

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
BLA 125268

MEDICAL REVIEW(S)



Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 6, 2008

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Florence Moore
Regulatory Project Manager
Division of Medical Imaging and Hematology Products

Subject: QT-IRT Consult to BLA 125268/0

This memo responds to your consult to us dated April 25, 2008 seeking our opinion on Amgen's proposal for not further evaluating the impact of romiplostim on the QTc interval.

The QT-IRT received and reviewed the following materials:

- Your consult
- Overview of supporting data demonstrating the low risk for delayed cardiac repolarization with romiplostim

Background

Nplate (Romiplostim) is an Fc fusion protein (peptibody) that increases platelet production via the thrombopoietin (TPO) receptor (also known as cMpl), which activates intracellular transcriptional pathways. The peptibody molecule is comprised of a human immunoglobulin G1 (IgG1) Fc domain, with each single-chain subunit covalently linked at the C-terminus to a peptide chain containing two TPO receptor-binding domains. Romiplostim has no amino acid sequence homology to endogenous TPO (eTPO). Romiplostim is produced by recombinant DNA technology in Escherichia coli (E coli).

Romiplostim is being developed as a treatment for thrombocytopenia associated with immune (idiopathic) thrombocytopenic purpura (ITP). The sponsor submitted the current BLA seeking the full approval of Romiplostim for the treatment of ITP and this BLA is under priority review.

The recommended initial dose is 1 mcg/kg administered once weekly as sc injection. The dose should be adjusted to the appropriate platelet count to a maximum dose of 10 mcg/kg.

2281

Sponsor's Justification for not further characterizing the QT effects:

"Amgen believes that romiplostim does not prolong the QTc interval through either direct or indirect effects. The following conclusions can be made:

- Romiplostim represents an important therapeutic for treating ITP
- Romiplostim, a peptibody, with a molecular weight of 59 kDaltons and high specificity for the Mpl receptor is not anticipated to have off target binding to the hERG channel.
- Preclinical evaluation of the potential for romiplostim to prolong the QTc interval was negative. The evaluation included a cardiovascular safety pharmacology study in cynomolgus monkeys. Additionally, electrocardiographic parameters were evaluated as part of the 1 month and 3/6 month repeat dose toxicity studies in non-human primates.
- Phase 1 studies in healthy Caucasian and Japanese volunteers explored doses up to 10 mcg/kg (maximum recommended clinical dose) and demonstrated no effect on the QTc interval.

"Based on the above Amgen believes that romiplostim does not prolong the QTc interval and that a further evaluation of the impact of romiplostim on QTc interval is not warranted. A post marketing requirement for further evaluation is not necessary."

Romiplostim Pharmacokinetics

Source: Clinical Overview

"In healthy subjects, the pharmacokinetics of AMG 531 was nonlinear after a single IV dose of AMG 531 from 0.3 to 10.0 µg/kg. As the dose increased, the time-averaged clearance and volume of distribution measured by noncompartmental analysis decreased.

"After a single 2-µg/kg SC dose, peak serum concentrations were observed between 24 and 36 hours post-dose in healthy subjects (Study 20000109). For subjects with ITP, peak serum concentrations after chronic once-weekly SC administration were observed about 7 to 50 hours (median t_{max} = 14 hours) post-dose over a dose range of 3 to 15 µg/kg (Study 20030213-Subset A/B). No clear relationship was observed between the serum concentration-time profiles with doses over a range of 3 to 15 µg/kg (Study 20030213-Subset A/B). However, higher exposures were observed in subjects with lower platelet counts at a given dose, possibly because serum concentrations of AMG 531 are modulated by the receptor pool on platelets and megakaryocytes, which varies by time, subject, and disease state. Due to limited data available, the absolute bioavailability of AMG 531 after SC administration could not be estimated."

Clinical ECG Evaluation

A total of 11 clinical studies including 2 studies in healthy subjects and 7 studies in subjects with ITP were conducted as part of the development program. ECGs were collected in the 2 studies in healthy volunteers. A summary of the study design including ECGs are shown in the following table.

Summary of Phase 1 Studies Collecting ECGs

Study	Design	Population	Doses	Timing of ECGs	ECG Results
20000109	Randomized, first-in-human, phase 1 study to assess the safety, tolerability, PK, and PD of a single dose of romiplostim	Healthy volunteers Total: 32	Subjects (n=4 per cohort) received <i>single doses</i> of 0.1, 0.3, 1, or 2 mcg/kg romiplostim administered SC and 0.3, 1, or 10 mcg/kg romiplostim administered IV	ECGs were collected pre-dose, 5 min, 8 and 24 hours post dose	Sponsor's Tables 3 and 5
20040134	phase 1 study conducted to assess the safety, tolerability, PD and PK profiles of romiplostim in healthy Japanese subjects.	Healthy volunteers Total: 24	Subjects (n=8) received a <i>single SC injection</i> of romiplostim at doses of 0.3, 1.0, 2.0, or 3.0 mcg/kg.	ECGs were collected pre-dose, 5 min, 8 and 24 hours post dose	Sponsor's Tables 9 and 12

Table 3. Summary of Post-Baseline Maximum Change QTcF Interval
Study 20000109 - All Treated Subjects

Parameter	Placebo (N=16)	0.1 ug/kg SC (N=4)	0.3 ug/kg SC (N=4)	1.0 ug/kg SC (N=4)	2.0 ug/kg SC (N=4)	2.0 ug/kg SC (N=4)	0.3 ug/kg IV (N=4)	1.0 ug/kg IV (N=4)	10 ug/kg IV (N=4)	All AMG531 (N=32)
Post-Baseline Maximum Change QTcF Interval in msec										
n	16	4	4	4	4	4	4	4	4	32
Mean	6	3	-2	8	0	3	4	23	6	6
SD	17.9	6.8	16.4	8.6	24.6	18.8	3.7	24.3	34.3	18.8
Median	8	2	3	7	9	11	5	32	4	5
Min, Max	-49, 30	-3, 13	-25, 13	-0, 18	-36, 19	-24, 15	-1, 7	-12, 41	-33, 50	-36, 50

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Bazett-Corrected QT Interval (QTcB) (millisecond) = $QT/(RR/1000)^{1/2}$
Fridericia-Corrected QT Interval (QTcF) (millisecond) = $QT/(RR/1000)^{1/3}$

Baseline is defined as the Day 1 Predose measure.

There are two columns for 2.0 ug/kg SC groups because the cohort was repeated per protocol.

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Program: Table3.sas

Output: 110-08_003_001_SumMax.rtf (Date generated: 18APR2008:09:19) Source data: /data/csp/pharm/AMG531/20000109/SC3/tables/cr/1/c_vitals.26472001

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Table 6. Maximum Change From Baseline QTcF and QTcB by Category- Study 20000109

Parameter	Category	Placebo (N=10)	0.1 ug/kg SC (N=4)	0.3 ug/kg SC (N=4)	1.0 ug/kg SC (N=4)	2.0 ug/kg SC (N=4)	2.0 ug/kg SC (N=4)	0.3 ug/kg IV (N=4)	1.0 ug/kg IV (N=4)	10 ug/kg IV (N=4)	All AMG531 (N=32)
QTcF (msec)	≤ 30	15 (94)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	2 (50)	3 (75)	20 (91)
	>30 - 60	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (50)	1 (25)	3 (9)
	> 60	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
QTcB (msec)	≤ 30	16 (100)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	3 (75)	3 (75)	30 (94)
	>30 - 60	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)	1 (25)	2 (6)
	> 60	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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Bazett-Corrected QT Interval (QTcB) (millisecond) = $QT/(RR/1000)^{1/2}$

Fridericia-Corrected QT Interval (QTcF) (millisecond) = $QT/(RR/1000)^{1/3}$

Baseline is defined as the Day 1 Predose measure.

There are two columns for 2.0 ug/kg SC groups because the cohort was repeated per protocol.

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Program: Table1.sas

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Table 9. Summary of Post - Baseline Maximum Change QTcF Interval
Study 20040134 - All Treated Subjects

Parameter	Placebo (N=6)	0.3 ug/kg (N=8)	1.0 ug/kg (N=8)	2.0 ug/kg (N=8)	All AMG531 (N=24)
Post-Baseline Maximum Change QTcF Interval in msec					
n	6	8	8	8	24
Mean	3	-2	0	7	2
SD	9.2	5.7	5.6	4.6	6.2
Median	2	-0	1	8	2
Min, Max	-5, 20	-10, 4	-11, 9	-1, 15	-11, 15

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Bazett-Corrected QT Interval (QTcB) (millisecond) = $QT/(RR/1000)^{1/2}$

Fridericia-Corrected QT Interval (QTcF) (millisecond) = $QT/(RR/1000)^{1/3}$

Summaries are based on the means of measurements at each time point (triplicate for Day -1 time point, single measure for all other time points) and baseline is defined as the average of Day -1 triplicate mean and the Day 1 Predose measure.

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Program: Table3.sas

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Table 11. Maximum Change From Baseline QTcF and QTcB by Category – Study 20040134

Parameter	Category	Placebo (N=8)	0.3 ug/kg (N=8)	1.0 ug/kg (N=8)	2.0 ug/kg (N=8)	All AMG531 (N=24)
QTcF (msec)	≤ 30	6 (100)	8 (100)	8 (100)	8 (100)	24 (100)
	>30 - 60	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	> 60	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
QTcB (msec)	≤ 30	6 (100)	8 (100)	8 (100)	8 (100)	24 (100)
	>30 - 60	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	> 60	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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Bazett-Corrected QT Interval (QTcB) (millisecond) = $QT/(RR/1000)^{1/2}$

Fridercia-Corrected QT Interval (QTcF) (millisecond) = $QT/(RR/1000)^{1/2}$

Summaries are based on the means of measurements at each time point (triplicate for Day -1 time point, single measure for all other time points) and baseline is defined as the average of Day -1 triplicate mean and the Day 1 Predose measure.

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Program: Table1.sas

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QT-IRT Comments for DMIHP

1. There is no real consensus on the best approach to evaluate the QT effects of biologic therapeutics. The classic mechanism of directly inhibiting the hERG channel via the intracellular pore is not probable due to the large size of these agents. We do recognize, however, that these molecules can have off-target cardiac effects. For example, trastuzumab (Herceptin®) causes off-target cardio-toxicity by binding to an extracellular site on the cardiac myocyte. In addition, it is possible to block hERG from the exterior with large molecules. For example, snake and scorpion venom peptide toxins can bind to an extracellular surface site of the hERG receptor. With monoclonal antibodies, we recommend that routine ECG monitoring in Phase 1, 2 and 3 clinical studies should be performed to capture any important cardiac effects and do not recommend a 'thorough QT' study. A TQT study may be more appropriate for small peptides, such as cytokines, hormones. At this time, the appropriate ECG monitoring plan for biologic therapeutics that are not monoclonal antibodies are handled on a case-by-case basis.
2. Since romiplostim is a peptibody with molecular weight of 59 kDa, we do not believe that this molecule will not have access to the hERG pore from the intracellular side. Therefore, we do not recommend a TQT study. We do recommend that ECGs are collected in clinical trials to rule out off-target cardiac effects.
3. In our opinion, the sponsor has not collected adequate ECGs during the development of romiplostim to rule out off-target cardiac effects. ECGs were collected in two small phase 1 dose-escalating studies in healthy volunteers (n=56) who were administered only a single dose of romiplostim. Three ECGs were collected within 24 hours after dosing. Given the long $t_{1/2}$ of this product (range 1 to 34 days) and

ECGs were collected within 24 hours after a single dose, delayed or off-target effects cannot be ruled out.

4. We recommend that the sponsor continues routine ECG monitoring in the post-marketing clinical studies to capture any important cardiac effects in the patient population with chronic dosing of romiplostin. ECGs should be collected after multiple doses of romiplostin.

Thank you for requesting our input into the development of this product under BLA. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cdcrpqt@fda.hhs.gov

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On Original*



MEMORANDUM

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

FROM: Steven Lemery, Medical Review Officer, DBOP
THROUGH: Jeffrey Summers, Team Leader, DBOP
TO: File
SUBJECT: BLA application 125268: Consult to DMIHP regarding
MDS progression safety review for study 20050159
SUBMIT DATE: 10/23/2007
PRODUCT: AMG 531 / Nplate
APPLICANT: Amgen, Inc.
DATE: May 5, 2008

Executive Summary

- This review contains a summary of myelodysplastic syndrome (MDS) progression events and increased blast counts that occurred during study 20050159.
- Pre-clinical literature showed evidence of c-mpl overexpression in a variable percentage of acute myelogenous leukemia (AML) blasts and MDS blasts derived from patient samples. Some of these blasts proliferated in-vitro in response to thrombopoietin.
- Key findings of this review include increased blasts occurring in 18 out of 44 patients with MDS in study 20050159. Four additional patients experienced a cytogenetic progression event.
- This review summarizes these cases; some of these cases involved MDS progression or AML progression.
- This reviewer recommends publicizing the potential risk of MDS progression during the March Oncology Drugs Advisory Committee meeting.
- This reviewer recommends revising Amgen's proposed labeling to accurately reflect the experience of patients enrolled in this study.

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Background

During FDA review of the Amgen meeting package submitted for a Type B meeting scheduled on April 30, 2007, FDA noted that 6 out of 44 patients in a phase 1/2 clinical trial (study 20050159) in patients with myelodysplastic syndrome (MDS) appeared to develop acute myelogenous leukemia or chloroma within one year of follow-up after receiving AMG 531. This approximate extrapolated 40% conversion rate at three years was higher than that predicted for a patient population of low risk and intermediate-1 risk MDS patients (the median 25% time point for acute myelogenous leukemia (AML) conversion is (greater than) 9.4 years for low risk patients and 3.3 years for intermediate-1 risk subjects [Greenberg et al., 1997]).

During the April 30, 2007 meeting, Amgen stated that three of the five patients classified as having experienced an AML progression event actually had transient increased blast counts; therefore, the definition of AML was met in only two of the 44 patients. FDA requested during the meeting that Amgen provide a detailed report of increased blast counts occurring during study 20050159 to better assess this safety signal. Furthermore, FDA requested that Amgen update the informed consent forms in IND to discuss the potential for leukemia progression.

Amgen submitted a safety analysis for MDS and leukemia progression on October 31, 2007 describing increased blast counts or chloroma occurring in 10 of 44 patients. Data from the phase 1/2 MDS clinical trial was presented December 10, 2007 during an oral session at the annual American Society of Hematology meeting (Kantarjian et al, 2007). The abstract for this study summarized that two confirmed cases of transformation to AML occurred and that six additional patients experienced temporary blast cell increases. The cases submitted to the IND on October 31, 2007 were subsequently submitted to the BLA for review.

Additional information for this review was obtained from the 20050159 study report and data tables submitted with the BLA, the 120-day safety update submitted on 2/22/2008, additional patient narratives submitted by Amgen on 2/25/2008 and 2/29/2008, and a CIOMS safety report from a separate open-label extension study (in a patient previously enrolled in study 20050159).

Review

Review of the Literature

A review of the literature was conducted to determine whether non-clinical or theoretical models exist that may support the hypothesis that thrombopoietin (or thrombopoietin analogues) may increase the risk for leukemia or MDS progression in MDS patients treated with AMG531. Table 1 contains studies that evaluated c-mpl expression in patients with AML or MDS and studies evaluating whether increased proliferation was observed after the administration of thrombopoietin or pegylated thrombopoietin. None of these studies specifically evaluated AMG 531.

Table 1: Synopsis of Reviewed Nonclinical Studies

Study	Findings (see bottom of table for list of abbreviations)
Vigon et al., 1993	c-mpl expression (Northern Blot analysis) was increased in 26 of 51 patients with acute myeloblastic leukemia (AML) and in 5 of 16 patients with MDS. There was no significant correlation between c-mpl expression and the FAB classification of AML. The authors stated that c-mpl was barely detectable in normal bone marrow cells, and transcripts were not increased in lymphoid malignancies or chronic myeloproliferative disorders.
Bouscary et al., 1995	c-mpl expression (Northern Blot analysis) was increased in 45% (n=59) of patients with AML compared to barely detectable transcript levels in normal bone marrow samples. c-mpl levels were increased in 33% of MDS samples (limited to CMML, RAEB, and RAEBt).
Matsumura et al., 1995	Northern blot analysis demonstrated increased c-mpl expression in 26 out of 50 (52%) patients with AML (including 4 of 4 patients with the M7 subtype). Increased c-mpl was not detected in acute lymphoblastic leukemia (ALL) samples. RT-PCR detected c-mpl in all cases of AML. The investigators subsequently demonstrated a dose-dependent proliferative effect in response to rhTPO over a range of 1 to 100 ng/ml in two cell lines. Finally, the investigators evaluated the effect of rhTPO on the proliferation of patient AML cells. At 20 ng/mL, the proliferation of AML cells was induced in 19 of 26 c-mpl positive cases (by Northern blot) versus 3 of 24 cases in which c-mpl was barely detectable.
Quentmeier et al., 1996	Using flow cytometry, 13/21 cases had greater than 10% mpl-positive cells. Recombinant TPO overexpressed in hamster cells induced a mitogenic response in 3/21 AML specimens as measured by 3H-thymidine incorporation.
Motoji et al., 1996	Thrombopoietin stimulated blast colony formation in 11/20 patient samples studied with AML. The authors noted a "remarkable" increase in CD41 in three of the cases after thrombopoietin administration. The thrombopoietin receptor was detected in all five cases in which positive colony formation occurred after thrombopoietin versus one of three cases where colony formation did not occur.
Matsumura et al., 1996	The investigators evaluated AML cells from 15 patients that showed growth response to rhTPO in short term culture. The investigators studied these cells when subjected to a long-term suspension culture with or without rhTPO. In four cases (FAB M 0, 2, 4, and 7), rhTPO supported proliferation of AML cells for two to four weeks. When exposed to rhTPO, all AML cells tested demonstrated rapid tyrosine phosphorylation of c-mpl and STAT3; however, only in two cases were specific erythroid/megakaryocyte specific transcription factors markedly induced (GATA-1, GATA-2, and NF-E2).

