FDA Advisory Committee Briefing Document

Oncologic Drugs Advisory Committee
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Biological License Application (BLA) 125268: Romiplostim for the treatment of thrombocytopenia in certain adult patients with chronic immune (idiopathic) thrombocytopenia purpura

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Topics for Questions for Advisory Committee Members:

1. The committee will be asked to discuss the clinical efficacy data.

2. The FDA anticipates a focused discussion upon the following major safety considerations:

- Bone marrow reticulin deposition and risk for marrow fibrosis
- Increased blast cell counts in peripheral blood and the potential risk for leukemia, among patients with chronic immune thrombocytopenia purpura (ITP) as well as patients with myelodysplasia (MDS) or other conditions associated with thrombocytopenia
- Immunogenicity
- Thrombotic events
- Potential effects of decreased/suppressed intrinsic thrombopoietin (TPO) levels/activity by Romiplostim with worsening of thrombocytopenia after cessation of the drug.

3. FDA plans to request advice regarding the overall benefits and risks of Romiplostim for the proposed indication.

4. If recommended for approval, FDA anticipates additional discussion of:

- Dosing considerations, specifically,
  - should dosing attempt to achieve a specific platelet goal (if so, what is/are appropriate goals or ranges) and/or other therapeutic effect?
  - should dosing be continuous or include attempts at drug discontinuation?

- Patient Population:
  - whether the product should be reserved for use only after failure of one or more ITP medications

- Need for a risk management plan to ensure that, outside of clinical trials, Romiplostim is limited to patients with chronic ITP until additional data are available

- Additional clinical studies as post-marketing commitments, e.g.:
  - studies that compare continuous drug administration to intermittent drug administration
  - long term safety studies.

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Executive Summary

1. Product Background:

Romiplostim (Amgen, Inc.) is the subject of a Biological License Application (BLA) for marketing the product with the following clinical indication:

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

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

- Who are splenectomized and have an insufficient response to splenectomy."

Romiplostim is a recombinant protein that binds to the thrombopoietin (TPO) receptor on blood and bone marrow cells, including megakaryocytes. Romiplostim, in animal and human studies, stimulates the production of platelets and the Romiplostim clinical development program has focused upon use of the product in the treatment of certain patients with chronic ITP. Two major phase 3 studies in patients with chronic ITP have been completed and supply the major data assessing Romiplostim safety and efficacy. Two other areas of clinical development consist of Romiplostim use among patients with myelodysplasia and patients with chemotherapy-induced thrombocytopenia (CIT). The clinical data for these non-ITP usages are limited and preliminary, due to the on-going nature of the exploratory studies but available data are included within the Romiplostim license application.

Romiplostim is proposed for distribution as a lyophilized powder in single-use vials that contain 250 or 500 mcg of the product. The proposed starting dose is 1 mcg/kg administered subcutaneously every week by a healthcare provider. Dose adjustments are proposed to maintain platelet counts $\geq$ 50,000/mcL.

2. Clinical Background

Chronic ITP is generally regarded as an immunologically-mediated condition in which antibody development to platelet epitopes results in platelet destruction and thrombocytopenia, the laboratory hallmark of the condition. ITP occurs in adults and pediatric patients although the manifestations importantly differ between these two groups. In pediatric patients, thrombocytopenia frequently resolves spontaneously. In adults, ITP frequently results in chronic thrombocytopenia and a risk for life-threatening hemorrhage. Throughout this document chronic ITP will refer to the condition among adults.

The treatment for chronic ITP consists of various medications and, in some situations, splenectomy. The major goal of chronic ITP therapy is to reduce the risk for hemorrhage. In general, the risk for bleeding correlates with the severity of thrombocytopenia and a response to most therapy is indicated by improvement in platelet counts. Medications for chronic ITP consist of corticosteroids, intravenous gamma

globulin (IVIG), anti-D immunoglobulin and, in more refractory situations, a variety of immunomodulatory medications (such as rituximab or azathioprine).

Thrombocytopenia in chronic ITP is thought to result primarily from enhanced platelet destruction. However, inappropriately reduced platelet formation is also proposed as a contributor to the thrombocytopenia, as evidenced by "inappropriately low" blood levels of thrombopoietin (TPO) among thrombocytopenic patients with chronic ITP. Conceivably, Romiplostim functions to stimulate the formation of platelets in the setting of "inappropriately low" blood TPO levels among patients with chronic ITP.

The initial clinical experience with the use of TPOs as a stimulant of platelet production was complicated by the development of neutralizing antibodies in some subjects that resulted in thrombocytopenia. Romiplostim binds to the same cellular receptor as TPO and is thought to function similarly to stimulate platelet production. However, Romiplostim has no amino acid homology to TPO and, in clinical studies to date, has not been associated with the development of antibodies that cause thrombocytopenia.

3. Efficacy Data:

Two clinical studies provide the major data assessing effects of Romiplostim among patients with chronic ITP. Study 20030212 enrolled patients who had not undergone splenectomy and Study 20030105 enrolled patients who were refractory to splenectomy. Except for difference in eligibility criteria based upon splenectomy status, the studies had largely the same design features. Specifically, the studies used randomized (2:1; active: placebo), double-blind, placebo controlled designs with the enrollment of patients who were thrombocytopenic despite prior therapy with at least one prior ITP medication. Patients were exposed to the study drug for six months with weekly measurement of platelet counts. At the end of the study, patients were observed for another 12 weeks without administration of the study drug.

Within the two major clinical studies, the primary endpoint was "durable platelet response," defined as at least six weekly platelet counts ≥ 50,000/mcL during the last eight weeks of study drug treatment, in the absence of "rescue medications" at any time during the 24 week treatment period. The major secondary endpoints involved various comparisons of platelet count "responses" (defined as any weekly platelet count ≥ 50,000/mcL) and comparison of the use of thrombocytopenia "rescue medications." During the first 12 weeks of the study, investigators could decrease or eliminate the use of any concomitant ITP medications, based upon the observed platelet counts. Certain patient reported assessments (various scales) were also performed during the studies.

The baseline characteristics of enrolled subjects were similar between the randomized groups, with most subjects having received multiple prior ITP medications. Within the dataset pool of both studies, 11 patients had received a single prior ITP medication (2 in the placebo group and 9 in the Romiplostim group).

In both studies, statistically significant differences were observed for the primary endpoint and secondary endpoints, as shown below:

Table 1. Primary and Secondary Endpoint Results

Outcome	Study 20030105 (splenectomy)		Study 20030212 (no splenectomy)		p-value*
	Placebo n = 21	Romiplo-stim n = 42	Placebo n = 21	Romiplo-stim n = 41	
Durable platelet response, n (primary EP)	0 (0%)	16 (38%)	1 (5%)	25 (61%)	< 0.01
Major secondary Endpoints					
Overall platelet response, n	0 (0%)	33 (79%)	3 (14%)	36 (88%)	< 0.01
Weeks with platelet response, mean (SD)	0.2 (0.5)	12.3 (7.9)	1.3 (3.5)	15.2 (7.5)	< 0.01
Subjects requiring rescue medication, n	12 (57%)	11 (26%)	13 (62%)	7 (17%)	< 0.01
Subjects with durable platelet response with "stable dose", n	0 (0%)	13 (31%)	0 (0%)	21 (51%)	< 0.01

*p-value was similar for each study; "stable dose" was defined as a dose maintained within ± 1 mcg/kg during the last 8 weeks of treatment

Other notable efficacy findings included the number of subjects who were able to discontinue all baseline concomitant ITP medications, as shown in Table 2.

Table 2. Incidence of Concurrent ITP Medication Discontinuation from Baseline

	Study 20030105 (splenectomy)		Study 20030212 (no splenectomy)	
	Placebo	Romiplo-stim	Placebo	Romiplo-stim
Number of subjects receiving con ITP med at baseline	6	12	10	11
Subjects with con ITP meds discontinued at week 13	0/6	5/12	3/10	2/11
Subjects with con ITP meds discontinued at week 25	0/6	8/12	3/10	4/11

Overall, an increase in platelet counts from baseline by ≥ 20,000/mcL at any time point in either study (exclusive of eight weeks following a rescue medication) was achieved by approximately 90% of all subjects receiving Romiplostim and approximately 30% of subjects receiving placebo.

After a median of approximately 39 weeks of Romiplostim therapy in the long term extension study, patients continued to maintain platelet count responses in a pattern similar to those achieved during the 24 weeks of the two phase 3 clinical studies.

A large number of patient reported outcomes were assessed using the "ITP-PAQ scales" and most components of these scales showed no statistically significant difference between subjects who received placebo and those who received Romiplostim in the two studies.

Bleeding events were not prospectively defined efficacy endpoints but are important to assessment of the clinical meaningfulness of the platelet alterations. Bleeding is summarized within a pooled analysis of the two studies, as shown in Table 3.

Table 3. Bleeding Events (Pooled Analyses of Studies 20030105 and 20030212)

Outcome	Placebo, n = 41	Romiplostim, n = 84
Any bleeding event	25 (61%)	48 (57%)
Serious bleeding event	4 (10%)	5 (6%)

Platelet function studies have not been performed upon the platelets recovered from patients with chronic ITP. A study of the platelets obtained from healthy Japanese subjects did not reveal alterations (from baseline) in ADP-stimulated platelet aggregation following administration of Romiplostim.

4. Safety

The Romiplostim safety database consists of information from 204 patients with chronic ITP who were exposed to the product. Additionally, interim study data are available from patients exposed to Romiplostim in studies of its use in the treatment of thrombocytopenia associated with myelodysplasia (MDS) and cancer chemotherapy.

The two phase 3 clinical studies provide the placebo-comparative information. Within these two studies, the proportion of patients who were reported as having any adverse event was 100% for the Romiplostim group and 95% for the placebo group. Any serious adverse event was reported for 17% for the Romiplostim group and 20% for the placebo group. Four deaths occurred during the two studies (3 in the placebo group and one in the Romiplostim group).

The major safety concern from the clinical development program relates predominantly to five items: a) reticulin formation and risk for marrow fibrosis, b) risk for malignancy or progression of malignancy, c) thrombotic risks, d) re-occurrence of thrombocytopenia after cessation of Romiplostim therapy and e) immunogenicity.

a. Reticulin formation and risk for marrow fibrosis:

Reticulin is a bone marrow stromal structural fiber usually identified with a silver stain of the marrow. Increased reticulin staining ("reticulin fibrosis") has been associated with many benign and malignant conditions. Stromal structural fibers that are identified with a trichrome stain are thought to represent the presence of type 1 collagen, a type of fiber that has been associated with bone marrow fibrosis and severe hematological

complications. Laboratory and animal data suggest that TPOs stimulate megakaryocytes (and perhaps other cells) to secrete molecules (such as transforming growth factor beta) which culminate in the deposition of reticulin within the bone marrow.

Repeated-dose studies of Romiplostim in rats showed dose-related marrow fibrosis that resolved following discontinuation of the doses. Marrow fibrosis was not detected in studies of Romiplostim administration to monkeys. Consequently, one of the safety concerns for long term administration of Romiplostim to humans is the potential for progressive marrow stromal structural fiber deposition that may culminate in marrow fibrosis and hematocytopenias.

Within the phase 3 clinical studies, no patients receiving placebo had a bone marrow abnormality reported as an adverse event while one event (serious) was reported for a patient who received Romiplostim. This subject was a 40 year old man participating in Study 20030105 (splenectomy) who had a history of "reticulin fibrosis" at the time of study enrollment. A baseline bone marrow sample taken four months prior to study entry revealed generalized marrow hypoplasia and a "mild, patchy increase in reticulin." Over a five week period, Romiplostim was administered weekly to a maximum dose of 9 mcg/kg with no increase in platelet counts above 10,000/mcL. At week six, increased nucleated red blood cells were detected on a peripheral blood examination and a subsequent bone marrow examination revealed "increase of reticulin fibrosis" that was assessed as a serious event. The patient discontinued Romiplostim and the study. A three month follow-up bone marrow examination revealed a return to "mild, patchy increase in reticulin" similar to baseline.

Within the initially filed Romiplostim safety database of 204 patients with chronic ITP, increased reticulin fiber deposition was reported as an adverse event in six patients. One additional finding of increased bone marrow reticulin was detected in a marrow sample from a patient who did not have the event recorded as an adverse event. In general, abnormalities in peripheral blood smear examinations triggered the bone marrow examinations.

Within a recently supplied safety update to the BLA, the sponsor reports that nine of 219 patients with chronic ITP had an adverse event related to a bone marrow abnormality (increased reticulin in eight).

Overall, the safety database indicates that Romiplostim administration was associated with increased reticulin in approximately 4% (9/219) of exposed subjects. Two patients had "localized collagen" detected, in addition to the reticulin deposition. Follow-up marrow results are available for five of the nine patients. Two patients had improved reticulin findings and three had stable reticulin findings, all following Romiplostim discontinuation.

b. Risk for malignancy or progression of malignancy

The TPO receptor (cMpl) is expressed on the surface of hematopoietic cells and *in vitro* studies have indicated that high concentrations of TPO can stimulate the proliferation of myeloid blast cells. Limited data suggest that TPO may serve as an *in vivo* myeloid leukemic growth factor. To date, detection of the cMpl receptor has not been confirmed on the surface of solid tumors.

In the two phase 3 studies, only seven adverse events for "neoplasia" were reported, five in the placebo group (n = 41) and two in the Romiplostim group (n = 84). The two neoplasms in the Romiplostim group consisted of a basal cell carcinoma in one subject and a B cell lymphoma in another subject. Hematologic malignancies in the phase 3 studies consisted of multiple myeloma (placebo-exposed patient) and the previously noted B-cell lymphoma (Romiplostim-exposed patient).

One of the important considerations for Romiplostim marketing is the potential use of the product among patients who have thrombocytopenia that is not due to chronic ITP, especially patients who may have underlying conditions that increase the risk for hematologic malignancy. The preliminary findings (data cut-off of February, 2007) from a study of patients with MDS (Study 20050159) importantly inform the potential use of Romiplostim and raises concerns regarding blast cell proliferation and the potential risk for leukemia. The preliminary study findings indicate that Romiplostim may increase the proportion of blast cells in the peripheral blood of some patients with MDS.

Study 20050159 was an uncontrolled study of Romiplostim in patients with thrombocytopenia and MDS (low or intermediate risk). The study used an open label design in which subjects were enrolled into sequential dose cohorts of 300, 700, 1000 and 1500 mcg Romiplostim, administered weekly for three consecutive weeks. Follow-up was assessed on week four and thereafter subjects could elect to continue Romiplostim in a treatment extension study. Follow-up in this study is ongoing but, as of February, 2007, 44 subjects had been enrolled and completed the treatment period (4 weeks) and 25 subjects were receiving Romiplostim in the extension period. At the data cut-off point, five subjects had discontinued receiving Romiplostim due to progression of MDS to acute myelogenous leukemia (AML), based upon initial site assessment. Further investigation by the sponsor determined that, of these five patients, two subjects had MDS progression without progression to AML, one subject had disease progression to chronic myelomonocytic leukema (CMML) and two subjects had transient increases in blast cell counts that resolved following Romiplostim discontinuation. Additionally, three other subjects had increased blast cells detected in peripheral blood (evaluation is ongoing to determine whether the increases are transient). FDA's review of these data is on-going.

Within the ITP safety dataset that includes the phase 3 studies and uncontrolled studies, 12/204 patients experienced adverse events recorded as neoplasms with two of these events recorded as hematologic (B-cell lymphoma; multiple myeloma).

c. Thrombotic risks:

Within the pool of the two phase 3 studies, only three thrombotic events were reported:

Placebo group: 1) pulmonary embolus

Romiplostim group: 2) peripheral arterial embolus in a patients with atrial fibrillation

3) cerebrovascular accident

Overall, within the safety dataset of 204 patients with chronic ITP, a total of 14 patients experienced thrombotic events following Romiplostim initiation, inclusive of the uncontrolled exposure.

d. Alteration of intrinsic TPO/worsening of thrombocytopenia after cessation of Romiplostim therapy

Conceivably, administration of Romiplostim may suppress intrinsic thrombopoietin levels such that patients develop severe thrombocytopenia following discontinuation of the product. Additionally, the discontinuation of concomitant ITP medications may increase the risk for thrombocytopenia following discontinuation of Romiplostim. The phase 3 studies did not address the risks for post-discontinuation thrombocytopenia since patients who did not retain platelet responses were allowed to enroll in an extension study, In the phase 1 and 2 studies, (n = 57 receiving Romiplostim) four subjects experienced decreases in platelet counts below the pretreatment baseline levels; all counts approximated baseline levels within 14 days of the thrombocytopenia onset (generally following increases in concomitant ITP medications).

e. Immunogenicity:

During the clinical development program, monitoring was performed for antibody formation to Romiplostim, TPO and the peptide portion of Romiplostim using a "binding assay." The bioactivity of any antibody formation was assessed using a cellular proliferation assay, referred to as the "neutralization assay."

Overall, 17/204 (8%) of patients exposed to Romiplostim developed binding antibodies against the drug and 9/204 (4%) developed binding antibodies against TPO. No patient developed neutralizing antibodies to TPO.

One patient with chronic ITP developed neutralizing antibodies to Romiplostim in the open-label, extension study. At week 60 the subject has positive anti-Romiplostim binding antibody and negative anti-TPO and anti-Romiplostim neutralizing antibody results. The subject chose to discontinue the study at week 79 and that week's laboratory results revealed formation of anti-Romiplostim binding and neutralizing antibodies (no anti-TPO binding antibodies). Four months later, the anti-Romiplostim neutralizing antibodies were undetectable although anti-Romiplostim binding antibodies were still present (anti-TPO antibodies remained negative). This subject had a history of splenectomy and had platelet counts generally within the range of 40,000 to 100,000/mcl over the last many weeks prior to Romiplostim discontinuation. At the time of Romiplostim "tapering" on week 78, the platelet count was 76,000/mcL. At week 79, the

platelet count was 37,000/mcL and no reports of adverse events were recorded between week 79 and the time of the final antibody test (four months after the detection of the neutralizing antibody).

5. Risk Management Plan

The proposed risk management plan involves the following major components:

a) Product labeling, including a Medication Guide
b) Completion of on-going clinical studies
c) Careful review of spontaneously submitted adverse reaction reports of myeloid malignancy progression or reticulin formation, including completion of a physician questionnaire
d) Prospective registry study to be conducted in Scandinavian countries, focused upon detection of bone marrow fibrosis and reticulin deposition
e) Prospective, open-label, follow-up study of ~ 200 subjects with ITP to assess bone marrow morphologic changes (at month 24 and 60 over baseline), hematologic alterations and antibody formation
f) Retrospective observational studies to characterize rates of thrombotic events among patients with ITP; as well as to define the prevalence of bone marrow reticulin
g) Drug utilization study to evaluate patterns of Romiplostim use applying two US databases and Scandinavian national health registries.

At the present time, the sponsor does not propose to restrict the distribution of Romiplostim in a manner that will limit its use to patients with chronic ITP.

Medical Summary Document

This summary consists of the most pertinent components of the medical officer's draft review document

In this document, Romiplostim is occasionally referred to as "AMG 531"

1.0 SUMMARY OF CLINICAL FINDINGS

1.1 Overview of Clinical Program

The clinical development program consists primarily of two (with or without splenectomy) blinded pivotal studies providing controlled data on safety and efficacy, and an open-label extension study providing uncontrolled long-term clinical experience. Study 20030105 (study 105), conducted in patients status post splenectomy, enrolled 21 patients receiving placebo versus 42 patients receiving AMG 531. Study 20030212 (study 212), conducted in patients who have not yet undergone splenectomy, enrolled 21 patients receiving placebo and 41 patients receiving AMG 531. Study 20030213 (study 213), an uncontrolled open-label extension study conducted in patients who have completed an earlier AMG 531 study, provided clinical experience supporting the continued safety and effectiveness of AMG 531 with long-term use. Patients in the extension study included 100 patients who completed one of the pivotal studies, either in the treatment or the placebo arm.

