1. TITLE PAGE

Study Title:	A Randomized, Placebo Controlled Study Evaluating the Efficacy and Safety of AMG 531 Treatment of Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) Prior to Splenectomy
Investigational Product:	AMG 531
Indication:	Thrombocytopenia associated with ITP
Brief Description:	Phase 3, double-blind, multicenter, 24-week study assessing efficacy and safety of AMG 531 vs placebo
Study Sponsor:	Amgen Inc., Thousand Oaks, CA USA
Study No.:	20030212
IND No.:	10205
Study Phase:	Phase 3
Study Initiation Date:	04 April 2005 (first subject enrolled)
Study Completion Date:	21 December 2006 (last subject visit)
Clinical Study Manager:	Reggie Kelly Phone: (805) 447-7807 Fax: (805) 480-1291
Good Clinical Practice:	This study was conducted in accordance with the principles of the Food and Drug Administration and the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents will be retained in accordance with ICH GCP.
Report Date:	28 June 2007

2. SYNOPSIS

Name of Sponsor: Amgen Inc., Thousand Oaks, CA USA

Name of Finished Product: AMG 531

Name of Active Ingredient: AMG 531

Title of Study: A Randomized, Placebo Controlled Study Evaluating the Efficacy and Safety of AMG 531 Treatment of Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) Prior to Splenectomy

Publication(s): None

Study Period: 04 April 2005 (first subject enrolled) to 21 December 2006 (last subject visit)

Development Phase: Phase 3

Introduction and Objectives:
AMG 531 stimulates platelet production by a mechanism similar to that of endogenous thrombopoietin (eTPO), but no amino acid sequence homology exists between AMG 531 and eTPO. Initial studies suggest that AMG 531 is able to increase platelet counts in thrombocytopenic subjects with ITP regardless of splenectomy status or concurrent ITP medication use. The primary objective of this study is to evaluate the efficacy of AMG 531 in the treatment of thrombocytopenia in subjects with ITP as measured by durable platelet response during the last 8 weeks of treatment and other platelet response parameters. The secondary objectives are to evaluate the overall safety of AMG 531; to evaluate possible reductions in concurrent ITP therapies while receiving AMG 531; and to evaluate changes in Patient Reported Outcomes (PRO) and Health Resource Utilization due to treatment with AMG 531.

Methodology:
This was a randomized, double-blind, placebo-controlled, 24-week study designed to assess the efficacy and safety of AMG 531 in adult thrombocytopenic subjects with ITP who had not received a splenectomy. Approximately 60 subjects were planned to be enrolled in a 2:1 ratio to AMG 531 or placebo (40 AMG 531 and 20 placebo). Randomization was stratified by concurrent ITP therapy (yes or no) at baseline. Investigational product was administered by subcutaneous (SC) injection once per week starting at a dose of 1 µg/kg. Dose adjustment was allowed throughout the 24-week treatment period to allow subjects to maintain platelet counts in the target range of 50 to 200 x 10^9/L. The maximum permitted dose was 15 µg/kg. After 24 weeks of treatment, investigational product was withdrawn and the platelet count was monitored. Participation was complete once platelet counts were $\leq$ 50 x10^9/L or the subject reached week 36 with a platelet count > 50 x10^9/L, whichever occurred first. Rescue medication was permitted for bleeding or wet purpura, or if the investigator felt the subject was at immediate risk. Subjects in both arms were eligible to receive rescue medication throughout the duration of the study.

Reductions in concurrent ITP therapies could occur during the first 12 weeks of treatment once platelet counts were > 100 x 10^9/L. A pharmacokinetic sample was drawn once a subject reached a dose of $\geq$ 10 µg/kg. The sample was drawn before dosing. Additional pharmacokinetic samples could be requested by either Amgen or the investigator at doses of $\geq$ 10 µg/kg.

All subjects who completed the study were eligible to screen for the open-label extension Study 20030213.

Number of Subjects Planned: Approximately 60 subjects were planned to be enrolled in a 2:1 ratio to AMG 531 or placebo (40 AMG 531 and 20 placebo).

Number of Subjects Enrolled: A total of 62 subjects were enrolled: 21 received placebo and 41 received AMG 531.

Sex: placebo: 16 (76.2%) women, 5 (23.8%) men.