Study	Findings (see bottom of table for list of abbreviations)
Hirai et al, 1997	In vitro proliferative responses (H3 thymidine incorporation) to TPO were observed in 4 out of 4 cases of transient abnormal myelopoiesis (TAM) that occurs in patients with Down's syndrome. In vitro proliferative responses to TPO were also observed in 11 of 28 cases of AML. The maximum response to rhTPO in M7 cells occurred at a TPO concentration of 1 ng/ml. A proliferative response to TPO occurred in 5 of 6 AML cases demonstrating expression of c-mpl and none of 7 that did not.
Piacibello et al, 1997	A significant proliferative response to MGDF occurred in 9 of 23 AML cases (H3 thymidine incorporation). MGDF also enhanced proliferation associated with other hematopoietic growth factors.
Wetzler et al., 1998	c-mpl protein was detected in 59% of AML patients. Proliferation of AML blasts occurred in response to MGDF in six of 25 patient samples. The authors stated that there was no correlation between receptor expression and response to MDGF. The authors stated that the combination of G-CSF and MGDF was significantly more active in stimulating DNA synthesis compared to G-CSF alone.
Tokunaga et al., 1998	The investigators studied proliferation of AML blasts to TPO (20 ng/ml or in combination with other growth factors) by phenotype (CD7+ and CD34+) using the H3 thymidine incorporation assay. Proliferation was observed in 10/10 CD7+ cases, 5/9 CD7-CD34+ cases, and no cases that were CD7-CD34-. Significant growth in a leukemic blast colony assay was observed in 5/6 CD7+ samples tested and 4/17 CD7- samples tested. C-mpl RNA by Northern blot analysis was detected in 2/2 CD7+ cases, 1/2 CD7-CD34+ cases, and 0/1 CD7-CD34- case.
Takeshita et al., 1998	Using a ligand binding assay, the TPO receptor was expressed in 53 out of 114 cases of AML (47%); detection of TPO receptor was not correlated with FAB subtype except for M7 (all five cases expressed TPO). Thirteen of 66 (20%) AML cases showed proliferation in response to in-vitro TPO (200ng/ml) administration (H3 thymidine uptake). The authors stated that there was no significant correlation between the amount of TPO-R and proliferative response; however all of the AML cases that showed an in-vitro response had TPO-R expression.
Fontenay-Roupie et al., 1998	In short term liquid culture and progenitor assays (culturing with or without 20 ng/mL rhMGDF plus IL-3, IL6, EPO, GM-CSF, and SCF), the investigators discovered that TPO potentiated leukemic cluster growth (by day 10) of bone marrow mononuclear cells in 10/38 MDS cases (predominately limited to patients with RAEB, RAEBt, and CMML). Cytogenetically malignant colonies were detectable by FISH in three of three cases tested. The authors in this study concluded that rhMGDF-induced blast cell proliferation correlated with elevated expression of c-MPL in MDS cases.

Study	Findings (see bottom of table for list of abbreviations)
Lou et al., 2000	Marrow cells from 37 MDS patients were cultured (100 ng/ml for 48 hours) with pegylated TPO. TPO increased the blast count number in 9 of 19 cases of RAEB and RAEBt, and in 4 of 10 cases with MDS transformed to acute leukemia. The investigators concluded that high risk patients with MDS should be monitored with particular care in clinical studies evaluating TPO.
Schroder et al., 2000**	c-MPL expression was observed in 27 of 53 AML patients (51%).
Kalina et al., 2000	Cells from two patients with refractory anemia (MDS) showed low basal levels of phosphorylated STAT3 and STAT5 molecules that were enhanced by stimulation with recombinant PEG-rhMDGF (100 ng/ml for 10 minutes). In RAEBt (n=2) and AML M7 cells (n=2), STAT1, 3, 6 and MAPK were upregulated and showed a strong activation of STAT3 and 5 by Peg-rhMDGF.
Corazza et al., 2006	The authors concluded that in patients with AML, inadequate TPO levels are secondary to TPO clearing by functional c-mpl receptors on myeloid blasts and that TPO levels increased as blasts disappeared. TPO did not induce proliferation in c-mpl negative samples tested. TPO induced proliferation (cell cycle analysis using immunofluorescence staining of incorporated bromodeoxyuridine and flow cytometry analysis) or decreased apoptosis (using Aportarget Annexin-V FITC Apoptosis kit) of AML cells in 6 of 11 cases.
Abbreviations used in table that were not previously defined	TPO : thrombopoietin; rhTPO : recombinant human thrombopoietin; c-mpl : thrombopoietin receptor; CMML : chronic myelomonocytic leukemia; RAEB : refractory anemia with excess blasts; RAEBt : refractory anemia with excess blasts in transformation; ALL : acute lymphoblastic leukemia; RT-PCR : reverse transcriptase polymerase chain reaction; FAB : French-American-British (leukemia classification system that designated AML cases as M0 through M7); MGDF : megakaryocyte growth and differentiation factor (thrombopoietin); G-CSF : granulocyte-colony stimulating factor; FISH : fluorescent in situ hybridization

**Abstract reviewed only

Summary of findings from the literature review

1. Increased expression of c-MPL was detected in a variable percentage of blasts in patients with AML and MDS. No distinct pattern was detected regarding AML FAB subtype and c-MPL overexpression, with the possible exception of more consistent overexpression in AML M7.
2. A variable percentage of AML cells demonstrated in-vitro proliferation after exposure to different concentrations of TPO. Concordance of in-vitro proliferation with TPO overexpression by Northern blot analysis was not universal, although a higher

percentage of c-mpl overexpressing cells demonstrated in-vitro proliferation in most studies.

3. The reviewed non-clinical studies provided evidence that blasts can proliferate due to c-mpl ligation in some patients with AML or MDS.
4. The studies do not provide definitive evidence to determine whether TPO induced blast proliferation is a transient phenomenon or if some blasts remain hyperproliferative after exogenous thrombopoietin administration.
5. Markers such as c-mpl overexpression or CD7 expression might predict a higher risk of leukemic blast proliferation. Further studies would have to be conducted in patients to determine if these or other biomarkers might be useful in predicting which patients might be at risk for leukemic blast proliferation after treatment with TPO (or AMG 531).

Review of Clinical Cases

Amgen's BLA submission included narrative summaries for 10 potential cases of increases in blast counts, MDS progression, chloroma, or progression to AML (narrative summaries were provided for these cases). Available CIOMS forms were also reviewed.

Table 2 summarizes the 10 cases in the original BLA submission with narrative summaries. Included in the right-hand column are summaries where the interpretation of cases by this reviewer differs from the Amgen interpretation. All cases described below involved patients with MDS IPSS scores of 0 to 1 at baseline. All but one of the events included in the table initially presented within four months.

Table 2: Summary of Narrative Cases Submitted by Amgen in the Initial BLA submission

Subject No. Age; Sex; IPSS Score	Dose meg-sc weekly	A. Date start B. Date stop C. Date of Event	Event
1590102; 84; Male; 0.5	300	A. 4/7/2006 B. 11/3/2006 C. 7/28/2006	• Chloroma occurred approximately three and a half months after treatment began, and treatment continued for 8 additional injections. • AMG531 was discontinued on November 3, 2006 due to worsening chloroma. • The blast count increased from less than 5% at screening to 11-20% at week 12 and 5-10% at week 24.

Subject No.; Age; Sex; IPSS Score	Dose mcg/sq weekly	A. Date start B. Date stop C. Date of Event	Event
1590108; 81; Male; 1.0	700	A. 5/31/2006 B. 8/16/2006 C. 8/16/2006	• During screening (central laboratory), this patient's blast percentage was 4%. • He developed myelofibrosis resulting in study discontinuation and died later. • By week 12, he had cytogenetic progression from good to intermediate risk cytogenetics. • At the time of treatment discontinuation, the patient had a reported marrow blast count of less than 5%; however, he had a reported WBC of 57,700 /mcl, and the peripheral blast count was 4,040/mcl. Peripheral blasts from the local laboratory were 1-2% or missing. • This patient was considered by the Applicant to have progression of disease with myelofibrosis; <i>Because of his death shortly after acutely developing myelofibrosis, this may have been a developing case of acute panmyelosis with myelofibrosis.</i>
1590401; 76; Male; 0.5	700	A. 2/16/2006 B. 10/27/2006 C. 10/19//2006	• At screening, the patient had a central laboratory blast count of 3% versus 5-10% when originally evaluated for the IPSS score. • The patient stopped due to "AML progression." The blast count on October 19 was 21-30%. • The blast count at the site was 25% on Nov 21, 2006; the central blast count was 19% so the patient was deemed by the Applicant to have MDS progression rather than AML. • This patient received alternative therapy (azacitidine). • <i>Based on the average of the two marrow evaluations, this patient should be classified as having AML. This patient lost contact with the study site and had no additional follow-up information provided.</i>
1590408; 60; Female; 0.5	1,500	A. 9/11/2006 B. 9/25/2006 C. 10/3/2006	• This patient was diagnosed with RARS (<5% blasts). • Less than one month after starting study drug, she progressed from less than 5% blasts to 12% blasts with near 100% cellularity in the marrow; peripheral blasts were present. She received azacitidine, but died prior to the end of study visit. • On October 3, 2006, she had a WBC of 96,700/mcl and peripheral blasts of 6,770/mcl. (her peripheral blasts were 3,370/mcl on the day of AMG531 discontinuation). • The Applicant deemed this patient to have MDS progression (not AML); <i>however, this patient died after stopping study drug and had increasing disease burden at the time.</i>

Subject No. Age; Sex; IPSS Score	Dose mcg/sq weekly	A. Date start B. Date stop C. Date of Event	Event
1591208; 89; Male; 0.5	1,000	A. 9/14/2006 B. 10/18/2006 C. 10/10/2006	• The patient had 2% blasts in the marrow at screening and started hydroxyurea about one month later due to an increased white count with monoblasts suggestive of CMML. • The blast percentage in the Oct 10th marrow had increased to 20% as read at the local site. An October 27 marrow showed "Grade II" CMML with 11% blasts. Hydroxyurea may have temporarily masked the rate of rise of the blast counts (following treatment, the white count decreased from 123,100/mcl to 14,400/mcl in an 8-day span). • Off treatment, the blast differential improved and the patient had features of nonproliferative CMML and was alive as of 2/8/2008. He is red cell dependent.
1591210; 86; Female; 0.5	1,000	A. 9/14/2006 B. 10/11/2006 C. 10/11/2006	• The blast count at study initiation was 3%. • The bone marrow blast percentage had increased to 20% by week 5 and decreased to 10% at the end of the study evaluation. • As of August 2007, she had 8% blasts in the marrow. • She died on _____ of unknown causes. • <i>The increase in blast percentage increased her IPSS score and thus she would be considered to have experienced MDS progression.</i>
1590603#; 72; male; 1.0	1,500	A. 11/8/2006 B. 11/22/2006 C. 11/15/2006	• The patient's baseline marrow blasts were 5-10%. • The central lab reading showed a blast count of 4% pre study. The blast differential increased to 10% at week 1 and 24% by week 2 (unclear if this was marrow versus peripheral). The blasts returned to 9% by week 4, and 7% at week 8. • This patient, who was considered by the Applicant to have transient increased blast counts, progressed to AML and started treatment with gemtuzumab ozogamacin and arsenic less than 6 weeks after stopping study drug. He died of AML on _____

Subject No.; Age; Sex; IPSS Score	Dose mcg/sc weekly	A. Date start B. Date stop C. Date of Event*	Event
1591001; 86; male; 0	1,500	A. 11/29/2006 B. 5/16/2007 C. 12/20/2006	• By week 4, the patient's blasts increased from 0% in the periphery to 3% with 10% marrow blasts (marrow performed on 1/3/2007). The total white count increased to 20,000/mcl. • The blasts displayed aberrant expression of CD7 by flow cytometry and increased reticulin staining was observed in the 1/3/2007 bone marrow. Blasts were also CD45 dim and positive for CD13, CD33, CD34, CD117, and HLA-DR. • The peripheral blast count decreased to 2.2% when the study drug was withheld and the dose of AMG was reduced and restarted on 15 Feb 2007 (with a peripheral blast count of 0). • The marrow blast count increased again on March 14, 2007 (with a marrow blast count of 9%) and the drug was held a second time. The investigator stated that he has had stable counts. • <i>Without further information, this is a potential case of MDS disease progression.</i>
1591102; 79; Female; 0	1,500	A. 9/21/2006 B. 11/9/2006 C. 11/7/2006	• The patient discontinued AMG531 due to loss of response by week 6. • The bone marrow at week 6 showed a blast count in the bone marrow of 8%; she had a baseline marrow blast count of 2%. • The case was (<i>reasonably</i>) described at the time as a patient with a transiently increased blast count. • Follow-up information showed that she developed AML and died on '_____'
1591207; 66; Female; 1.0	1,500	A. 9/14/2006 B. 11/2/2006 C. 11/8/2006	• The marrow blast count increased from 5% at screening to 20% at week 9 with 27% peripheral blasts in October 2006. • The blast count decreased to 7% by November 28, 2006 (and March 13, 2007). • Bone marrow in March 2007 showed 7% blasts. • The blast count increased markedly, but was considered transient and not consistent with AML progression.

* Approximate or Estimated Event Dates based on narratives and data tables

There was a narrative report for a 72 year old man with a subject identification number of 1590602 who received a 1,500 mcg dose of AMG 531. No patient with this number was enrolled into study 20050159. Upon review, patient number 1590603 had the same age, same sex, received the same dose, and had the same start and stop dates for AMG 531. Thus the narrative for patient 1590602 appears to refer to patient number 1590603.

The Applicant identified one additional case of AML progression in the 120-day safety update.

- 1590406: This patient was a 71-year-old man enrolled into the 1,000 mcg cohort of AMG531 with an IPSS score of 0. This patient had less than 5% blasts at screening. During his week 24 visit, he had 7% blasts, and during his week 36 visit, this patient had 23% blasts. No additional information was submitted.

The following additional observations were based on laboratory data assessed from the 20050159 data tables included in the 120 day safety update.

- 1590101: This patient was a 78 year-old-man enrolled in the 300 mcg cohort who presented with an IPSS score of 0.5. He had a white blood cell count (WBC) of 5,900/mcl and 0% blasts (on March 15, 2007). On August 9, 2006, he presented with a WBC of 20,000/mcl and 2.4% peripheral blasts (on August 16, the WBC was 22,600/ul with 0.65% blasts and 3.16% myelocytes). He received darbepoetin alfa on study day 58. This patient died from CNS hemorrhage on _____ prior to undergoing a repeat bone marrow biopsy to evaluate for the presence of leukemic progression.
- 1590109: This patient was a 64-year-old man enrolled in the 700 mcg cohort who presented with an IPSS score of 0.5. He presented with less than 5 percent blasts and good cytogenetics at the beginning of treatment (June 8, 2006) and progressed to a blast count percentage of 11-20% by the end of treatment (week 6). The IPSS score increased from 0.5 to 2.5. This patient was receiving prior granulocyte growth factors; however, G-CSF was not allowed on study. This person did receive darbepoetin alfa during the study. He stopped study treatment due to lack of response and progression of disease, and he died of unknown causes on _____.
- 1590116: This patient was a 61-year-old man enrolled into the 700 mcg cohort. This patient had an IPSS score of 1.0 with poor risk cytogenetics and less than 5% blasts at screening. By week four, this patient had 21-30% blasts, and by the end of treatment 2 weeks later, this patient had 5-10% blasts indicating potential MDS progression. This man was removed from the study prematurely due to "administrative decision." This patient had stable disease one year after stopping study drug.
- 1590106: This patient was a 71-year-old woman enrolled into the 700 mcg cohort and had an IPSS score of 0.0. This patient had a transient increased blast count from less than 5% to 5-10% on week 24. During this visit, the patient had intermediate risk cytogenetics. Her cytogenetics were considered good risk during her week 36 and week 48 visits. This patient started study treatment on 5/23/2006 and discontinued the roll-over study on 9/4/2007. Her bone marrow on 9/14/2007 showed 14.5% blasts and she ultimately started treatment with decitabine on 10/29/2007. She died of MDS and pneumonia on _____.
- 1590114: This patient was an 80-year-old man enrolled into the 1,500 mcg cohort of AMG 531 with an IPSS score of 1.0. This patient had intermediate risk cytogenetics at screening. By week 12 (1/12/2007), this patient developed poor risk cytogenetics and 11-20% blasts with an IPSS score of 3.0. This patient was removed from the study prematurely due to "administrative decision." A marrow performed 3 months (4/6/2007) later showed 3% blasts. No other marrow examinations were performed and he died of MDS 7 months after starting study drug.
- 1590407: This patient was a 72-year-old man enrolled into the 1,500 mcg cohort with an IPSS score of 0.5. This patient had a blast count percentage of less than 5% at screening and approximately 2 months later had a blast count percentage of 21-30%. This patient was removed from the study prematurely due to "increasing white count." He started treatment with azacitidine on study day 51 (October 31, 2006). He died approximately \ _____ after he started treatment with romiplostim. The

cause of death submitted by the Applicant was determined to be anemia caused by underlying MDS.

- 1591206: This patient was a 48-year-old woman who was enrolled into the 1,000 mcg cohort with an IPSS score of 0. According to the patient data tables, she discontinued the study after 248 days due to moderate disease progression with a mild increase in marrow blasts reported by the local site. Her blast percentage at the local site was 8% versus less than 1% when treatment started. The patient was alive as of 12/19/2007. She received romiplostim from 8/14/2006 to 3/21/2007.

The following four patients exhibited cytogenetics progression without a notable increase in blasts while being treated with AMG 531.