1.2 Efficacy

The pivotal studies and the extension study show that AMG 531 is an effective agent for the long-term management of chronic ITP in adults. Overall, the nearly 90% (88%, 36/41) overall platelet response in patients refractory to first-line medical therapies (prior to splenectomy) is substantially higher than that reported in the literature for therapy-naive patients. AMG 531 is less effective in patients refractory to second-line therapy (splenectomy) but remains significantly more effective than currently available therapies.

- In both of the two controlled pivotal studies, the primary efficacy endpoint was durable platelet response, defined as at least 6 weekly platelet counts of $\geq$ 50,000/uL during the last 8 weeks of treatment, in the absence of rescue medication at any time during the 24-week treatment period. Between the two studies, about one-half of all patients on AMG 531 (41 of 83 subjects, 49%) achieved a durable platelet response, compared with only one of 42 patients on placebo (2.4%, $p < 0.0001$). As might be expected, the rate of durable platelet response (on AMG 531 therapy) was greater in patients who have not undergone splenectomy (61%, study 212) than in those status post splenectomy (38%, study 105). Most patients on AMG 531 responded quickly, reaching a median platelet count of 50,000/uL after one to three doses (30% by week 2, 42% by week 3, 54% by week 4). These platelet counts remained within 50-200 (x 10^3/uL) for the remainder of the study. In study 105, the median platelet counts at baseline were 14.7 (placebo) and 13.5 (AMG 531), and the platelet counts after one dose were 15.0 (placebo) and 27.0 (AMG 531). Similar platelet responses were observed in study 212: median platelet counts at baseline were 19.3 (placebo) and 18.7 (AMG 531), and the platelet counts after one dose were 23.0 (placebo) and 43.5 (AMG 531).
- In the open-label extension study (study 213), platelet responses to long-term AMG 531 dosing (mean 29.3 weeks, SD 16.4 weeks, range 1-60 weeks) were similar to those seen in the pivotal studies, without unexpected long-term adverse events.

The data from these three studies indicate that, in patients with ITP refractory to current fist-line (low-dose corticosteroids) or second-line (splenectomy) therapies, AMG 531 is a

safe and effective alternative in raising the platelet count to levels where the patients are considered to be no longer at increased risk for serious bleeding (>100,000/uL).

1.3 Safety

Irrespective of splenectomy status, common non-serious adverse events occurred in greater proportions in the AMG 531 group than in the placebo group, but the proportions of patients experiencing severe, serious, or fatal events were not appreciably different between the two groups. Severe, serious, or fatal events occurred in greater proportions among patients with more refractory ITP (splenectomy) than in less refractory disease (non-splenectomy).

Study 105 (Splenectomy)

Nearly all patients experienced at least one adverse event (95.2% placebo, 100% AMG 531). Severe (grade 3 or worse) events occurred in similar proportions (38% placebo, 36% AMG 531), as did serious events (24% placebo, 21% AMG 531).

- The most common adverse events were (placebo, AMG 531): headache (33%, 43%), epistaxis (33%, 38%), and fatigue (24%, 31%). The common events occurred more frequently in the AMG 531 group than in the placebo group. None of the common events were considered serious.
- Adverse events occurring at $\geq$ 10% higher incidence in the AMG 531 group than in the placebo group were (placebo, AMG 531): myalgia (0%, 21%), dizziness (0%, 17%), laryngopharyngeal pain (0%, 14%), fever (0%, 14%), arthralgia (14%, 29%), insomnia (5%, 19%), and diarrhea (10%, 21%).
- Fewer patients in the AMG 531 group (4 patients, 19%) experienced a clinically significant bleeding (11 events) than in the placebo group (4 patients, 10%). All of these bleeding events occurred at a platelet count < 20 (x 10^3/uL).
- Three patients (14%) in the placebo group and none in the AMG 531 group died. The causes of death in the three patients were: pneumonia/intracranial hemorrhage, pulmonary embolism, and intracranial hemorrhage.
- One patient discontinued AMG 531 due to moderate arthralgia and myalgia, and another patient on AMG 531 experienced severe arthralgia and myalgia (considered treatment-related).
- Two patients in the AMG 531 group (versus none in the placebo group) withdrew from the study due to adverse events. One patient withdrew due to "reticulin fibrosis of the bone marrow," a condition that predated AMG 531 therapy. A second patient discontinued treatment due to moderate arthralgia and myalgia.

Study 212 (Non-Splenectomy)

Nearly all patients experienced an adverse event (95% placebo, 100% AMG 531). Severe adverse events occurred in similar proportions (30% placebo, 24% AMG 531), as did serious adverse events (15% placebo, 12% AMG 531).

- The most common adverse events were (placebo, AMG 531): fatigue (35%, 36%), contusion (35%, 31%), headache (30%, 26%), epistaxis (15%, 26%), and arthralgia (25%, 24%).
- Adverse events that occurred at $\geq$ 10% higher incidence in the AMG 531 group than in the placebo group were (placebo, AMG 531): dizziness (0%, 17%), abdominal pain (0%, 12%), shoulder pain (0%, 12%), and epistaxis (15%, 26%).

- One patient in the AMG 531 group died. The patient experienced a cerebrovascular accident 3 days after 22 doses of AMG 531, at which time the platelet count was 107 (x 10^3/uL). Ten days after starting antiplatelet and antihypertensive agents to treat the cerebrovascular accident, the patient suffered intracranial hemorrhage which ultimately led to death.
- One patient in each group withdrew from the study due to an adverse event. The patient in the placebo group discontinued due to metastasis to liver, and the patient in the AMG 531 group withdrew due to life-threatening B-cell lymphoma.

2.0 INTRODUCTION AND BACKGROUND

2.1 PRODUCT INFORMATION

AMG 531, an Fc fusion protein produced by recombinant DNA technology in Escherichia coli, stimulates platelet production by binding to the thrombopoietin receptor. The fusion protein consists of a human IgG_1 Fc domain covalently linked to two peptides that bind to the thrombopoietin receptor. The fusion protein shares no amino acid sequence homology with the endogenous thrombopoietin molecule. AMG 531 is indicated for treatment of thrombocytopenia in adults with ITP refractory to low-dose corticosteroid therapy or splenectomy.

The drug product is supplied as a sterile, preservative-free lyophilized white powder (ready for reconstitution with sterile water for injection) in glass vials containing 250 or 500 ug of deliverable product per vial. The concentration of AMG 531 after reconstitution is the same for both vial presentations (500 ug/mL), and the volume of the reconstituted product to be administered by subcutaneous injection will range typically between 0.1 mL (initial dose of 1 ug/kg for a 50 kg patient) and 2 mL (maximum dose of 10 ug/kg for a 100 kg patient).

2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS

In immune thrombocytopenic purpura (ITP), platelets or platelet precursors are destroyed through mechanisms involving autoimmune antibodies and thrombocytopenia results when the rate of platelet destruction exceeds that of production. Current management of ITP consists of initial therapy using corticosteroids and immune globulins, followed by splenectomy in poor responders, and the use of cytotoxic chemotherapy agents and androgens in those responding poorly to splenectomy. All of the current therapies aim to modulate the immune system to decrease the rate of platelet destruction. Significant side effects (corticosteroids, cytotoxic agents, androgens), the need for major surgery (splenectomy), or the inability to consistently deliver long-term therapy (intravenous immune globulins) have limited the effectiveness of current therapies. Many patients with ITP remain inadequately treated and remain at increased risk for bleeding (relative to patients without ITP), including life-threatening bleeding. A significant unmet medical need exists in the management of ITP refractory to current therapies viable for long-term use (low-dose corticosteroids and splenectomy).

3.0 INDICATION

Romiplostim (AMG 531) is indicated for the treatment of thrombocytopenia in adult patients with chronic ITP, who are (sponsor's wording):

- Nonsplenectomized and have had an inadequate response or are intolerant to corticosteroids and/or immunoglobulins, or
- Splenectomized and have had an inadequate response to splenectomy.

4.0 MAJOR CLINICAL STUDIES

4.1.1 Methods (Studies 105, 212, and 213)

Objectives:

- Primary: To evaluate the efficacy of AMG 531 in the treatment of thrombocytopenia in adult subjects with ITP, as measured by durable platelet response during the last 8 weeks of treatment, and other platelet response parameters
- Secondary: To evaluate the following:
  - Overall safety of AMG 531
  - Possible reductions in concurrent ITP therapies while receiving AMG 531
  - Changes in Patient Reported Outcomes (PRO) and Health Resource Utilization

Investigational Treatment:

- AMG 531 administered by subcutaneous injection (SC) once weekly (QW) for 24 weeks
- Weekly dose adjustment as needed based on weekly platelet counts
- Target maintenance platelet count range of 50 and 200 x 103/uL
- Initial starting dose of 1 ug/kg, maximum dose of 15 ug/kg
- Discontinue treatment upon detection of neutralizing antibodies to AMG 531 or eTPO
- After 24 weeks, monitor patients though week 36 or until platelet counts < 50 ($x10^3$/uL).

Concurrent Therapies:

- Concurrent therapies for ITP permitted if at constant dose and schedule
- Reductions in concurrent ITP therapies could occur once platelet counts were > 100 x 10^3/uL
- Rescue medication permitted for bleeding or wet purpura, or if at immediate risk for bleeding
- Use of rescue medication disqualifies the patient for achieving durable platelet response
- Platelet counts within 8 weeks of rescue medication excluded for response analyses

Subject Selection:

- Inclusion criteria specific to each study:
  - Study 105: Splenectomy at least 4 weeks prior to study entry and refractory to splenectomy
  - Study 212: Patients who had not undergone splenectomy
  - Study 213: Prior completion of studies 105 or 212
- Inclusion criteria common to all three studies:
  - At least 18 years old
  - Diagnosis of ITP according to American Society of Hematology (ASH) guidelines
  - Must have completed at least 1 previous treatment for ITP
  - Pretreatment platelet count $\leq$ 30 x 103/uL (mean of 3 counts during screening)
  - No pretreatment Individual platelet count > 35 x 103/uL
  - Hemoglobin of at least 9.0 g/dL at baseline
  - Over 60 years of age: Chronic ITP documented by bone marrow to exclude MDS

Table 4: Dose Adjustment in Pivotal Studies (Study 105 and 212)

Platelet Count ($x 10^9$/L)	Action
Start-up (to a platelet count of > 50 x 10^9/L):	
≤ 10	Dose increase by 2 µg/kg every week in which counts ≤ 10 x 10^9/L; can be increased every week.
> 10 to ≤ 50	Dose increase by 2 µg/kg after 2 consecutive weeks of counts ≤ 50 x 10^9/L; can be increased every 2 weeks.
> 50	Dose remains constant on weekly schedule; maintenance rules below.
Maintenance (once platelet count > 50 x 10^9/L):	
≤ 10	Dose increase by 1 µg/kg every week in which counts ≤ 10 x 10^9/L; 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 constant
> 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 on which count ≤ 200 x 10^9/L.

Table 5: Dose Adjustment in Extension Study (Study 213)

Platelet Count ($x 10^9$/L)	Action
≤ 10	Dose increased by 2 µg/kg every week when platelet counts are ≤ 10. Dose can be increased every week.
> 10 to < 50	Dose increased by 2 µg/kg after two consecutive weeks of platelet counts < 50. Dose can be increased every two weeks.
50 to 250	Dose may be adjusted by 1 µg/kg (increased or decreased) at the investigators discretion, no more frequently than every two weeks. The maximum dose is 10 µg/kg weekly.
> 250 to < 400	Dose reduced by 1 µg/kg after two consecutive weeks of platelet counts in this range. Dose can be reduced every two weeks.
≥ 400	Next scheduled dose held, and the dose will be reduced by 1 µg/kg on the next scheduled dosing day that the platelet count is < 250 x 10^9/L.

When the dose needed to be reduced in a patient receiving 1 µg/kg, the dose was held until the platelet count fell to 50 (x 10^3/uL), and dosing was resumed at 1 µg/kg according to the maintenance dose adjustment guidelines shown above.

Analysis Sets:

- Phase 3 Efficacy Set: All patients randomized in studies 105 or 212
- Long-term Efficacy Set: All patients in phase 3 efficacy set and enrolled in study 213

In evaluating long-term efficacy, efficacy data were collected from the start of treatment in studies 105 or 212 through data cut-off in study 213 (28 November 2006). This analysis set does not include patients who did not enroll in either study 105 or study 212.

4.1.2 General Discussion of Endpoints (Pivotal Studies)

- Primary: Proportion of patients achieving a durable platelet response
- Major Secondary Endpoints:
  - Incidence of overall platelet response (durable and transient)
  - Number of weekly platelet responses
  - Proportion of patients requiring rescue medication
  - Incidence of durable platelet response on stable dose
- Endpoint Definitions:
  - Durable Response: $\geq$ 6 weekly platelet counts $\geq$ 50 x 10^3/uL during last 8 weeks of treatment with no rescue medication use at any time during treatment
  - Transient Response: $\geq$ 4 weekly platelet counts $\geq$ 50 x 10^3/uL between weeks 2 and 25 in the absence of a durable platelet response
  - Overall Response: Achieving either of the two mutually exclusive response types (transient response or durable response)
  - Non-Response: Fewer than 4 weekly platelet counts $\geq$ 50 x 10^3/uL between weeks 2 and 25
  - Stable dose: Dose within 1 µg/kg during the last 8 weeks of treatment (weeks 17 to 24)

4.1.3 Study Design (Pivotal Studies)

- Randomized, double-blind, placebo-controlled, 24-weeks, planned 60 subjects
- Stratification by presence or absence of baseline ITP therapy
- 2/1 randomization (AMG 531/placebo)

4.1.4 Efficacy Findings (Studies 105, 212, and 213)

Subject Disposition

A total of 125 patients enrolled in the two pivotal efficacy studies (105 and 212). Due to 2:1 randomization, 83 subjects were assigned to AMG 531 and 42 to placebo. Patient disposition are shown in the tables.

- Discontinuation of Investigational Therapy: Most of the 25 patients who discontinued the investigational therapy had been assigned to receive placebo. Nearly one-half of placebo patients discontinued the investigational therapy (49% placebo, 6.0% AMG 531). The most common reasons for discontinuation were (placebo vs AMG 531): subject request (17% vs 1%), other (17% vs 0%), and adverse events (2% vs 5%).
- Study completion rate was higher in the AMG 531 group (86% placebo vs 95% AMG 531). The most common reasons for withdrawing from study were (placebo vs AMG

531): adverse events (2.4% vs 3.6%), withdrawal of consent (4.8% vs 1.2%), and death (4.8% vs 0.0%).

- Of the 115 patients completing a pivotal study, 100 enrolled in study 213: 34 of 42 patients (81%) on placebo and 66 of 83 patients (80%) on AMG 531.

Table 6: Numbers of Patients in Phase 3 Studies by Region

	Study 20030105		Study 20030212		Both Studies		
	Placebo (N = 21) n (%)	AMG 531 (N = 42) n (%)	Placebo (N = 21) n (%)	AMG 531 (N = 41) n (%)	Placebo (N = 42) n (%)	AMG 531 (N = 83) n (%)	Total (N = 125) n (%)
North America	17 (81.0)	32 (76.2)	17 (81.0)	37 (90.2)	34 (81.0)	69 (83.1)	103 (82.4)
United States	17 (81.0)	32 (76.2)	17 (81.0)	37 (90.2)	34 (81.0)	69 (83.1)	103 (82.4)
European Union	4 (19.0)	10 (23.8)	4 (19.0)	4 (9.8)	8 (19.0)	14 (16.9)	22 (17.6)
France	0 (0.0)	5 (11.9)	2 (9.5)	0 (0.0)	2 (4.8)	5 (6.0)	7 (5.6)
Netherlands (The)	3 (14.3)	1 (2.4)	0 (0.0)	1 (2.4)	3 (7.1)	2 (2.4)	5 (4.0)
Spain	0 (0.0)	3 (7.1)	1 (4.8)	3 (7.3)	1 (2.4)	6 (7.2)	7 (5.6)
United Kingdom	1 (4.8)	1 (2.4)	1 (4.8)	0 (0.0)	2 (4.8)	1 (1.2)	3 (2.4)

Table 7: Numbers of Patients in Phase 3 Studies and Study 213

	Study 20030105		Study 20030212		Both Studies		
	Placebo n (%)	AMG 531 n (%)	Placebo n (%)	AMG 531 n (%)	Placebo n (%)	AMG 531 n (%)	Total n (%)
Randomized to Phase 3 Study	21 (100.0)	42 (100.0)	21 (100.0)	41 (100.0)	42 (100.0)	83 (100.0)	125 (100.0)
Discontinued Phase 3 Study	2 (9.5)	2 (4.8)	4 (19.0)	2 (4.9)	6 (14.3)	4 (4.8)	10 (8.0)
Completed Phase 3 Study	19 (90.5)	40 (95.2)	17 (81.0)	39 (95.1)	36 (85.7)	79 (95.2)	115 (92.0)
Enrolled in Study 20030213[a]	18 (85.7)	34 (81.0)	16 (76.2)	32 (78.0)	34 (81.0)	66 (79.5)	100 (80.0)
Discontinued from Study 20030213	0 (0.0)	5 (11.9)	1 (4.8)	4 (9.8)	1 (2.4)	9 (10.8)	10 (8.0)
Continuing in Study 20030213	18 (85.7)	29 (69.0)	15 (71.4)	28 (68.3)	33 (78.6)	57 (68.7)	90 (72.0)

Percentages were based on number of subjects randomized to phase 3 studies.

[a] All subjects received AMG 531 in Study 20030213 but were listed under their randomized treatment in a previous phase 3 study.

Table 8: Disposition of Patients in Phase 3 Studies and Enrolled in Study 213

	Study 20030105		Study 20030212		From Both Studies		
	Placebo n (%)	AMG 531 n (%)	Placebo n (%)	AMG 531 n (%)	Placebo n (%)	AMG 531 n (%)	Total n (%)
Completed Phase 3 Study	19	40	17	39	36	79	115
Enrolled in Study 20030213[a]	18 (100.0)	34 (100.0)	16 (100.0)	32 (100.0)	34 (100.0)	66 (100.0)	100 (100.0)
Completed Study 20030213	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Continuing in Study 20030213	18 (100.0)	29 (85.3)	15 (93.8)	28 (87.5)	33 (97.1)	57 (86.4)	90 (90.0)
Discontinued from Study 20030213	0 (0.0)	5 (14.7)	1 (6.3)	4 (12.5)	1 (2.9)	9 (13.6)	10 (10.0)
Protocol deviation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Noncompliance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Adverse event	0 (0.0)	2 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.0)	2 (2.0)
Consent withdrawn	0 (0.0)	2 (5.9)	1 (6.3)	3 (9.4)	1 (2.9)	5 (7.6)	6 (6.0)
Requirement for alternative therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Administrative decision	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	1 (2.9)	0 (0.0)	1 (3.1)	0 (0.0)	2 (3.0)	2 (2.0)
Protocol-specified criteria	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject request	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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[a] All subjects received AMG 531 in Study 20030213 but were listed under their randomized treatment in a previous phase 3 study.

Baseline Characteristics

- In both pivotal studies, demographic and other baseline characteristics were typical for patients with ITP and were well balanced between placebo and AMG 531 groups. The baseline characteristics are shown in the tables.
  - Median age was 52 years (range 21-88), with a higher proportion of patients $\geq$ 65 years of age in the placebo group (31% placebo vs 22% AMG 531). The median weight was 81 kg (range 52-169) in the placebo group and 78 kg (range 44-138) in the AMG 531 group. There were more women (65%) than men (35%) and most patients (82%) were white.
  - Baseline platelet counts were severely thrombocytopenic: median 18 (range 2 - 31) x 10^3/uL in the placebo group and 16 (range 2 - 29) x 10^3/uL in the AMG 531 group. Median values for RBC, WBC, hemoglobin, and endogenous thrombopoietin were balanced between the two treatment groups and across the two studies.
  - Per patient selection criteria, all patients had received at least 1 previous ITP therapy: most (94%) patients had received corticosteroids and most patients (66% in study 212, 94% in study 105) had received IVIG. All patients had been extensively treated and had failed current first-line therapies for ITP.

