the week-79 sample was positive for anti-romiplostim binding antibodies, and negative for anti-romiplostim neutralizing and anti-TPO binding antibodies.

Plans for managing the potential risk of neutralizing antibodies that cross react with eTPO are discussed in Section 6.

5.9.6 Bleeding Events

As explained in Section 4.4, which describes the primary endpoint, bleeding events were not prespecified efficacy endpoints because they are subjective in nature, no validated scale exists for bleeding events in ITP, and their assessment is likely to be confounded by rescue medication given when the platelet count reaches levels at which intervention is recommended by treatment guidelines ($30 \times 10^9/L$).

Because bleeding events are obvious outcomes of the efficacy endpoint, platelet counts, bleeding events have been assessed as post-hoc analyses and the results are presented under Efficacy (Section 4.13).

5.9.7 Potential for Dosing Errors

Romiplostim is a highly potent peptide administered SC as a low volume dose. The proposed dosage form for marketing is as a powder for reconstitution with sterile water for injection. Two vial sizes are proposed that when reconstituted provide a solution of 500 mcg/mL: the 250 mcg single-use vial contains 375 micrograms of active ingredient which has to be reconstituted with 0.72 mL. Due to hold up in the vial and syringe, the deliverable amount of romiplostim is 250 micrograms in 0.5mL. The 500 mcg single-use vial contains 625 micrograms of active ingredient which has to be reconstituted with 1.2 mL. Due to hold up in the vial and syringe, the deliverable amount of romiplostim is 500 micrograms in 1.0 mL. In patients requiring low weekly doses as well as during the titration phase, a smaller amount of romiplostim may be required for

the weekly injection. Amgen is currently evaluating a smaller volume vial for these situations.

In the case of an excessive dose, thrombocytosis could be expected. The outcome in the case of overdose could be thrombotic/thromboembolic events due to high platelet counts. If too large a dose of romiplostim is given, platelet counts should be monitored weekly and the dosing guidance followed. The label states that in case of overdose, romiplostim should be discontinued and platelet counts monitored; treatment with romiplostim should be in accordance with dosing and administration recommendations. Individual patients may show variability in their platelet response to romiplostim.

In the case of underdosing, low platelet counts due to inadequate treatment could be expected. The outcome could be bleeding events. If too small a dose of romiplostim is given, platelet counts should be monitored weekly and the dosing guidance followed. Individual patients may show variability in their platelet response to romiplostim.

Amgen's plans for minimizing the risk of mistakes due to reconstitution or accidental under- or overdosing are discussed in Section 6.

6. Risk Management Program and Risk Minimization Plan

6.1 Key Points

- Amgen is committed to establishing a comprehensive risk management program including cautionary instructions in the prescribing information, pharmacovigilance (both routine and proactive), risk management activities, and additional clinical studies. Amgen believes these actions are appropriate and adequate to minimize the potential safety risks.
- The Risk Minimization Action Plan (RiskMAP) for romiplostim is designed to ensure appropriate use of romiplostim in ITP patients, minimize use of romiplostim in patients with thrombocytopenia caused by conditions other than ITP, and promote informed risk-benefit decisions regarding romiplostim use.
- The potential risks of romiplostim therapy will be managed in the RiskMAP through the following tools: prescribing information, Medication Guide, targeted education and outreach (including physician education initiatives, patient and patient advocacy group initiatives) and systems to measure and demonstrate program effectiveness.
- The RiskMAP tools will be evaluated prior to implementation via focus groups with both health care providers and patient advocacy; post-implementation, Amgen is committed to evaluating the RiskMAP program on a biannual basis.
- Amgen will provide a semi-annual report to the FDA regarding the status and progress of the RiskMAP program, with a discussion of the impact of the program and potential modifications as deemed appropriate.

6.2 Risk Management and Risk Minimization Action Plan (RiskMAP)

Based on experience in pre-clinical and/or clinical studies, and in light of what is known about thrombopoiesis, the following identified and potential risks have been determined for romiplostim in the setting of ITP:

Identified Risks

- Re-occurrence of thrombocytopenia after cessation of treatment
- Increased bone marrow reticulin

Potential Risks

- Thrombotic / thromboembolic complications
- Neutralizing antibodies that cross react with eTPO
- Progression of existing hematopoietic malignancies or MDS (with TPO receptor expression)
- Progression of increased reticulin to an irreversible bone marrow fibrotic state
- Potential for off-label use in indications where risk-benefit ratio has not been adequately studied
- Risk for medication errors due to the potency of romiplostim and the small volumes administered.

Amgen is committed to setting risk management tools in place to manage these identified and potential risks described in the RMP utilizing a combination of risk management tools, primarily instructions in the prescribing information, a patient Medication Guide, active surveillance, and additional studies. In addition, a formal RiskMAP is proposed (education, targeted outreach, and utilization studies) to address romiplostim utilization and to minimize off-label use. The Applicant believes these actions are appropriate and adequate to manage and minimize the safety risks of romiplostim.

The Risk Management Plan is outlined below.

6.2.1 Identified Risk: Re-occurrence of Thrombocytopenia After Cessation of Treatment

FDA-approved prescribing information remains the cornerstone of risk management. The risk of recurrent thrombocytopenia following treatment cessation is managed through inclusion of language in the proposed labelling in the warnings and precautions sections and inclusion as an ADR. The proposed warning language will state that

thrombocytopenia may reoccur upon discontinuation of romiplostim, increasing the patient's risk of bleeding, particularly if romiplostim is discontinued while the patient is on anticoagulants or anti-platelet agents. In addition, physicians will be advised to monitor patients closely for a decrease in platelet count and evaluate ITP treatments according to current treatment guidelines.