AMG 531: 27 (65.9%) women, 14 (34.1%) men

Age: placebo: median 46.0 years (range 23 to 88 years)

AMG 531: median 52.0 years (range 21 to 88 years)

Ethnicity (Race): placebo: 18 subjects (85.7%) white; AMG 531 31 subjects (75.6%) white

Diagnosis and Main Criteria for Eligibility: Eligible subjects were men or women at least 18 years of age with a diagnosis of ITP according to American Society of Hematology (ASH) guidelines (George et al, 1996). Subjects > 60 years of age had to have a documented history of chronic ITP with bone marrow confirmation. Platelet count (mean of 3 counts taken during the screening and pre-treatment periods) was required to be $\leq 30 \times 10^9$/L, with no individual count $> 35 \times 10^9$/L. Subjects were required to have adequate liver and renal function, and hemoglobin > 9.0 g/dL. Subjects with a history of bone marrow stem cell disorder or with prior splenectomy were excluded. The only current ITP treatments permitted were corticosteroids, azathioprine, and/or danazol administered at a constant dose and schedule. Subjects who received IV Ig or anti-D Ig within 2 weeks before the screening visit, rituximab within 14 weeks before the screening visit, or hematopoietic growth factors within 4 weeks before the screening visit were ineligible.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: AMG 531 was supplied in 5-mL single-use vials as a sterile, white, preservative-free, lyophilized powder containing a protein concentration of 0.5 mg/mL when reconstituted with 1.2 mL of sterile water for injection. AMG 531 was administered subcutaneously (SC) once weekly at a starting dose of 1 µg/kg, with dose adjustment as shown in the table below, to a maximum permitted dose of 15 µg/kg.

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

Duration of Treatment: 24 weeks

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: Placebo consisted of the excipient ingredients supplied as a lyophilized powder in 5 mL

single-use glass vials, to be reconstituted with 1.2 mL sterile water for injection. Doses of placebo were volume-matched to AMG 531 doses.

Study Endpoints

Primary: Incidence of durable platelet response (at least 6 weekly platelet responses during the last 8 weeks of treatment in the absence of rescue medication).

Key Secondary Endpoints: Incidence of overall platelet response (mutually exclusive categories of durable platelet response [defined above] plus transient platelet response [at least 4 weekly platelet responses, without durable platelet response]; number of weeks with platelet response; proportion of subjects requiring rescue medication; incidence of durable platelet response with stable dose (dose maintained within ± 1 µg/kg during the last 8 weeks of treatment).

Descriptive secondary endpoints: adverse events (including clinically significant changes in laboratory values and incidence of antibody formation); proportion of subjects able to reduce or discontinue concurrent ITP therapies during the first 12 weeks of treatment; change from baseline in health resource use at each scheduled visit; and change from baseline at each scheduled visit for the following PRO instruments: ITP Patient Assessment Questionnaire (PAQ) scales, Short-Assessment.

Statistical Methods: The incidences of durable and overall platelet responses, proportion of subjects requiring rescue medication, and incidence of achieving stable dose was compared between the AMG 531 and placebo groups by using the Cochran-Mantel-Haenszel test stratified by baseline concurrent ITP therapy (yes/no). Exact 95% confidence intervals (CIs) for the incidence were provided for each treatment group and for the difference between treatment groups. A normal approximation was used for the CI of the difference between treatment groups. The common odds ratio was estimated along with its 95% CI.

The number of weeks with platelet response for both treatment groups was summarized and compared by using the analysis of variance (ANOVA) model with treatment, baseline ITP therapy (yes/no) in the model. To mitigate violation of the model assumptions, Cochran-Mantel-Haenszel test using rank and stratified by baseline concurrent ITP therapy (yes/no) was performed as a secondary analysis to ensure the robustness of the result. A sequential testing scheme was used as follows to adjust for multiplicity for the primary and key secondary endpoints in comparing AMG 531 and placebo:

- test incidence of durable platelet response, if significant then
- test incidence of overall platelet response (durable platelet response plus transient platelet response), if significant then
- test number of weeks with platelet response, if significant then
- test proportion of subjects requiring rescue medications, if significant then
- test incidence of durable platelet response with stable dose.

Summary of Results:

Subject Disposition: Twenty-six study centers screened a total of 70 subjects, from which 25 centers randomized 62 subjects (21 to placebo and 41 to AMG 531). All randomized subjects received at least 1 dose of investigational product. Subject 3651 randomized to placebo inadvertently received 3 doses of AMG 531 (weeks 19, 22, and 24). The full analysis set and efficacy analysis set included all randomized subjects; and therefore, the 1 subject randomized to placebo who inadvertently received 3 doses of AMG 531 is counted in the placebo group. Thus, these analysis sets included 62 subjects (21 subjects in the placebo group and 41 subjects in the AMG 531 group). The safety analysis set included all randomized subjects who received at least one dose of investigational product. If a placebo subject received at least 1 dose of AMG 531, then that subject's safety data were included in the AMG 531 group. Therefore, the one subject randomized to placebo who inadvertently received 3 doses of AMG 531 is counted in the AMG 531 group. Thus, the safety analysis consisted of 20 subjects in the placebo group and 42 subjects in the AMG 531 group.