- In study 212, about one-half of the patients (47%) had received one or two prior ITP therapies, and 39% had received 3 or 4 prior therapies.
- In study 105, patients had been treated even more extensively for ITP: 27% had received 8 to 10 prior treatments, 54.0% had received 5 to 7 prior treatments, and none had received fewer than 3 treatments.

Table 9: Demographics of Patients in Phase 3 Studies

	Study 20030105		Study 20030212		Both Studies		
	Placebo (N = 21)	AMG 531 (N = 42)	Placebo (N = 21)	AMG 531 (N = 41)	Placebo (N = 42)	AMG 531 (N = 83)	Total (N = 125)
Age Group in Years - n (%)							
18-29	2 (9.5)	3 (7.1)	3 (14.3)	2 (4.9)	5 (11.9)	5 (6.0)	10 (8.0)
30-39	1 (4.8)	10 (23.8)	3 (14.3)	5 (12.2)	4 (9.5)	15 (18.1)	19 (15.2)
40-49	4 (19.0)	8 (19.0)	5 (23.8)	10 (24.4)	9 (21.4)	18 (21.7)	27 (21.6)
50-59	5 (23.8)	8 (19.0)	1 (4.8)	11 (26.8)	6 (14.3)	19 (22.9)	25 (20.0)
60-64	4 (19.0)	3 (7.1)	1 (4.8)	5 (12.2)	5 (11.9)	8 (9.6)	13 (10.4)
≥ 65	5 (23.8)	10 (23.8)	8 (38.1)	8 (19.5)	13 (31.0)	18 (21.7)	31 (24.8)
Age (years)							
n	21	42	21	41	42	83	125
Mean	53.9	51.1	55.0	53.3	54.5	52.2	53.0
SD	13.4	15.6	21.7	15.5	17.8	15.5	16.3
Median	56.0	50.5	46.0	52.0	52.0	52.0	52.0
Q1, Q3	46.0, 62.0	38.0, 64.0	39.0, 73.0	41.0, 63.0	43.0, 70.0	40.0, 63.0	40.0, 64.0
Min, Max	26, 72	27, 88	23, 88	21, 80	23, 88	21, 88	21, 88
Sex - n (%)							
Male	10 (47.6)	15 (35.7)	5 (23.8)	14 (34.1)	15 (35.7)	29 (34.9)	44 (35.2)
Female	11 (52.4)	27 (64.3)	16 (76.2)	27 (65.9)	27 (64.3)	54 (65.1)	81 (64.8)
Race - n (%)							
White or Caucasian	19 (90.5)	34 (81.0)	18 (85.7)	31 (75.6)	37 (88.1)	65 (78.3)	102 (81.6)
Black or African American	2 (9.5)	3 (7.1)	1 (4.8)	3 (7.3)	3 (7.1)	6 (7.2)	9 (7.2)
Hispanic or Latino	0 (0.0)	3 (7.1)	2 (9.5)	3 (7.3)	2 (4.8)	6 (7.2)	8 (6.4)
Asian	0 (0.0)	2 (4.8)	0 (0.0)	3 (7.3)	0 (0.0)	5 (6.0)	5 (4.0)
Japanese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (1.2)	1 (0.8)
Aborigine	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 10: Baseline Hematology and Endogenous Thrombopoietin (Phase 3 Studies)

	Study 20030105		Study 20030212		Both Studies		
	Placebo (N = 21)	AMG 531 (N = 42)	Placebo (N = 21)	AMG 531 (N = 41)	Placebo (N = 42)	AMG 531 (N = 83)	Total (N = 125)
Platelet Count(10^9/L)							
n	21	42	21	41	42	83	125
Mean	14.1	15.0	19.1	17.9	16.6	16.4	16.5
SD	8.1	7.8	8.3	7.6	8.5	7.8	8.0
Median	14.7	13.5	19.3	18.7	17.7	15.7	16.0
Q1, Q3	7.7, 20.7	8.7, 22.3	14.7, 25.7	11.7, 24.3	8.0, 24.0	9.3, 24.0	9.2, 24.0
Min, Max	2, 28	3, 29	5, 31	2, 29	2, 31	2, 29	2, 31
Red Blood Cells (10^{12}/L)							
n	21	42	20	41	41	83	124
Mean	4.55	4.53	4.43	4.53	4.49	4.53	4.52
SD	0.53	0.53	0.60	0.56	0.56	0.55	0.55
Median	4.64	4.57	4.45	4.52	4.60	4.55	4.55
Q1, Q3	4.22, 4.94	4.21, 4.96	3.92, 4.93	4.20, 4.95	4.10, 4.94	4.20, 4.96	4.19, 4.96
Min, Max	3.3, 5.4	3.1, 5.5	3.1, 5.4	3.4, 5.8	3.1, 5.4	3.1, 5.8	3.1, 5.8
White Blood Cells (10^9/L)							
n	21	42	20	41	41	83	124
Mean	9.64	10.42	7.70	6.63	8.69	8.55	8.59
SD	4.87	4.81	3.74	3.04	4.41	4.44	4.41
Median	8.40	8.94	7.70	5.87	8.20	7.30	7.66
Q1, Q3	7.40, 9.30	7.18, 13.40	5.01, 8.61	4.70, 7.55	6.50, 9.10	5.40, 10.14	5.66, 9.55
Min, Max	4.2, 26.9	3.6, 21.4	2.9, 18.7	2.6, 16.2	2.9, 26.9	2.6, 21.4	2.6, 26.9
Hemoglobin (g/L)							
n	21	42	20	41	41	83	124
Mean	142.24	136.29	128.50	136.66	135.54	136.47	136.16
SD	18.77	16.00	16.45	14.64	18.79	15.25	16.43
Median	145.00	137.00	125.00	136.00	133.00	137.00	137.00
Q1, Q3	133.00, 155.00	129.00, 145.00	118.00, 138.00	127.00, 148.00	123.00, 149.00	128.00, 147.00	125.00, 147.50
Min, Max	89.0, 177.0	91.0, 174.0	103.0, 165.0	105.0, 160.0	89.0, 177.0	91.0, 174.0	89.0, 177.0
eTPO (pg/mL)							
n	20	41	20	41	40	82	122
Mean	200.0	130.2	176.7	132.8	188.4	131.5	150.2
SD	198.8	120.2	398.5	184.7	311.1	154.8	219.0
Median	124.3	113.0	81.4	93.8	108.3	102.1	103.1
Q1, Q3	92.6, 210.3	63.4, 134.8	36.7, 122.1	59.8, 145.6	51.2, 150.0	59.8, 142.2	57.3, 144.6
Min, Max	31, 744	31, 586	31, 1848	31, 1228	31, 1848	31, 1228	31, 1848

Baseline platelet count = Mean of platelet counts at Days -8, -2 and pre-dose Day 1.
For others, baseline = pre-treatment value closest to the first dosing.

Table 11: ITP Treatment History (Phase 3 Study subjects)

	Study 20030105		Study 20030212		Both Studies		
	Placebo (N = 21)	AMG 531 (N = 42)	Placebo (N = 21)	AMG 531 (N = 41)	Placebo (N = 42)	AMG 531 (N = 83)	Total (N = 125)
Number of Subjects with Prior ITP Treatment - n (%)							
Corticosteroid	20 (95.2)	42 (100.0)	19 (90.5)	37 (90.2)	39 (92.9)	79 (95.2)	118 (94.4)
Immunoglobin	20 (95.2)	41 (97.6)	18 (85.7)	29 (70.7)	38 (90.5)	70 (84.3)	108 (86.4)
Anti-D Antibody (WinRho)	9 (42.9)	19 (45.2)	6 (28.6)	20 (48.8)	15 (35.7)	39 (47.0)	54 (43.2)
IV Immune Gamma Globulin	20 (95.2)	39 (92.9)	15 (71.4)	26 (63.4)	35 (83.3)	65 (78.3)	100 (80.0)
Chemotherapy	17 (81.0)	26 (61.9)	7 (33.3)	6 (14.6)	24 (57.1)	32 (38.6)	56 (44.8)
Vinscristine/vinblastine	10 (47.6)	17 (40.5)	0 (0.0)	0 (0.0)	10 (23.8)	17 (20.5)	27 (21.6)
Cyclophosphamide	14 (66.7)	21 (50.0)	7 (33.3)	6 (14.6)	21 (50.0)	27 (32.5)	48 (38.4)
Azathioprine	5 (23.8)	10 (23.8)	1 (4.8)	2 (4.9)	6 (14.3)	12 (14.5)	18 (14.4)
Danazol	10 (47.6)	13 (31.0)	1 (4.8)	6 (14.6)	11 (26.2)	19 (22.9)	30 (24.0)
Rituximab	15 (71.4)	30 (71.4)	5 (23.8)	13 (31.7)	20 (47.6)	43 (51.8)	63 (50.4)
Other	11 (52.4)	21 (50.0)	6 (28.6)	10 (24.4)	17 (40.5)	31 (37.3)	48 (38.4)
Number of Splenectomy Subjects - n (%)	21 (100.0)	42 (100.0)	0 (0.0)	0 (0.0)	21 (50.0)	42 (50.6)	63 (50.4)
Total Number of ITP Treatments Subject Ever Received[a] - n (%)							
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	2 (9.5)	9 (22.0)	2 (4.8)	9 (10.8)	11 (8.8)
2	0 (0.0)	0 (0.0)	9 (42.9)	9 (22.0)	9 (21.4)	9 (10.8)	18 (14.4)
3	1 (4.8)	3 (7.1)	5 (23.8)	8 (19.5)	6 (14.3)	11 (13.3)	17 (13.6)
4	1 (4.8)	7 (16.7)	2 (9.5)	9 (22.0)	3 (7.1)	16 (19.3)	19 (15.2)
5	4 (19.0)	9 (21.4)	2 (9.5)	4 (9.8)	6 (14.3)	13 (15.7)	19 (15.2)
6	5 (23.8)	6 (14.3)	0 (0.0)	1 (2.4)	5 (11.9)	7 (8.4)	12 (9.6)
7	4 (19.0)	6 (14.3)	1 (4.8)	1 (2.4)	5 (11.9)	7 (8.4)	12 (9.6)
8	5 (23.8)	5 (11.9)	0 (0.0)	0 (0.0)	5 (11.9)	5 (6.0)	10 (8.0)
9	0 (0.0)	6 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (7.2)	6 (4.8)
10	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (0.8)

[a] ITP treatments include: Corticosteroid, Anti-D Antibody, IV Immune Gamma Globulin, Vincristine/Vinblastine, Danazol, Cyclophosphamide, Azathioprine, Rituximab, other, and splenectomy status (Yes).

Efficacy Results

Study 105 (Splenectomy)

- Primary Endpoint: A significantly greater proportion of patients in the AMG 531 group achieved the primary endpoint, durable platelet response (see definition above), than in the placebo group (38% vs 0%, $p = 0.0013$).
- Major Secondary Endpoints: The results were consistent with those for the primary endpoint. In comparison with the placebo group, the AMG 531 group achieved an overall platelet response more frequently (79% vs 0%, $p < 0.0001$) and required rescue medication less frequently (26% vs 57%, $p < 0.05$).

Study 212 (Non-Splenectomy)

For the primary and the major secondary endpoints, the results obtained in patients who had not undergone splenectomy were consistent with those obtained in patients who had undergone splenectomy (61% vs 5%); AMG 531 appears to be effective in increasing the platelet count in patients with ITP, irrespective of splenectomy status.

Controlled Studies (Studies 105 and 212)

- When results of the two pivotal studies were combined, 7% of the patients on placebo and 83% of patients on AMG 531 achieved an overall response (odds ratio of 71, AMG 531 over placebo, $p < 0.0001$).
- The efficacy results are summarized in the tables. Compared to patients in study 212 (prior to splenectomy), patients in study 105 (splenectomy) took longer to reach an effective dose and stabilized at a higher dose (1.9 µg/kg median dose in study 212 vs 2.9 µg/kg in study 105). A comparison across the two studies suggests:
  - As might be expected, AMG 531 is more effective in patients less refractory to current standard therapy for ITP (e.g., prior to requiring splenectomy), than in more refractory patients (e.g., status post splenectomy).
  - Although AMG 531 appeared to be more effective in patients prior to splenectomy (study 212) than after splenectomy (study 105), these results likely reflect underlying disease severity (selection bias): splenectomy may actually increase the effectiveness of AMG 531.
  - In patients with ITP refractory to current first-line therapies (low dose steroids, IVIG, anti-D), AMG 531 reduces, but does not eliminate, the need for rescue medication. Whether or not AMG 531 can eliminate the need for rescue medication in therapy-naive patients remains to be seen in future studies.

Table 12: Major Efficacy Endpoints in Study 105

Endpoint	Placebo (N = 21)	AMG 531 (N = 42)	Treatment group comparison p-value
Primary Endpoint			
Durable Platelet Response[a]			
Incidence Rate	0 (0.0%)	16 (38.1%)	0.0013
95% CI	(0.0%, 16.1%)	(23.6%, 54.4%)	
Key Secondary Endpoints			
Overall Platelet Response[a]			
Incidence Rate	0 (0.0%)	33 (78.6%)	< 0.0001
95% CI	(0.0%, 16.1%)	(63.2%, 89.7%)	
No. Weeks with Platelet Response[b]			
Mean	0.2 weeks	12.3 weeks	< 0.0001
SD	0.5 weeks	7.9 weeks	
Proportion of Subjects Requiring Rescue Medication[a]			
Incidence Rate	12 (57.1%)	11 (26.2%)	0.0175
95% CI	(34.0%, 78.2%)	(13.9%, 42.0%)	
Durable Platelet Response with Stable Dose[a]			
Incidence Rate	0 (0.0%)	13 (31.0%)	0.0046
95% CI	(0.0%, 16.1%)	(17.6%, 47.1%)	

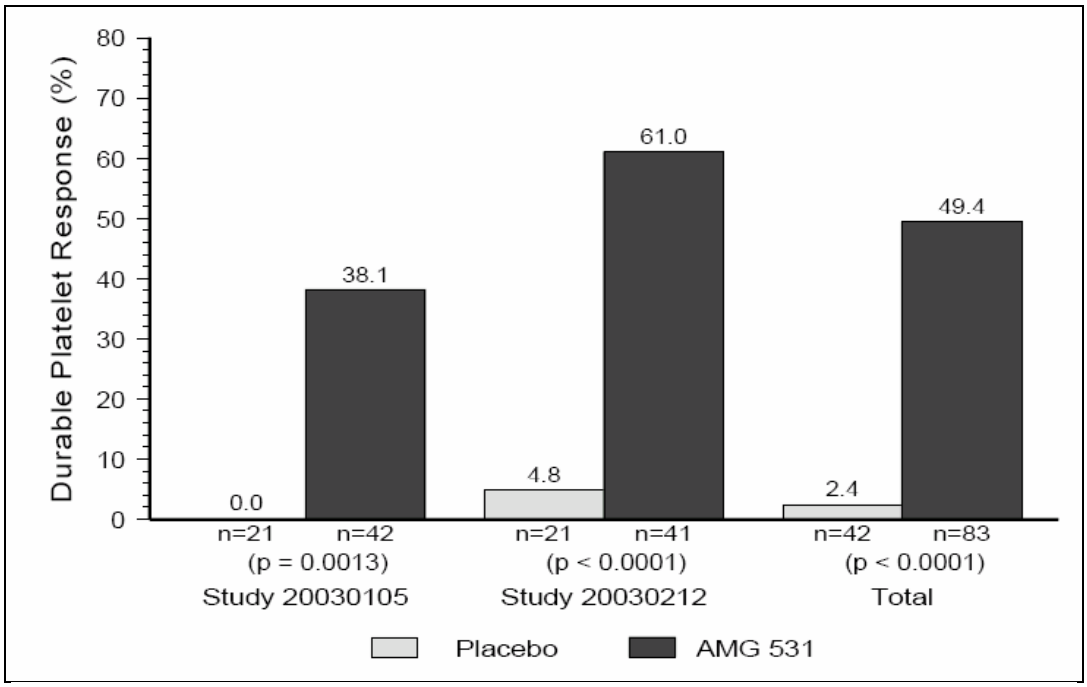
[a] From Cochran-Mantel-Haenszel controlling for baseline concurrent ITP therapy.
[b] From analysis of variance, or CMH based on rank.

Table 13: Major Efficacy Endpoints in Study 212

Endpoint	Placebo (N = 21)	AMG 531 (N = 41)	Treatment group comparison p-value
Primary Endpoint			
Durable Platelet response[a]			
Incidence Rate	1 (4.8%)	25 (61.0%)	< 0.0001
95% CI	(0.1%, 23.8%)	(44.5%, 75.8%)	
Key Secondary Endpoints			
Overall Platelet Response[a]			
Incidence Rate	3 (14.3%)	36 (87.8%)	< 0.0001
95% CI	(3.0%, 36.3%)	(73.8%, 95.9%)	
Number of Weeks with Platelet Response[b]			
Mean	1.3 weeks	15.2 weeks	< 0.0001
SD	3.5 weeks	7.5 weeks	
Proportion of Subjects Requiring Rescue Medications[a]			
Incidence Rate	13 (61.9%)	7 (17.1%)	0.0004
95% CI	(38.4%, 81.9%)	(7.2%, 32.1%)	
Durable Platelet Response with Stable Dose[a]			
Incidence Rate	0 (0.0%)	21 (51.2%)	0.0001
95% CI	(0.0%, 16.1%)	(35.1%, 67.1%)	

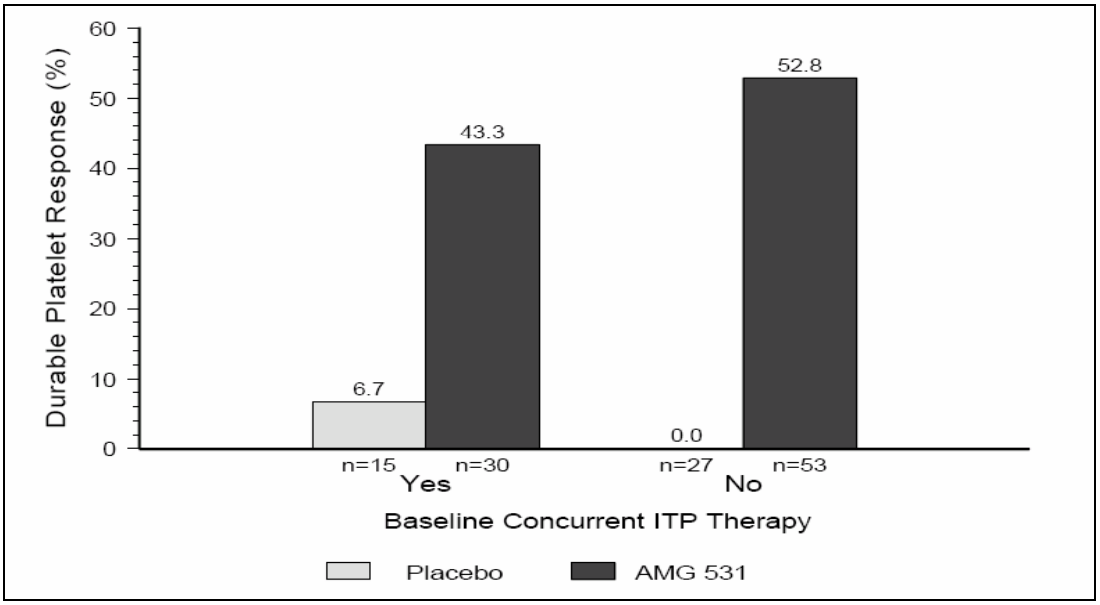
[a] From Cochran-Mantel-Haenszel controlling for baseline concurrent ITP therapy.
[b] From analysis of variance, or CMH based on rank.

Figure 1: Patients in Phase 3 Studies Achieving Durable Platelet Response



Durable platelet response was defined as weekly platelet count >= 50 x 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.