6.2.2 Identified Risk: Increased Bone Marrow Reticulin

Increased reticulin staining (reticulin fibrosis) is associated with many benign and malignant conditions while increased trichrome staining (collagen fibrosis) is particularly prominent in late stages of severe myeloproliferative diseases or following tumour metastasis to the bone marrow, typically irreversible.

Recent evidence has shown that the amount of bone marrow reticulin 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 and a poorer prognosis (Kuter et al, 2007).

Diagnosis of chronic idiopathic myelofibrosis is based on WHO criteria.

The risk management plan employs the following strategies: proposed labelling, a patient Medication Guide, active surveillance, and additional studies described below.

Warning of the risk of bone marrow fibrosis with cytopenia is included in the warnings and precautions sections of the prescribing information, and this risk is listed as an ADR in the appropriate sections of the prescribing information. The proposed label will state that reticulin has been observed in the bone marrow of some patients receiving TPO mimetics. In addition, the risk of progression of reticulin to an irreversible myelofibrotic state in the setting of long-term TPO receptor activation cannot be excluded. During treatment with romiplostim, the peripheral blood smear and complete blood count (CBC) should be examined for new or worsening morphological abnormalities (eg, teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). Furthermore, physicians will be advised that if a patient develops new or worsening morphological abnormalities or cytopenia(s), physicians should consider discontinuing treatment with romiplostim and consider bone marrow biopsy, including appropriate staining for fibrosis.

In addition, the applicant proposed a patient Medication Guide which will state that long-term use of medicines like romiplostim may cause changes in the bone marrow. In

addition, these changes may lead to abnormal or reduced blood cells. A physician will decide if these changes mean that the patient should stop taking romiplostim.

Active surveillance for cases of increased bone marrow reticulin will continue to be assessed from ongoing and future clinical trials, and post-marketing reports. These activities will include:

- Ongoing review by an expert bone marrow panel: an independent panel will review individual cases of bone marrow abnormalities from ongoing clinical studies and post-market reports and advise Amgen on potential risks and required actions.
- Proposed Physician Questionnaire: Amgen will request that reporting physicians complete a standard questionnaire for all reports of increased reticulin in the bone marrow of patients participating in romiplostim clinical trials or spontaneous reports received from post-marketing use. The aim of the questionnaire is to obtain comprehensive data on the nature of the reported event. Data on demographic characteristics, risk factors, ITP history, concurrent therapy, physical findings, CBC, bone marrow aspirates/biopsies, reticulin/collagen staining, time to onset, dose, action taken with romiplostim in response to the event and follow-up information will be collected. These data will be reported in periodic safety update reports.

In addition, Amgen proposes the following studies to assess the risk of increased bone marrow reticulin and bone marrow fibrosis.

6.2.2.1 Retrospective Observational Study to Define Prevalence of Bone Marrow Reticulin Who Have Not Received Romiplostim

Study 20070796 is being planned to assess the prevalence and nature of bone marrow reticulin and bone marrow fibrosis in adults with chronic ITP who have not received romiplostim. Historical data on 1,500 patients with ITP will be collected from 1996 to 2007 (ie, non-romiplostim patients) using the National Health Registry Databases of Denmark. Denmark gathers all health-related data on their citizens through a system of interlinked databases, recording all the health-related data on every inhabitant, including pathology and laboratory measurements, from birth until death. The Danish National Health Registry databases have been previously used to determine the safety profile of

pharmaceuticals and are considered as to be among the best pharmacovigilance and epidemiology tools by regulatory authorities, epidemiologists, and safety specialists in both the medical and scientific communities.

Cases of bone marrow fibrosis will be ascertained using electronic medical record review. Confirmation of the diagnosis will be carried out by an evaluation of the results of bone marrow biopsies and clinical presentation. The primary endpoint is the prevalence of increased reticulin as confirmed by bone marrow biopsies and potentially associated clinical signs, including splenomegaly, hepatomegaly, leukocytosis, cytopenia, peripheral blast cells, tear-drop shaped RBCs, nucleated RBCs, or granulocyte precursors. Secondary endpoints include the frequency of collagen fibrosis and incidence of primary myelofibrosis.

The study is descriptive in nature for the primary endpoint because bone marrow fibrosis is a rare event. All cases observed will be described in detail with regard to underlying disease, comorbidities, treatment history, medications, possible risk factors, and demographic characteristics. It is anticipated that a final report will be published in a peer-reviewed scientific journal in 2009.

6.2.2.2 Prospective Registry to Monitor the incidence of increased bone Marrow reticulin and the potential risk of Bone Marrow Fibrosis

Heightened post-marketing surveillance activities will take place, including an active prospective surveillance registry to monitor this risk. This is Protocol 20070797, "A Prospective Annual Assessment of Bone Marrow Fibrosis Risk in Adult Patients with Chronic Immune (Idiopathic) Thrombocytopenic Purpura Exposed or not Exposed to AMG 531 Using Existing Databases".

This will be a database safety cohort registry of all patients with chronic ITP registered in Denmark, Sweden, and Finland between January 1, 2009 (starting date) and December 31, 2019 (ending date). All adult patients identified as having chronic ITP (incident and prevalent cases through both hospital discharge registry and outpatient clinic registry as described by Frederiksen and Schmidt (1999)) on or after the starting date and up until 1 year before the ending date will be followed-up for at least 1 year and up to 10 years in either of two cohorts: Romiplostim Exposed Cohort or Romiplostim Unexposed Cohort. Incident and recurrent outcomes of interest will be assessed on an annual basis.

Cases with bone marrow abnormalities will be ascertained using electronic medical record review. Confirmation of the diagnosis of increased reticulin or collagen fibrosis in the bone marrow will be carried out by evaluation of the results of bone marrow biopsies.