- 1591204: This patient was a 58-year-old man enrolled into the 1,000 mcg cohort of AMG 531 with an IPSS score of 0.5. This patient had good risk cytogenetics at screening and developed intermediate risk cytogenetics approximately two months after starting treatment. This man stopped study treatment after he withdrew consent. No additional information was provided. He started treatment with azacitidine with improvement in his cytopenias and was alive as of 1/29/2008 (he received romiplostim from 8/7/2006 to 9/20/2006).
- 1590103: This patient was a 76-year-old man enrolled in the 300 mcg cohort who presented with an IPSS score of 0.0. He presented with thrombocytopenia and good risk cytogenetics and progressed to having anemia and thrombocytopenia with intermediate risk cytogenetics by week 12. Furthermore, his marrow demonstrated no evidence of fibrosis using a trichrome stain at week 12; however, approximately 2 months later, his marrow demonstrated a moderately positive trichrome stain. This patient withdrew his consent from the study after experiencing hematuria.
- 1590402: This patient was a 76-year-old man enrolled in the 300 mcg cohort who presented with an IPSS score of 0.5 and good risk cytogenetics. By week 36, he developed poor risk cytogenetics. He died shortly thereafter with the cause of death determined to be related to a fall and myelodysplasia.
- 1590110: This patient was a 76-year-old man in the 1000 mcg cohort who presented with an IPSS score of 0.0. He progressed from good to intermediate cytogenetics after approximately three months. No additional information was available at the time of this review.

An additional safety report was received by FDA of a patient originally enrolled into study 20050159 who was switched to an open-label rollover study. This patient (1590501) was a 72-year-old woman who was enrolled into the initial study with chromosomal rearrangements involving chromosomes 1, 5, and 20 (poor risk cytogenetics). Approximately 13 months post-initiation of study 2005019, she transitioned into the rollover study, 20060197. At the time of enrollment into the rollover study, she was found to carry a BCR-ABL fusion transcript (p190) with rare blasts in the marrow. *This patient technically would not be considered to have cytogenetics progression by IPSS because she had poor risk cytogenetics at baseline. It is included in this review because of the unusual nature of the finding in a patient with MDS.*

In the 120-day safety update to the BLA submission, Amgen summarized the MDS progression events occurring as of February 2007 as follows:

- One patient had chloroma consistent with disease progression to AML.
- One additional patient (1590406) was noted to have increases in bone marrow blast cells that appear to be consistent with AML.
- Six patients experienced transient increases in the bone marrow blast cell count, not consistent with progression to AML (1591207, 1591208, 1591210, 1590603, 1591001, 1591102).
- Three patients (1590408, 1590108, 1590401) experienced MDS disease progression.

This review summarizes the MDS progression events as follows:

- Four patients progressed to AML (1590102, 1590401, 1590603, and 1590496). The average of the blast count measurements at the time of progression for patient 1590401 was greater than 20%. Patient 1590603 was considered to have a transient blast count elevation by the Applicant. However, he developed AML approximately six weeks after stopping study drug (requiring treatment with gemtuzumab, ozogamycin and arsenic).
- Two patients (1590108 and 1590408) died after experiencing rapid MDS progression possibly consistent with the development of AML (patient 1590108 could be consistent with developing panmyelosis).
- One patient (1590407) with an IPSS score of 0.5 and less than 5% blasts at screening developed a blast count percentage between 21-30% at approximately 2 months and then started treatment with azacitidine on day 51. He was removed prematurely from the study due to an "increasing white count". This case was also suspicious for AML.
- Four additional patients (1591210, 1590116, 1591207, 1591208) developed blast counts greater than or equal to twenty percent while receiving romiplostim. All blast counts decreased off treatment; however, two patients progressed to a higher IPSS score compared to their baseline status. One patient (1591210) in this group died approximately one year after starting study drug of unknown cause.
- Three patients (1590109, 1590114, 1591001) developed blasts counts between 10 percent and 19 percent while receiving romiplostim. One of these three patients also experienced cytogenetics progression. This patient's blasts improved off treatment, but he died of MDS seven months after romiplostim treatment began. A second patient experienced MDS progression and died of unknown causes 15 months after beginning romiplostim.
- Four additional patients (1590101, 1591206, 1591102, 1590106) experienced increases in blast counts while receiving study drug. Among these patients, one woman (1591102) with an IPSS of 0 who was considered to have a transiently increased blast count developed AML one year later. One man (1590101) developed an increase in peripheral blasts up to 2,400/ul; he died of CNS hemorrhage prior to undergoing a repeat bone marrow aspirate. Additionally, one woman with an IPSS score of 0 experienced a transient elevation in her blast count during week 24. Her blast counts increased again after 16 months of therapy and she died of MDS after subsequently receiving decitabine.

- Finally, four patients (1591204, 1590103, 1590402, and 1590110) had cytogenetics progression alone without a notable increase in blasts. One of these patients who progressed to poor risk cytogenetics at week 36 died shortly thereafter with the cause of death determined to be related to myelodysplasia. A second patient had a bone marrow biopsy moderately positive for the trichrome stain indicating the possible presence of collagen fibrosis.

Summary of all Patients

In summary, at least seven of forty-four patients developed acute leukemia or rapid MDS progression and death during or shortly after romiplostim administration. At least seven additional MDS patients died within nineteen months of beginning romiplostim, albeit one was due to CNS hemorrhage. Additional long-term follow-up information was not available to determine if more cases of AML or death occurred in patients who were not found to have blast count elevations during study drug administration.

Conclusions

The percentage of patients who experienced MDS progression (increased blasts or worsening cytogenetics), AML, or a temporary increase in number of blasts cells (22/44 [50%]) is concerning for a potential safety signal that AMG 531 may increase the risk of hematologic progression in patients with MDS in at least a subset of patients. All patients studied in the phase 1/2 trial had low or intermediate-1 risk disease. The occurrence of disease progression (or transient blast count increases) by three months in 15 out of 22 patients appears to be greater than what would be expected in the general MDS population with low risk or intermediate-1 risk MDS. Blast count increases or MDS progression occurred at all doses of AMG 531 tested. Because study 20050159 was uncontrolled, the possibility that this cohort of patients may have been at higher risk cannot be ruled out (for example, due to older age, degree of thrombocytopenia, or other unknown variables).

The data reviewed above highlights the possibility for more rapid hematologic progression after treatment of MDS patients with AMG 531. Increased blast proliferation after thrombopoietin administration was observed in multiple pre-clinical studies as described in the review section. In the BLA submission, data were not submitted that would enable an analysis to determine whether potential disease specific risk factors could predict which patients might experience increased blast cell proliferation. Potential candidate disease specific risk factors (biomarkers) in preclinical studies included overexpression of c-mpl by Northern blot analysis, M7 subtype of AML, and CD7; however, overexpression of c-mpl was not universally concordant with in-vitro blast cell proliferation in all studies that were reviewed. Additional studies to determine the phenotype of the proliferating blasts may be useful in some instances (if abnormal blast populations can be identified).

Finally, the risk of AML progression in MDS patients should be differentiated versus the risk of AML in patients with immune thrombocytopenia (treated with AMG531), the indication for which the Applicant is seeking Licensure. Patients with MDS have an abnormal hematopoietic clonal population and defective hematopoiesis. The stimulation

of this abnormal clonal population with genetic abnormalities may increase the risk of disease progression in patients with MDS. ITP is an immunologic disorder, and patients with ITP are not known to have an abnormal clonal population of hematopoietic cells. Neoplasia events occurring during ITP studies were reviewed by DMIHP.

Recommendations

1. The potential risk of MDS progression should be publicly communicated to physicians and patients during the March 12, Oncology Drugs Advisory Committee meeting. *Comment: this initial recommendation was adopted and this reviewer summarized these events in the March 12, 2008 ODAC meeting.*
2. The adverse reaction of MDS progression should be communicated to the Office of Surveillance and Epidemiology if AMG 531 is approved (for ITP). *Comment: OSE has been involved in discussions regarding product risks and involved in the proposed REMS (Risk Evaluation and Mitigation Strategies).*
3. The product label should accurately reflect, as a Warning, the experience of blast count elevations, MDS progression, and leukemia that occurred during study 20050159 (as described in this review and the presentation by FDA at the March 12, 2008 ODAC meeting). The summary by Amgen of these cases did not encompass the additional cases observed in data tables submitted by Amgen.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

MEMORANDUM

Date: March 5, 2008 **Date Consulted:** October 29, 2007

From: Richardae Araujo, Pharm.D. *Richardae Araujo 3/31/08*
Regulatory Reviewer, Pediatric and Maternal Health Staff

Through: Karen Feibus, MD *KF Feibus 4/1/08*
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, MD *LM 3/31/08*
Associate Director, Pediatric and Maternal Health Staff

To: Division of Medical Imaging and Hematology Products (DMIHP)

Drug: STN — Nplate (romiplostim)

Subject: New Molecular Entity/Orphan Product for the treatment of idiopathic thrombocytopenia purpura (ITP)

Materials Reviewed: Relevant data submitted in STN — FDA and Amgen Advisory Committee Meeting Background Packages, Interim Clinical Review, Office of Surveillance and Epidemiology (OSE) Review, and Pharmacology/Toxicology Review

Consult Question: Please review the Pregnancy, Labor and Delivery, and Nursing Mothers subsections of labeling and provide advice on appropriate language.

EXECUTIVE SUMMARY

On October 23, 2007, Amgen, Inc. submitted a new orphan biologic license application (STN _____) to the Division of Medical Imaging and Hematology Products (DMIHP) for romiplostim (AMG 531). Romiplostim is an Fc fusion protein that increases platelet production through binding to the thrombopoietin (TPO) receptor on blood and bone marrow cells, including megakaryocytes. The protein consists of a human immunoglobulin G1 (IgG1) Fc domain covalently linked to two peptides that bind to the thrombopoietin receptor. The sponsor's proposed indication for romiplostim is treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who are (1) non-splenectomized and have an insufficient response or are intolerant to corticosteroids and/or immunoglobulins, or (2) who are splenectomized and have an insufficient response to splenectomy.

Amgen submitted two randomized, double blind, placebo controlled, multi-center, phase three clinical trials to demonstrate romiplostim safety and efficacy in ITP patients. The primary efficacy endpoint was durable platelet response defined as at least six weekly platelet counts $\geq 50 \times 10^9/L$ during the last eight weeks of study drug treatment in the absence of rescue medication at any time during the 24 week treatment period. The major secondary endpoints included various comparisons of platelet count responses and comparison of the use of thrombocytopenia rescue medications. In addition, Amgen conducted an open-label extension study providing uncontrolled long-term clinical experience with romiplostim.

Five major safety concerns were identified in the clinical development program for romiplostim including (1) reticulin formation and risk for marrow fibrosis, (2) risk for malignancy or progression of malignancy, (3) thrombotic events, (4) alteration of intrinsic TPO/worsening of thrombocytopenia after cessation of romiplostim therapy, and (5) immunogenicity. However, these safety concerns have not been well characterized.

Chronic ITP is a serious and life threatening autoimmune disease characterized by a low platelet count and mucocutaneous bleeding.¹ ITP often occurs in the second or third decade of life and has a female to male ratio of about 3:1.² Because ITP is predominantly a disease of young adults, particularly females, it is may be encountered in pregnancy. Estimates of ITP incidence during pregnancy vary widely and has been reported to range from 1/1,000 to 1/10,000.³

Current treatment of ITP in pregnancy includes IVIG, corticosteroids, and/or splenectomy. Romiplostim, a first-in-class biologic product under review for the treatment of thrombocytopenia in adult patients with chronic ITP, may be considered an option for pregnant woman who fail current available therapies. However, pregnant women were excluded from romiplostim clinical studies; therefore, there is no human data on the effects of romiplostim during pregnancy.

¹ Halevy R, Ellis MH, Fejgin MD. Management of Immune Thrombocytopenic Purpura in Pregnancy. *Obstet Gynecol Surv.* 2008 Mar; 63(3):182-188.

² American College of Obstetricians and Gynecologists Practice Bulletin. Thrombocytopenia in Pregnancy. *Clinical Management Guidelines for Obstetrician Gynecologists.* 1999. Sept;6: 1-12.

In animal studies, romiplostim crossed the placental barrier in rats and resulted in significant fetal concentrations of romiplostim (approximately 50% of maternal serum concentration). In addition, significant dose-dependent increases in fetal platelet counts (1.7 to 6 times baseline values) and binding antibodies to romiplostim were observed in rat offspring. In developmental toxicity studies, adverse fetal effects including post-implantation loss and an increase in pup mortality was observed. Due to the lack of human data and adverse effects observed in animals, Amgen proposes a pregnancy category C for romiplostim.

If approved, romiplostim will be a new novel therapy for the treatment of ITP. Therefore, the possibility exists that women with ITP, who are of childbearing potential, may conceive while on romiplostim therapy, resulting in inadvertent exposure to the drug. There may be situations where a woman, who uses romiplostim to manage her ITP, has failed other therapies and wants to get pregnant. A clinician may choose to continue romiplostim therapy in such an ITP patient. During pregnancy, women with ITP may fail currently available therapies, and a clinician may choose to prescribe romiplostim after considering the serious risks associated with treatment and the benefits of the drug to the mother.

While there are no human data on the effects of romiplostim during pregnancy, adverse fetal effects were observed in animal studies. In addition, based on the immunological aspects of romiplostim and animal data, it is highly likely that romiplostim will cross the human placenta. However, because animal studies are not always predictive of human response, data on romiplostim exposure during human pregnancy and associated pregnancy and fetal outcomes is needed.

DMIHP consulted the MHT and requested review of the Pregnancy, Labor and Delivery, and Nursing Mothers sub-sections of labeling. The MHT's recommendations and revisions to the sponsors proposed labeling are provided below.

RECOMMENDATIONS

1. The MHT recommends that the sponsor develop and maintain a prospective, observational pregnancy exposure registry that compares the pregnancy and fetal outcomes of women exposed to romiplostim during pregnancy to an unexposed control population. The registry should be conducted as a post-marketing requirement for this application. The outcomes of the registry should include major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, platelet number and function, neoplasm formation, reticulatin formation, thrombotic events, and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life. For guidance on how to establish a pregnancy exposure registry, the sponsor should review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at <http://www.fda.gov/cder/guidance/3626fn1.htm>. The sponsor should submit a draft pregnancy registry protocol for review by DMIHP and MHT within six months of product approval. A final protocol should be submitted

approval and should include revised labeling to incorporate pregnancy registry contact information.

2. The MHT also recommends that Amgen consider conducting a lactation study in a subset of women enrolled in the registry, who choose to breastfeed their infants, to assess the presence of romiplostim in breast milk and potential effects in nursing infants. For guidance on how to conduct a lactation study, the sponsor should review the Draft Guidance for Industry, Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling <http://www.fda.gov/cder/guidance/5918dft.pdf>. The sponsor should submit a draft protocol for review by DMIHP and MHT within six months of product approval.
3. The MHT recommended revisions to the sponsors proposed labeling are provided on pages 11-13 of this review.

INTRODUCTION

On October 23, 2007, Amgen, Inc. submitted a new orphan biologic license application (STN) to the Division of Medical Imaging and Hematology Products (DMIHP) for romiplostim (AMG 531). Romiplostim is an Fc fusion protein that increases platelet production through binding to the thrombopoietin (TPO) receptor on blood and bone marrow cells, including megakaryocytes. The protein consists of a human immunoglobulin G1 (IgG1) Fc domain covalently linked to two peptides that bind to the thrombopoietin receptor. The fusion protein has no amino acid sequence homology with endogenous thrombopoietin. The sponsor's proposed indication for romiplostim is treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who are (1) non-splenectomized and have an insufficient response or are intolerant to corticosteroids and/or immunoglobulins, or (2) who are splenectomized and have an insufficient response to splenectomy. Based on data submitted in STN this review responds to DMIHP's consult to the Maternal Health Team (MHT) and recommends language for the Pregnancy, Labor and Delivery, and Nursing Mothers sub-sections of romiplostim proposed labeling.

BACKGROUND

Overview of ITP in Pregnancy

Chronic ITP is a serious and life threatening autoimmune disease characterized by a low platelet count and mucocutaneous bleeding.³ ITP often occurs in the second or third decade of life and has a female to male ratio of about 3:1.⁴ Because ITP is predominantly a disease of young adults,

³ Halevy R, Ellis MH, Fejgin MD. Management of Immune Thrombocytopenic Purpura in Pregnancy. *Obstet Gynecol Surv.* 2008 Mar; 63(3):182-188.

⁴ American College of Obstetricians and Gynecologists Practice Bulletin. Thrombocytopenia in Pregnancy. *Clinical Management Guidelines for Obstetrician Gynecologists.* 1999. Sept;6: 1-12.

particularly females, it may be encountered in pregnancy. Estimates of ITP incidence during pregnancy vary widely and has been reported to range from 1/1,000 to 1/10,000.³

The diagnosis of ITP during pregnancy is one of exclusion and is more difficult because the presentation may resemble that of gestational thrombocytopenia (GT) or incidental thrombocytopenia of pregnancy.⁵ GT is the most common cause of thrombocytopenia during pregnancy and accounts for at least 75% of all cases of pregnancy-associated thrombocytopenia.⁶ GT occurs late in gestation and is characterized by asymptomatic, mild thrombocytopenia with a platelet count $\geq 70,000 \times 10^9/L$. GT is not associated with fetal thrombocytopenia and resolves spontaneously after delivery. In contrast, according to the American Society of Hematology, ITP is a relatively uncommon cause of thrombocytopenia in pregnancy.⁵ When ITP is first diagnosed during pregnancy, thrombocytopenia occurs early in gestation and platelet counts are usually below $50,000 \times 10^9/L$.³ Other causes of thrombocytopenia during pregnancy include HELLP syndrome (hemolysis, elevated liver function tests, and low platelet count), which accounts for about 25% of cases, and preeclampsia.^{3,5}

The American Society of Hematology (ASH) and the British Committee for Standards in Hematology (BCSH) have guidelines on the medical management of ITP during pregnancy. A summary of these guidelines is provided in Tables 1 and 2 below.⁶

Table 1 Medical management of immune thrombocytopenic purpura in pregnancy: American Society of Hematology guidelines

Treatment indications	Platelets $< 10\,000/\mu l$ Platelets $10\text{--}30\,000/\mu l$ in second or third trimester Bleeding
Intravenous immunoglobulin	Initial treatment: third trimester, platelets $< 10\,000/\mu l$ Initial treatment: platelets $10\text{--}30\,000/\mu l$ and bleeding After steroid failure: platelets $< 10\,000/\mu l$ After steroid failure: platelets $10\text{--}30\,000/\mu l$ and bleeding After steroid failure: third trimester, platelets $10\text{--}30\,000/\mu l$, asymptomatic
Splenectomy	Second trimester, platelets $< 10\,000/\mu l$, bleeding
Safe platelet count for delivery	$50\,000/\mu l$

⁵ George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood*. 1996; 88:3-40.