Figure 2: Durable Platelet Response in Phase 3 Studies by Baseline ITP Therapy



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

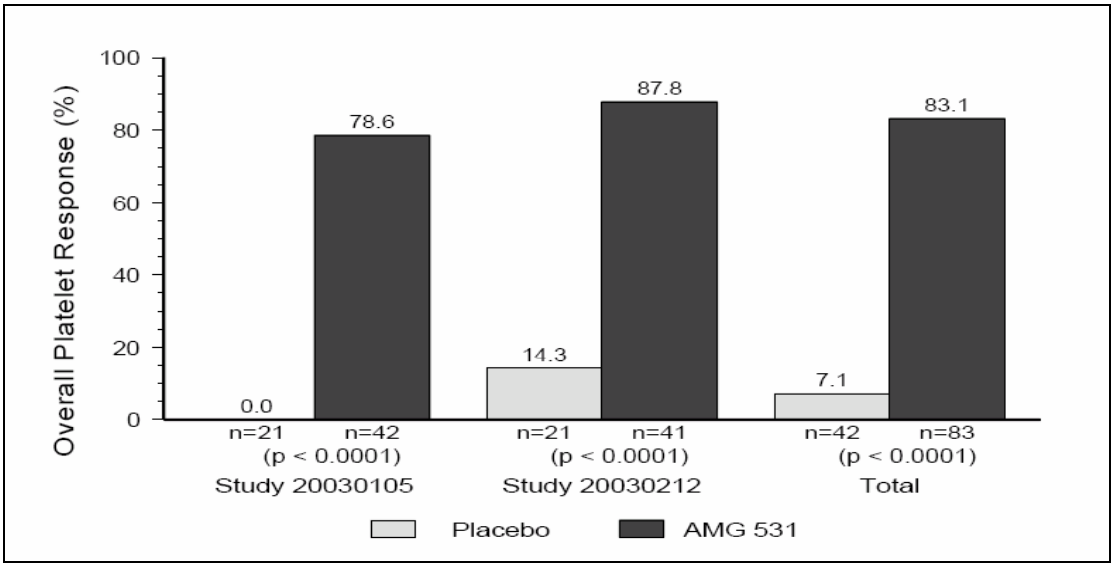
Table 14: Durable Platelet Response in Phase 3 Studies by Baseline ITP Therapy

Incidence of Durable Platelet Response	Study 20030105 Placebo (N = 21)	Study 20030105 AMG 531 (N = 42)	Study 20030212 Placebo (N = 21)	Study 20030212 AMG 531 (N = 41)	Total Placebo (N = 42)	Total AMG 531 (N = 83)
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%)
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%)
Incidence rate of (AMG 531 - 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 (AMG 531/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	

Durable platelet response was defined as weekly platelet count ≥ 50 x 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.

Figure 3: Overall Platelet Response in Phase 3 Studies



Overall platelet response was defined as either a durable or transient platelet response. Durable platelet response was defined as weekly platelet count >= 50 x 10^9/L for 6 or more times during weeks 18-25 in the absence of rescue medication any time during the treatment period. Transient platelet response was defined as weekly platelet count >= 50 x 10^9/L for 4 or more times during weeks 2-25 but without durable platelet response.
Platelet counts within 8 weeks after rescue medication use were excluded.
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 15: Overall Platelet Response in Phase 3 Studies by Baseline ITP Therapy

Incidence of Overall Platelet Response	Study 20030105 Placebo (N = 21)	Study 20030105 AMG 531 (N = 42)	Study 20030212 Placebo (N = 21)	Study 20030212 AMG 531 (N = 41)	Total Placebo (N = 42)	Total AMG 531 (N = 83)
By Baseline Concurrent ITP Therapy						
Yes	0/7 (0.0%)	12/14 (85.7%)	2/8 (25.0%)	13/16 (81.3%)	2/15 (13.3%)	25/30 (83.3%)
No	0/14 (0.0%)	21/28 (75.0%)	1/13 (7.7%)	23/25 (92.0%)	1/27 (3.7%)	44/53 (83.0%)
Overall						
Incidence rate	0/21 (0.0%)	33/42 (78.6%)	3/21 (14.3%)	36/41 (87.8%)	3/42 (7.1%)	69/83 (83.1%)
95% exact binomial CI	(0.0%, 16.1%)	(63.2%, 89.7%)	(3.0%, 36.3%)	(73.8%, 95.9%)	(1.5%, 19.5%)	(73.3%, 90.5%)
Incidence rate of (AMG 531 - Placebo)	78.6%		73.5%		76.0%	
95% normal approximation CI	(66.2%, 91.0%)		(55.5%, 91.5%)		(64.8%, 87.2%)	
Mantel-Haenszel common odds ratio of (AMG 531/Placebo)	-		34.739		71.087	
95% confidence interval	(-, -)		(7.767, 155.382)		(16.376, 308.583)	
Treatment group comparison p-value[a]	< 0.0001		< 0.0001		< 0.0001	

Overall platelet response was defined as either a durable or transient platelet response. Durable response was defined as achieving weekly platelet count for 6 or more times during weeks 18-25 in the absence of rescue medication any time in the treatment period. Transient response was defined as achieving weekly platelet response for 4 or more times between weeks 2 and 25 but without durable response. Weekly platelet response was defined as platelet count ≥ 50 x 10^9/L during Weeks 2-25 without rescue medication use in the past 8 weeks.

[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.

Table 16: Platelet Response Weeks in Phase 3 Studies

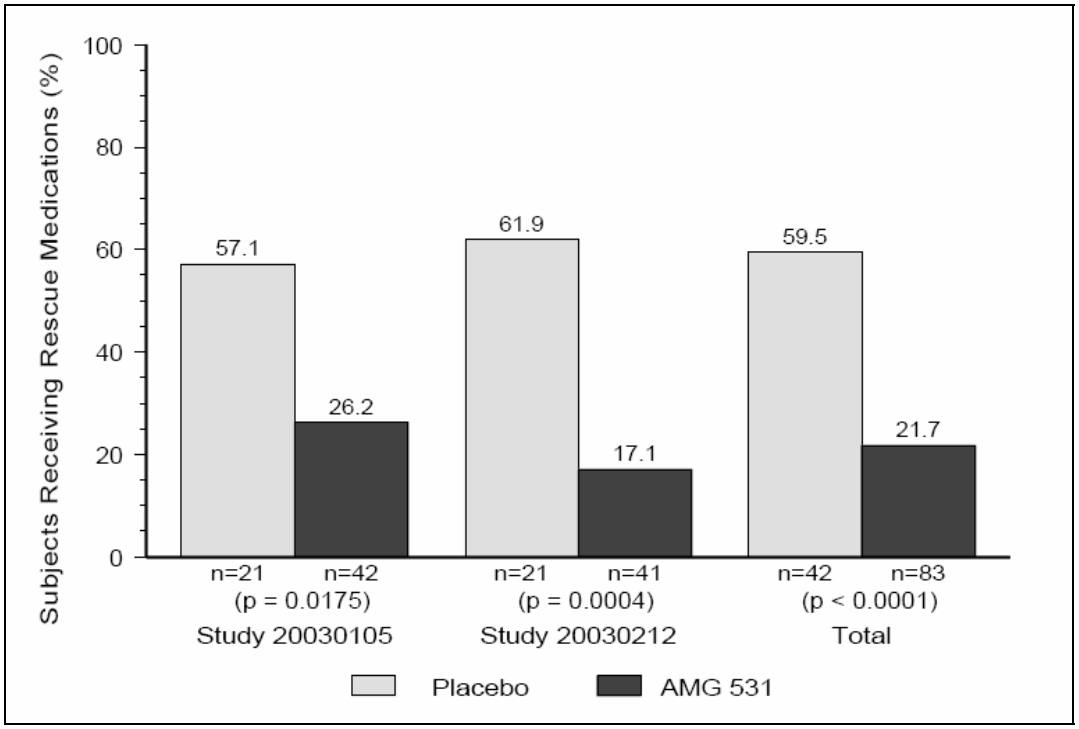
	Study 20030105 Placebo (N = 21)	Study 20030105 AMG 531 (N = 42)	Study 20030212 Placebo (N = 21)	Study 20030212 AMG 531 (N = 41)	Total Placebo (N = 42)	Total AMG 531 (N = 83)
Number of Weeks with Platelet Response[a]						
n	21	42	21	41	42	83
Mean	0.2	12.3	1.3	15.2	0.8	13.8
SD	0.5	7.9	3.5	7.5	2.5	7.8
Median	0.0	14.0	0.0	18.0	0.0	16.0
Q1, Q3	0.0, 0.0	5.0, 20.0	0.0, 1.0	11.0, 21.0	0.0, 0.0	8.0, 20.0
Min, Max	0, 2	0, 24	0, 15	0, 24	0, 15	0, 24
p-value for Treatment Group Comparison:						
From analysis of variance[b]	< 0.0001		< 0.0001		< 0.0001	
From CMH[c] based on rank	< 0.0001		< 0.0001		< 0.0001	

[a] Number of weeks with platelet response = Number of weeks with platelet count ≥ 50 x 10^9/L during Weeks 2 - 25. Platelet counts within 8 weeks after rescue medication use were excluded.

[b] For 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).

[c] p-value is from Cochran-Mantel-Haenszel test (row mean scores differ). For individual studies, the test is adjusted by baseline concurrent ITP therapy; For total, the test is adjusted by splenectomy status and baseline concurrent ITP therapy.

Figure 4: Patients in Phase 3 Studies Requiring Rescue Medication



Rescue medication was defined as any medication that was administered for the intended purpose of raising platelet count.
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 17: Patients in Phase 3 Studies Requiring Rescue Medication

	Study 20030105		Study 20030212		Total	
Requiring Rescue Medications During Treatment Period	Placebo (N = 21)	AMG 531 (N = 42)	Placebo (N = 21)	AMG 531 (N = 41)	Placebo (N = 42)	AMG 531 (N = 83)
By Baseline Concurrent ITP Therapy						
Yes	6/7 (85.7%)	3/14 (21.4%)	4/8 (50.0%)	5/16 (31.3%)	10/15 (66.7%)	8/30 (26.7%)
No	6/14 (42.9%)	8/28 (28.6%)	9/13 (69.2%)	2/25 (8.0%)	15/27 (55.6%)	10/53 (18.9%)
Overall						
Incidence rate	12/21 (57.1%)	11/42 (26.2%)	13/21 (61.9%)	7/41 (17.1%)	25/42 (59.5%)	18/83 (21.7%)
95% exact binomial CI	(34.0%, 78.2%)	(13.9%, 42.0%)	(38.4%, 81.9%)	(7.2%, 32.1%)	(43.3%, 74.4%)	(13.4%, 32.1%)
Incidence rate of (AMG 531 - Placebo)	-31.0%		-44.8%		-37.8%	
95% normal approximation CI	(-55.9%, -6.0%)		(-68.6%, -21.1%)		(-55.1%, -20.5%)	
Mantel-Haenszel common odds ratio of (AMG 531/Placebo)	0.278		0.143		0.204	
95% confidence interval	(0.094, 0.822)		(0.044, 0.465)		(0.093, 0.450)	
Treatment group comparison p-value[a]	0.0175		0.0004		< 0.0001	

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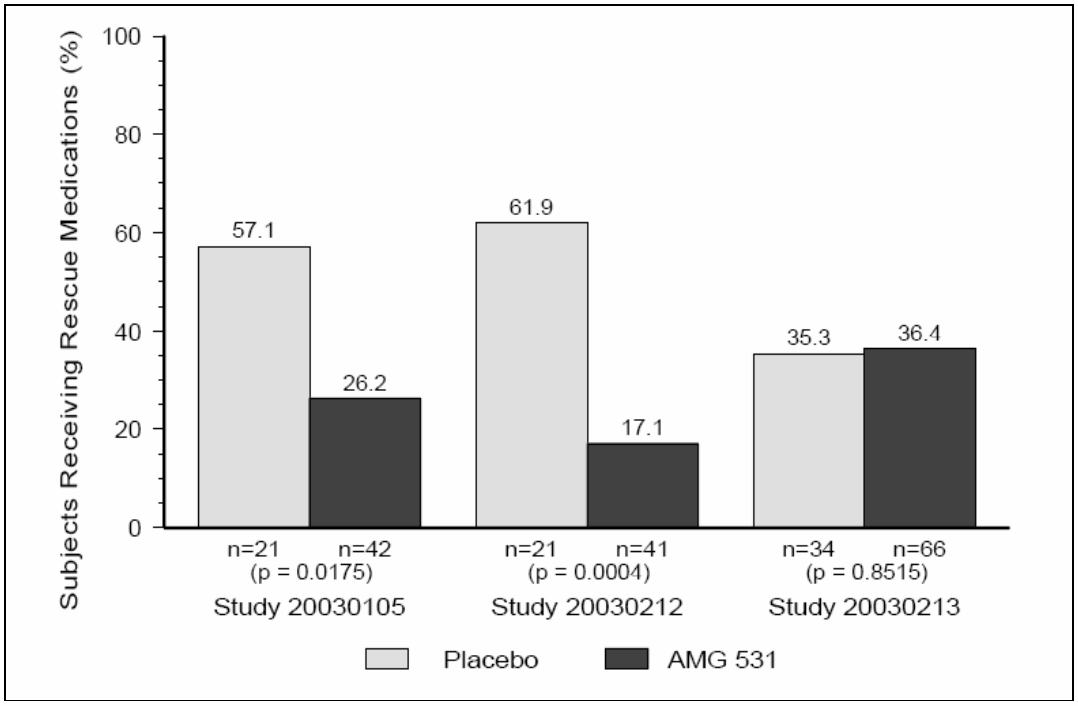
Rescue medication was defined as any medication that was administered for the intended purpose of raising platelet count.
[a] For individual studies, p-value is from Cochran-Mantel-Haenszel controlling for baseline concurrent ITP therapy; For total, p-value is from Cochran-Mantel-Haenszel controlling for splenectomy status and baseline concurrent ITP therapy.

Table 18: Rescue Medication Use in studies 105 and 212

		Splenectomized 20030105		Non-splenectomized 20030212	
		Placebo (n=21)	AMG 531 (n=42)	Placebo (n=21)	AMG 531 (n=41)
Subjects receiving rescue medications – n (%)		12 (57.1)	11 (26.2)	13 (61.9)	7 (17.1)
Category	Terms Reported				
Corticosteroids	Prednisone Methylprednisolone Methylprednisolone sodium succinate Dexamethasone Prednisolone sodium sulfobenzoate	8 (38.1)	7 (16.7)	6 (28.6)	7 (17.1)
IVIG	Immunoglobulin human normal Immunoglobulins	11 (52.4)	7 (16.7)	7 (33.3)	4 (9.8)
Anti-D	Immunoglobulin human anti-RH Anti-D immunoglobulin	0 (0.0)	0 (0.0)	4 (19.0)	2 (4.9)
Transfusions	Platelets, human blood Blood transfusion, auxiliary products	4 (19.0)	5 (11.9)	2 (9.5)	0 (0.0)
Cyclosporin	Ciclosporin	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4))
Rituximab	Rituximab	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)
Azathioprine	Azathioprine	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)

- The use of rescue medication increased gradually over the 25-week treatment period in patients on placebo, while it remained constant in patients on AMG 531.
  - o Study 105 (splenectomy): In patients on placebo, the use of rescue medication rose from 5-10 percent per week during weeks 1-5 to 20-30 percent per week in weeks 20-25 (final weeks). In patients on AMG 531, the use of rescue medication remained between 2 and 10 percent per week.
  - o Study 212 (prior to splenectomy): In patients on placebo, the use of rescue medication remained between 5 and 10 percent per week through week 6, and between 11 and 33 percent per week after week 7. In patients on AMG 531, the use of rescue medication remained between 5 and 10 percent per week.
  - o Study 213: About 25% of patients required rescue medication during weeks 1-12 and also during weeks 12-24. The proportion decreased during later 12-week intervals (see tables and figures).

Figure 5: Use of Rescue Medication in Phase 3 Studies



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.

Table 19: Durable Platelet Response on Stable Dose (Phase 3 Studies)

	Study 20030105		Study 20030212		Total	
Incidence of Durable Platelet Response with Stable Dose	Placebo (N = 21)	AMG 531 (N = 42)	Placebo (N = 21)	AMG 531 (N = 41)	Placebo (N = 42)	AMG 531 (N = 83)
By Baseline Concurrent ITP Therapy						
Yes	0/7 (0.0%)	3/14 (21.4%)	0/8 (0.0%)	7/16 (43.8%)	0/15 (0.0%)	10/30 (33.3%)
No	0/14 (0.0%)	10/28 (35.7%)	0/13 (0.0%)	14/25 (56.0%)	0/27 (0.0%)	24/53 (45.3%)
Overall						
Incidence rate	0/21 (0.0%)	13/42 (31.0%)	0/21 (0.0%)	21/41 (51.2%)	0/42 (0.0%)	34/83 (41.0%)
95% exact binomial CI	(0.0%, 16.1%)	(17.6%, 47.1%)	(0.0%, 16.1%)	(35.1%, 67.1%)	(0.0%, 8.4%)	(30.3%, 52.3%)
Incidence rate of (AMG 531 - Placebo)	31.0%		51.2%		41.0%	
95% normal approximation CI	(17.0%, 44.9%)		(35.9%, 66.5%)		(30.4%, 51.5%)	
Mantel-Haenszel common odds ratio of (AMG 531/Placebo)	-		-		-	
95% confidence interval	(-, -)		(-, -)		(-, -)	
Treatment group comparison p-value[a]	0.0046		< 0.0001		< 0.0001	

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Durable platelet response was defined as weekly platelet count ≥ 50 x 10^9/L for 6 or more times for Weeks 18 - 25 measurements in the absence of rescue medication any time during the treatment period.
Stable dose was defined as a dose maintained within ± 1 µg/kg during the last 8 weeks of treatment.
[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.