6.2.2.3 Long Term Prospective Study to Assess changes in Bone Marrow Morphology

In order to prospectively capture long-term bone marrow changes in patients with ITP receiving romiplostim, Amgen proposes to conduct a longitudinal bone marrow morphology study. Approximately 200 subjects with ITP will be recruited and a baseline bone marrow biopsy with reticulin and trichrome staining will be required prior to romiplostim exposure. Eligible subjects will be men or women > 18 years of age with a platelet count below $30 \times 10^9/L$, and a diagnosis of ITP according to the American Society of Hematology (ASH) guidelines (George et al, 1996) who have failed at least 1 prior therapy. Continuous monitoring will include monthly assessments of peripheral blood smear for morphological abnormalities, sampling for antibody testing at baseline as well as after 24 months and 60 months of romiplostim exposure, bone marrow biopsy with reticulin and trichrome staining at screening/baseline and after 24 months and 60 months of romiplostim exposure. The primary endpoint of the trial will be the incidence of increased reticulin at month 24 and month 60 over baseline. The study will have adequate statistical power (> 80%) to conclude a significant increase if 10% of reticulin-naive subjects develop reticulin during the study using McNemar's test (type I error = 0.05, 2-sided).

6.2.3 Potential Risk: Thrombotic/Thromboembolic Complications

The risk management plan employs the following strategies: proposed labelling, a patient Medication Guide, active surveillance, and additional studies described below.

Warning of this potential risk will be included in the Warnings and Precautions sections of the proposed prescribing information. The proposed label will state that platelet counts above the normal range present a risk for thrombotic / thromboembolic complications. The incidence of thrombotic / thromboembolic events observed in clinical trials was similar between romiplostim and placebo and no association between these events and elevated platelet counts was observed. Dose adjustment guidelines should be followed.

The proposed Medication Guide will advise patients that they may have an increased chance of a blood clot, if their blood platelet count is too high during treatment with romiplostim.

Active surveillance activities include continuous assessment of cases from ongoing and future clinical trials, and post-marketing reports. In addition, Amgen proposed the following:

- Formation of an external expert advisory panel that will:
 - review reported thrombotic / thromboembolic adverse events that occur among subjects across the romiplostim clinical program and postmarketing reports
 - review Amgen's methods of analysis of reported thrombotic / thromboembolic events and make recommendations regarding additional analyses that could be used to further evaluate thrombotic / thromboembolic events

Amgen also proposes the following studies to assess the risk of thrombotic/thromboembolic complications.

Retrospective observational study to define rates of thromboembolic events: As described under increased bone marrow reticulin and bone marrow fibrosis (Section 5.9.3), Study 20070796 is being planned to determine the incidence rates of bone marrow reticulin, bone marrow fibrosis, and thromboembolic events in patients with chronic ITP. The incidence of thromboembolic events will be ascertained using electronic medical record review to identify terms from a predefined list. The cases identified will be described in detail with regard to underlying disease, comorbidities, treatment history, medications, possible risk factors, and demographic characteristics.

6.2.4 Potential Risk: Neutralizing Antibodies That Cross React With eTPO

The risk management plan employs the following strategies: proposed labelling, active surveillance, and additional studies described below.

The proposed prescribing information for romiplostim will provide a statement advising physicians that should hyporesponsiveness or failure to maintain a platelet response with romiplostim occur, they should undertake a search for causative factors including neutralizing antibodies to romiplostim and bone marrow fibrosis.

If formation of neutralizing antibodies is suspected, the label advises that Amgen should be contacted and provides a contact telephone number. As outlined in the Risk Management Plan, Amgen should be provided with a serum sample to test for the presence of binding and neutralizing antibodies to romiplostim and TPO.

The proposed label also provides instructions for monitoring for peripheral blood smear morphological abnormalities or cytopenias in the context of possible bone marrow fibrosis (see Section 5.9.3).

Active surveillance activities include continuous assessment of cases from ongoing and future clinical trials, and post-marketing reports including testing for both binding and neutralizing antibodies to romiplostim, eTPO, and any correlation with adverse events.

6.2.5 Potential Risk: Progression of Existing Hematopoietic Malignancies or MDS

The risk management plan employs the following strategies: proposed labelling, a patient Medication Guide, active surveillance, and additional studies described below.

Warning of this risk will be included in the Warnings and Precautions sections of the proposed prescribing information. Since the TPO receptor is predominantly expressed on the surface of cells of the hematopoietic lineage, there is a theoretical possibility that TPO receptor stimulators may enhance the progression of existing hematopoietic malignancies or MDS.

In addition, the Medication Guide will advise patients that if they have certain types of hematopoietic malignancies or MDS, using romiplostim might cause their disease to progress faster.

Active surveillance for cases of progression of existing hematopoietic malignancies or MDS will continue to be assessed from ongoing and future clinical trials, and post-marketing reports. These surveillance activities will include:

- Proposed Physician Questionnaire: Amgen will request that reporting physicians complete a standard questionnaire for all reports of progression of existing hematopoietic malignancies or MDS in patients participating in romiplostim clinical trials or spontaneous reports received from post-marketing use. The aim of the questionnaire is to obtain comprehensive data on the nature of the reported event. Data on demographic characteristics, risk factors, past medical history, concurrent therapy, physical findings, CBC, bone marrow aspirates/biopsies, time to onset, dose, action taken with romiplostim in response to the event and follow-up information will be collected. This data will be reported in periodic safety update reports.

Additional risk minimization activities are further described in the proposed RiskMAP (Section 6.2.9) and will involve an educational / training program and materials for prescribers, and a utilization study with the goal to minimize use of TPO receptor agonists to treat thrombocytopenia among patients with existing hematopoietic malignancies, MDS, or other thrombocytopenic conditions.