⁶ Gernsheimer T, McCrae KR. Immune thrombocytopenia purpura in pregnancy. *Current Opinion in Hematology*. 2007;14:574-580.

Table 2 Maternal management of immune thrombocytopenic purpura in pregnancy: British Committee for Standards in Haematology guidelines

Treatment indications	Platelets <20 000/ μ l, unless delivery imminent
Intravenous immunoglobulin (IVIg)	Oral corticosteroids and IVIg have similar responses as in nonpregnant state
Splenectomy	If essential, in the second trimester, laparoscopic advantageous
Safe platelet count for delivery	50 000/ μ l vaginal 80 000/ μ l cesarean section or epidural

As described in Tables 1 and 2 above, the medical management of ITP in pregnancy includes the use of IVIG, corticosteroids, and/or splenectomy. According to the ASH, pregnant women with ITP and platelet counts >50,000 do not routinely require treatment and should not receive corticosteroids or IVIG as routine initial therapy. In addition, ASH recommends that pregnant women in the first or second trimester with platelet counts of 30,000 to 50,000 not receive routine initial treatment. However, treatment is recommended for women with platelet counts <10,000 and for those with platelet counts of 10,000 to 30,000 who are in their second or third trimester or are bleeding. ASH and the American College of Obstetrics and Gynecology (ACOG) consider IVIG appropriate initial treatment for women in the third trimester when:

- Platelet counts are less than 10,000,
- Platelet counts are 10,000 to 30,000 and there is clinical evidence of bleeding
- When delivery is planned and platelets are less than 50,000.⁴

In pregnant women who fail corticosteroid and IVIG therapy, splenectomy is considered appropriate in the second trimester when platelet counts are <10,000 and bleeding is occurring. ASH recommends that splenectomy not be performed in asymptomatic pregnant women with platelet counts >10,000.⁵

The course of ITP is usually not affected by pregnancy, although there have been anecdotal reports of patients' conditions worsening during pregnancy and improving postpartum.⁴ However, pregnancy may be adversely affected by severe thrombocytopenia. The primary risk to the mother is hemorrhage during the peripartum period.⁴ Although pregnant women with ITP may experience several maternal and fetal complications, in most cases, there is neither maternal nor fetal morbidity or mortality, even with very low maternal platelet counts.³

REVIEW OF DATA

This review discusses relevant data submitted in the romiplostim application, and pertinent information included in the medical officer, pharmacology/toxicology, and Office of Surveillance and Epidemiology (OSE) application reviews. In addition, this review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of labeling and recommendations for postmarketing requirements to monitor maternal and fetal exposures to romiplostim during pregnancy and associated pregnancy and fetal outcomes.

Studies to support product approval

Amgen submitted two randomized, double blind, placebo controlled, multi-center, phase three clinical trials to demonstrate romiplostim safety and efficacy in ITP patients. One study enrolled subjects who had not undergone splenectomy (Study 20030212) and the other enrolled splenectomized patients (Study 20030105). Patients enrolled in both studies had a diagnosis of ITP and a mean of 3 platelet counts (taken during the screening and pre-treatment periods) that were $\leq 30 \times 10^9/L$ with no individual count $> 35 \times 10^9/L$. The 62 patients enrolled in Study 20030212 had a median age of 52.0 years (range 21 to 88 years) and had a higher proportion of women (69.4%) than men (30.6%).⁷ Similarly, the 63 patients enrolled in Study 20030105 had a median age of 52.0 years (range 26 to 88 years) and also had a higher proportion of women (60.3%) than men (39.7%).⁷ Both study populations had inadequate platelet responses to existing ITP treatments.

The primary efficacy endpoint for both studies was durable platelet response, defined as at least six weekly platelet counts $\geq 50 \times 10^9/L$ during the last eight weeks of study drug treatment in the absence of rescue medication at any time during the 24 week treatment period. The major secondary endpoints included various comparisons of platelet count responses and comparison of the use of thrombocytopenia rescue medications. In the 2 pivotal studies combined, the primary endpoint, durable platelet response, was achieved by half of all subjects who received romiplostim (41 of 83 subjects; 49.4%) compared with one of 42 subjects who received placebo (2.4%) ($p < 0.0001$).⁷ Romiplostim was also found to be statistically significant when compared to placebo for all key secondary efficacy endpoints in the combined population as well as for each individual study.⁷ In addition, Amgen conducted an open-label extension study providing uncontrolled long-term clinical experience with romiplostim. Please see the medical officer review, conducted by Dr. John Lee, for a detailed analysis of the safety and efficacy data submitted for romiplostim.

Safety concerns

The medical officer and OSE reviews for this application describe five major safety concerns identified from the clinical development program for romiplostim:

- Reticulin formation and risk for marrow fibrosis
- Risk for malignancy or progression of malignancy
- Thrombotic events

⁷ Amgen background document for Oncology Drugs Advisory Committee Meeting. February 8, 2008.

- Alteration of intrinsic TPO/worsening of thrombocytopenia after cessation of romiplostim therapy
- Immunogenicity.

Based on the safety concerns identified above, Amgen has proposed a risk management plan that involves the following major components.⁸

- Product labeling, including a Medication Guide
- Targeted education and outreach
- Completion of on-going clinical studies
- Advisory panels/safety monitoring committee involvement in on-going and future clinical studies
- Review of spontaneously submitted adverse reaction reports of myeloid malignancy progression or reticulin formation, including completion of a physician questionnaire
- Prospective registry to be conducted in Scandinavian countries, focused on detection of bone marrow fibrosis and reticulin deposition
- Prospective, open-label, follow-up study of about 200 subjects with ITP to assess bone marrow morphologic changes (at month 24 and 60 over baseline), hematologic alterations, and antibody formation
- Retrospective observational studies to characterize rates of thrombotic events among patients with ITP and define the prevalence of bone marrow reticulin
- Drug utilization study using two U.S. databases and Scandinavian national health registries to evaluate patterns of romiplostim use

Reviewer comments:

- *The OSE review provides a detailed evaluation and description of the sponsors proposed risk management plan.*
- *Throughout the review of this application, the Division has discussed whether or not the sponsor should restrict the distribution of romiplostim to limit its use to only those patients with chronic ITP. At the time of this review, this issue is still being discussed.*

Romiplostim Effects during Pregnancy

Human Data

Pregnant women were excluded from romiplostim clinical studies; therefore, there is no human data on the effects of romiplostim during pregnancy. Due to the lack of human data and adverse effects observed in animals, Amgen proposes a pregnancy category C for romiplostim.

Romiplostim is a large molecule with a theoretical molecular weight of 59,085 Daltons. Large molecules do not readily cross the human placenta; however, based on the immunological characteristics of romiplostim and the animal data described below, it is highly likely that romiplostim will cross the human placenta.

Current drug therapy for pregnant women with ITP includes IVIG and corticosteroids. Prednisone and other glucocorticoids are associated with fetal growth impairment and may be

⁸ FDA Advisory Committee background package and OSE review.

associated with an increased risk of oral clefts in humans⁹ Corticosteroid use during pregnancy can be associated with serious adverse events including hypertension, hyperglycemia, osteoporosis, excessive weight gain, and psychosis, and patients should be monitored for these potential complications.¹⁰ Clinicians may see a role for romiplostim treatment in pregnant women with ITP who are refractory to IVIG and corticosteroid therapy or may consider romiplostim as alternative therapy if the product appears to offer a better risk/benefit profile for certain patients. Clinicians caring for pregnant women should be advised of the serious adverse events associated with romiplostim use in clinical trials as well as the lack of data on romiplostim use during human pregnancy.

Animal Data

Amgen conducted reproduction studies in rats and embryo-fetal studies in mice, rats, and rabbits. Based on these studies, romiplostim crossed the placental barrier in rats and resulted in significant fetal concentrations of romiplostim, approximately 50% of maternal serum concentration. In addition, significant dose-dependent increases in fetal platelet counts (1.7 to 6 times baseline values) and binding antibodies to romiplostim were observed in rat offspring. Developmental toxicity studies performed in rodents and rabbits at doses six to ten times the maximum recommended human dose (MRHD) revealed no evidence of harm to the developing fetus. In embryo-fetal development studies in mice, rats, and rabbits at doses ranging from six to ten times the MRHD, reductions in maternal body weight and increased post-implantation loss were observed only in mice. In addition, a rat prenatal and postnatal development study revealed an increase in pup mortality at a dose ten times the MRHD.

Reviewer comment:

Please see the pharmacology/toxicology review by Dr. Tushar Kokate for a detailed analysis of the reproductive and developmental toxicity studies submitted in support of this application.

Romiplostim Effects during Lactation

Breastfeeding women were excluded from participation in romiplostim clinical trials; therefore, there is no data on the effects of romiplostim during human lactation. Amgen recommends that caution be exercised when romiplostim is administered to breastfeeding women.

Reviewer comment:

While published data suggest that immunoglobulins are minimally absorbed, if at all, from the intestinal tract, there are no clinical pharmacology studies evaluating the oral bioavailability of romiplostim. These studies will likely be part of a postmarketing commitment. Immunoglobulins generally do transfer to breast milk from maternal serum.

⁹ REPROTOX information for Prednisone: <http://csi.micromedex.com/DATA/RX/RX1169.HTM?Top=Yes>

¹⁰ British Society for Haematology. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children, and in pregnancy. British Journal of Haematology. 2003;120: 574-596.

Sponsors Proposed Pregnancy and Nursing Mothers Labeling

The sponsors proposed Pregnancy and Nursing Mothers subsections of labeling are provided below. The MHT recommended revisions to this labeling are provided on pages 11 to 13 of this review.

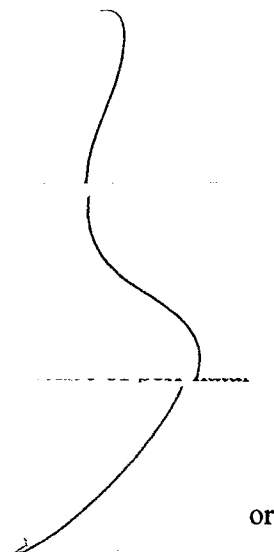
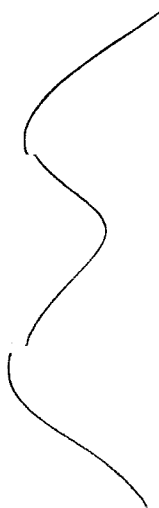
Highlights

Sponsors proposed language – None

8.1 Pregnancy

Pregnancy Category C

J



8.3 Nursing Mothers



MEDICATION GUIDE

What should I tell my doctor before taking Nplate?



DISCUSSION/CONCLUSIONS

Chronic ITP is a serious and life threatening autoimmune disease that may be encountered in pregnancy. Current treatment of ITP in pregnancy includes IVIG, corticosteroids, and/or splenectomy. Romiplostim, a first-in-class biologic product under review for the treatment of

thrombocytopenia in adult patients with chronic ITP, may be considered an option for pregnant woman who fail current available therapies. However, there are no data on the effects of romiplostim during human pregnancy. In addition, five major safety concerns were identified in the clinical development program for romiplostim including (1) reticulin formation and risk for marrow fibrosis, (2) risk for malignancy or progression of malignancy, (3) thrombotic events, (4) alteration of intrinsic TPO/worsening of thrombocytopenia after cessation of romiplostim therapy, and (5) immunogenicity. However, these safety concerns have not been well characterized.

If approved, romiplostim will be a new novel therapy for the treatment of ITP. Therefore, the possibility exists that women with ITP, who are of childbearing potential, may conceive while on romiplostim therapy, resulting in inadvertent exposure to the drug. There may be situations where a woman, who uses romiplostim to manage her ITP, has failed other therapies and wants to get pregnant. A clinician may choose to continue romiplostim therapy in such an ITP patient. During pregnancy, women with ITP may fail currently available therapies, and a clinician may choose to prescribe romiplostim after considering the serious risks associated with treatment and the benefits of the drug to the mother.

While there are no human data on the effects of romiplostim during pregnancy, adverse fetal effects including post-implantation loss and an increase in pup mortality was observed in animal studies. In addition, based on the immunological aspects of romiplostim and animal data, it is highly likely that romiplostim will cross the human placenta. However, because animal studies are not always predictive of human response, data on romiplostim exposure during human pregnancy and associated pregnancy and fetal outcomes is needed. There are no data available about the oral bioavailability of romiplostim or whether romiplostim is present in human milk; however, IgG does transfer into breast milk from maternal serum.

DMIHP consulted the MHT and requested review of the Pregnancy, Labor and Delivery, and Nursing Mothers sub-sections of labeling. The MHT's recommendations and revisions to the sponsors proposed labeling are provided below.

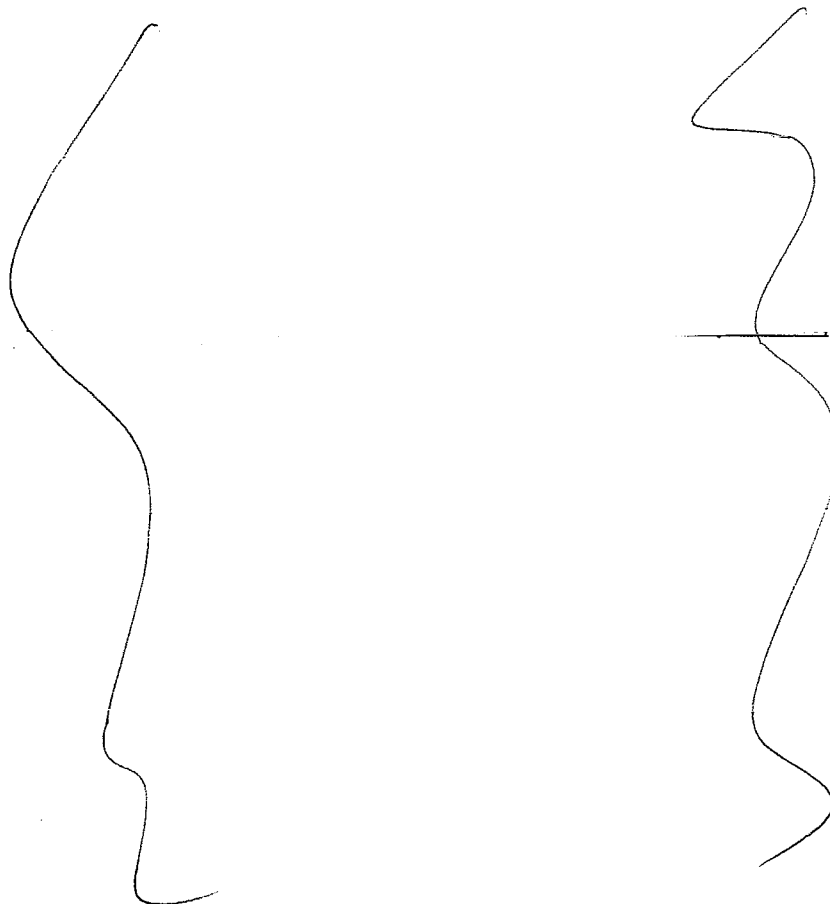
RECOMMENDATIONS

1. The MHT recommends that the sponsor develop and maintain a prospective, observational pregnancy exposure registry that compares the pregnancy and fetal outcomes of women exposed to romiplostim during pregnancy to an unexposed control population. The registry should be conducted as a post-marketing requirement for this application. The outcomes of the registry should include major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, platelet number and function, neoplasm formation, reticulin formation, thrombotic events, and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life. For guidance on how to establish a pregnancy exposure registry, the sponsor should review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at <http://www.fda.gov/cder/guidance/3626fnl.htm>. The sponsor should submit a draft

pregnancy registry protocol for review by DMIHP and MHT within six months of product approval. A final protocol should be submitted no later than _____ product approval and should include revised labeling to incorporate pregnancy registry contact information.

2. The MHT also recommends that Amgen consider conducting a lactation study in a subset of women enrolled in the registry, who choose to breastfeed their infants, to assess the presence of romiplostim in breast milk and potential effects in nursing infants. For guidance on how to conduct a lactation study, the sponsor should review the Draft Guidance for Industry, Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling <http://www.fda.gov/cder/guidance/5918dft.pdf>. The sponsor should submit a draft protocol for review by DMIHP and MHT within six months of product approval.
3. The MHT recommended revisions to the sponsors proposed labeling are provided below. Recommended additions are underlined and deletions are struck-out.

Highlights



1 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 X § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

INTERIM CLINICAL REVIEW

Application Type BLA
Submission Number STN 125268/0
Submission Code

Letter Date October 23, 2007
Stamp Date October 23, 2007
PDUFA Goal Date April 23, 2008

Reviewer Name John Lee
Interim Review Date January 2, 2008

Established Name Romiplostim
(Proposed) Trade Name NPlate
Therapeutic Class
Applicant Amgen, Inc.

Priority Designation

Formulation
Dosing Regimen SC injection QW

Indication Treatment of Thrombocytopenia in
Immune Thrombocytopenic
Purpura (ITP)

Intended Population Adult Patients with Chronic ITP
Refractory to Low-Dose
Corticosteroids or Splenectomy

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1. EXECUTIVE SUMMARY

1.1 RECOMMENDATION ON REGULATORY ACTION

Approval, with recommendations on postmarketing actions (see Section 1.2) for continued proactive monitoring of long-term efficacy and safety (including immunogenicity), the development of a more comprehensive dosing strategy to optimize product safety, and completion of a formal QT cardiac safety study.