Figure 6: Increase in Platelet Counts ≥ 20 x 10^3/uL (Phase 3 Studies)

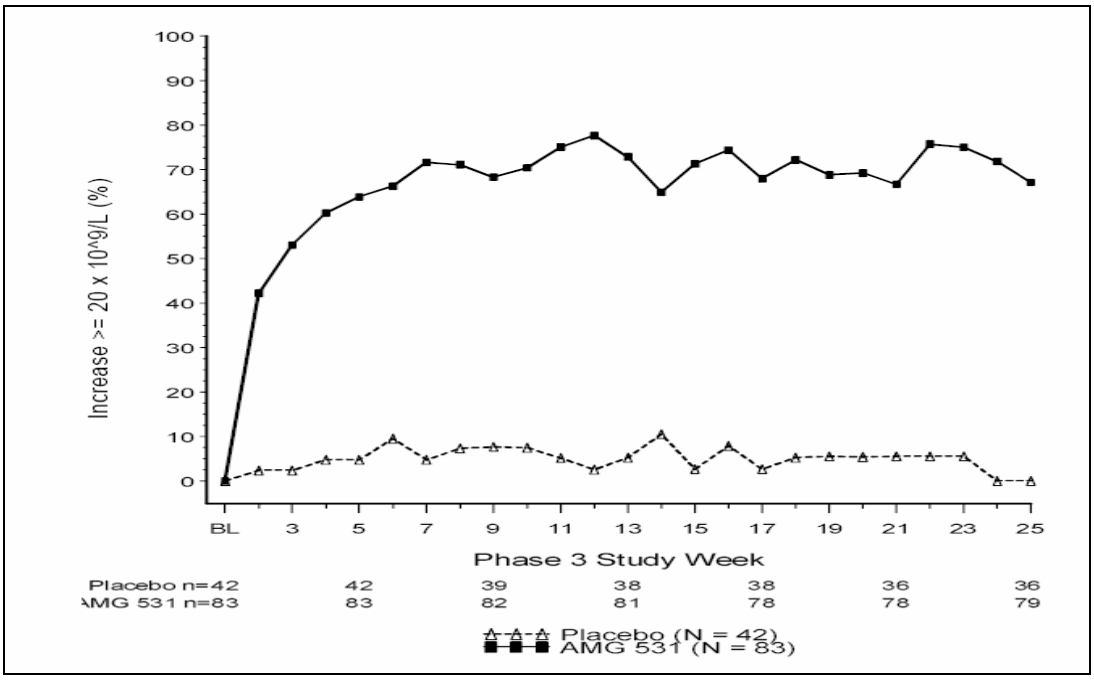
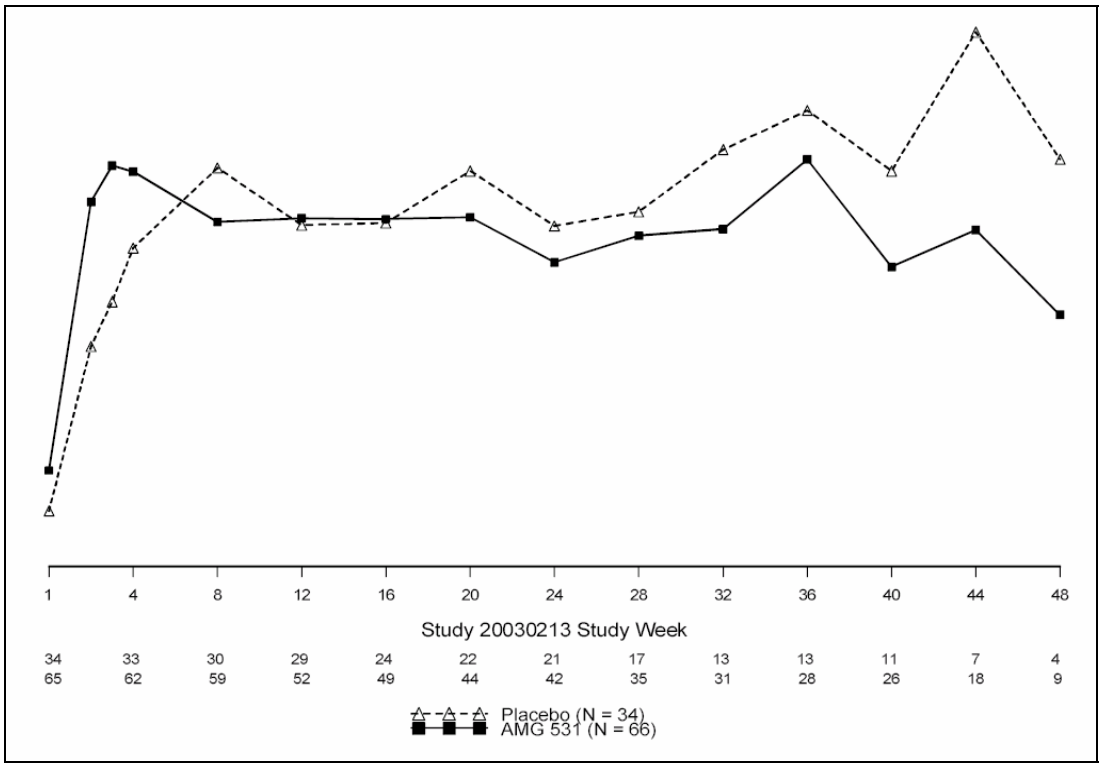


Figure 7: Increase in Platelet Counts ≥ 20 x 10^3/uL (Study 213)



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 increase within 8 weeks after receiving any rescue medications.
Baseline platelet count = Mean of platelet counts at Days -8, -2 and pre-dose Day 1 in phase 3 studies.
All subjects received AMG 531 in Study 20030213 but were listed under their randomized treatment in a previous phase 3 study.

5. INTEGRATED REVIEW OF SAFETY

5.1 METHODS AND FINDINGS

Table 20: Safety Analysis Sets

	Received Placebo Only n	Received Placebo and AMG 531[a] n	Received AMG 531 Only n	Total n
AMG 531 safety set	33	35	249	317
ITP safety set	11	35	169	215
Phase 3 ITP safety set	41	1	83	125
Phase 3 ITP long-term safety set	8	34	83	125
MDS safety set	0	0	20	20
CIT safety set	0	0	4	4
Healthy volunteer safety set	22	0	56	78

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[a]Subjects who started on placebo and later received AMG 531 in the open label extension study 20030213. One 20030212 subject randomized to placebo who inadvertently received three doses of AMG 531.
The AMG 531 safety set consists of all subjects in the ITP safety set, the MDS safety set, the CIT safety set or the healthy volunteer safety set.
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).
The phase 3 ITP safety set consists of all subjects who received investigational product in either ITP phase 3 study, 20030105 or 20030212.
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 extension study (20030213).
MDS safety set consists of all subjects who received investigational product in an MDS study (20050159) by the date of data cutoff (September 15, 2006) for this filling.
CIT safety set consists of all subjects who received investigational product in a CIT study, 20050144 (data cutoff by August 14, 2006).
The healthy volunteer safety set consists of all subjects who received investigational product in a healthy volunteer study (20000109 or 20040134).

Table 21: Baseline Demographics (Phase 3 ITP Safety Set)

	Placebo (N=41)	AMG 531 (N=84)	Total (N=125)
Age Group in Years - n (%)			
< 18	0 (0.0)	0 (0.0)	0 (0.0)
18 - 29	4 (9.8)	6 (7.1)	10 (8.0)
30 - 39	4 (9.8)	15 (17.9)	19 (15.2)
40 - 49	9 (22.0)	18 (21.4)	27 (21.6)
50 - 59	6 (14.6)	19 (22.6)	25 (20.0)
60 - 64	5 (12.2)	8 (9.5)	13 (10.4)
65 - 69	1 (2.4)	7 (8.3)	8 (6.4)
70 - 74	7 (17.1)	1 (1.2)	8 (6.4)
≥ 75	5 (12.2)	10 (11.9)	15 (12.0)
Age Group - n (%)			
< 65 yrs	28 (68.3)	66 (78.6)	94 (75.2)
≥ 65 yrs	13 (31.7)	18 (21.4)	31 (24.8)
Age Group - n (%)			
< 75 yrs	36 (87.8)	74 (88.1)	110 (88.0)
≥ 75 yrs	5 (12.2)	10 (11.9)	15 (12.0)
Age (yrs)			
n	41	84	125
Mean	55.1	51.9	53.0
SD	17.4	15.7	16.3
Median	52.0	52.0	52.0
Q1, Q3	44.0, 70.0	39.5, 63.0	40.0, 64.0
Min, Max	23, 88	21, 88	21, 88
Sex - n (%)			
Female	26 (63.4)	55 (65.5)	81 (64.8)
Male	15 (36.6)	29 (34.5)	44 (35.2)
Race - n (%)			
White or Caucasian	37 (90.2)	65 (77.4)	102 (81.6)
Black or African American	3 (7.3)	6 (7.1)	9 (7.2)
Hispanic or Latino	1 (2.4)	7 (8.3)	8 (6.4)
Asian	0 (0.0)	5 (6.0)	5 (4.0)
Japanese	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (1.2)	1 (0.8)
Aborigine	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Race - n (%)			
Caucasian	37 (90.2)	65 (77.4)	102 (81.6)
African American	3 (7.3)	6 (7.1)	9 (7.2)
Japanese	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (2.4)	13 (15.5)	14 (11.2)
Baseline Weight (kg)			
n	41	84	125
Mean	86.8	82.1	83.7
SD	25.2	22.3	23.3
Median	81.0	78.1	79.1
Q1, Q3	69.3, 98.2	66.7, 94.6	67.0, 96.5
Min, Max	52, 169	44, 138	44, 169
Baseline Weight Category - n (%)			
< 70 kg	11 (26.8)	29 (34.5)	40 (32.0)
≥ 70 kg	30 (73.2)	55 (65.5)	85 (68.0)

- In comparison with the demographic profile of the placebo group, the AMG 531 group consisted of appreciably younger (mean age 52 vs 55 years), lighter (82 kg vs 87 kg), and more non-Caucasian (16% vs 2%) patients.
- The appreciably older placebo group may be associated with an observed safety and "efficacy" profiles that appear less favorable than they would be, if age had been more closely matched between the two groups.
- However, the small difference in age (mean age, age distribution) between the two groups does not invalidate statistically significant conclusions about the safety and efficacy of AMG 531, since the small difference in age is itself not statistically significant.
- Nevertheless, the following points may be kept in mind in assessing the "magnitude" of the safety and efficacy of AMG 531 therapy as administered in the two pivotal studies:
  - The higher (than "true") rate in the placebo group may make AMG 531 therapy appear safer than it actually is.
  - The higher rate of adverse events may include bleeding events, and the higher (than "true") rate of bleeding in the placebo group may make AMG 531 therapy appear more effective than it actually is in preventing bleeding.
  - Younger patients may respond to AMG 531 therapy (in increasing the platelet count) more readily than do older patients. The observed difference in platelet response between the two groups may be larger than it actually is.

Table 22: ITP History (Phase 3 ITP Safety Set)

	Placebo (N = 41)	AMG 531 (N = 84)	Total (N = 125)
Years since ITP Diagnosis			
n	41	84	125
Mean	7.72	8.40	8.18
SD	7.95	10.52	9.73
Median	4.30	4.50	4.30
Q1, Q3	1.40, 12.40	1.15, 10.15	1.30, 12.30
Min, Max	0.1, 31.4	0.1, 44.8	0.1, 44.8
Years Since ITP Diagnosis - n (%)			
< 3 years	18 (43.9)	32 (38.1)	50 (40.0)
≥ 3 years	23 (56.1)	52 (61.9)	75 (60.0)
Years since Splenectomy			
n	21	42	63
Mean	10.23	10.68	10.53
SD	8.50	11.44	10.49
Median	8.08	5.83	6.56
Q1, Q3	3.47, 14.26	2.39, 18.05	2.51, 17.95
Min, Max	0.9, 31.4	0.2, 43.0	0.2, 43.0
Time since Splenectomy - n (%)			
< 6 months	0 (0.0)	7 (16.7)	7 (11.1)
≥ 6 months	21 (100.0)	35 (83.3)	56 (88.9)
Subjects with ITP Medication Treatment History - n (%)			
No	0 (0.0)	0 (0.0)	0 (0.0)
Yes	41 (100.0)	84 (100.0)	125 (100.0)
Subjects with Baseline Concurrent ITP Therapy - n (%)			
No	26 (63.4)	60 (71.4)	86 (68.8)
Yes	15 (36.6)	24 (28.6)	39 (31.2)

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

Percentages are based on number of subjects treated. If subject received at least one dose of AMG 531, then subject is counted in AMG 531 group, otherwise is counted in Placebo group.

Splenectomy status is defined by study design. Subjects from pre-splenectomy study 20030212 were excluded from this summary.

The value of baseline concurrent ITP therapy is based on the CRF database value.

- Patients in the AMG 531 group have had clinically evident (diagnosed) ITP appreciably longer (8.4 vs 7.7 mean years since diagnosis) than did patients in the placebo group.
- ITP in patients in the AMG 531 group may be less refractory to current first-line ITP therapies; a significant fraction of patients (17%) in the AMG 531 group had recent (< 6 months) splenectomy, versus none in the placebo group. In comparison with the placebo group, the AMG 531 group may consist of patients with potentially less refractory disease.

- Prior bleeding and prior ITP medication histories (not shown) are consistent with this interpretation regarding splenectomy. These considerations (which suggest less refractory disease in the AMG 531 group, as compared with the placebo group) should be kept in mind in interpreting the results of the pivotal studies.

Table 23: Overall Summary of Adverse Events (Phase 3 ITP Safety Set)

	Placebo (N = 41) n (%)	AMG 531 (N = 84) n (%)
Subjects Reporting Any Adverse Events	39 (95.1)	84 (100.0)
Subjects Reporting Adverse Events with Severity of		
Severe	12 (29.3)	23 (27.4)
Life-threatening	1 (2.4)	4 (4.8)
Fatal	3 (7.3)	1 (1.2)
Subjects Reporting Any Serious Adverse Events[a]	8 (19.5)	14 (16.7)
Subjects Reporting Any Treatment-Related Adverse Events	11 (26.8)	34 (40.5)
Subjects Reporting Treatment-Related Adverse Events with Severity of		
Severe	0 (0.0)	8 (9.5)
Life-threatening	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)
Subjects Reporting Any Treatment-Related Serious Adverse Events[a]	0 (0.0)	2 (2.4)
Subjects Who Withdrew from Study Due to Adverse Events	1 (2.4)	3 (3.6)

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

[a]Serious adverse event includes any event that is fatal, life threatening (places subject at immediate risk of death), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, a congenital anomaly / birth defect, or other significant medical hazard.

A subject can be counted in more than one category of severity grade.

Only adverse events starting after the first dose of investigational product are tabulated.

- A higher fraction of patients in the AMG 531 group (100% vs 95%) reported at least one adverse event. However, rates of life-threatening or fatal events were lower in the AMG 531 group (6% vs 10%).
- These results suggest that AMG 531 therapy is associated with clinically evident adverse events (safety) but reduces the rate of serious and life-threatening bleeding events (efficacy). The risk-benefit ratio favors the use of AMG 531 in patients with ITP refractory to current first-line therapies.

Table 24: Adverse Events ≥ 5% of Patients (Phase 3 ITP Safety Set)

Preferred Term	Placebo (N = 41) n (%)	AMG 531 (N = 84) n (%)
Headache	13 (31.7)	29 (34.5)
Fatigue	12 (29.3)	28 (33.3)
Epistaxis	10 (24.4)	27 (32.1)
Arthralgia	8 (19.5)	22 (26.2)
Contusion	10 (24.4)	21 (25.0)
Petechiae	9 (22.0)	14 (16.7)
Diarrhoea	6 (14.6)	14 (16.7)
Upper Respiratory Tract Infection	5 (12.2)	14 (16.7)
Dizziness	0 (0)	14 (16.7)
Insomnia	3 (7.3)	13 (15.5)
Myalgia	1 (2.4)	12 (14.3)
Back Pain	4 (9.8)	11 (13.1)
Nausea	4 (9.8)	11 (13.1)
Pain in Extremity	2 (4.9)	11 (13.1)
Cough	7 (17.1)	10 (11.9)
Anxiety	5 (12.2)	9 (10.7)
Gingival Bleeding	5 (12.2)	9 (10.7)
Abdominal Pain	0 (0)	9 (10.7)
Muscle Spasms	4 (9.8)	8 (9.5)
Injection Site Bruising	2 (4.9)	8 (9.5)
Nasopharyngitis	7 (17.1)	7 (8.3)
Oral Mucosal Blistering	3 (7.3)	7 (8.3)
Pain	3 (7.3)	7 (8.3)
Pharyngolaryngeal Pain	2 (4.9)	7 (8.3)
Shoulder Pain	0 (0)	7 (8.3)
Ecchymosis	6 (14.6)	6 (7.1)
Asthenia	2 (4.9)	6 (7.1)
Oedema Peripheral	2 (4.9)	6 (7.1)
Haematoma	1 (2.4)	6 (7.1)
Pyrexia	1 (2.4)	6 (7.1)
Dyspepsia	0 (0)	6 (7.1)
Rash	4 (9.8)	5 (6.0)
Anaemia	1 (2.4)	5 (6.0)
Injection Site Pain	1 (2.4)	5 (6.0)
Paraesthesia	0 (0)	5 (6.0)
Vomiting	3 (7.3)	4 (4.8)
Chest Discomfort	3 (7.3)	3 (3.6)
Urinary Tract Infection	3 (7.3)	3 (3.6)
Injection Site Haematoma	3 (7.3)	1 (1.2)
Toothache	3 (7.3)	1 (1.2)

The Phase 3 ITP safety set consists of all subjects who received investigational product in either ITP phase 3 study, 20030105 or 20030212.
Incidence of adverse events are selected based on ≥ 5% occurrence in either AMG 531 or placebo treatment group.
Only adverse events starting after the first dose of investigational product are tabulated.
MedDRA version 9.0 was used.

- In either placebo or AMG 531 group, 40 adverse events types (Preferred Terms, MedDRA version 9.0) were reported in ≥ 5% of patients, see tables.

- Of these 40 events (event types), 27 were reported in a greater proportion of patients on AMG 531: headache, fatigue, epistaxis, arthralgia, contusion, diarrhea, upper respiratory tract infection, dizziness, insomnia, myalgia, back pain, nausea, pain in extremity, abdominal pain, injection site bruising, oral mucosal blistering, pain, pharyngolaryngeal pain, shoulder pain, aesthenia, peripheral edema, hematoma, pyrexia, dyspepsia, anemia, injection site pain, and paresthesia.
- Of the 27 events that were reported in a greater proportion of patients on AMG 531 group, 10 were reported by $\geq$ 5% of patients (proportion of patients on AMG 531 $\geq$ 5% than proportion of patients on placebo): epistaxis, arthralgia, dizziness, insomnia, myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia, and paresthesia.
- Of the 10 events that were reported by $\geq$ 5% of patients for the AMG 531 group, 8 events were reported at $\geq$ 2-fold rate for the AMG 531 group than for the placebo group: dizziness, insomnia, myalgia, pain in extremity, abdominal pain, shoulder pain, dyspepsia, and paresthesia.
- The 8 adverse events that appear to be true AMG 531 treatment-related adverse events ($\geq$ 5% rate and $\geq$ twice the rate) may be grouped into 3 major organ systems: neurologic (dizziness, insomnia, and paresthesia), gastrointestinal (abdominal pain/dyspepsia), and musculoskeletal (myalgia and extremity/shoulder pain).

Table 25: Adverse Events ≥ 5% of Patients by Age (Phase 3 ITP Safety Set)

	Age < 65		Age ≥ 65	
Preferred Term	Placebo (N=28) n (%)	AMG 531 (N=66) n (%)	Placebo (N=13) n (%)	AMG 531 (N=18) n (%)
Headache	10 (35.7)	25 (37.9)	3 (23.1)	4 (22.2)
Fatigue	8 (28.6)	25 (37.9)	4 (30.8)	3 (16.7)
Epistaxis	8 (28.6)	22 (33.3)	2 (15.4)	5 (27.8)
Arthralgia	5 (17.9)	17 (25.8)	3 (23.1)	5 (27.8)
Contusion	5 (17.9)	16 (24.2)	5 (38.5)	5 (27.8)
Petechiae	6 (21.4)	11 (16.7)	3 (23.1)	3 (16.7)
Diarrhoea	6 (21.4)	12 (18.2)	0 (0.0)	2 (11.1)
Upper Respiratory Tract Infection	4 (14.3)	9 (13.6)	1 (7.7)	5 (27.8)
Dizziness	0 (0.0)	9 (13.6)	0 (0.0)	5 (27.8)
Insomnia	2 (7.1)	10 (15.2)	1 (7.7)	3 (16.7)
Myalgia	1 (3.6)	8 (12.1)	0 (0.0)	4 (22.2)
Back Pain	4 (14.3)	10 (15.2)	0 (0.0)	1 (5.6)
Nausea	4 (14.3)	9 (13.6)	0 (0.0)	2 (11.1)
Pain in Extremity	2 (7.1)	5 (7.6)	0 (0.0)	6 (33.3)
Cough	6 (21.4)	7 (10.6)	1 (7.7)	3 (16.7)
Anxiety	3 (10.7)	7 (10.6)	2 (15.4)	2 (11.1)
Gingival Bleeding	4 (14.3)	9 (13.6)	1 (7.7)	0 (0.0)
Abdominal Pain	0 (0.0)	6 (9.1)	0 (0.0)	3 (16.7)
Muscle Spasms	3 (10.7)	4 (6.1)	1 (7.7)	4 (22.2)
Injection Site Bruising	1 (3.6)	8 (12.1)	1 (7.7)	0 (0.0)
Nasopharyngitis	5 (17.9)	6 (9.1)	2 (15.4)	1 (5.6)
Oral Mucosal Blistering	2 (7.1)	5 (7.6)	1 (7.7)	2 (11.1)
Pain	2 (7.1)	5 (7.6)	1 (7.7)	2 (11.1)
Pharyngolaryngeal Pain	1 (3.6)	5 (7.6)	1 (7.7)	2 (11.1)
Shoulder Pain	0 (0.0)	4 (6.1)	0 (0.0)	3 (16.7)
Ecchymosis	4 (14.3)	4 (6.1)	2 (15.4)	2 (11.1)
Asthenia	2 (7.1)	5 (7.6)	0 (0.0)	1 (5.6)
Oedema Peripheral	2 (7.1)	5 (7.6)	0 (0.0)	1 (5.6)
Haematoma	1 (3.6)	4 (6.1)	0 (0.0)	2 (11.1)
Pyrexia	1 (3.6)	5 (7.6)	0 (0.0)	1 (5.6)
Dyspepsia	0 (0.0)	5 (7.6)	0 (0.0)	1 (5.6)
Rash	4 (14.3)	3 (4.5)	0 (0.0)	2 (11.1)
Anaemia	0 (0.0)	5 (7.6)	1 (7.7)	0 (0.0)
Injection Site Pain	1 (3.6)	4 (6.1)	0 (0.0)	1 (5.6)
Paraesthesia	0 (0.0)	4 (6.1)	0 (0.0)	1 (5.6)
Vomiting	3 (10.7)	4 (6.1)	0 (0.0)	0 (0.0)
Chest Discomfort	2 (7.1)	3 (4.5)	1 (7.7)	0 (0.0)
Urinary Tract Infection	3 (10.7)	2 (3.0)	0 (0.0)	1 (5.6)
Injection Site Haematoma	2 (7.1)	0 (0.0)	1 (7.7)	1 (5.6)
Toothache	2 (7.1)	1 (1.5)	1 (7.7)	0 (0.0)

Footnotes: See **Table** above

- Among patients on AMG 531, the following 8 adverse events were reported in appreciably greater proportions of patients (≥ 5%) for the group < 65 years old than for the group ≥ 65 years old: headache (38% vs 22%), fatigue (38% vs 17%), diarrhea (18% vs 11%), back pain (15% vs 6%), gingival bleeding (14% vs 0%), injection site bruising (12% vs 0%), anemia (8% vs 0%), and vomiting (6% vs 0%).
- None of these 8 events (reported in appreciably greater proportions of patients for the group ≤ 65 years old) were in common with the 8 events that appear to be related to AMG 531 therapy. All other adverse events listed in the table above, including the 8

adverse events identified as being potentially AMG 531 treatment-related, were reported in similar or greater proportions in patients ≥ 65 years old.