6.2.6 Progression of Increased Reticulin to an Irreversible Bone Marrow Fibrotic State

The potential risk of progression of increased reticulin to an irreversible bone marrow fibrotic state is described in Section 6.2.2. The actions proposed by Amgen to evaluate this risk are addressed in Section 6.2.2.

6.2.7 Potential Risk: Potential for Off-Label Use in Indications Where Risk-Benefit Ratio has not Been Adequately Studied

The risk management plan addresses the potential risk of non-indicated use of romiplostim in patients with thrombocytopenia caused by conditions other than ITP through proposed labelling guidance and post marketing activities.

The launch of romiplostim will be a specialty launch, focused on prescribers who have patients diagnosed with ITP in their practice setting. As such, field representative contact will be directed at hematology, medical oncology, hematology-oncology specialists. No Direct to Consumer media advertising will be used.

Additional risk minimization activities are further described in the proposed Risk MAP (Section 6.2.9) and will involve an educational / training program and materials for prescribers, and a utilization study with the goal to minimize use of TPO receptor agonists to treat thrombocytopenia caused by disorders other than ITP.

6.2.8 Potential Risk: Medication Errors and Overdose

The risk management plan addresses the potential risk of dosing errors and overdose through proposed labelling guidance. The proposed labelling will provide clear guidance on dose calculation, reconstitution, and administration for health care professionals. In addition, recommendations for the use of syringes with adequate graduations for low volume administration.

Healthcare providers will receive careful instruction on how to reconstitute the product, calculate the dose required, and adjust dose on the basis of routine platelet count monitoring. In addition, the following have been carefully evaluated to minimize the potential for medication errors: product brand name, product presentation (eg, package, vial, and healthcare provider reconstitution kits), and instructions for use. Additionally, the 2 strengths of romiplostim (500 and 250 µg) will be differentiated by the use of different color packaging. To further minimize this potential risk, a third smaller SKU size is under consideration.

6.2.9 Risk Minimization Action Plan (RiskMAP)

The term risk minimization action plan (RiskMAP) means a strategic safety program designed to meet specific *goals* and *objectives* in minimizing known risks of a product while preserving its benefits. A RiskMAP targets one or more safety-related health outcomes or goals and uses one or more *tools* to achieve those goals (Guidance for Industry - Development and Use of Risk Minimization Action Plans, March 2005; Guidance for Industry - Premarketing Risk Assessment, March 2005).

The proposed RiskMAP for romiplostim is designed to encourage appropriate use of romiplostim in chronic ITP patients thereby minimizing inadvertent exposure of romiplostim to patients with hematopoietic malignancy, MDS, or other thrombocytopenic conditions (off-label use).

The RiskMAP objectives for appropriate use are addressed through the following tools:

- proposed prescribing information and the patient Medication Guide previously described,
- targeted physician education and outreach
- patient and patient advocacy initiatives
- a post approval product utilization study.

6.2.9.1 Proposed Prescribing Information

The proposed prescribing information will clearly delineate the approved indication and patient population for the use of romiplostim.

6.2.9.2 Patient Medication Guide

The proposed Medication Guide will be provided to all patients at the initiation of romiplostim therapy with the objective of ensuring the appropriate use of romiplostim. This tool will work in coordination with physician education tools to ensure patient-physician dialog on the approved indication and risks associated with romiplostim use.

6.2.9.3 Targeted Physician Education and Outreach

The educational tools in this category employ specific, targeted education and outreach efforts in regard to safety risks and their main goal is to increase appropriate knowledge and behaviors of key groups (health care practitioners and to a certain extent patients) to prevent or mitigate the product risks and ensure appropriate product use. The educational efforts will be specifically addressing different audience groups in order to ensure adequate information to health care providers, patients, and payors. All tools will be driven by the US Prescriber Information which describes the approved indication, risks, warnings and precautions associated with use of romiplostim.

6.2.9.3.1 Health Care Professional Education Tools

Planned initiatives to educate physicians and other healthcare providers on the risks of romiplostim and ensure appropriate use include the following:

- Distribution of the Medication Guide to healthcare providers with the request to review the full prescribing information with their patients.
- Training and education program for health care professionals:
 - Continuing education for healthcare practitioners including product-focused programs developed by sponsor-supported accredited CE programs (independently developed)
 - Targeted face-to-face education and training of all purchasers on the differential diagnosis of ITP, the appropriate use of romiplostim, and the risks, warnings and precautions
 - Dissemination of safety information through sales force and Regional Medical Liaisons (RMLs) to prescribers
 - Education through Medical and Scientific Associations (ASH, etc.): Health care associations are another means by which healthcare providers keep current on new developments regarding various treatment options. Amgen has been engaged and will continue to do so in the future with relevant organisations (eg, ASH) to determine how to best communicate and educate their membership.

To minimize the risk of physicians inadvertently treating an MDS or hematopoietic malignancy patient with romiplostim, Amgen created a rigorous risk communications platform that is supported by three interconnected components:

- Internal Amgen systems that target promotion to qualified specialists and triggers training of every physician who purchases romiplostim
- A custom reminder system that delivers to the point of care a pre-use checklist along with each product purchase. The checklist specifies critical points about differential diagnosis of ITP and avoiding the administration of romiplostim to patients with MDS or hematopoietic malignancies.