1.2 RECOMMENDATION ON POSTMARKETING ACTIONS

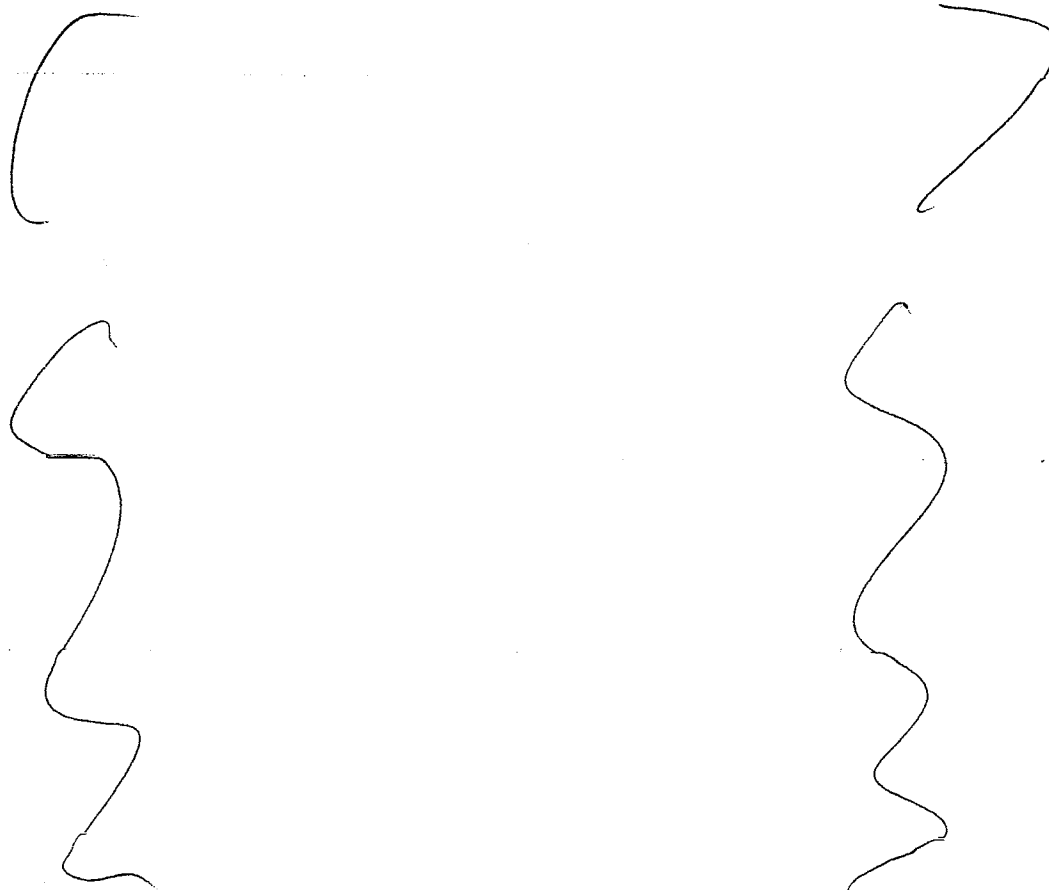
1.2.1 Risk Management Activity

- The clinical experience to date is limited under the sponsor's development program for the orphan indication of immune thrombocytopenic purpura (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).
 - The sponsor should distribute AMG 531 under a program that permits active safety monitoring to accurately determine the incidence of these events, until the lack of an increase in their incidence is demonstrated with statistical rigor. The low prevalence of ITP should permit the effective implementation of such an active safety monitoring program.
 - Data collected as part of standard of care (including work-up of significant ITP complications) may be proactively captured under the sponsor's postmarketing surveillance, in lieu of performing a formal phase 4 study.

- Further, the results of the long-term extension study (study 213) suggest that the efficacy of AMG 531 in treating thrombocytopenia of ITP may decline modestly with prolonged use (over 30 weeks). The sponsor should proactively collect long-term efficacy data to include baseline platelet counts, maintenance platelet counts, and trends in changes in AMG 531 dose requirements with prolonged therapy.

1.2.2 Required Phase 4 Commitments

- -



- A formal QT cardiac safety study has not been performed to date under the sponsor's AMG 531 clinical development program. The adequacy of safety monitoring to date, the lack of adverse event reports implicating cardiac arrhythmias or sudden deaths, and no expected mechanism for AMG 531 to have a QT effect support that a formal QT study may be completed as a postmarketing commitment.

1.3 SUMMARY OF CLINICAL FINDINGS

1.3.1 Overview of Clinical Program

The clinical development program for the use of AMG 531 (romiplostim, Nplate) in ITP consists of 9 clinical studies in patients and 2 pharmacology studies in healthy volunteers. The core data that support the safety and efficacy of AMG 531 in ITP were obtained primarily in two pivotal controlled blinded studies (with or without splenectomy). An open-label extension study provided uncontrolled long-term safety 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.

The protocols for the three major studies (105, 212, 213) were reviewed by FDA (Special Protocol Assessment) and by EMEA (Protocol Assistance). AMG 531 has received orphan designation for the treatment of ITP in the United States (2003),

1.3.2 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-naïve 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 $\geq 50,000/\mu\text{L}$ 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 $50,000/\mu\text{L}$ after one to three doses (30% by week 2, 42% by week 3, 54% by week 4). These platelet counts remained within $50\text{--}200 \times 10^3/\mu\text{L}$ 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.

Based on these three studies, AMG 531 appears to be a safe and effective alternative in managing severe thrombocytopenia of ITP refractory to current first-line (low-dose corticosteroids) or second-line (splenectomy) therapies.

1.3.3 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 ($\times 10^3/\mu\text{L}$).
- 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 (see narrative corresponding to case 1 in **Table 29**). 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 ($\times 10^3/\mu\text{L}$). 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.

1.3.4 Dosing Regimen and Administration

AMG 531 is to be administered by an experienced healthcare provider. Therapy should be started at an initial dose of 1 $\mu\text{g}/\text{kg}$ once weekly as a subcutaneous injection. The dose is to be adjusted based on weekly platelet counts to achieve and maintain the platelet count $> 50 \times 10^3/\mu\text{L}$, not to exceed a maximum weekly dose of 10 $\mu\text{g}/\text{kg}$ (**Table 1**).

Table 1: Dose Adjustment

Platelet Count ($\times 10^9/L$)	Action	Adjustment Frequency
Initial dose is 1 mcg/kg, based on actual body weight		
<50	Increase dose in 1 mcg/kg increments	Every week
50 to 400	Adjust dose in 1 mcg/kg increments (increase or decrease) at the physician's discretion to achieve a recommended platelet count <u>50</u>	Every 2 weeks
>400	Do not administer, hold scheduled dose. Reinitiate therapy when platelet count is $< 200 \times 10^9/L$. - Consider decreasing the dose by 1 mcg/kg at the next scheduled dose - Consider maintaining the dose of Nplate if the platelet count increase was due to the initiation or increase in dose of a concurrently administered ITP medication	Every week

AMG 531 is available in single-use vials (5 mL) containing 250 ug or 500 ug of deliverable lyophilized product. The drug product  refrigerated storage protected from light, and should be administered within 24 hours of reconstitution using sterile water for injection.

2. 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 IgG₁ 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. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

The following discipline reviews are pending (as of Jan 2, 2008): Toxicology; Clinical Pharmacology; Chemistry, Manufacturing, and Controls; and Statistics.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

This BLA contains clinical data from 9 studies in ITP patients (safety and efficacy) and from 2 studies in healthy volunteers (pharmacology). The clinical review focused on controlled data from study 212 (non-splenectomy) and from study 105 (splenectomy). Uncontrolled data from study 213 were reviewed for consistency with those obtained in controlled studies.

5. CLINICAL PHARMACOLOGY

Clinical Pharmacology review is pending as of Jan 2, 2008.

6. INTEGRATED REVIEW OF EFFICACY

6.1 INDICATION

Nplate (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.

6.1.1 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 (see **Tables 2-3**).
- 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 through week 36 or until platelet counts < 50 (x10³/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 10³/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 ≤ 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 2: 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 10⁹/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 10⁹/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 3: Dose Adjustment in Extension Study (Study 213)

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

When the dose needed to be reduced in a patient receiving 1 $\mu g/kg$, the dose was held until the platelet count fell to 50 ($\times 10^3/uL$), and dosing was resumed at 1 $\mu g/kg$ 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.

6.1.2 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: ≥ 6 weekly platelet counts $\geq 50 \times 10^3/uL$ during last 8 weeks of treatment with no rescue medication use at any time during treatment
 - Transient Response: ≥ 4 weekly platelet counts $\geq 50 \times 10^3/uL$ 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 $\geq 50 \times 10^3/uL$ between weeks 2 and 25
 - Stable dose: Dose within 1 $\mu g/kg$ during the last 8 weeks of treatment (weeks 17 to 24)

6.1.3 Study Design (Pivotal Studies)

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

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

Subject Disposition

125 patients enrolled in the two pivotal efficacy studies (105 and 212) at 2:1 randomization ratio (83 AMG 531, 42 placebo), as shown in **Tables 4-6**.

- 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 4: Numbers of Patients in Phase 3 Studies by Region

	Study 20030105		Study 20030212		Both Studies		
	Placebo	AMG 531	Placebo	AMG 531	Placebo	AMG 531	Total
	(N = 21) n (%)	(N = 42) n (%)	(N = 21) n (%)	(N = 41) n (%)	(N = 42) n (%)	(N = 83) n (%)	(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 5: Numbers of Patients in Phase 3 Studies and Study 213

	Study 20030105		Study 20030212		Both Studies		
	Placebo	AMG 531	Placebo	AMG 531	Placebo	AMG 531	Total
	(N = 21) n (%)	(N = 42) n (%)	(N = 21) n (%)	(N = 41) n (%)	(N = 42) n (%)	(N = 83) n (%)	(N = 125) 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.

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Table 6: 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)

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

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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 **Tables 7-9**.
 - Median age was 52 years (range 21-88), with a higher proportion of patients ≥ 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) $\times 10^3/\mu\text{L}$ in the placebo group and 16 (range 2 - 29) $\times 10^3/\mu\text{L}$ 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 7: 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, 83.0	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 8: 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 9: ITP Treatment History (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)
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)
Immunoglobulin	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)
Vincristine/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

Results for the major efficacy endpoints are summarized separately for each controlled study in **Table 10** (study 105, splenectomy) and in **Table 11** (study 212, non-splenectomy). Pooled results are shown in **Tables 12-17** and in **Figures 1-5**. Results from the uncontrolled long-term extension study are compared with pooled results of controlled studies in **Figures 6-7**.

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%, $p < 0.0001$).
 - 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.
 - In patients on placebo, the use of rescue medication increased from 5% - 10% per week to 20% - 30% per week, from weeks 1 - 5 to weeks 20 - 25 (final weeks).
 - In patients on AMG 531, the use of rescue medication remained between 2% and 10% per week. Patients on AMG 531 required rescue medication less frequently (26% vs 57%, $p < 0.05$).

Table 10: Major Efficacy Results 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.

Study 212 (Non-Splenectomy)

The results obtained in patients who had not undergone splenectomy were consistent with those obtained in patients who had undergone splenectomy. In general, the response rates (proportions of patients) in patients who have not undergone splenectomy (both placebo and AMG 531 groups) were higher than the response rates in patients who have undergone splenectomy (corresponding treatment groups).

AMG 531 appears to be effective in increasing the platelet count in patients with ITP, irrespective of splenectomy status, and the effectiveness appears to be greater in patients with less severe disease (splenectomy not required for adequate management) than in patients with more severe disease (splenectomy performed to manage refractory disease).

- Primary Endpoint: A significantly greater proportion of patients in the AMG 531 group achieved a durable platelet response than in the placebo group (61% vs 5%, $p < 0.0001$).
- Major Secondary Endpoints:
 - A significantly greater proportion of patients in the AMG 531 group achieved an overall platelet response than in the placebo group (88% vs 14%, $p < 0.0001$).
 - As in patients status post splenectomy, 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.
 - In patients on placebo, the use of rescue medication remained between 5% and 10% per week through week 6, and increased to between 11% and 33% per week after week 7.
 - In patients on AMG 531, the use of rescue medication remained between 5% and 10% per week throughout the study.

Table 11: Major Efficacy Results in Study 212

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

Comparison of Studies 105 and 212

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), and 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-naïve patients remains to be seen in future studies.

Pooled Results (Studies 105 and 212)

- Primary Endpoint: A significantly greater proportion of patients in the AMG 531 group achieved a durable platelet response than in the placebo group (49% vs 2%, $p < 0.0001$).
- Major Secondary Endpoints:
 - A significantly greater proportion of patients in the AMG 531 group achieved an overall platelet response than in the placebo group (83% vs 7%, $p < 0.0001$).
 - A significantly smaller proportion of patients in the AMG 531 group required rescue medication than in the placebo group (22% vs 60%, $p < 0.0001$).

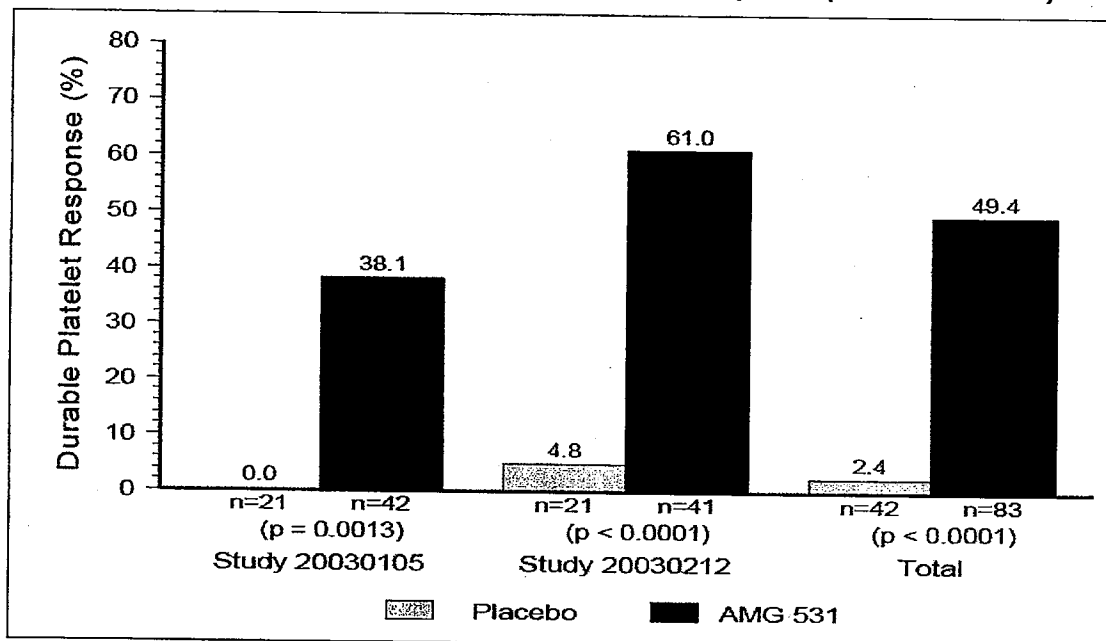
Table 12: Durable Platelet Response by Baseline ITP Therapy (Phase 3 Studies)

Incidence of Durable Platelet Response	Study 20030105		Study 20030212		Total	
	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%)	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

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

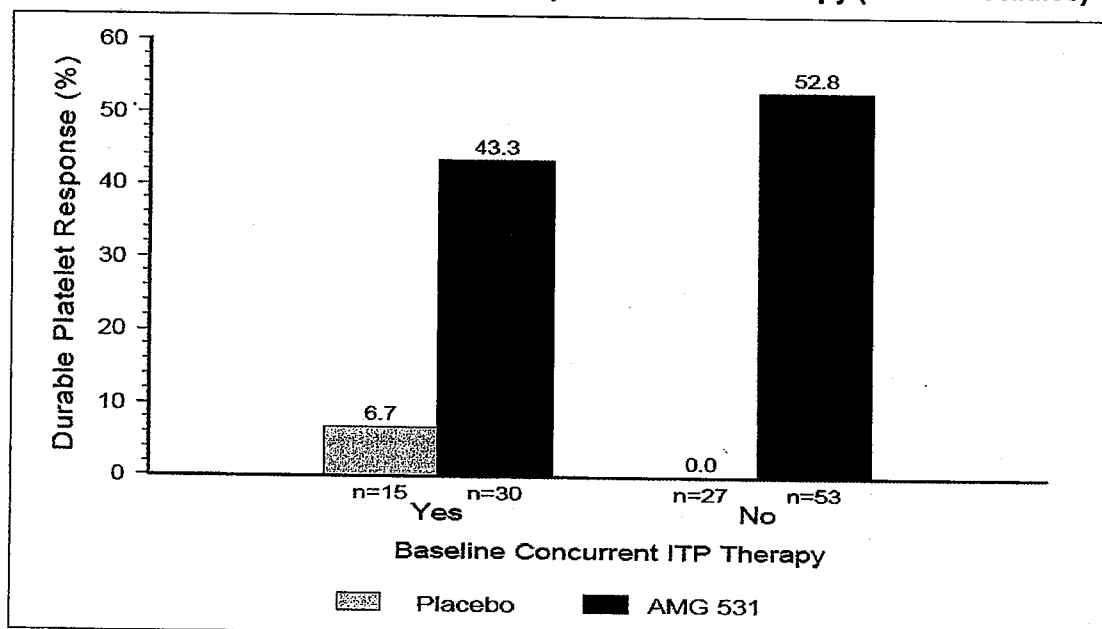
^a For individual studies, p-value is from Cochran-Mantel-Haenszel controlling for baseline concurrent ITP therapy; For total, p-value is from Cochran-Mantel-Haenszel controlling for splenectomy status and baseline concurrent ITP therapy.