- Of the 8 events that appear to be related to AMG 531 therapy (from the table above), 3 were reported in similar proportions in both age groups (insomnia, dyspepsia, and paresthesia), and 5 were reported in appreciably greater proportions in the group ≥ 65 years old (dizziness, myalgia, extremity pain, abdominal pain, and shoulder pain). None were reported in appreciably greater proportions in the group < 65 years old.

Table 26: Serious Adverse Events (Phase 3 ITP Safety Set)

Preferred Term	Placebo (N = 41) n (%)	AMG 531 (N = 84) n (%)
Number of Subjects Reporting Serious Adverse Events	8 (19.5)	14 (16.7)
Gastrointestinal Haemorrhage	0 (0)	2 (2.4)
Platelet Count Decreased	2 (4.9)	1 (1.2)
Haemorrhage Intracranial	1 (2.4)	1 (1.2)
Angioneurotic Oedema	0 (0)	1 (1.2)
Appendicitis	0 (0)	1 (1.2)
B-Cell Lymphoma	0 (0)	1 (1.2)
Bone Marrow Disorder	0 (0)	1 (1.2)
Cerebrovascular Accident	0 (0)	1 (1.2)
Ecchymosis	0 (0)	1 (1.2)
Epistaxis	0 (0)	1 (1.2)
Haematochezia	0 (0)	1 (1.2)
Head Injury	0 (0)	1 (1.2)
Hypersensitivity	0 (0)	1 (1.2)
Hypertension	0 (0)	1 (1.2)
Hypovolaemia	0 (0)	1 (1.2)
Idiopathic Thrombocytopenic Purpura	0 (0)	1 (1.2)
Oral Mucosal Petechiae	0 (0)	1 (1.2)
Pericardial Effusion	0 (0)	1 (1.2)
Peripheral Embolism	0 (0)	1 (1.2)
Peripheral Ischaemia	0 (0)	1 (1.2)
Road Traffic Accident	0 (0)	1 (1.2)
Sternal Fracture	0 (0)	1 (1.2)
Suicide Attempt	0 (0)	1 (1.2)
Thrombocytopenia	0 (0)	1 (1.2)
Pneumonia	2 (4.9)	0 (0)
Anaemia Haemolytic Autoimmune	1 (2.4)	0 (0)
Cerebral Haemorrhage	1 (2.4)	0 (0)
Evan's Syndrome	1 (2.4)	0 (0)
Gastric Haemorrhage	1 (2.4)	0 (0)
Headache	1 (2.4)	0 (0)
Petechiae	1 (2.4)	0 (0)
Pneumonia Primary Atypical	1 (2.4)	0 (0)
Pulmonary Embolism	1 (2.4)	0 (0)
Purpura	1 (2.4)	0 (0)

The Phase 3 ITP safety set consists of all subjects who received investigational product in either ITP phase 3 study, 20030105 or 20030212.
Serious adverse event includes any event that is fatal, life threatening (places subject at immediate risk of death), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, a congenital anomaly / birth defect, or other significant medical hazard.
Only adverse events starting after the first dose of investigational product are tabulated.

- Rates of serious adverse events were not appreciably different between placebo and AMG 531 groups (20% placebo vs 17% AMG 531). AMG 531 therapy does not appear to pose a serious safety risk, based on short-term (6 months of treatment) results obtained from a small number of patients (N = 84).
- As might be expected, rates of 3 serious bleeding events (intracranial, cerebral hemorrhage, and gastric hemorrhage) were lower for the AMG 531 group, and rates of 3 serious thrombotic events (cerebrovascular accident, peripheral embolism, and peripheral ischemia/embolism) were higher for the AMG 531 group.
- A higher rate of gastrointestinal hemorrhage in the AMG 531 group and a higher rate of pulmonary embolism in the placebo group are inconsistent with the mechanism of action of AMG 531, but patient numbers are small (one patient versus none for each event).
- The thrombotic events shown in the table above were reported more often in patients with platelet counts < 450 (x 10^3/uL) than in patients with counts $\geq$ 450 (8 vs 3 patients).
  - However, the apparent lack of a temporal association between elevated platelet counts and clinical thrombosis does not indicate that AMG 531-induced thrombocytosis is without thrombotic risks.
  - In the setting of ITP under AMG-531 therapy (rapid turnover of young platelets, thrombocytopenia, and marked fluctuations in platelet counts), elevated counts of active young platelets may be too transient to correlate with clinical thrombosis, even with weekly platelet count monitoring.

Table 27: Fatal Adverse Events (Phase 3 ITP Safety Set)

Preferred Term	Placebo (N = 41) n (%)	AMG 531 (N = 84) n (%)
Number of Subjects Reporting Fatal Adverse Events	3 (7.3)	1 (1.2)
Haemorrhage Intracranial	0 (0)	1 (1.2)
Cerebral Haemorrhage	1 (2.4)	0 (0)
Pneumonia Primary Atypical	1 (2.4)	0 (0)
Pulmonary Embolism	1 (2.4)	0 (0)

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The Phase 3 ITP safety set consists of all subjects who received investigational product in either ITP phase 3 study, 20030105 or 20030212.
Only adverse events starting after the first dose of investigational product are tabulated.

Table 28: Fatal Adverse Events (ITP Safety Set)

Preferred Term	Placebo (N = 46) n (%)	AMG 531 (N = 204) n (%)
Number of Subjects Reporting Fatal Adverse Events	3 (6.5)	5 (2.5)
Acute Respiratory Distress Syndrome	0 (0)	1 (0.5)
Cardiac Arrest	0 (0)	1 (0.5)
Haemorrhage Intracranial	0 (0)	1 (0.5)
Hepatic Failure	0 (0)	1 (0.5)
Pneumonia Pneumococcal	0 (0)	1 (0.5)
Renal Failure	0 (0)	1 (0.5)
Cerebral Haemorrhage	1 (2.2)	0 (0)
Pneumonia Primary Atypical	1 (2.2)	0 (0)
Pulmonary Embolism	1 (2.2)	0 (0)

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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).
N = number of subjects who received at least one dose of investigational products over the course of all ITP studies.
Thirty five subjects who started on placebo and later received AMG 531 were counted in both treatment groups. Adverse events were assigned to treatment group by start date of the event.

- In the two pivotal studies, fatality rate for the AMG 531 group was lower than that for the placebo group (1% vs 7%). The single death in the AMG 531 group was due to intracranial hemorrhage, a complication of ITP expected not to be exacerbated by AMG 531 therapy.
- When the data from the pivotal studies are pooled with other uncontrolled ITP studies in the AMG 531 development program, the fatality rate for the AMG 531 group increased from 1.2% (pivotal studies) to 2.5% (all studies) but remained well below a placebo rate of 6.5% (all studies).

Table 29: Serious Bleeding Events (Phase 3 ITP Safety Set)

Preferred Term	Placebo (N = 41) n (%)	AMG 531 (N = 84) n (%)
Subjects reporting serious bleeding adverse events of interest	4 (9.8)	5 (6.0)
Gastrointestinal Haemorrhage	0 (0)	2 (2.4)
Haemorrhage Intracranial	1 (2.4)	1 (1.2)
Ecchymosis	0 (0)	1 (1.2)
Epistaxis	0 (0)	1 (1.2)
Haematochezia	0 (0)	1 (1.2)
Oral Mucosal Petechiae	0 (0)	1 (1.2)
Cerebral Haemorrhage	1 (2.4)	0 (0)
Gastric Haemorrhage	1 (2.4)	0 (0)
Petechiae	1 (2.4)	0 (0)
Purpura	1 (2.4)	0 (0)

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The Phase 3 ITP safety set consists of all subjects who received investigational product in either ITP phase 3 study, 20030105 or 20030212.
The adverse event terms that map to bleeding events were prospectively identified by the sponsor before the unblinding of the pivotal studies.
Serious adverse event includes any event that is fatal, life threatening (places subject at immediate risk of death), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, a congenital anomaly / birth defect, or other significant medical hazard.
Only adverse events starting after the first dose of investigational product are tabulated.

- As might be expected based on the therapeutic effect of AMG 531, the rate of adverse bleeding events, including serious bleeding events, were lower for the AMG 531 group than for the placebo group.

Table 30: Bone Marrow Abnormality (ITP Safety Set)

Preferred Term	Placebo (N = 46) n (%)	AMG 531 (N = 204) n (%)
Subjects reporting bone marrow abnormality adverse events of interest	0 (0)	6 (2.9)
Bone Marrow Disorder	0 (0)	5 (2.5)
Myelofibrosis	0 (0)	1 (0.5)

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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).
N = number of subjects who received at least one dose of investigational product over the course of all ITP studies.
Thirty five subjects who started on placebo and later received AMG 531 were counted in both treatment groups. Adverse events were assigned to treatment group by start date of the event.
The adverse event terms that map to bone marrow abnormality were prospectively identified by the sponsor before the unblinding of the pivotal studies.
MedDRA version 9.0 was used.

- Bone marrow abnormality was reported in 6 patients, all in the AMG 531 group: one case in a controlled pivotal study (study 105 in patients status post splenectomy), and 5 cases in study 213, an uncontrolled single-arm extension study:
- Narrative of the single case of bone marrow abnormality reported in study 105:

  A 40-year-old Caucasian man with ITP status post splenectomy: This patient had a prior history of on-going "reticulin fibrosis" of bone marrow, with a baseline peripheral nucleated red blood cell (NRBC) count ranging between 1 and 5 (per 100 WBC). Baseline marrow studies (4 months prior to study enrollment) showed hypoplastic marrow with mild patchy increase in reticulin. The patient received 5 weekly injections of AMG 531 over 5 weeks at doses ranging from 1 - 9 ug/kg, during which the platelet count failed to rise much above a baseline of 5 ($x10^3$/uL). Treatment was temporarily withheld at week 6 due to increased peripheral NRBC. By week 7 (two weeks after the fifth and last dose at 9 ug/kg), NRBC had increased to 93. The marrow findings were reported as "increased reticulin fibrosis of marrow" as a severe and serious adverse event, and the subject was withdrawn from study.

  Compared with baseline, the marrow study showed moderate increases in cellularity (myeloid and megakaryocytic), reticulin, and megakaryocytic dyspoiesis. There was no evidence of a lymphoproliferative disorder or collagen deposition. A follow-up marrow study at 3 months showed a significant reduction in megakaryocytic hyperplasia and dyspoiesis, with a return to the baseline level of "reticulin fibrosis." No clinical sequelae were associated with this event.
- Narratives of the 5 cases of bone marrow abnormality reported in study 213:
  - A 31-year-old Caucasian man with ITP status post splenectomy: This patient had received two doses of AMG 531 in a prior ITP study (10 ug/kg on days 1 and 22 of study 2000137). A platelet count of 27 (x 10^3/uL) at baseline increased to a maximum count of 523 during the prior study. No bone marrow abnormalities were reported at that time (baseline).

    Ten months after completing the prior study, the patient enrolled in study 213 with a baseline platelet count of 19 and received weekly injections of AMG 531 for 22 weeks at doses increasing from 1-18 ug/kg. Platelet counts ranged from 12 to 93, peripheral NRBC were noted at weeks 15 and 22, and peripheral blast count of 1% noted at week 20 increased to 6% at week 22. A marrow study at week 22 showed increased cellularity with tri-lineage hematopoiesis, megakaryocytic hyperplasia, moderate to focally dense reticulin deposits, and no evidence of leukemia or significant collagen fibrosis. The investigator reported "moderate increased reticulin" as a serious adverse event. AMG 531 was discontinued at week 24.

    Follow up marrow study at week 33 showed mild diffuse reticulin fibrosis (suggestive of improvement since week 22) and no evidence of acute leukemia or collagen fibrosis. A second follow up marrow study at week 46 showed mild reticulin fibrosis (unchanged from the week 33) and continued no evidence of collagen fibrosis.
  - A 53-year-old Caucasian man with ITP status post splenectomy: This patient's notable medical history included gammopathy, coagulopathy, and alcoholism. He had received AMG 531 under study 105 at doses escalating from 1-5 ug/kg over 24 weeks and had achieved a durable platelet response. Upon completion of study 105, he enrolled immediately into study 213 at a baseline platelet count of 6 (x 10^3/uL). Under study 213, an initial AMG 531 dose of 5 ug/kg was gradually increased to 8 ug/kg by week 44, with corresponding platelet counts between 45 and 90.

At week 12, a bone marrow biopsy was taken as part of study 20050123 (marrow study 123), in which he was also enrolled. A local interpretation of the biopsy led to the only adverse event reported for this patient between weeks 1 to 44 of study 213 (data cut-off): mild increase in reticulin fibrosis considered to be non-serious and treatment-related. Retrospective review of previous marrow studies obtained as baseline at enrollment into study 105 and under study 123 showed no evidence of reticulin.

- A 58-year old African-American man with ITP and status post splenectomy: This patient had received weekly injections of AMG 531 under study 105 at doses escalating from 1-15 ug/kg over 24 weeks. Baseline marrow studies (obtained 2 years earlier) showed marked erythroid and megakaryocytic hyperplasia with mild increased reticulin. Baseline platelet count was 7 (x 10^3/uL) with no peripheral NRBC. At week 14, at AMG 531 dose of 14 ug/kg and a platelet count of 58, peripheral NRBC were noted (47 per 100 WBC). Marrow studies showed marked granulocytic and megakaryocytic hyperplasia with mild-moderate increase in reticulin with no evidence of collagen. Between weeks 15-22, the AMG 531 dose remained at 14 ug/kg with platelet counts ranging between 30 and 70. Final two doses of AMG 531 at weeks 23 and 24 were administered at 15 µg/kg in response to platelet counts of 15 and 37.

  Five weeks after completing study 105, the patient enrolled into study 213 at an initial AMG 531 dose of 15 ug/kg, a baseline platelet count of 7 (x 10^3/uL), and a peripheral NRBC count of 1 per 100 WBC. Over the first 8 weeks, the AMG 531 dose remained constant at 15 µg/kg, the platelet count peaked at 33, and NRBC count peaked at 15 per 100 WBC. Marrow studies at week 8 showed no significant change in cellularity and reticulin from week 14 of study 105, and the marrow findings were reported as moderate increase in reticulin (considered serious and treatment-related). AMG 531 was withheld and a 4-day course of pulse dexamethasone. At week 23, AMG 531 was resumed at 15 ug/kg and continued through week 52 (data cut-off). Platelet counts ranged between 6 and 22 from weeks 9 through 22 (AMG 531 withheld), and ranged between 9 and 42 from weeks 23 through 50 (AMG 531 resumed). At week 51, the platelet count rose to 204 after pulse dexamethasone given as ITP rescue medication.

- A 55-year old Caucasian woman with ITP and systemic lupus erythematosus (SLE): This patient had received AMG 531 under study 212 at doses escalating from 1 to 9 ug/kg over 24 weeks (missed doses at weeks 12, 14, 16, 17, 19, 22, and 23 due to study noncompliance). Corresponding platelet counts during the 24 weeks ranged between 3 (x 10^3/ul) and 71 (baseline of 12). No marrow abnormality was reported for this patient under study 212.

  Upon completing study 212, the patient enrolled immediately into study 213 at a baseline platelet count of 22 and an initial AMG 531 dose of 9 ug/kg. Over the next 3 weeks, AMG 531 dose was increased to 13 ug/kg and the platelet count peaked at 54 at week 2. At week 3, the patient developed severe thrombocytopenia (platelet count of 3) with bleeding from the ear (moderate, non-serious). The patient was hospitalized and received IVIG, corticosteroids, and a platelet transfusion (AMG 531 therapy not interrupted), and the platelet count increased to 14. On study day 30, one day following hospital discharge (platelet count 8, resolving symptoms), the patient withdrew (consent) from the study.

  Three weeks later, the subject was again hospitalized for severe thrombocytopenia (platelet count 4), hemolytic anemia (hemoglobin 6.1 g/dL), and elective splenectomy. Marrow studies showed increased cellularity with diffuse grade 2 to 3 reticulin fibrosis

without evidence of collagen. Immunohistochemistry evaluation showed no evidence of lymphoproliferative disorder or lymphoma, mild increase in T cells (interpreted as a reactive process). The patient received IVIG, corticosteroids, and blood transfusion, and the hemoglobin increased to 11 g/dL (hospital day 4) and the platelet count increased to 78 (hospital day 7). On hospital day 9, the patient underwent splenectomy, following which the platelet count stabilized for several days but decreased to 18 on hospital day 11. The patient again received IVIG and the platelet count increased to 75 and the patient was discharged on day 13.

- A 37-year old Caucasian man with ITP status post splenectomy and history of hemolytic anemia: This patient had received AMG 531 under study 105 over 24 weeks at doses escalating from 1 to 9 ug/kg. Baseline marrow studies showed mild interstitial lymphocytosis (small mature CD3+ T lymphocytes). No marrow abnormality was reported for the subject during study 105. Three weeks after completing study 105, the patient enrolled into study 213 and received two doses of AMG 531 (initial 7 ug/kg, final 9 ug/kg on day 8) before withdrawing from the study on day 23. The platelet counts were 5 (x 10^3/uL) at baseline and 4, 3, and 12 on days 8, 15, and 22, respectively.

  On study day 8, the patient was hospitalized for severe thrombocytopenia (platelet count 3) and gingival bleeding, which did not respond to platelet transfusion, pulse methylprednisolone, and erythropoietin. Marrow studies showed erythrocytic and magakaryocytic dyspoiesis with significantly increased reticulin, and without evidence of collagen, cytogenetic abnormalities, or clonal disorder. The patient was discharged on prednisone. Repeat marrow studies (10 weeks after withdrawing from the study) showed no change from previous studies.

- The 6 narratives above are summarized in the tables. In all 6 cases, the primary bone marrow abnormality reported was increase in reticulin, with or without increased cellularity or cellular dyspoiesis. None of the 6 cases progressed to true myelofibrosis (deposition of collagen).
  - All had received AMG 531 in a setting of ITP sufficiently refractory to require splenectomy. AMG 531 therapy was typically complicated by poor platelet response, bleeding, or poor patient tolerance/compliance leading to patient withdrawal from study (3 patients) or discontinuing therapy (additional 2 patients).
  - Peripheral NRBC were noted in 3 of the 6 cases, which contributed to the decision to perform marrow studies.
  - Resolution of increased reticulin was reported in one patient (patient 1), and partial resolution was reported in two patients (patients 2 and 4). Results of follow up marrow studies were not reported in patients 3 and 5, and no significant resolution was noted in patient 6.