- An integrated training kit, to be delivered to every purchasing physician, that provides the curriculum and tools to guide appropriate use of romiplostim. The training kit includes:
 - Education materials on ITP diagnosis and management based on ASH guidelines, including the importance of bone marrow biopsy and other diagnostic tools in ruling out hematopoietic malignancies, MDS, and bone marrow fibrosis.
 - Education materials on bone marrow biopsy assessment of hematopoietic malignancy/MDS
 - Specialist referral resource list for health care providers when using romiplostim: list of ITP treating specialists in different geographic regions to enable primary care provider referrals and/or consultation
 - Patient/caregiver disease state educational materials in office: ITP disease state educational materials to be distributed to ITP treating offices to help patient/caregivers understand their disease and various treatment options
 - Amgen will evaluate the performance of the program post-launch and continuously improve the communications program. The evaluation plan includes metrics that: 1) assesses monthly the effectiveness of systems implementation by Amgen, 2) assesses semi-annually the awareness of target stakeholders of key program components and messages, and 3) assesses annually the actual incidence of romiplostim use in patients diagnosed with MDS or hematopoietic malignancies.

The applicant will evaluate the performance of the program post-launch and continuously improve the communications program. The evaluation plan includes metrics that: 1) assesses monthly the effectiveness of systems implementation by The applicant, 2) assesses semiannually the awareness of target stakeholders of key program components and messages, and 3) assesses annually the actual incidence of romiplostim use in patients diagnosed with MDS or hematopoietic malignancies.

6.2.9.3.2 Sales Force and Promotional Activities

Promotional materials and sales force activities will be designed to meet risk minimization objectives:

- Amgen to only call on specialists: Amgen Sales Representatives will only promote romiplostim to targeted specialists, ie, Hematologists, Hematologists/Oncologists, Medical Oncologists and their office staff
- No Direct to Consumer media advertising will be used

- Product promotion messages define benefit/risk profile: the romiplostim benefit/risk profile will be highlighted in all promotional materials
- Monitoring of Utilization: Amgen will monitor all romiplostim purchases to trigger education. A periodic review of wholesaler/distributor sales data will be used to monitor romiplostim purchases by health care providers to trigger initial and follow-up education and training programs.

6.2.9.3.3 Prospective Romiplostim Utilization Study

A study is planned to prospectively analyze data from the PharMetrics Patient-Centric Database and HealthCore Managed Care Database, as well as data from the national health registry systems of Denmark, Sweden, and Finland. The following groups of patients will be identified:

- All patients who received at least one treatment of romiplostim.
- All chronic ITP patients (defined as individuals whose ITP lasts longer than 6 months and who have used any of the conventional treatment for ITP, regardless of romiplostim utilization).
- Estimate the proportion of romiplostim users who do not have an ITP condition as described in the romiplostim product label and to describe for what indications romiplostim was used in those situations.
- Investigate the proportion of romiplostim users who received more than the maximum dose of 10 µg/kg and to describe demographic and clinical characteristics of these patients and their utilization pattern.
- Describe romiplostim treatment and utilization patterns (up to 39 months) among chronic ITP patients (as described in the romiplostim product label).
- Compare treatment and utilization patterns among chronic ITP patients who receive romiplostim with those who are not receiving romiplostim.

The study will have 2 major components: (1) 3 annual cross-sectional assessments for all romiplostim users and (2) a cohort analysis (up to 36 months follow-up) for chronic ITP patients, regardless of romiplostim treatment status.

The cross-sectional assessments will be conducted at 9, 15 and 27 months after

launch of romiplostim in the respective country. The proposed analyses are descriptive in nature.

6.2.9.3.4 Evaluation of the RiskMAP and Monitoring of Risk Minimization Activities

The RiskMAP tools will be evaluated prior to implementation using the following approaches:

- Focus groups will be conducted with health care providers to evaluate the education tools
- Focus groups will be conducted with patient advocacy group members to evaluate the Medication Guide and patient-oriented tools and their value to patients

Post-implementation, the evaluation of the RiskMAP will take several forms; most critical is determining the performance of the overall RiskMAP in achieving its goals.

Amgen is committed to evaluating the RiskMAP program on a regular basis (biannually) for the following:

- Assessment of comprehension, knowledge, attitudes, and desired safety behaviors about drug safety risks in healthcare providers as result of the educational efforts (provider, pharmacist, nurse)
- Evaluation of the effectiveness of the Medication Guide delivery through surveys (web based) and other tools
- Market research on platelet counts at the time of treatment initiation and values achieved during treatment, duration of therapy, doses used, monitoring of off label use
- Surveys of patients and patient advocacy groups on knowledge regarding ITP and romiplostim

6.2.9.3.5 Periodic Reporting to the FDA on the Effectiveness of the Risk Minimization Program

Amgen proposes to report semiannually on the overall program, with an option to reduce or expand use of particular tools. The Agency will be notified of any change through an amendment to the program.

We propose that approximately 2 years after introduction of the RiskMAP, Amgen and the Agency discuss the impact of this Risk Minimization Action, the modifications and additions that might be made to the program, and the discontinuation of other aspects that based on findings do not appear to be adding value.

6.2.10 Risk Management - Conclusions

Amgen is committed to establishing a comprehensive risk management program including cautionary instructions in the prescribing information, pharmacovigilance (both routine and proactive), risk management activities, and additional clinical studies. In addition, a formal RiskMAP is proposed (education, targeted outreach, and utilization studies) to address romiplostim utilization and to minimize off label use. The applicant believes these actions are appropriate and adequate to manage and minimize the safety risks of romiplostim.

This approach is a reasonable alternative to the risk management tool of a performance-based access system (ie, restricted distribution), which in the speciality practice setting in which romiplostim will be used has no clear additional advantages over the RiskMAP proposed. Monitoring of the RiskMAP will assure appropriate utilization and allow for additional measures to be implemented if concerns arise.