Figure 1: Patients Achieving Durable Platelet Response (Phase 3 Studies)

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

For individual studies, p-value is from Cochran-Mantel-Haenszel controlling for baseline concurrent ITP therapy;

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

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

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

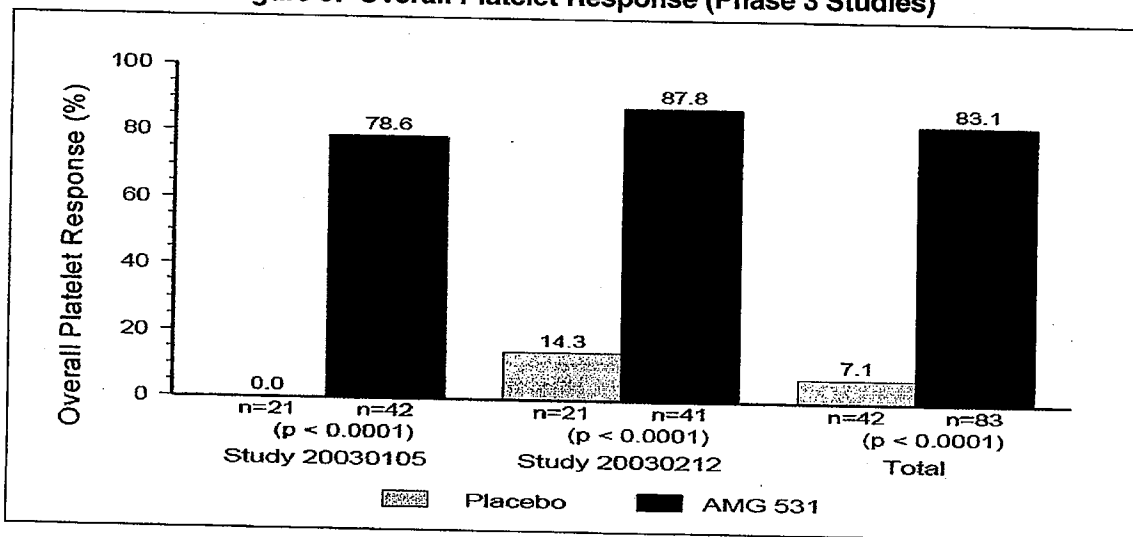
Table 13: Overall Platelet Response by Baseline ITP Therapy (Phase 3 Studies)

Incidence of Overall Platelet Response	Study 20030105		Study 20030212		Total	
	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%)	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	

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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 $\geq 50 \times 10^9/L$ 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.

Figure 3: Overall Platelet Response (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 $\geq 50 \times 10^9/L$ for 6 or more times during weeks 18-25 in the absence of rescue medication any time during the treatment period. Transient platelet response was defined as weekly platelet count $\geq 50 \times 10^9/L$ 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 14: Platelet Response Weeks (Phase 3 Studies)

	Study 20030105		Study 20030212		Total	
	Placebo (N = 21)	AMG 531 (N = 42)	Placebo (N = 21)	AMG 531 (N = 41)	Placebo (N = 42)	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	

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^a Number of weeks with platelet response = Number of weeks with platelet count $\geq 50 \times 10^9/L$ 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.

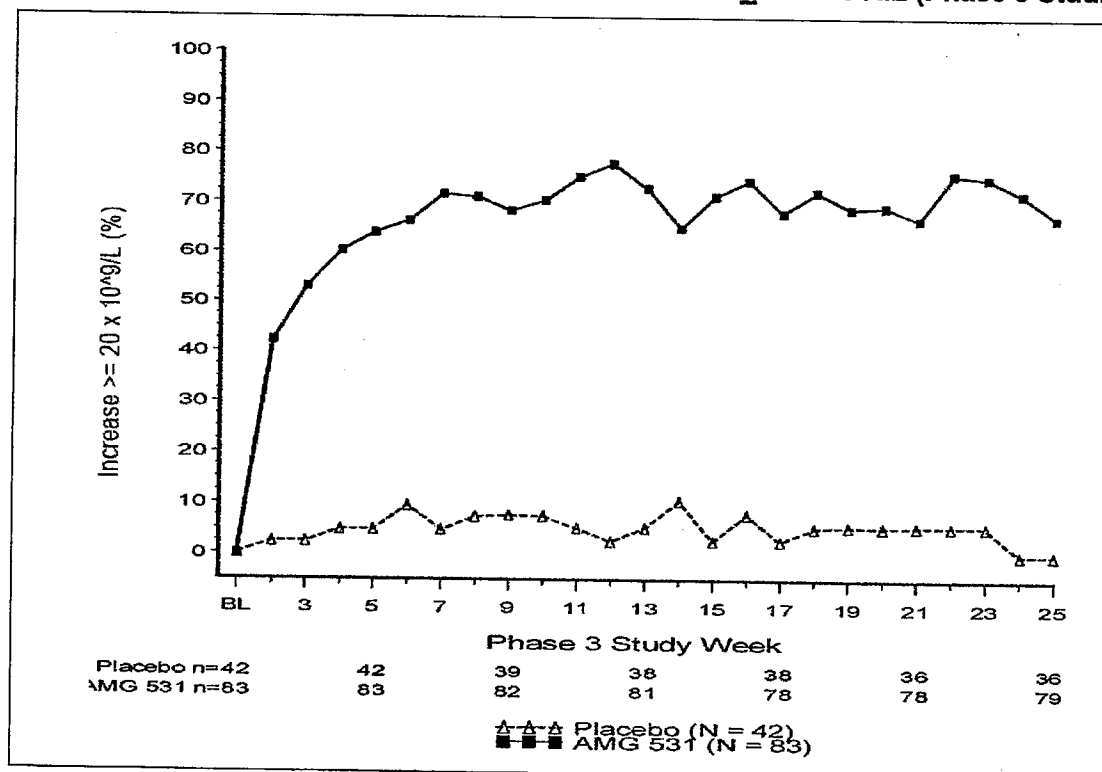
Figure 4: Proportions of Patients with Platelet Increases $\geq 20 \times 10^3/uL$ (Phase 3 Studies)

Table 15: Durable Platelet Response on Stable Dose (Phase 3 Studies)

Incidence of Durable Platelet Response with Stable Dose	Study 20030105		Study 20030212		Total	
	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 $\geq 50 \times 10^9/L$ 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 $\pm 1 \mu g/kg$ 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.

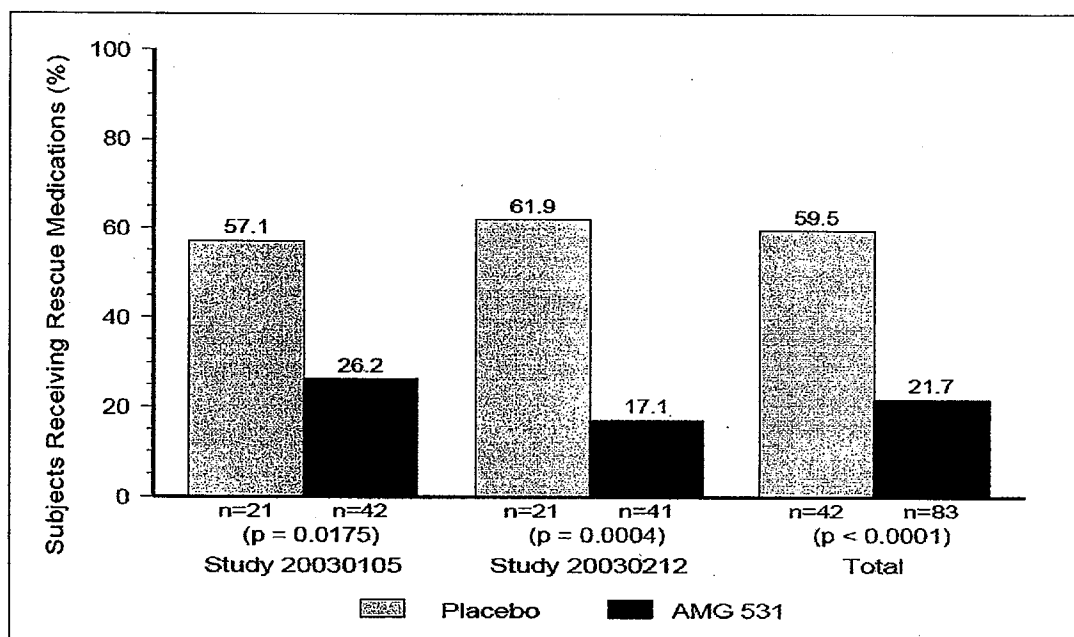
Table 16: Patients Requiring Rescue Medication (Phase 3 Studies)

Requiring Rescue Medications During Treatment Period	Study 20030105		Study 20030212		Total	
	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.

Figure 5: Patients Requiring Rescue Medication (Phase 3 Studies)

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: Use of Rescue Medication (Phase 3 Studies)

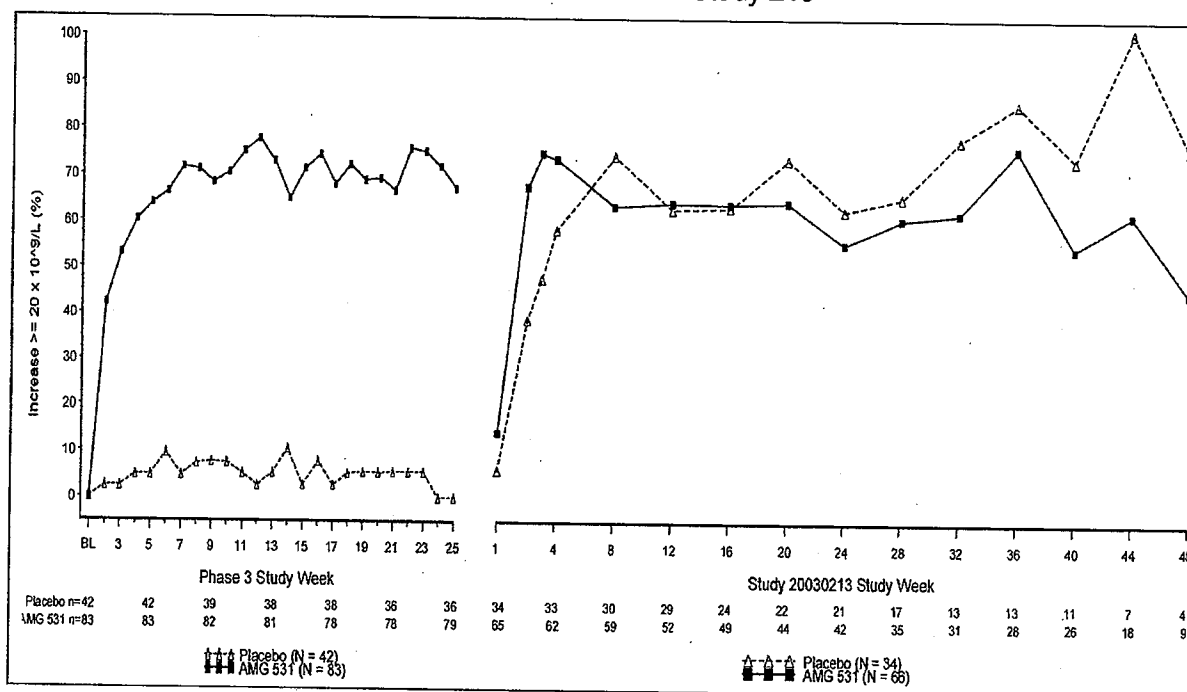
		Splenectomized 20030105		Non-splenectomized 20030212	
		Placebo (n=21)	AMG 531 (n=42)	Placebo (n=21)	AMG 531 (n=41)
Subjects receiving rescue medications – n (%)		12 (57.1)	11 (26.2)	13 (61.9)	7 (17.1)
Category	Terms Reported				
Corticosteroids	Prednisone Methylprednisolone Methylprednisolone sodium succinate Dexamethasone Prednisolone sodium sulfobenzate	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)

Study 213: Comparison with Controlled Studies

The efficacy results obtained from the uncontrolled long-term extension study were consistent with those obtained from the controlled pivotal studies. However, the uncontrolled experience suggests that efficacy of AMG 531 may decline over time with prolonged use.

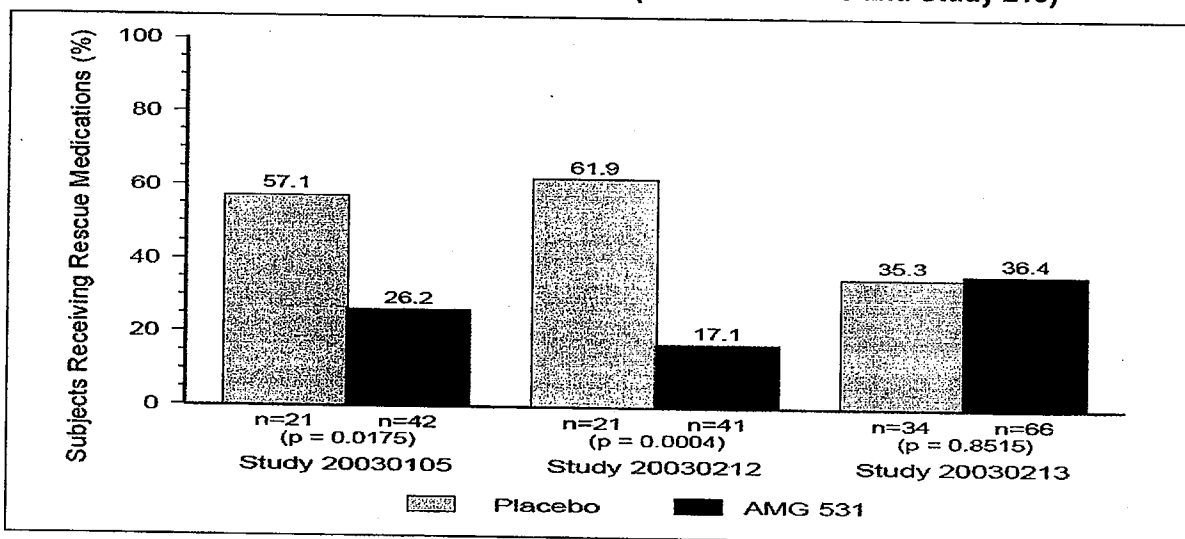
- **Figure 6** shows the proportions of patients with an increase in platelet count ≥ 20 ($\times 10^3/\mu\text{L}$) above baseline, in controlled studies (pooled data, left panel) and in uncontrolled long-term extension study (right panel).
 - During the first 30 weeks of AMG 531 therapy, the response rates (proportions of patients) over time among "placebo patients" in study 213 (previously randomized to placebo in controlled studies, but on AMG 531 in study 213; dashed curve, right panel) parallel the response rates in patients randomized to AMG 531 in controlled studies (solid curve, left panel).
 - Beyond 30 weeks, the response rates in the "placebo patients" appear to exceed modestly the response rates in patients randomized to AMG 531 in controlled studies. The apparent greater response rates in these patients may have resulted from a more liberal dosing guideline used in study 213. A comparison of dosing guidelines in controlled studies (**Table 2**) and in study 213 (**Table 3**) show that dose adjustments (upward or downward) were permitted for platelet counts between 50 - 250 ($\times 10^3/\mu\text{L}$) in study 213, whereas doses were to remain constant for platelet counts between 50 - 200 in the controlled studies.
 - Despite more liberal dosing, the response rates among "AMG 531 patients" in study 213 (previously randomized to AMG 531 in controlled studies, and on AMG 531 in study 213; solid curve, right panel) appear to decline modestly, to fall below the response rates in patients randomized to AMG 531 in controlled studies (solid curve, left panel). The apparent decline in response rates over time in these patients suggest that treatment-induced thrombopoiesis may decline with prolonged use of AMG 531 (about one year, between two studies).
 - The initial rate of rise in the response curve for the "AMG 531 patients" in study 213 (solid curve, right panel) exceeds those for the "placebo patients" in study 213 (dashed curve, right panel) and for the patients randomized to AMG 531 in controlled studies (solid curve, left panel). The more rapid rate of rise in previously treated patients likely reflects the dosing guideline used in study 213, which permitted previously determined stable doses in controlled studies as the starting doses in study 213.
- **Figure 7** compares the use of rescue medication in study 213 versus controlled studies. As might be expected, the use of rescue medication did not differ appreciably among patients in 213, irrespective of treatment status (AMG 531 vs placebo) in previous controlled studies.
 - The proportion of patients requiring rescue medication in study 213 was about 25% for each of the first two 12-week periods, and the proportion decreased during subsequent 12-week periods. The overall rate was about 36% for the entire duration.
 - Among patients receiving AMG 531 therapy, the proportion of patients requiring rescue medication appears to be significantly greater in study 213 than in controlled studies. The greater proportion (nearly two-fold) in study 213 likely reflects greater treatment duration in study 213 (nearly two-fold), and possibly a decline in the efficacy of AMG 531 over time with prolonged use (as discussed above).

Figure 6: Proportions of Patients with Platelet Increase $\geq 20 \times 10^3/\mu\text{L}$ Controlled Studies and 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.

Figure 7: Use of Rescue Medication (Phase 3 Studies and Study 213)



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.

6.1.5 Efficacy Conclusions

In patients with ITP refractory to current first-line (low-dose corticosteroids) or second-line (splenectomy) therapies, AMG 531 appears to be 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 ($\geq 100 \times 10^3/\mu\text{L}$).

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-naïve patients. AMG 531 is less effective in patients refractory to second-line therapy (splenectomy) but remains significantly more effective than currently available therapies.

7. INTEGRATED REVIEW OF SAFETY

7.1 SAFETY DATA SETS

Seven safety analysis sets are presented in **Table 18**. Three involve ITP, of which one (phase 3 safety set) consists of placebo-controlled data. This safety review focuses on controlled ITP data set. Uncontrolled ITP data are reviewed for consistency with the controlled data.

Four other data sets, less relevant to the ITP indication, involve myelodysplastic syndrome (MDS set), chemotherapy-induced thrombocytopenia (CIT set), healthy volunteers, or anyone who received AMG 531 under any study (AMG 531 set). These data sets are not presented in this interim review.

Table 18: 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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^aSubjects 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 filing.

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).

- Phase 3 ITP safety set (controlled data): All safety data collected from patients who received at least one dose of an investigational product in the two controlled studies (study 105, splenectomy; study 212, non-splenectomy)
- Phase 3 ITP long-term safety set (uncontrolled data): All safety data collected from patients who received at least one dose of an investigational product in the two controlled studies, plus any extension data collected for those patients subsequently participating in the uncontrolled long-term extension study (study 213)
- ITP safety set (uncontrolled data): All safety data collected from patients who received at least one dose of an investigational product in any ITP study, including phase 1 studies.

7.2 PATIENT DEMOGRAPHICS

Table 19 shows that the AMG 531 and placebo groups were generally well matched for baseline patient demographic profile, with the following potential caveats.

- 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.

7.3 ITP HISTORY

Table 20 shows that the AMG 531 and placebo groups were generally well matched for ITP status as evaluated by ITP history, with the following potential caveats.

- 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 19: 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)

Table 20: 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.

7.4 ADVERSE EVENTS

7.4.1 Overview of Adverse Events

Table 21 presents an overview of the controlled safety experience in using AMG 531 to treat thrombocytopenia in ITP.

- 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 21: 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.

^aSerious 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.