  This case series suggests that increased reticulin in bone marrow occurs typically in the setting of highly refractory disease (less responsive to AMG 531 therapy) and is often heralded by the appearance of bone marrow cells (typically NRBC) in the peripheral circulation. This condition appears to be a dose-dependent adverse effect of AMG 531 therapy related to its therapeutic effect (megakaryopoietic stimulation) and not an idiosyncratic treatment complication. The narrative in patient 1 also suggests that the condition may result from any state with a high level of platelet turnover in the absence of AMG 531 therapy (endogenous compensation in ITP).

Table 31: Increased Reticulin in Bone Marrow

Patient		Splenectomy	History	Response	BM Trigger	Resolution
1	40 WM	yes	none	poor	NRBC	yes
2	31 WM	yes	none	good	NRBC, peripheral blasts	partial
3	53 WM	yes	none	good	routine per study protocol	NR
4	58 BM	yes	none	good	NRBC	partial
5	55 WF	(yes)	HA, SLE	poor	poor response to ITP therapy	NR
6	37 WM	yes	HA	poor	poor response to ITP therapy	no

Patient = patient number and demographics (age, race, sex); Splenectomy = splenectomy status; History = additional medical history in addition to splenectomy status (HA = hemolytic anemia; SLE = systemic lupus erythematosus); Response = platelet or clinical response to AMG 531 therapy; BM Trigger = primary trigger for performing bone marrow studies (NRBC = nucleated red blood cells); Resolution = resolution of reticulin in bone marrow (NR = not reported).

Patient 5 enrolled in study 213 after completing study 212 (non-splenectomy). The patient underwent splenectomy soon after withdrawing from study 213.

Table 32: Neoplasms (ITP Safety Set)

Preferred Term	Placebo (N = 46) n (%)	AMG 531 (N = 204) n (%)
Subjects reporting neoplasm adverse events of interest	5 (10.9)	12 (5.9)
Basal Cell Carcinoma	0 (0)	3 (1.5)
Lung Neoplasm	1 (2.2)	2 (1.0)
Multiple Myeloma	1 (2.2)	1 (0.5)
B-Cell Lymphoma	0 (0)	1 (0.5)
Colon Cancer	0 (0)	1 (0.5)
Haemangioma of Liver	0 (0)	1 (0.5)
Hepatic Neoplasm Malignant	0 (0)	1 (0.5)
Laryngeal Neoplasm	0 (0)	1 (0.5)
Malignant Melanoma	0 (0)	1 (0.5)
Melanocytic Naevus	0 (0)	1 (0.5)
Mvelofibrosis	0 (0)	1 (0.5)
Benign Ovarian Tumour	1 (2.2)	0 (0)
Fibroma	1 (2.2)	0 (0)
Metastases to Liver	1 (2.2)	0 (0)
Uterine Leiomyoma	1 (2.2)	0 (0)

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).
N = number of subjects who received at least one dose of investigational product over the course of all ITP studies.
Thirty five subjects who started on placebo and later received AMG 531 were counted in both treatment groups. Adverse events were assigned to treatment group by start date of the event.
Neoplasm events were determined by MedDRA version 9.0 SOC "Neoplasms benign, malignant and unspecified (incl cysts and polyps)"

Table 33: Serious Neoplasms (Phase 3 ITP Safety Set)

Preferred Term	Placebo (N = 41) n (%)	AMG 531 (N = 84) n (%)
Subjects reporting serious neoplasm adverse events of interest	0 (0)	1 (1.2)
B-Cell Lymphoma	0 (0)	1 (1.2)

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The Phase 3 ITP safety set consists of all subjects who received investigational product in either ITP phase 3 study, 20030105 or 20030212.
Neoplasm events were determined by MedDRA version 9.0 SOC "Neoplasms benign, malignant and unspecified (incl cysts and polyps)".
Serious adverse event includes any event that is fatal, life threatening (places subject at immediate risk of death), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, a congenital anomaly / birth defect, or other significant medical hazard.
Only adverse events starting after the first dose of investigational product are tabulated.

Table 34: Serious Neoplasms (ITP Safety Set)

Preferred Term	Placebo (N = 46) n (%)	AMG 531 (N = 204) n (%)
Subjects reporting serious neoplasm adverse events of interest	0 (0)	5 (2.5)
B-Cell Lymphoma	0 (0)	1 (0.5)
Colon Cancer	0 (0)	1 (0.5)
Hepatic Neoplasm Malignant	0 (0)	1 (0.5)
Multiple Myeloma	0 (0)	1 (0.5)
Myelofibrosis	0 (0)	1 (0.5)

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).
Neoplasm events were determined by MedDRA version 9.0 SOC "Neoplasms benign, malignant and unspecified (incl cysts and polyps)".
N = number of subjects who received at least one dose of investigational product over the course of all ITP studies.
Thirty five subjects who started on placebo and later received AMG 531 were counted in both treatment groups. Adverse events were assigned to treatment group by start date of the event.
Serious adverse event includes any event that is fatal, life threatening (places subject at immediate risk of death), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent
or significant disability / incapacity, a congenital anomaly / birth defect, or other significant medical hazard.
MedDRA version 9.0 was used.

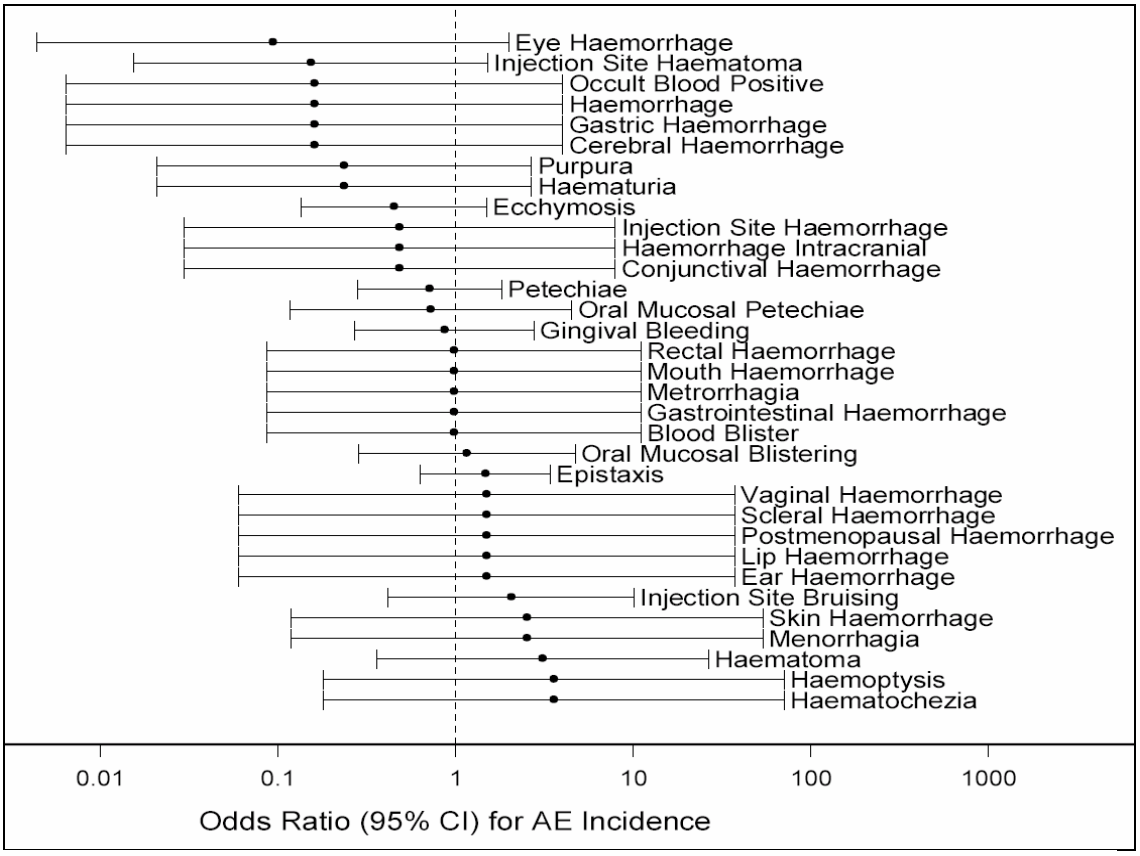
Table 35: Change from Baseline in P-Selectin (Phase 3 ITP Safety Set)

P-Selectin (GMP-140) (ug/L)

	Placebo (N=41)	AMG 531 (N=84)
Week 13		
n	30	70
Mean	6.20	50.20
SD	30.14	68.37
Median	1.00	35.00
Q1, Q3	-6.00, 8.00	12.00, 62.00
Min, Max	-35.00, 118.00	-22.00, 447.00
Week 25[a]		
n	31	68
Mean	2.19	37.38
SD	21.36	45.07
Median	4.00	33.00
Q1, Q3	-9.00, 11.00	7.50, 52.50
Min, Max	-45.00, 62.00	-45.00, 256.00

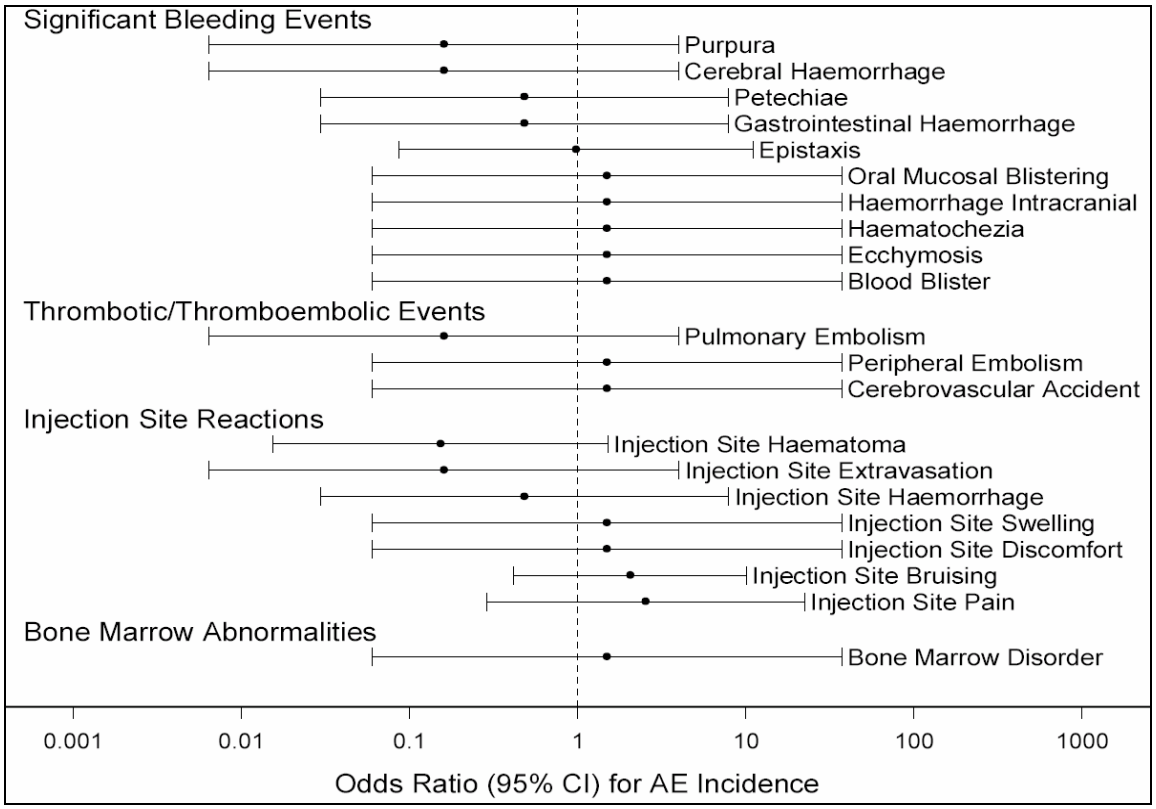
The Phase 3 ITP safety set consists of all subjects who received investigational product in either ITP phase 3 study, 20030105 or 20030212.
Baseline = pre-treatment value closest to the first dose.
[a] End of treatment measurements of subjects who were on study at Week 25 are summarized.

Figure 7: Bleeding Events
Odds Ratio and 95% Confidence Interval (Phase 3 ITP Safety Set)



Odds ratio: AMG 531 vs Placebo. The logit estimator with a correction of 0.5 in every cell, was used for those graphs that contain zero cells. Confidence intervals are estimates based upon log transformation.
The Phase 3 ITP safety set consists of all subjects who received investigational product in either ITP phase 3 study, 20030105 or 20030212.
The adverse event terms that map to bleeding events were prospectively identified by the sponsor before the unblinding of the pivotal studies.
MedDRA version 9.0 was used.

Figure 8: Selected Adverse Events of Interest
Odds Ratio and 95% Confidence Interval (Phase 3 ITP Safety Set)



Odds ratio: AMG 531 vs Placebo. The logit estimator with a correction of 0.5 in every cell, was used for those graphs that contain zero cells. Confidence intervals are estimates based upon log transformation.
The Phase 3 ITP safety set consists of all subjects who received investigational product in either ITP phase 3 study, 20030105 or 20030212.
The adverse events terms that map to bleeding, thrombotic/thromboembolic, injection site events, and bone marrow abnormalities were prospectively identified by the sponsor before the unblinding of the pivotal studies
Significant bleeding events are bleeding events with investigator defined severity grade 3 or above. MedDRA version 9.0 was used.

7. OVERALL ASSESSMENT

The data submitted under this BLA indicate that AMG 531 therapy is safe and effective in increasing the platelet count and in reducing the incidence of serious bleeding in adult patients with ITP refractory to long-term low-dose corticosteroid therapy or splenectomy. However, the clinical experience to date under the sponsor's development program is limited for the orphan indication of ITP, and the current experience may be inadequate to detect important safety concerns that may be anticipated based on the mechanism of action of AMG 531: the potential to increase the incidence of thromboembolic events (including stroke and myocardial infarction) and hematologic disorders (including myelodysplasia, leukemia, and myelofibrosis).

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 12, 2008
To:	Rafel (Dwaine) Rieves, M.D., Director (Acting) Division of Medical Imaging and Hematology Products (DMIHP)
Thru:	Gerald Dal Pan, M.D., M.H.S., Director Office of Surveillance and Epidemiology (OSE) s/2/12/08
From:	OSE Risk Management Team Richard Abate, R.Ph., Safety Evaluator (DMEP) Janet Anderson, Pharm.D., Project Manager (OSE-IO) Suzanne Berkman, Pharm.D., Senior Risk Management Analyst (DRM) Mary Dempsey, Risk Management Program Coordinator (DRM) Susan Lu, R.Ph., Team Leader (DAEA) Rita Ouellet-Hellstrom, Ph.D., M.P.H., Epidemiologist and Acting Team Leader (DE) Claudia Karwoski, Pharm.D., Acting Director (DRM) Betsy Scroggs, Pharm.D., Safety Evaluator (DAEA) Kellie Taylor, Pharm.D., M.P.H., Team Leader (DMEP)
Subject:	Review of risk management proposal and additional considerations
Drug Name(s):	Romiplostim/AMG 531
Application Type/Number:	BLA 125268
Applicant/Sponsor:	Amgen Inc.
OSE RCM #:	2007-2270

CONTENTS

EXECUTIVE SUMMARY

Because the clinical trial experience involved relatively small numbers of patients and limited duration of exposure, the extent and significance of the available safety data are inadequate to elucidate fully the significance of certain safety concerns.

If the Advisory Committee concludes that romiplostim provides a meaningful therapeutic benefit and/or fulfills an unmet need for patients in whom the benefit exceed the potential (long term) risks, approval of this product should be contingent upon the Sponsor's commitment to a comprehensive risk management plan with elements to assure safe use and further study of the drug to resolve the stated uncertainties. This would include clear identification of the appropriate population for use and selection of the appropriate tools to (1) communicate the risks, (2) ensure appropriate patient selection, and (3) provide consistent monitoring. In addition, the risk management plan should incorporate an assessment tool to provide for data collection to evaluate fully the effects of romiplostim over time.

1 BACKGROUND

1.1 Product Information

Romiplostim is a first-in-class fusion peptibody that binds to and activates thrombopoietin receptor, inducing the proliferation and maturation of megakaryocytes into platelets. This mechanism of action makes romiplostim appealing for broad use in a variety of diseases associated with thrombocytopenia. At present, the Sponsor is proposing romiplostim for the treatment of thrombocytopenia in adult patients with chronic idiopathic (autoimmune) thrombocytopenic purpura (ITP) who are (1) non-splenectomized and have an inadequate response or are intolerant to corticosteroids and/or immunoglobulins or (2) are splenectomized and have an insufficient response to splenectomy. Studies are ongoing for the use of romiplostim to treat thrombocytopenia associated with myelodysplastic syndrome (MDS) and chemotherapy-induced thrombocytopenia (CIT).

For the treatment of ITP, the Sponsor studied a weight-based dosing regimen (initial dose 1 mcg/kg subcutaneously once weekly). Dosing is titrated weekly to maintain a platelet count $\geq 50x10^9$/L. The maximum dose is 10 mcg/kg. Prior to administration, the lyophilized drug product must be mixed with sterile water for injection. Because of a dosing error in the clinical trials, the Sponsor recommends that romiplostim be administered by a healthcare professional.

1.2 Safety Concerns

While the efficacy appears robust based on the outcomes of two placebo-controlled, blinded clinical studies, the drug product has certain risks that are not yet completely characterized. There is biologic plausibility that romiplostim has the potential to induce unexpected cell proliferation, platelet activation and/or thrombosis. Based on these theoretical concerns and the adverse events noted in clinical trials, the following risks were identified for further risk management consideration:

- **Neoplasm progression**: Thrombopoietin receptors are expressed on the surface of myeloid cells. There is no confirmed expression on solid tumors.[1] Patients with any known history of marrow stem cell disorder or any "active" (no "active" cancer in past 5 years) cancer were excluded from the ITP studies.[2] The Agency noted development of acute myelogenous leukemia or chloroma in patients with MDS treated with romiplostim in phase 1 and 2 clinical trials for treatment of thrombocytopenia associated with MDS. Questions arise regarding how to screen patients effectively and what is the risk of malignancy progression with long term romiplostim exposure in ITP patients with a history of malignancy.

- **Reticulin formation/marrow fibrosis**: There is concern that with prolonged exposure to romiplostim, increased reticulin will lead to adverse clinical sequelae (e.g., myelofibrosis, collagen fibrosis, chronic idiopathic myelofibrosis, or bone marrow fibrosis with cytopenia). Overall, increased reticulin was reported in six subjects exposed to romiplostim in the ITP safety database.[3] All patients had undergone splenectomy and all had nucleated red blood cells on peripheral smear. None had bone marrow consistent with myelofibrosis. The doses used were high, ranging from 7 to 15 mcg/kg/dose.[3] Based on the observed cases, the medical officer states that increased reticulin appears to be a dose-dependent adverse effect. All cases were in patients with highly refractory disease which coincides with the possible need for dose escalation. The Sponsor states that this safety concern has been detected through routine monitoring of peripheral blood smear and a decline in platelet count response. However, the Sponsor also states that no well-characterized biomarkers are available that could help predict the incidence of reticulin in ITP subjects. Bone marrow biopsy is the only reliable way to determine the presence of reticulin. Biopsy is not consistent with routine management of ITP patients.[4] Questions arise regarding the significance of the event, the long-term sequelae, how best to monitor this finding, and if/how best to treat this finding/event (lower dose, discontinue romiplostim, watchful waiting). If romiplostim discontinuation is warranted, the risk of possibly significant rebound thrombocytopenia must be considered.