7. CONCLUSIONS

7.1 Key Points

- Chronic ITP carries risks for serious bleeding, such as intracranial and gastrointestinal bleeding. Existing treatments are insufficiently efficacious, and are associated with significant adverse effects. New options are needed to treat thrombocytopenia in this population.
- The results of the phase 3 studies both individually and in the integrated analysis support the use of romiplostim in patients with chronic ITP.
- Amgen is committed to establishing a comprehensive risk management program including cautionary instructions in the prescribing information, pharmacovigilance (both routine and proactive), risk management activities, and additional clinical studies. Amgen believes these actions are appropriate and adequate to minimize the potential safety risks).
- In conclusion, the benefit-to-risk ratio for romiplostim as demonstrated by the clinical data is considered supportive for regulatory approval of the proposed indication. Potential safety risks can be appropriately and adequately minimized in the post marketing setting through the proposed risk management tools and RiskMAP.

7.2 Overall Conclusions

The efficacy of available medical therapies is inadequate for many patients with severe chronic ITP and for patients who are refractory to the surgical treatment of splenectomy, and tolerability and toxicity of many of these treatments limit their chronic use. Thus, a significant unmet medical need exists for a safe and effective long-term therapy to increase platelet counts in patients with chronic ITP.

Historically, there has been no general agreement on a standard definition of response in ITP, and definitions of response in the literature vary widely (Ruggeri, 2008). The endpoint of durable platelet response was stringently defined to capture a stable increase in platelet count. Overall platelet response (durable plus transient response) may be more comparable to definitions in the literature. The overall platelet response in the combined analysis of the 2 romiplostim pivotal studies was 83.1%, which compares

favourably to the results summarized in Table 1 for other agents. Many of the reports in Table 1 are from studies of ITP patients with less chronic disease than those enrolled in the romiplostim pivotal studies, and treatments were given as acute rather than long-term therapy.

Romiplostim had a tolerable safety profile in the clinical program. Most adverse events were mild and manageable. Individual risks were identified for risk mitigation activities beyond routine pharmacovigilance. The Applicant believes these actions are adequate to minimize the potential safety risks.

In consideration of the benefits and risks of romiplostim therapy, the overall profile of romiplostim can be considered favorable and the data are a strong basis for regulatory approval of the proposed indication. The risks will be addressed through appropriate instructions in the prescribing information and the development of a Risk Management Program addressing risk assessment, post-marketing pharmacovigilance studies and a RiskMAP.

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Appendix 1. Dose Adjustment Rules for Pivotal Studies

Platelet Count (x 10 ⁹ /L)	Action
Start-up (to a platelet count of > 50 x 10⁹/L):	
≤ 10	Dose increase by 2 µg/kg every week counts ≤ 10; can be increased every week.
> 10 to ≤ 50	Dose increase by 2 µg/kg after 2 consecutive weeks of counts ≤ 50; can be increased every 2 weeks.
> 50	Dose remains constant on weekly schedule; maintenance rules below.
Maintenance (once platelet count > 50 x 10⁹/L):	
≤ 10	Dose increase by 1 µg/kg every week when counts ≤ 10; can be increased every week.
> 10 to ≤ 50	Dose increase by 1 µg/kg after 2 consecutive weeks of counts in this range. Dose can be increased every 2 weeks.
> 50 to ≤ 200	Dose remains constant on weekly schedule
> 200 to ≤ 400	Dose reduced by 1 µg/kg after 2 consecutive weeks of platelet counts in this range. Dose can be reduced every 2 weeks.
> 400	Next scheduled dose held, and dose reduced by 1 µg/kg on next scheduled dosing day that count is ≤ 200 x 10 ⁹ /L.

Source: CSR 20030212 and CSR 20030105.

Dose adjustment based on local platelet counts was allowed weekly during weeks 2 through 12. After the first 12 weeks, dose adjustment was allowed every 4 weeks unless the investigator considered the subject at immediate risk. If a dose reduction was required in a subject receiving 1 µg/kg, the dose was held until the platelet count fell to ≤ 50 x 10⁹/L; at that point dosing resumed at 1 µg/kg using the maintenance dose adjustment rules.

Appendix 4. Bone Marrow Reticulin Questionnaire



Bone Marrow Reticulin Questionnaire for Subjects Receiving Romiplostim (AMG 531)

Page 1 of 2

1. Subject Information

AER #: _____ Male Female Subject Initials: ____ Date of Birth: __/__/__ (DD/MM/YY)

Report Source: Clinical Trial Spontaneous Report Other (specify): _____

If the subject was receiving Romiplostim in a clinical trial, please record the study #: _____

Romiplostim Start Date: __/__/__ (DD/MM/YY) Romiplostim Starting Dose: ____ µg/kg	Is Romiplostim still being administered? <input type="checkbox"/> Yes <input type="checkbox"/> No	If YES, what is the current dose: ____ µg/kg
		If NO, date and dose of the last administration? ____/____/____ (DD/MM/YY) ____ µg/kg

For which indication is/was the subject receiving treatment with romiplostim?	<input type="checkbox"/> ITP (complete sections 2, 3 & 6 below)
	<input type="checkbox"/> MDS (complete sections 2, 4 & 6 below)
	<input type="checkbox"/> Other (specify): _____ (complete sections 2 & 6 below)

2. Documentation of Bone Marrow Reticulin (please append all relevant source documentation)

How would you best characterize the bone marrow reticulin? (check only one)	<input type="checkbox"/> New diagnosis (no prior documentation of bone marrow reticulin)
	<input type="checkbox"/> Progression/worsening of previously documented bone marrow reticulin

What was the date of new diagnosis or the date of progression/worsening? __/__/__ (DD/MM/YY)

Please indicate which of the following procedures were performed in support of the current diagnosis (below):