7.4.2 Common Adverse Events

Table 22 presents the 40 adverse events (event types, as Preferred Terms of MedDRA version 9.0) reported in $\geq 5\%$ of patients, in either placebo or AMG 531 group.

- Of the 40 events, 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 (and pain), oral mucosal blistering, pain, pharyngolaryngeal pain, shoulder pain, aesthenia, peripheral edema, hematoma, pyrexia, dyspepsia, anemia, 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 ≥ 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 22: Adverse Events $\geq$ 5% of Patients (Phase 3 ITP Safety Set)

Preferred Term	Placebo (N = 41)	AMG 531 (N = 84)
	n (%)	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 $\geq$ 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.

Table 23 presents the adverse events reported in $\geq 5\%$ of patients by age (above or below age 65), in either placebo or AMG 531 group.

- Among patients on AMG 531, the following 8 adverse events were reported in appreciably greater proportions of patients ($\geq 5\%$) 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 **Table 23**, 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.

Table 23: Adverse Events $\geq 5\%$ of Patients by Age (Phase 3 ITP Safety Set)

Preferred Term	Age < 65		Age ≥ 65	
	Placebo	AMG 531	Placebo	AMG 531
	(N=28) n (%)	(N=66) n (%)	(N=13) n (%)	(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)

- Of the 8 events that appear to be related to AMG 531 therapy (from **Table 22**), 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.

7.4.3 Serious Adverse Events

Table 24 presents the serious adverse events. 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).

Table 24: Serious Adverse Events (Phase 3 ITP Safety Set)

Preferred Term	Placebo (N = 41)	AMG 531 (N = 84)
	n (%)	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.

- 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 **Table 24** above were reported more often in patients with platelet counts < 450 ($\times 10^3/\mu\text{L}$) than in patients with counts ≥ 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.

7.4.4 Fatal Adverse Events

Table 25 presents the fatal adverse events for the controlled phase 3 ITP safety set, and **Table 26** presents the fatal adverse events for the larger but uncontrolled ITP safety set.

- 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 25: Fatal Adverse Events (Phase 3 ITP Safety Set)

	Placebo (N = 41)	AMG 531 (N = 84)
Preferred Term	n (%)	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 26: Fatal Adverse Events (ITP Safety Set)

	Placebo (N = 46)	AMG 531 (N = 204)
Preferred Term	n (%)	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.

7.4.5 Serious Bleeding Events

Table 27 presents the serious bleeding events for the controlled phase 3 ITP safety set. 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 27: Serious Bleeding Events (Phase 3 ITP Safety Set)

	Placebo (N = 41)	AMG 531 (N = 84)
Preferred Term	n (%)	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)

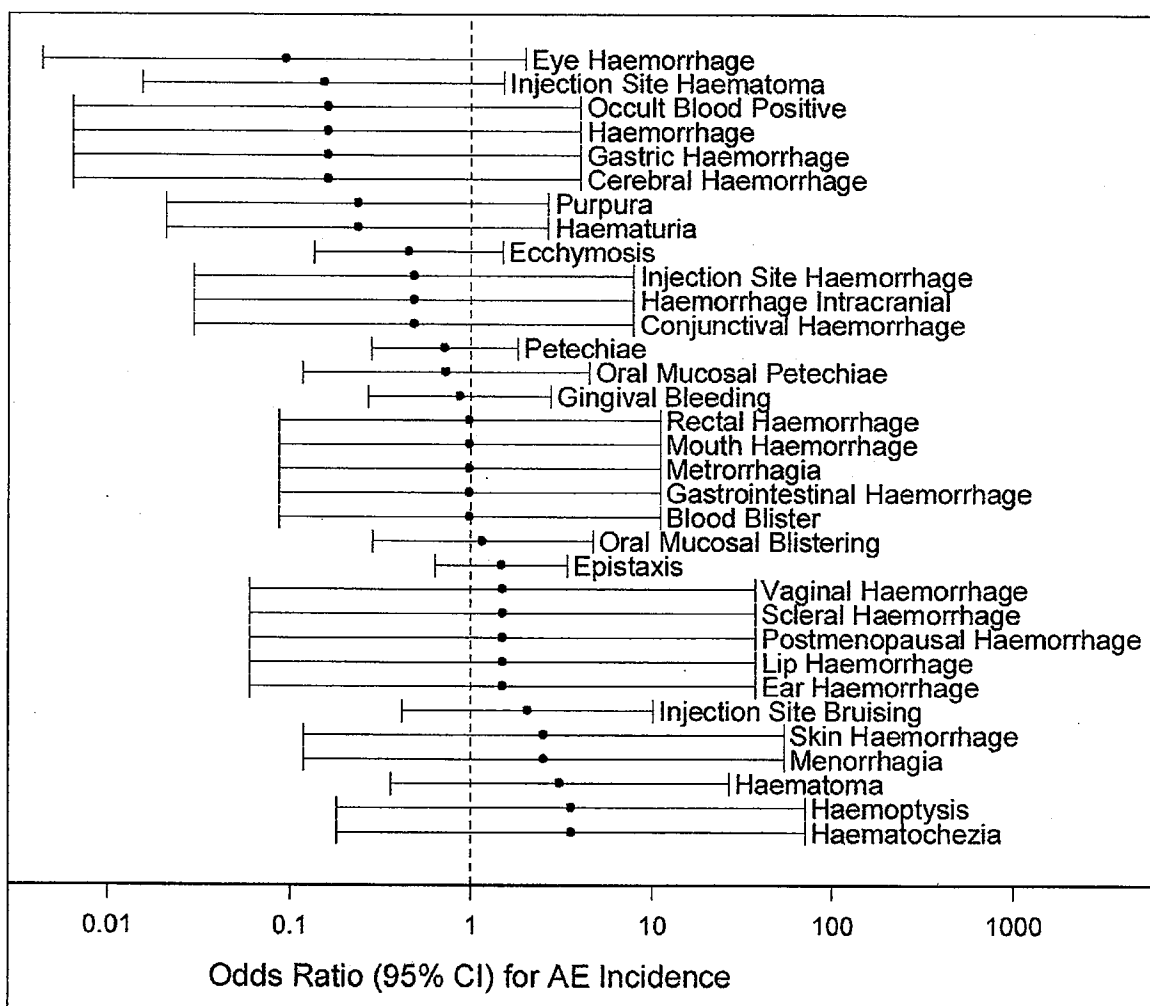
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The Phase 3 ITP safety set consists of all subjects who received investigational product in either ITP phase 3 study, 20030105 or 20030212. The adverse event terms that map to bleeding events were prospectively identified by the sponsor before the 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.

7.4.6 Overview of Bleeding Events

Figure 8 presents an overview of bleeding events reported in the two controlled studies (study 105, splenectomy; study 212, non-splenectomy). Although the incidence of all clinical bleeding events as reported does not appear to be appreciably reduced, thrombocytopenia-associated bleeding (including serious bleeding) does appear to be appreciably (although not significantly) reduced. These results are consistent with the limited number of patients, the relatively brief treatment duration, and artifacts of reporting.

Figure 8: 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.

7.4.7 Bone Marrow Abnormalities

Table 28 presents the bone marrow abnormalities reported for the uncontrolled ITP safety set. 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.

Table 28: Bone Marrow Abnormality (ITP Safety Set)

	Placebo (N = 46)	AMG 531 (N = 204)
Preferred Term	n (%)	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.

- **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 "reticulosis" 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 reticulosis. 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 $5 \times 10^3/\mu\text{L}$. 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 reticulosis 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), reticulosis, 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 "reticulosis." 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 $27 \times 10^3/\mu\text{L}$ 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 ($\times 10^3/\mu\text{L}$). 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 ($\times 10^3/\mu\text{L}$) 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 $\mu\text{g/kg}$ 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 ($\times 10^3/\mu\text{L}$), and a peripheral NRBC count of 1 per 100 WBC. Over the first 8 weeks, the AMG 531 dose remained constant at 15 $\mu\text{g/kg}$, 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 ($\times 10^3/\text{ul}$) 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.

- o 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 ($\times 10^3/\text{uL}$) 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 megakaryocytic 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 below in **Table 29**. 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).
 - o 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).
 - o 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 29: 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.

7.4.8 Selected Adverse Events of Special Interest

The limited data to date do not suggest that the use of AMG 531 in ITP induces serious bone marrow abnormalities. However, since AMG 531 induces the proliferation and maturation of megakaryocytes, the potential to induce unexpected cell proliferation or platelet activation and thrombosis remains a theoretical long-term safety concern.

- As with bone marrow abnormalities, limited data to date do not suggest that the use of AMG 531 in ITP induces neoplasms (**Tables 30-32**) or platelet activation (**Table 33**).
- **Figure 9** presents the odds ratios (placebo/AMG 531) for the incidence of selected adverse events reported in the two controlled studies (study 105, splenectomy; study 212, non-splenectomy). The selected adverse events serve as an overview of safety (thrombosis, injection site reactions, bone marrow abnormalities) as well as clinical efficacy (bleeding).

Table 30: Neoplasms (ITP Safety Set)

	Placebo (N = 46)	AMG 531 (N = 204)
Preferred Term	n (%)	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)
Myelofibrosis	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 31: Serious Neoplasms (Phase 3 ITP Safety Set)

	Placebo (N = 41)	AMG 531 (N = 84)
Preferred Term	n (%)	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 32: Serious Neoplasms (ITP Safety Set)

	Placebo (N = 46)	AMG 531 (N = 204)
Preferred Term	n (%)	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)

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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).

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 33: 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

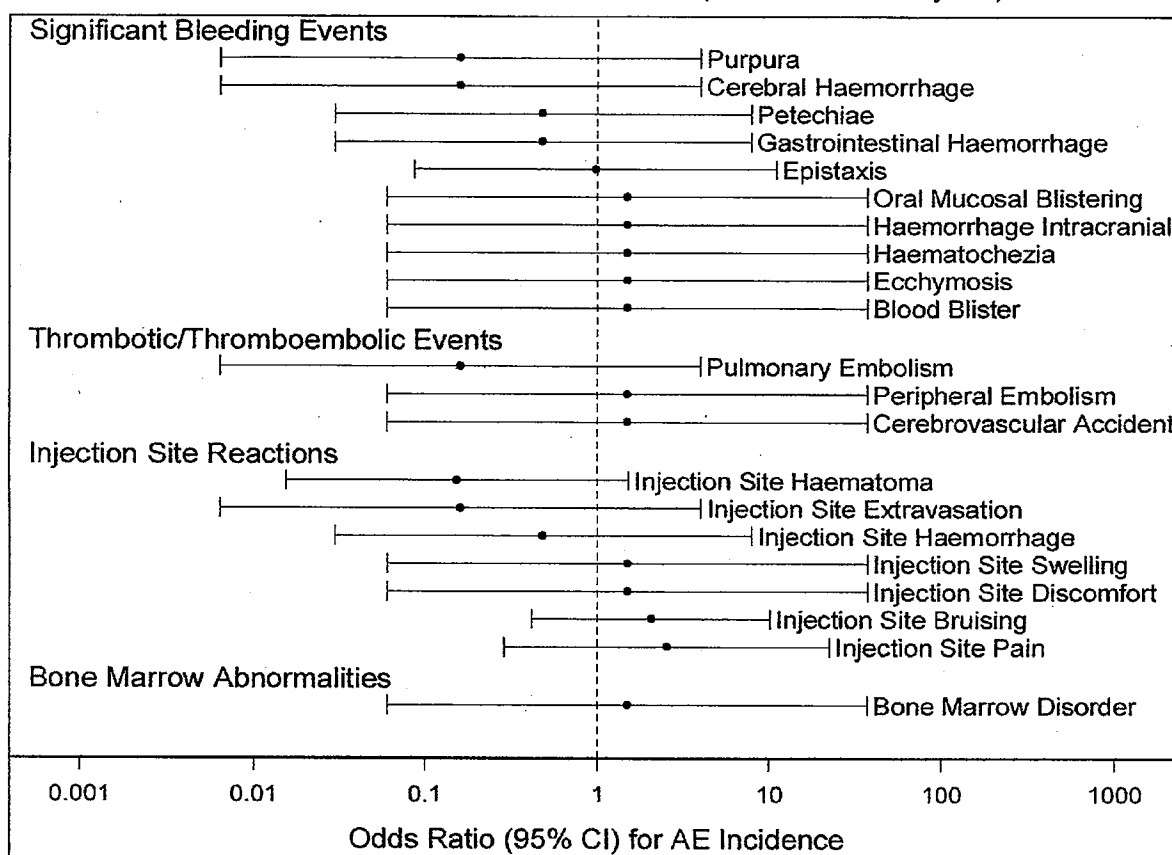
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The Phase 3 ITP safety set consists of all subjects who received investigational product in either ITP phase 3 study, 20030105 or 20030212.

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 9: 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.

8. ADDITIONAL CLINICAL ISSUES

The following case narrative suggests that the current AMG 531 formulation may not consistently permit accurate dosing or permit dose adjustment in increments smaller than 1 ug/kg.

A 64-year-old Hispanic woman with ITP had received AMG 531 under study 212 (non-splenectomy) with excellent platelet response. Platelet counts increased from a baseline of 16 ($\times 10^3/\mu\text{L}$) to 40-70 through week 7 in response to an AMG 531 dose of 1 ug/kg, and adjusting the dose upward by 1 ug/kg at week 10 resulted in a rapid rise in platelet count to 320 ($\times 10^3/\mu\text{L}$), a level that exceeded the target range (50-200). Lowering the dose back to 1 ug/kg resulted in a gradual decline in the platelet count to 15 at week 19, and increasing the dose back to 2 ug/kg again resulted in a rapid increase in the platelet count to 192 at week 24 (last dose per protocol). The platelet counts (off AMG 531) through week 27 (study completion) were 182, 54, and 5. Two weeks after completing study 212, the patient enrolled into study 213 at a baseline platelet count of 17. She received one dose of AMG 531 at 2 ug/kg and withdrew (consent) from the study. The reasons for withdrawing from study 213 remains unclear.

Accurate dosing and dose adjustment in increments smaller than 1 ug/kg may be necessary in patients sensitive to AMG 531 dosing (large platelet increase after small AMG 531 dose), particularly if the treatment-sensitive patient is small (low body weight). The patient described above may be one of such treatment-sensitive patients. In such patients, the dose of AMG 531 necessary to consistently maintain the platelet count within the desired target range may require the accurate and consistent delivery of small volumes (as low as 0.1 mL) of the drug product, which may be difficult using the current AMG 531 formulation. Although the platelet count is expected to fluctuate in ITP, the degree of fluctuation observed in the sponsor's clinical studies may have resulted, at least in part, from inconsistent dosing.

9. 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).

Date: Jan 16, 2008

From: John Lee, M.D., Medical Officer, DMIHP, OODP

 1/16/08

Through: Dwaine Rieves, M.D., Acting Director, DMIHP, OODP

 1-22-08

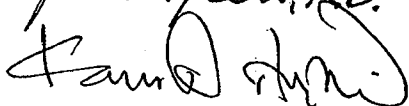
To: BLA File, STN 125268

Subject: Interim Clinical Review (as of Jan 2, 2008) of BLA (STN 125268): Romiplostim (Nplate) for the treatment of thrombocytopenia in immune thrombocytopenic purpura (ITP)

CLINICAL REVIEW

Application Type BLA
Submission Number STN 125268/0

Letter Date October 23, 2007
Stamp Date October 23, 2007
PDUFA Date July 23, 2008

Reviewer Name Faranak Jamali, M.D. 
Acting Team Leader Kassa Ayalew, M.D. 
Review Completion Date May 20, 2008

Established Name Romiplostim
(Proposed) Trade Name Nplate
Therapeutic Class TPO mimetic
Applicant Amgen, Inc.

Priority Designation Priority Review
Formulation Injection
Dosing Regimen SC injection QW
Strength: 250 mcg (5mL vial), 500 mcg (5mL vial)
Indication Treatment of Thrombocytopenia in Chronic Immune (Idiopathic) Thrombocytopenic Purpura (ITP)

Intended Population Adult Patients with Chronic ITP Refractory to Corticosteroids or Splenectomy

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical recommendation for this application is approval for the treatment of chronic immune (idiopathic) thrombocytopenic purpura in adults who are refractory to low-dose corticosteroids or splenectomy. This recommendation is based on a review of safety and efficacy information on adult patients with ITP who are refractory to low-dose corticosteroids or splenectomy treated with Nplate.

It is recommended that the application be approved provided that the sponsor agrees with recommendations on postmarketing actions for continued proactive monitoring of long-term efficacy and safety (including bone marrow fibrosis, thromboembolic events, post-cessation thrombocytopenia, and immunogenicity), completion of a formal QT cardiac safety study, and pregnancy exposure registry. Nplate has demonstrated substantial evidence of effectiveness in raising the platelet counts in chronic ITP patients who have insufficient response to corticosteroids, immunoglobulins or splenectomy.

It is also recommended that the sponsor perform the REMS (risk evaluation and mitigation strategy) to optimize the appropriate use of Nplate to treat adult patients with chronic ITP, improve understanding of the risk profile of Nplate by monitoring for and assessing the serious adverse events associated with the identified and potential risks.

The REMS should include education of patients and physicians about the risk profile of Nplate and appropriate use of this drug, limit off-label use in patients with other thrombocytopenic states, monitor, track, and assess identified and potential safety risks of Nplate in all patients with chronic ITP who will be receiving Nplate (for details please refer to Dr Suzanne Berkman's review).

1.2 Risk Benefit Assessment

Please refer to section 1.1.