- **Thrombotic events**: Thrombotic complications are a concern particularly when platelet counts exceed the normal range. The Sponsor lists it as theoretical concern and states that adverse event rates were similar between placebo and romiplostim. Difficulty with delivering a consistent dose along with the inability to make small dosage adjustments are contributing factors to this risk. Typical dose volumes range between 0.1 to 0.2 mL. Therefore, small volume changes can result in significant dose alterations. The degree of platelet count fluctuation observed in the clinical studies may have resulted, in part, from the difficulties of being able to deliver an accurate dose, consistently. Further, these fluctuations required the Sponsor to broaden the target platelet range from 50-100x10^9/L to 50-200x10^9/L in the absence of any justification for benefit for higher platelet

[1] Risk management plan. Amgen; dated September 14, 2007. p.78.
[2] Risk management plan. Amgen; dated September 14, 2007. p. 32.
[3] Lee J. Interim clinical review for romiplostim in ITP. January 16, 2008.
[4] Background information for ODAC meeting, March 12, 2008. Amgen; submitted on February 8, 2008.

counts in ITP patients.[3] The ability to modify precisely a patient's dose or deliver the same dose consistently could avoid such medication errors that may result from continually adjusting a patient's dose in reaction to fluctuations, exposing patients to higher doses than necessary and increasing the risk of experiencing an adverse event. The importance of proper dose preparation and administration and close platelet count monitoring need to be addressed.

- **Immunogenicity**: During clinical trials, antibody formation to romiplostim and endogenous thrombopoietin were noted. At least one case of neutralizing antibodies was also identified. Based on information provided at the time of submission, antibody formation did not affect the effectiveness of romiplostim. However, the sustained efficacy over the long term has not been fully assessed. Therefore, monitoring platelet counts, dose escalation, and creating a clear plan for antibody formation detection may be prudent.
- **Recurrence of thrombocytopenia after cessation of treatment**: Recurrence of thrombocytopenia, markedly below baseline, was reported in phase 1 and 2 dose-finding studies upon drug discontinuation. There were no reports of these events in phase 3 studies because patients were transitioned to the open-label extension study. Thrombocytopenia may be exacerbated by anticoagulant/anti-platelet therapy. It will be important to highlight this phenomenon to prescribers.

2 Risk Management of Romiplostim

Risk management encompasses risk minimization strategies as well as risk assessment strategies.[5] Both of these components are equally necessary in order to develop a sufficient program to minimize the known and potential risks and assess the potential effects of romiplostim in the long term.

Risk Minimization

The romiplostim RiskMAP should minimize risk by (1) ensuring appropriate patient selection; (2) educating prescribers about the appropriate patient selection, drug dosing, preparation, and administration technique and use the lowest effective dose to maintain a platelet count at the minimum concentration necessary to avoid negative sequelae; and (3) educating patients about the risks so that he or she can make an informed decision to proceed or to refuse treatment with romiplostim.

Various tools/strategies work to minimize risks associated with drugs and therapeutic biologics. Tools communicate specific risk information as well as information regarding optimal product use. Tools provide guidance and/or assure adherence to certain prescribing/dispensing requirements, and/or limit use of a product to only the most appropriate situations or patient populations.

Risk Assessment

The romiplostim RiskMAP should assess the risk of the following in all treated patients:

- Neoplasm progression (however this may be difficult if patients with a history of neoplasm are excluded)

[5] Guidance for Industry: *Development and Use of Risk Minimization Action Plans.* Finalized March 2005.

- Reticulin formation
- Thrombotic complications
- Antibody formation contributing to reduced efficacy through dose escalation and antibody testing
- Clinically important sequelae upon romiplostim discontinuation

2.1 Summary of Sponosor's Proposed Risk Management Plan

The RiskMAP submitted to the Agency on February 7, 2008, was reviewed. The program "is designed to ensure appropriate use of romiplostim in ITP patients, minimize use of romiplostim in patients with thrombocytopenia caused by a condition other than ITP, and promote informed risk-benefit decision regarding romiplostim use."[6] The Sponsor proposes to meet these goals through labeling, targeted education and outreach, routine pharmacovigilance and four studies to assess risk.

Proposed Labeling

The proposed Warnings and Precautions section of the label will include information regarding the risk of malignancies and progression of malignancies, recurrence of thrombocytopenia after treatment discontinuation, increased reticulin formation, thrombotic/thromboembolic complications, and antibody formation. The Dosage and Administration section provides additional information on calculating and preparing the dose of romiplostim. In addition, the label states that romiplostim "must be administered by a healthcare professional." The Sponsor does not explain how this will be ensured.

Targeted Education and Outreach

The Sponsor submitted a Medication Guide for patients. It is unclear who will be responsible for distributing the Medication Guide to the patient. Since a healthcare practitioner must administer the dose on a weekly basis, the Sponsor may utilize alternative drug distribution plans which may deviate from typical drug distribution (manufacturer → wholesaler → pharmacy → patient).

In order to "minimize the risk of physician inadvertently treating an MDS or hematopoietic malignancy patient with romiplostim, Amgen created a rigorous risk communications platform that is supported by three interconnected components."[7] Briefly, these components consist of targeting only qualified specialists for training, a "pre-use checklist along with each product purchase," and a "training kit." The "training kit" provided to prescribers will include patient-directed disease state information. None of the materials were provided in Amgen's background document.

Amgen proposes a variety of routine educational efforts directed at healthcare professionals such as continuing education programs, face-to-face education (detailing), and dissemination of safety information through sales force. In absence of the actual materials, it is difficult to determine if these efforts will truly serve an educational purpose or function primarily to promote and market romiplostim.

Pharmacovigilance

The Sponsor proposes the following measures:

[6] Background information for ODAC meeting, March 12, 2008. Amgen; submitted on February 8, 2008. p.79.
[7] Background information for ODAC meeting, March 12, 2008. Amgen; submitted on February 8, 2008. p. 90.

- Post-marketing safety surveillance for the required periodic safety update reporting
- Advisory panels/safety monitoring committee involvement in on-going and future clinical studies
- An adverse event questionnaire: This questionnaire will be used to document reticulin and progression of myeloid malignancy events reported through clinical trials and the Sponsor's spontaneous reporting system.

Risk Assessment

The Sponsor proposes the following studies:

- Retrospective observational study (Protocol 20070796) to define the background prevalence of bone marrow reticulin who have not received romiplostim: This study will assess the prevalence and nature of bone marrow reticulin and bone marrow fibrosis in adults with chronic ITP in Denmark. It will also evaluate the incidence of thrombotic events. Historical data on 1,500 patients with ITP will be collected from 1996 to 2007 using the National Health Registry Databases of Denmark.
- Registry to monitor the incidence of increased bone marrow reticulin and potential risk of bone marrow fibrosis (Protocol 20070797): This cohort study will include all adult patients identified as having chronic ITP in Denmark, Sweden, and Finland, between January 1, 2009, and December 31, 2019 from hospitalized and outpatient records regardless of romiplostim exposure. Study subjects would be followed from one to ten years. Cases with bone marrow abnormalities would be ascertained using electronic medical records. Of note, romiplostim is not approved in these countries.[8]
- Long term prospective study to assess changes in bone marrow morphology: This study will include 200 patients with ITP receiving romiplostim to capture long-term bone marrow changes. Bone marrow biopsy, peripheral blood smear, and sampling for antibody testing will be completed at baseline before romiplostim exposure as well as after 24 months and 60 months of romiplostim exposure. The primary endpoint will be the incidence of increased reticulin at month 24 and month 60 over baseline.
- Romiplostim utilization study: This study will use data form the PharMetrics Patient Centric Database, HealthCore Managed Care Database, and the national health registry systems of Denmark, Sweden, and Finland. Assessment will be conducted at 9, 15, and 27 months after launch. This study will attempt to:
    - estimate the proportion of patients treated with romiplostim for off-label indications,
    - estimate the proportion receiving more than the maximum labeled dose,
    - describe romiplostim treatment and utilization patterns (up to 39 months) among chronic ITP patients, and

[8] Risk management plan. Amgen; dated September 14, 2007. p. 80. Internal communication with the Division of Medical Imaging and Hematology Products (DMIHP) on February 11, 2008.

- compare treatment and utilization patterns among chronic TIP patients who are and are not treated with romiplostim.

Additional Measures
In addition to the strategies outlined above, the Sponsor states that no direct-to-consumer media advertising will be used.

Program Evaluation Plan
The Sponsor plans to report semiannually on the overall program with an option to reduce or expand use of particular tools based on the following:

- assessment of comprehension, knowledge, attitude, and desired safety behaviors about drug safety risks in healthcare providers as a result of the educational efforts (prescriber, 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/on-label use
- surveys of patients and patient advocacy groups on knowledge regarding ITP and romiplostim

2.1.1 Comments on Sponsor Proposal

The Sponsor proposes an education-based RiskMAP that focuses on appropriate patient selection and further risk assessment. While we agree with the risk assessment and minimization goals, certain components of the plan are missing that if included, would better ensure safe use and adequate risk assessment. Considering the biologic plausibility for significant adverse events coupled with the limited number patients exposed[9] over a relatively short period of time in the clinical development program[10] and the anticipated broader use in a traditional post-approval environment, these concerns build a case for implementation of additional risk mitigation strategies.

The proposal fails to identify the appropriate use population. Neither the RiskMAP nor the proposed label clearly outlines who should or should not receive romiplostim based on the risk/benefit profile. For example, the label does not state whether prescribers should expose ITP patients with a history of bone marrow disorder or "active" cancer to romiplostim.

The RiskMAP fails to describe how appropriate use will be ensured. Instead, it focuses on education-based initiatives designed to encourage appropriate use. These educational tools are important to communicate the message(s), but there is limited experience on their effectiveness in ensuring safe use of a product. Traditional risk communication tools such as labeling and dear healthcare professional letters have been shown to have little effect on impacting prescribing behavior or increasing compliance with labeled laboratory monitoring recommendations.[11,12,13,14]

[9] The ITP safety set consists of only 204 patients (284 total including all studies) who were exposed to at least one dose of romiplostim. Data from the risk management plan submitted by Amgen dated September 14, 2008. p.23.
[10] Only 74 patients had at least 52 weeks of exposure. Data from the background information for ODAC meeting, March 12, 2008. Amgen; submitted on February 8, 2008. p. 62.
[11] Willy M, et al. *A study of compliance with FDA recommendations for pemoline (Cylert)*. J Am Acad Child Adolesc Psychiatry. 2002 Jul;41(7):785-90.
[12] Graham D, et al. *Liver enzyme monitoring in patients treated with troglitazone*. JAMA. 2001 Aug 15;286(7):831-3.

- One focus of the proposal is the strategy to target only qualified specialists (hematology, medical oncology, hematology-oncology) to enhance appropriate use. This plan may be ineffective given that hematologists/oncologists are expected to comprise the vast majority of use, on and off-label. With only a proposed ITP indication at this time, the need to target oncologists is difficult to justify and may serve to encourage rather than discourage off-label use (e.g., use in CIT). Therefore, the impact of this initiative on minimizing off-label use is possibly unfavorable to inconsequential, at best.
- The Sponsor also proposes a checklist (not provided) with each product purchase. It is not clear if a checklist(s) will be provided with each vial or each shipment. It is not clear how the checklist will be implemented or what leverage this effort will ultimately have on appropriate patient selection in the absence of measures to ensure its appropriate use. How the checklist will be implemented will depend in part upon who purchases and receives the product. Since romiplostim is to be administered by healthcare professionals only, it is unclear if romiplostim will be sold directly to prescribers for administration or if retail pharmacies will order this product to dispense to the patient to take to a healthcare professional for administration. If the latter, it is unclear how the checklist will be of any value to the prescribing physician in selecting the appropriate patient when the decision to treat the patient has been made and the prescription has been written and dispensed.

Four studies are proposed to assess bone marrow reticulin risks, potential thromboembolic events, and patterns of prescribing. These studies are unlikely to adequately characterize and manage the identified and potential risks associated with romiplostim. Two of the four proposed studies will be completed in non-U.S. populations.

The Retrospective Observational Study (Protocol 20070796) proposes to evaluate the background prevalence and incidence of bone marrow reticulin and thrombotic events in non-US ITP populations. This study would provide information on background rates regardless of romiplostim approval since the study would evaluate incidence/prevalence in ITP patients through 2007. The Sponsor should consider evaluating the prevalence and incidence of bone marrow reticulin and thrombotic events in U.S. ITP populations also using population-based large claims databases with access to medical records. ITP patients can be reliably identified in administration data.[15]

The prospective registry proposes to follow all ITP patients identified from hospital and outpatient records over a ten-year period. The study, however, is limited to Danish, Swedish, and Finnish patients where romiplostim is not yet approved. In concept, this registry would have the potential to provide clinically significant information on bone marrow abnormalities but would be limited to clinical information captured by medical records. This registry, however, may or may not provide information on whether any potential increased risk for bone marrow reticulin abnormalities and neoplasms can be related to the disease progression itself or to romiplostim exposure. There are no estimates of the number of exposed and non-exposed ITP patients and it remains unknown if and when romiplostim will be approved in Denmark, Sweden, and Finland, all non-US populations.

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[13] Smalley W, Shatin D, Wysowski D, Gurwitz J, Andrade S, et al. *Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action.* JAMA 2000;284(23):3036-3039.
[14] Weatherby LB, Nordstrom BL, Fife D, Walker AM. *The Impact Of Wording in "Dear Doctor" Letters and In Black Box Labels*. Clin Pharmacol Ther. 2002;72:735-742.
[15] Segal BM, Powe NR. Accuracy of identification of patients with immune thrombocytopenic purpura through administrative records: A data validation study. Amer J of Hematology.2003;75(1): 12-17.

Although the Sponsor describes the third study as a "long term prospective study," this appears to be an open-label follow-up of study subjects treated with romiplostim. This study would be limited to assessing bone marrow morphology in 200 study subjects. Continuous monitoring would include monthly assessments of peripheral blood smears 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 would be the incidence of increased reticulin at month 24 and month 60 over baseline. This study would characterize the morphology of romiplostim-exposed patients. There is no mention of a comparator group. Also, no information is provided on the nationality of study subjects.

The fourth study proposes to evaluate patterns of romiplostim use using the PharMetrics Patient-Centric Database, HealthCore Managed Care Database, as well as data from the national health registry systems of Denmark, Sweden, and Finland. All databases are adequate to evaluate patterns of care and identify off-label use. The PharMetrics and HealthCore are US-based. Records from PharMetrics are de-identified, however, with no possibility of linking with medical records. The HealthCore database and the European registries offer access to electronic medical records and could be suitable to assess possible risks.

These studies do not provide immediate resolution to the concerns surrounding the risks associated with romiplostim now and cannot ensure safe use for patients who may receive romiplostim if the product is approved during the current review cycle. Therefore, a restricted distribution risk minimization action plan designed to assure safe use through appropriate patient selection and risk assessment should be considered in conjunction with risk assessments.

2.2 additional risk management strategy considerations

2.2.1 Risk communication

Communication strategies work to inform healthcare professional and patients about conditions of use contributing to produce risk and conditions of use that are important to achieve the products benefits. Dear healthcare professional letters, Medication Guides, informed consent forms (patient agreement forms), and training programs are all examples of different tools. The informed consent process facilitates communication between the patient and prescriber. The result of this communication is the patient's authorization or agreement to undergo treatment with the romiplostim. This process gives the patient the opportunity to ask questions to elicit a better understanding of the treatment, so that the patient can make an informed decision to proceed or to refuse treatment. The purpose is not to obtain agreement to participate in the RiskMAP. Agreement to share/disclose health information is a separate issue. Informed consent is utilized for several products with RiskMAPs including Lotronex, Accutane, Tysabri, Soriatane, and Thalomid.

2.2.2 Ensuring appropriate use

Patient Selection

The goal of risk minimization is to minimize a product's risks while preserving its benefits. The first step is to identify a patient population for whom this product has a favorable benefit risk profile and restrict its use to those patients until the risks and long term effects are understood and the need for such measures may no longer be needed. If such a patient population can be

identified, the RiskMAP should address how prescribers will identify the patients for whom a favorable benefit/risk profile exists, what risk minimization measures are needed for these patients to safely use the product, and what measures are needed to prevent use in patients for whom the benefit risk profile is not favorable.

Patient Monitoring and Data Collection

Specific goals and objectives are part of the development of a RiskMAP. The goals are translated into measurable program objectives that lead to achievement of the RiskMAP goals. These objectives often involve monitoring laboratory tests, imaging, and other examination findings.

Data collection should be comprehensive, and involve all patients prescribed romiplostim since the proposed patient population is limited and closely monitored. Data collection should include, but not be limited to, detection of neoplasm development and/or progression, reticulin formation and subsequent sequelae or absence thereof, thrombotic events, determination of the risk of immunogenicity, and characterization of the risk of thrombocytopenia upon treatment discontinuation. The merits of the proposed risk assessment studies versus data collection through the risk management plan will need further consideration and discussion.

2.3 Elements of a possible RiskMAP

The considerations described above to minimize exposure and assess long term risk with centralized sources for data collection can be accomplished through a restricted distribution program in which certain conditions for safe use must be met before the product can be distributed, prescribed, dispensed, and/or administered. These elements are in addition to the communication tools discussed above and might include the following:

a. Mandatory enrollment of prescribers with one or more of the following elements:
    i. Attestation of understanding the safe use condition(s) (e.g., appropriate patient selection, patient counseling and monitoring)
    ii. Agreement to comply with program monitoring and data collection

b. Required registration for distributors/pharmacies

    The Sponsor has not explained how the drug will be distributed. Requirements for the stakeholders involved in distribution will be dependent on how the Sponsor plans to distribute romiplostim.

c. Mandatory enrollment of patients:
    i. Patients sign informed consent
    ii. Comply with monitoring

d. Long-term data collection to assess the following:
    i. Risk of neoplasm progression
    ii. Risk of reticulin formation
    iii. Risk of thrombotic events
    iv. Risk of antibody formation/reduced efficacy
    v. Clinically important sequelae upon romiplostim discontinuation

3 DISCUSSION

The Sponsor's proposal for education, targeted detailing and a checklist may not be sufficient to minimize the risk and ensure appropriate use of the product. The Advisory Committee should discuss the utility of a restricted distribution program for romiplostim. There are a number of characteristics about the drug product and the nature of the disease that make a restricted distribution program feasible. The target patient population is limited and closely monitored. That patient-provider relationship is targeted to a single but significant medical problem that requires chronic, long-term treatment. We anticipate prescribing to be limited to one specialty, primarily hematology – even when potential off-label use is considered. The product's formulation (requires reconstitution, single-use vial vs. fixed dose, prefilled syringe) may limit use. In addition, the Sponsor plans to require administration by a healthcare provider.

There is a unique challenge with developing an adequate RiskMAP for romiplostim. There is not a single identifiable, preventable risk; rather there are several risks that require consideration and long term follow-up. For example, the significance of reticulin formation is not known nor is there an ideal method for detection/monitoring. In the case of malignancy progression, the RiskMAP can mitigate this risk by preventing exposure in patients at risk. However, there are no mitigation options that go beyond gatekeeping and monitoring. Further, the absence of neoplasm cases will not translate to lack of risk. The lack of malignancy cases could demonstrate the effectiveness of the RiskMAP but not provide further insight into malignancy progression. Additional data outside of the RiskMAP would be necessary to evaluate the significance of this risk.

By developing a RiskMAP in which prescribers and patients enroll provides the opportunity to create centralized data collection tools and to ensure appropriate monitoring is performed. It is particularly important to ensure safe use while risk assessment is ongoing. The Sponsor could choose to prompt the prescriber and monitor for neoplasm progression, reticulin formation/sequelae, and/or antibody formation at regular intervals. A special registry/protocol could be developed for patients for long-term follow-up, if necessary. While the additional studies proposed by the Sponsor could provide additional information, those studies should not be a substitute for or alleviate the need to ensure safe use through careful patient selection, observation and follow-up at the present time. The merits of the proposed risk assessment studies and the merits of data collection through the risk management plan will need further consideration and discussion.

4 CONCLUSION

If the Advisory Committee determines that romiplostim provides a meaningful therapeutic benefit and/or fulfills and unmet need for patients where the benefit exceeds the unknown long term risks, approval of this product should be contingent upon the Sponsor's commitment to a comprehensive risk management plan to assure safe use and to further study of the drug to resolve the stated uncertainties.