Bone marrow aspirate	<input type="checkbox"/> Yes	____/____/____ (DD/MM/YY)	Silver stain: <input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Not done	
	<input type="checkbox"/> No			
Bone marrow biopsy	<input type="checkbox"/> Yes	____/____/____ (DD/MM/YY)	Trichrome stain: <input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Not done	
	<input type="checkbox"/> No			
Cytogenetics	<input type="checkbox"/> Yes	____/____/____ (DD/MM/YY)	Abnormalities:	If YES, specify: _____
	<input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No	
Immunophenotype	<input type="checkbox"/> Yes	____/____/____ (DD/MM/YY)	Abnormalities:	If YES, specify: _____
	<input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No	

What clinical features were present at the time of diagnosis (check all that apply):

anemia granulocytopenia thrombocytopenia increased peripheral blasts

bleeding (petechiae, epistaxis, etc.) increased nRBCs loss of efficacy

Other (specify): _____

Please quantify the degree of bone marrow reticulin and collagen using the Bauermeister scale (check only one):	1 <input type="checkbox"/>	Occasional fine individual fibers and foci of a fine fiber network
	2 <input type="checkbox"/>	Fine fiber network throughout most of the section; no coarse fibers
	3 <input type="checkbox"/>	Diffuse fiber network with scattered thick coarse fibers but no mature collagen (negative trichrome staining)
	4 <input type="checkbox"/>	Diffuse, often coarse fiber network with areas of collagenization (positive trichrome staining)



Bone Marrow Reticulin Questionnaire for Subjects Receiving Romiplostim (AMG 531)

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3. ITP History (please append all relevant source documentation)

Date of initial ITP diagnosis: ___ / ___ (MM/YY)			Age at Diagnosis: _____			
Which of the following assessment were performed at the time of initial diagnosis? (check all that apply)			<input type="checkbox"/> Peripheral blood smear <input type="checkbox"/> Cytogenetics <input type="checkbox"/> Phenotype <input type="checkbox"/> Bone marrow aspirate <input type="checkbox"/> Bone marrow biopsy <input type="checkbox"/> Silver stain <input type="checkbox"/> Trichrome stain			
ITP Treatment History (check all that apply):		Prior Treatment	Current Treatment		Prior Treatment	Current Treatment
	steroids	<input type="checkbox"/>	<input type="checkbox"/>	splenectomy	<input type="checkbox"/>	<input type="checkbox"/>
	IVIG	<input type="checkbox"/>	<input type="checkbox"/>	azathioprine	<input type="checkbox"/>	<input type="checkbox"/>
	danazol	<input type="checkbox"/>	<input type="checkbox"/>	cyclophosphamide	<input type="checkbox"/>	<input type="checkbox"/>
	rituximab	<input type="checkbox"/>	<input type="checkbox"/>	eltrombopag	<input type="checkbox"/>	<input type="checkbox"/>
	interferon alfa	<input type="checkbox"/>	<input type="checkbox"/>	other (specify): _____	<input type="checkbox"/>	<input type="checkbox"/>

4. MDS History (please append all relevant source documentation)

Date of MDS Diagnosis: ___ / ___ (MM/YY)		IPSS score at initial diagnosis: _____	
Were the following assessments performed at the time of initial diagnosis? (check all that apply)		<input type="checkbox"/> Bone marrow aspirate <input type="checkbox"/> Bone marrow biopsy <input type="checkbox"/> Cytogenetics <input type="checkbox"/> Peripheral blood smear <input type="checkbox"/> Silver stain <input type="checkbox"/> Trichrome stain	
Prior MDS Treatment: (check all that apply)		<input type="checkbox"/> azacitidine <input type="checkbox"/> thalidomide <input type="checkbox"/> decitabine <input type="checkbox"/> lenalidomide <input type="checkbox"/> supportive care (specify): _____ <input type="checkbox"/> other (specify): _____	

6. Risk Factors (please append all relevant source documentation)

Please indicate if there is subject history of any of the following risk factors (check all that apply):	<input type="checkbox"/> radiation treatment <input type="checkbox"/> exposure to Thorotrast contrast agents <input type="checkbox"/> exposure to benzene/toluene <input type="checkbox"/> other (specify): _____
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Reporter Name (print): _____ Title: _____

Reporter Signature: _____ Date: _____

Appendix 5. Hematopoietic Malignancy Questionnaire



Myeloid Malignancy Questionnaire for Subjects Receiving Romiplostim (AMG 531)

Page 1 of 2

1. Subject Information

AER #: _____	<input type="checkbox"/> Male <input type="checkbox"/> Female	Subject Initials: ___ ___	Date of Birth: ___/___/___ (DD/MM/YY)
Report Source: <input type="checkbox"/> Clinical Trial <input type="checkbox"/> Spontaneous Report <input type="checkbox"/> Other (specify): _____			
If the subject was receiving Romiplostim in a clinical trial, please record the study #: _____			
Romiplostim Start Date: ___/___/___ (DD/MM/YY)	Is Romiplostim still being administered?	If YES, what is the current dose: ___ µg/kg	
Romiplostim Starting Dose: ___ µg/kg	<input type="checkbox"/> Yes <input type="checkbox"/> No	If NO, date and dose of the last administration? ___/___/___ (DD/MM/YY) ___ µg/kg	
For which indication is/was the subject receiving treatment with romiplostim?	<input type="checkbox"/> ITP (complete sections 2, 3 & 6 below) <input type="checkbox"/> MDS (complete sections 2, 4 & 6 below) <input type="checkbox"/> CIT (complete sections 2, 5 & 6 below) <input type="checkbox"/> Other (specify): _____ (complete sections 2 & 6 below)		