1.3 Recommendations for Postmarketing Risk Management Activities

The clinical experience with Nplate to date is limited. In addition, the current Nplate formulation does not consistently permit accurate dosing or dose adjustment in increments smaller than 1 ug/kg for the proposed indication. The following list of postmarketing Risk Management Activities are recommended to the applicant:

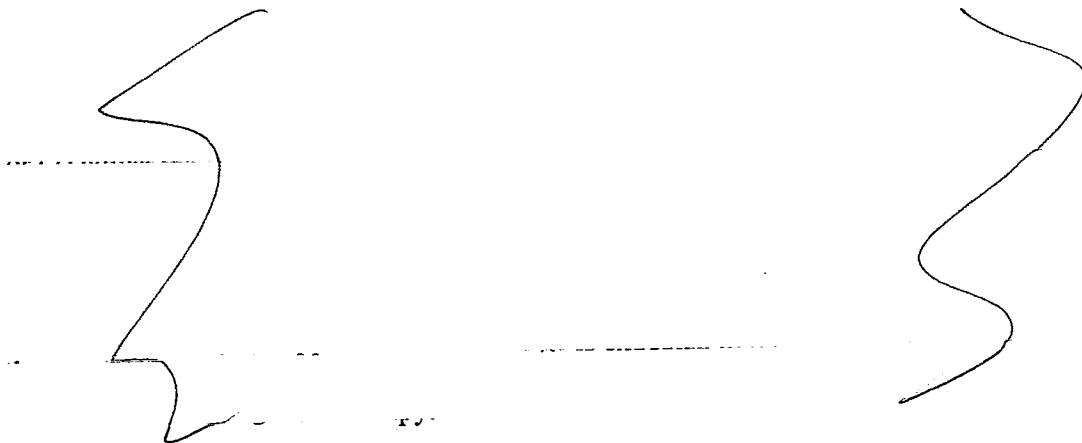
- The sponsor should distribute Nplate under a program that permits active safety monitoring to accurately determine the incidence of adverse events such as bone marrow fibrosis, thromboembolic events, post-cessation thrombocytopenia, and immunogenicity until the lack of an increase in their incidence is demonstrated with statistical rigor.

- Data collected as part of standard of care (including work-up of significant ITP complications) should be proactively captured under the sponsor's postmarketing surveillance, in lieu of performing a formal phase 4 study.
- All patients who participated in an ITP study during product development should be followed as a special subset of the active postmarketing safety monitoring program.
- The sponsor should proactively collect long-term efficacy data to include baseline platelet counts, maintenance platelet counts, and trends in changes in Nplate dose requirements with prolonged therapy.

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1.4 Recommendations for other Post Marketing Study Commitments

The following is a list of post-marketing requirements recommended to the sponsor:

1. To conduct Study 20070796: Determination of Frequency Rates of Bone Marrow Fibrosis and Thrombotic/Thromboembolic Events in Patients with Chronic Immune (Idiopathic) Thrombocytopenic Purpura in Denmark.
2. Given that Nplate is a peptibody with molecular weight of 59 kDa, it is unlikely that Nplate will have access to the hERG pore from the intracellular side. However, the sponsor has not collected adequate ECGs during the development of Nplate to rule out other off-target cardiac effects. We recommend that the sponsor continues routine ECG monitoring in the post-marketing clinical studies to capture any important cardiac effects in the patient population following chronic dosing of Nplate. ECGs should be collected after patients have received multiple doses of Nplate. Please submit your proposed study plan and the time frame.
3. The incidence of immunogenicity appears increasing with time during the clinical trials with Nplate treatment and one patient developed neutralizing antibodies to Nplate at week 79. The sponsor should continue collecting blood samples in patients with chronic ITP who receive long term Nplate treatment to test the incidence of binding and neutralizing antibodies to Nplate and/or to the endogenous thrombopoietin (TPO). The impact of the appearance of these antibodies on clinical efficacy and safety should be assessed. Please submit your proposed study plan and the time frame.
4. To develop and maintain a prospective, observational pregnancy exposure registry that compares the pregnancy and fetal outcomes of women exposed to Nplate during pregnancy to an unexposed control population. The registry should be conducted as a post-marketing requirement for this application. The outcomes of the registry should include major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, platelet number and function, neoplasm formation, reticulatin formation, thrombotic events, and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life. For guidance on how to establish a pregnancy exposure registry, please review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at <http://www.fda.gov/cder/guidance/3626fnl.htm>.
5. We recommend that you conduct a lactation study in a subset of women enrolled in the registry, who choose to breastfeed their infants, to assess the presence of Nplate in breast milk and potential effects in nursing infants. For guidance on how to conduct a lactation study, please review the Draft Guidance for Industry, Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling <http://www.fda.gov/cder/guidance/5918dft.pdf>.

6. Analysis of historical data on 633 patients with chronic ITP collected from 1996 to 2006 (i.e., patients not exposed to Nplate) by the National Health Registry of Denmark.
7. To conduct Study 20080009: A Prospective Phase IV, Open-Label, Multi-Center, Study Evaluating the Changes in Bone Marrow Morphology in Subjects Receiving Nplate for the Treatment of Thrombocytopenia associated with Immune (Idiopathic) Thrombocytopenia Purpura (ITP) .
8. To provide a registry to monitor the incidence of increase 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 Nplate 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, Nplate is not approved in these countries.

2 Introduction and Regulatory Background

2.1 Product Information

Nplate, 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 IgG1 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. Nplate indication is sought for treatment of thrombocytopenia in adults with ITP refractory to low-dose corticosteroid therapy or splenectomy. The 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 Nplate 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).

Nplate has received orphan designation for this proposed indication in major global regions, United States (US) (2003),

2.2 Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Sponsor	Amgen
Drug Product/ Generic	Romiplostim
Trade Name	Nplate
Chemical Class	NME (new molecular entity)
Pharmacological Class	TPO-mimetic agent
Dosage Forms	Initial dose of 1 mcg/kg once weekly as a subcutaneous (SC) injection. Adjust weekly dose by increments of 1 mcg/kg to minimize the risk of bleeding by achieving and maintaining a platelet count greater than $\times 10^9/L$



Routes of Administration SQ

Age Groups Adults $\geq$ 18 years

Indication Studied Treatment of thrombocytopenia in adults with ITP
refractory to low-dose corticosteroid therapy or
splenectomy

2.3 Currently available treatments for proposed indication

IVIg and anti-D immunoglobulin (WinRho®) are approved for use in ITP. Splenectomy is generally the next step for adults who have relapsed or not had a response to corticosteroids, IVIg, or anti-D immunoglobulin. Approximately 30% to 40% of adults who undergo splenectomy either fail to respond or relapse. There is no currently approved treatment for patients refractory to low-dose corticosteroid therapy or splenectomy.

2.4 Proposed Indications

The Applicant sought indication is treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy.

2.5 Availability of Proposed Active Ingredient in the United States

The active ingredient: Nplate. The inactive ingredients include: L-histidine, sucrose, mannitol, polysorbate-20 and hydrochloric acid

The ingredients are manufactured by Amgen Inc. and the ingredients production and/or its use may be covered by one or more US Patents, including US Patent Nos. 6,835,809; and 7,189,827, as well as other patents or patents pending.

2.6 Important Safety Issues With Consideration to Related Drugs

Not applicable.

2.7 Summary of Presubmission Regulatory Activity Related to this Submission

The applicant and Agency had several meetings prior to this Biologics License Application (BLA) submission where they agreed upon modifying PK, PD comparability bridging plan and the adequacy of proposed data package to support the BLA.

The applicant submitted a Biologics License Application for Nplate seeking the indication of the treatment of thrombocytopenia in adults with ITP refractory to low-dose corticosteroid therapy or splenectomy.

On October 23, 2007, the applicant submitted a BLA (STN 125268/0) seeking approval of Nplate for treatment of thrombocytopenia in adults with chronic ITP refractory to low-dose corticosteroid therapy or splenectomy. The BLA was supported by two double-blind, placebo controlled clinical studies and an open label, extension study.

The results of the above studies were reviewed by the agency and presented to Advisory Committee on March 12, 2008. At that time, the AC unanimously voted in favor of the adequacy of the data to support the safety and efficacy of Nplate.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of the reviewed submission were acceptable. Four sites were inspected regarding the two controlled phase 3 trials and the extension study. With the limited information provided for four sites, no major deficiencies were noted that could compromise the integrity of the data. For details of the inspection, please refer to Ms. Karen Storm's review, Division of Scientific Investigations.

3.2 Compliance with Good Clinical Practices

There was no evidence to suggest that the studies contained in this BLA were not conducted in accordance with accepted ethical standards and under good clinical practices. Valid consents were obtained from patients participating in the studies and the IRB had oversight of the studies.

3.3 Financial Disclosures

Financial disclosure information was submitted to the BLA. There was no evidence of financial conflict of interest.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There is no important CMC issue to affect the clinical interpretation of the data reviewed in this BLA.

For details of CMC issues, please refer to Dr. David M. Frucht's review, Product Quality Reviewer, Division of Monoclonal Antibodies.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

In a 4-week repeat dose toxicity study in rats, Nplate caused bone hyperostosis and marrow fibrosis at clinically equivalent and higher doses. This finding was not observed in animals after a 4-week post-treatment recovery period. Studies of long-term treatment with Nplate in rats have not been conducted; therefore, it is not known if the fibrosis of the bone marrow is reversible in rats after long-term treatment.

For details of Pharmacology/Toxicology issues, please refer to the review by Dr. Tushar Kokate's review, Product Pharmacology/Toxicology Reviewer.

4.4 Clinical Pharmacology

There were 9 clinical pharmacology studies (two studies in healthy subjects and 7 studies in subjects with chronic ITP). Based on the review of those studies the major clinical pharmacology recommendations are described below:

- Collection of immunogenicity data in chronic ITP studies with long-term Nplate exposure to assess the incidence of binding and neutralizing antibodies to Nplate or to eTPO and to evaluate the clinical impact of these antibodies on the degree of thrombocytopenia, if it ever occurs.
- Conducting a QTc study with ECG measurements in chronic ITP patients receiving Nplate treatment to evaluate the potential effect of Nplate treatment on QT- interval following the principles described in the ICH E14 Guidance (<http://www.fda.gov/cber/gdlns/iche14qtc.pdf>).

- Conducting a pharmacokinetic (PK) and pharmacodynamic (PD) study with Nplate in pediatric patient population to identify an appropriate initial dose and dosing regimen to be used in future clinical pediatric efficacy and safety trials.

For details of clinical pharmacology issues, please refer to Drs. Angela Men and Hong Zhao's review.

4.4.1 Mechanism of Action

Nplate increases platelet production through binding and activation of the TPO receptor(c-Mpl), a mechanism analogous to endogenous TPO.

4.4.2 Pharmacodynamics

In clinical studies, treatment with Nplate resulted in dose-dependent increases in platelet counts. After a single subcutaneous dose of 1 to 10 mcg/kg Nplate in patients with chronic ITP, the peak platelet count was 1.3 to 14.9 times greater than the baseline platelet count over a 2- to 3-week period. The platelet counts were above $50 \times 10^9/L$ for 7 out of 8 patients with chronic ITP who received six weekly doses of Nplate at 1mcg/kg.

4.4.3 Pharmacokinetics

In the long-term extension study in patients with ITP receiving weekly treatment of Nplate subcutaneously, the pharmacokinetics of Nplate over the dose range of 3 to 15 mcg/kg indicated that peak serum concentrations of Nplate were observed about 7 to 50 hours post-dose (median: 14 hours) with half-life values ranging from 1 to 34 days (median: 3.5 days). The serum concentrations varied among patients and did not correlate with the dose administered. The elimination of serum Nplate is in part dependent on the TPO receptor on platelets. As a result, for a given dose, patients with high platelet counts are associated with low serum concentrations and vice versa. In another ITP clinical study, no accumulation in serum concentrations was observed (n = 4) after six weekly doses of Nplate (3 mcg/kg). The accumulation at higher dose of Nplate is unknown.

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5 Sources of Clinical Data

The summary of the applicant's studies for the above indication are presented in table below.
The material reviewed in this BLA was derived from the clinical studies conducted by the Applicant.

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Table 1: Summary of Clinical Studies

Study identifier/Phase	Study design	Study drug, dose, route of administration	Number of patients	Type of patients	Duration of treatment	Study status
2000105/ Phase 3	Multicenter, double blind, randomized, placebo controlled	Nplate or placebo on 2:1 ratio, weekly SC, starting dose: 1 µg/kg, to max 15 µg/kg	63 (25 men, 38 women)	Adults, ITP splenectomized	24 weeks	Complete
20030212/ Phase 3	Multicenter, double blind, randomized, placebo controlled	Nplate or placebo on 2:1 ratio, weekly SC, starting dose: 1 µg/kg, to max 15 µg/kg	62 (19 men, 43 women)	Adults, ITP Non-splenectomized	24 weeks	Complete
20050123	Substudy in conjunction with 2 phase 3 & the open label extension studies	Evaluation of effects of Nplate on bone marrow	10 (2 men, 8 women)	Adults, ITP	N/A	Complete
20010218/ Phase 1/2	Multicenter, open-label, sequential cohort, unit dose escalation	4 patients per each cohort(4 cohorts of 30, 100,300, and 500 µg)	16 (6 men, 10 women)	ITP for ≥ 3 months	3 week treatment period and 8 week observation period	Complete
20030213/ Phase 3	Open label extension of phase 3 studies	Nplate, SC, once weekly: 1-30 µg/kg	137 (46 men, 91 women),	Adults, ITP completed another Nplate ITP study	No limit; once weekly dose	Ongoing
20040209	Open label, individual patient protocol	NPLATE starting dose: 3 µg/kg, SC,	17 (6 men, 11 women)	Severe ITP, refractory to standard Rx,	Cycles of 12-week intervals	ongoing
20010147	Observational study to assess patient reported outcomes	N/A	73 (56 women, 17 men)	Adults, ITP	N/A	Completed
20050159 /Phase 1/2	Multicenter, open-label, sequential cohort dose escalation study	4 dose cohorts: Nplate once weekly Doses :300, 700, 1000, and 1500 µg SC	20 (15 men, 5 women)	Adults diagnosed with MDS	3 weeks and up to 1 year for the treatment extension phase	Ongoing; abbreviated
20050144 /phase 1/2	Open-label, Multicenter, dose finding study	4 Nplate Dose cohorts: 100, 300, 700 and 1000 µg	4 (3 men, 1 women)	Chemotherapy induced thrombocytopenia	five 21- day treatment cycles	Ongoing; abbreviated

Source: Applicant Submission

5.1 Review Strategy

The clinical review is based on the data from the two controlled phase 3 studies and one open label extension study, which are described below.

1. Study 20030212 (study 1, non- splenectomized) conducted in patients who have not yet undergone splenectomy, enrolled 21 patients receiving placebo and 41 patients receiving Nplate.
2. Study 20030105 (study 2, splenectomized), conducted in patients status post splenectomy, enrolled 21 patients receiving placebo versus 42 patients receiving Nplate.
3. Study 20030213 (study 3, extension study), an uncontrolled open-label extension study conducted in patients who have completed an earlier Nplate study, provided clinical experience supporting the continued safety and effectiveness of Nplate 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.

Study reports, line listings, and Case Report Forms were reviewed for all efficacy endpoints and demographic subgroups. The safety review also consisted of a review of all adverse events by summary tables and line listings.

Dr John Lee a medical reviewer in the Division of Medical imaging and Hematology Products performed part of the clinical review of the submission. This clinical review recapitulated the findings by Dr John Lee and updated the safety and efficacy data. The review of the additional safety and efficacy data was done using study reports, summary tables and line listings. Safety was assessed by integrating the data of the applicant-sponsored trials and other studies, where the product was used. FDA presented the findings to the Advisory Committee on March 12, 2008.

6 Review of Efficacy

6.1 Summary of Efficacy Results and Conclusion

The principal focus of the review is the two double-blind, placebo-controlled clinical studies and an open label, extension study. Other clinical study information was used for safety evaluation.

A total of 125 patients were included in the two phase 3 studies (divided almost equally). Both studies were multicenter, double-blind, placebo controlled and patients were randomized (2:1; active: placebo). The study patients had at least one prior ITP medication prior to enrollment.

Except for the splenectomy status, the two studies had largely the same inclusion criteria and design features. The baseline characteristics of enrolled ITP patients were similar between the placebo and Nplate arms, with most subjects having received multiple prior ITP medications. In both studies the pretreatment platelet count was $\leq 30 \times 10^3/\mu\text{L}$ (mean of 3 counts during screening).

The primary endpoint in both studies was "durable platelet response," defined as at least six weekly platelet counts $\geq 50,000/\text{mcL}$ 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 comparisons of platelet count "responses" (defined as any weekly platelet count $\geq 50,000/\text{mcL}$) and the use of thrombocytopenia "rescue medications." Patients were exposed to the study drug for 24 weeks with weekly platelet count measurements followed by 12 weeks of observation with out the study drug administration.

Patients who had completed Study 1 and 2 and whose platelet counts subsequently decreased to $\leq 50 \times 10^9/\text{L}$ were allowed to receive Nplate in an open-label extension study with weekly dosing based on platelet counts. Following Nplate discontinuation in Study one and two, 8.3% (7/84) of patients maintained platelet counts of $\geq 50 \times 10^9/\text{L}$. Among 100 patients who subsequently entered the extension study, platelet counts were increased and sustained regardless of whether they had received Nplate or placebo in the prior placebo-controlled studies.

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In both studies, statistically significant differences were observed for the primary endpoint and secondary endpoints, as shown in Table 2 below:

Table 2: Primary and Secondary Endpoint Results

Outcome	Study 1 (no splenectomized patients)		Study 2 (splenectomized patients)		p-value*
	Placebo n = 21	Nplate n = 41	Placebo n = 21	Nplate n = 42	
Durable platelet response, n (primary end point)	1(5%)	25(61%)	0 (0%)	16 (38%)	< 0.01
Major secondary endpoints					
Overall platelet response, n	3 (14%)	36 (88%)	0 (0%)	33 (79%)	< 0.01
Weeks with platelet response, mean (SD)	1.3 (3.5)	15.2 (7.5)	0.2 (0.5)	12.3 (7.9)	< 0.01
Subjects requiring rescue medication, n	13 (62%)	7 (17%)	12 (57%)	11(26%)	< 0.01
Subjects with durable platelet response with "stable dose", n	0 (0%)	21 (51%)	0 (0%)	13 (31%)	< 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.

A significantly greater proportion of patients in the Nplate group achieved the primary endpoint, durable platelet response than in the placebo group (38% vs. 0%, $p = 0.0013$).

Nplate appears to be effective in increasing the platelet count in patients with ITP, irrespective of splenectomy status when compared to placebo, and the effectiveness appears to be greater in patients with less severe disease (splenectomy not required for adequate management) than in patients with more severe disease (splenectomy performed to manage refractory disease).