2. Documentation of Myeloid Malignancy (please append all relevant source documentation)

How would you best characterize the myeloid malignancy? (check only one)	<input type="checkbox"/> Diagnosis of a new myeloid malignancy <input type="checkbox"/> Progression/transformation of a pre-existing myeloid malignancy		
What was the date of new diagnosis or the date of progression/transformation? ___/___/___ (DD/MM/YY)			
Please indicate the medically confirmed diagnosis and provide details (where applicable): <input type="checkbox"/> AML (FAB subtype): _____ <input type="checkbox"/> MDS (IPSS score): _____ <input type="checkbox"/> CML <input type="checkbox"/> PMF <input type="checkbox"/> ET <input type="checkbox"/> PV			
What clinical features were present at the time of diagnosis (check all that apply):	<input type="checkbox"/> anemia <input type="checkbox"/> granulocytopenia <input type="checkbox"/> thrombocytopenia <input type="checkbox"/> increased nRBCs <input type="checkbox"/> bleeding manifestations (petechiae, epistaxis, etc.) <input type="checkbox"/> loss of efficacy <input type="checkbox"/> increased blast cells <input type="checkbox"/> lymphadenopathy <input type="checkbox"/> hepatosplenomegaly <input type="checkbox"/> abnormal peripheral smear (specify): _____ <input type="checkbox"/> Other (specify): _____		
Were the following assessments performed at the time of initial diagnosis?	Bone marrow aspirate <input type="checkbox"/> Yes <input type="checkbox"/> No	If YES, provide date: ___/___/___ (DD/MM/YY)	Silver stain: <input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Not done
	Bone marrow biopsy <input type="checkbox"/> Yes <input type="checkbox"/> No	If YES, provide date: ___/___/___ (DD/MM/YY)	Trichrome stain: <input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Not done
	Cytogenetics <input type="checkbox"/> Yes <input type="checkbox"/> No	If YES, provide date: ___/___/___ (DD/MM/YY)	Abnormalities: <input type="checkbox"/> Yes <input type="checkbox"/> No If YES, specify: _____
	Immunophenotype <input type="checkbox"/> Yes <input type="checkbox"/> No	If YES, provide date: ___/___/___ (DD/MM/YY)	Abnormalities: <input type="checkbox"/> Yes <input type="checkbox"/> No If YES, specify: _____



Myeloid Malignancy Questionnaire for Subjects Receiving Romiplostim (AMG 531)

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3. ITP History (please append all relevant source documentation)

Date of initial ITP diagnosis: ___ / ___ (MM/YY)			Age at Diagnosis: _____			
Which of the following assessment were performed at the time of initial diagnosis? (check all that apply)			<input type="checkbox"/> Peripheral blood smear <input type="checkbox"/> Cyto genetics <input type="checkbox"/> Phenotype <input type="checkbox"/> Bone marrow aspirate <input type="checkbox"/> Bone marrow biopsy <input type="checkbox"/> Silver stain <input type="checkbox"/> Trichrome stain			
ITP Treatment History (check all that apply):		Prior Treatment	Current Treatment		Prior Treatment	Current Treatment
	steroids	<input type="checkbox"/>	<input type="checkbox"/>	splenectomy	<input type="checkbox"/>	<input type="checkbox"/>
	IVIG	<input type="checkbox"/>	<input type="checkbox"/>	azathioprine	<input type="checkbox"/>	<input type="checkbox"/>
	danazol	<input type="checkbox"/>	<input type="checkbox"/>	cyclophosphamide	<input type="checkbox"/>	<input type="checkbox"/>
	rituximab	<input type="checkbox"/>	<input type="checkbox"/>	eltrombopag	<input type="checkbox"/>	<input type="checkbox"/>
	interferon alfa	<input type="checkbox"/>	<input type="checkbox"/>	other (specify): _____	<input type="checkbox"/>	<input type="checkbox"/>

4. MDS History (please append all relevant source documentation)

Date of MDS Diagnosis: ___ / ___ (MM/YY)		IPSS score at initial diagnosis: _____	
Were the following assessments performed at the time of initial diagnosis? (check all that apply)		<input type="checkbox"/> Bone marrow aspirate <input type="checkbox"/> Bone marrow biopsy <input type="checkbox"/> Cyto genetics <input type="checkbox"/> Peripheral blood smear <input type="checkbox"/> Silver stain <input type="checkbox"/> Trichrome stain	
Prior MDS Treatment: (check all that apply)		<input type="checkbox"/> azacitidine <input type="checkbox"/> thalidomide <input type="checkbox"/> decitabine <input type="checkbox"/> lenalidomide <input type="checkbox"/> supportive care (specify): _____ <input type="checkbox"/> other (specify): _____	

5. CIT History (please append all relevant source documentation)

What is the primary disease for which the subject is under treatment? _____	When was the underlying disease first diagnosed? ___ / ___ (MM /YY)
What regimen(s) has the subject received as treatment for the underlying disease? (check all that apply)	<input type="checkbox"/> Chemotherapy (specify): _____ <input type="checkbox"/> Radiotherapy (specify): _____

6. Risk Factors (please append all relevant source documentation)

Please indicate if there is subject history of any of the following risk factors (check all that apply):	<input type="checkbox"/> hematologic malignancy <input type="checkbox"/> Solid tumor <input type="checkbox"/> radiation treatment <input type="checkbox"/> chemotherapy treatment <input type="checkbox"/> benzene exposure <input type="checkbox"/> formaldehyde exposure <input type="checkbox"/> family history of cancer/other malignancy <input type="checkbox"/> other (specify): _____
	Reporter Name (print): _____ Title: _____ Reporter Signature: _____ Date: _____