Eight subjects (38.1%) in the placebo group and 3 subjects (7.3%) in the AMG 531 group discontinued treatment. Subjects who discontinued investigational product were asked to remain in the study, and 17 subjects (81.0%) in the placebo group and 39 subjects (95.1%) in the AMG 531 group completed the study.

Efficacy Results: AMG 531 was statistically significantly superior to placebo for the primary efficacy endpoint and for the key secondary endpoints (Table 2-1). One subject (4.8%) in the placebo group and 25 subjects (61.0%) in the AMG 531 group achieved a durable platelet response ($p < 0.0001$). The analyses for additional secondary efficacy endpoints and descriptive secondary endpoints also demonstrated the efficacy of AMG 531. A total of 3 subjects (14.3%) in the placebo group and 36 subjects (87.8%) in the AMG 531 group achieved an overall platelet response ($p < 0.0001$). The number of weeks with platelet response was also significantly greater for the AMG 531 group: mean 1.3 weeks, SD 3.5 weeks for placebo; mean 15.2 weeks, SD 7.5 for AMG 531 ($p < 0.0001$).

A total of 13 subjects (61.9%) in the placebo group and 7 subjects (17.1%) n the AMG 531 group received rescue medication during the treatment period ($p = 0.0004$). The placebo group had 61 occurrences of rescue medication use (0.13 per subject*weeks [ie, number of times rescue medication used/sum (total duration of subject's time in treatment period)]), while the AMG 531 group had 54 occurrences (0.06 per subject*weeks).

A total of 21 (51.2%) subjects were able to achieve a durable platelet response at a stable dose of AMG 531 (no subject in the placebo group) ($p = 0.0001$) ("stable dose" was defined as a dose maintained within ± 1 µg/kg during the last 8 weeks of treatment).

Ten subjects in the placebo group and 11 subjects in the AMG 531 group were receiving concurrent ITP therapies at baseline. At week-13 timepoint, 1 of the 10 placebo subjects (10.0%) who entered the study on baseline concurrent ITP treatment had a > 25% reduction in concurrent ITP treatment and an additional 3 placebo subjects (30%) discontinued all concurrent ITP treatment, while 5 of the 11 AMG 531 subjects (45.5%) with baseline concurrent ITP medication had a > 25% reduction and an additional 2 AMG 531 subjects (18.2%) had discontinued all concurrent ITP therapies. At week-25 timepoint, 2 placebo subjects (20.0%) had a > 25% reduction in concurrent ITP treatment and an additional 3 placebo subjects (30.0%) discontinued all concurrent ITP therapies, while 4 AMG 531 subjects (36.4%) had a > 25% reduction and an additional 4 AMG 531 subjects (36.4%) had discontinued all concurrent ITP therapies.

Platelet counts increased above their baseline values by ≥ 20 x 10^9/L at any time during the treatment period for 7 subjects (33.3%) in the placebo group and 38 subjects (92.7%) in the AMG 531 group ($p < 0.0001$). Platelet counts in the placebo group remained relatively steady throughout the study, while median platelet count in the AMG 531 group increased to a maximum of 100 x 10^9/L at week 11, and then remained at an increased level of between 62.5 x 10^9/L and 96 x 10^9/L for the remainder of the 25-week treatment period.

Table 2-1. Key Efficacy Endpoints

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

[a] From Cochran-Mantel-Haenszel controlling for baseline concurrent ITP therapy.
[b] From analysis of variance, or CMH based on rank.
Sources: *Table 14-4.1.1, Table 14-4.1.2, Table 14-4.1.3, Table 14-4.1.4, Table 14-4.1.5*

Compared to the placebo group, subjects in the AMG 531 group reported higher scores indicating better health status on all ITP-PAQ scales from week 1 to 25, except for Work Quality of Life. Although the AMG 531 group reported a greater improvement for 9 of the 10 ITP-PAQ scales, the Physical Health - Activity scale was the only scale that showed a statistically significant difference in means for AMG 531 – placebo of 21.98 (p = 0.0164). All other mean change scores for the PRO questionnaires were similar between treatment groups.

Safety Results: The percentage of subjects experiencing adverse events was similar in the 2 treatment groups: 95% of the placebo group and 100% of the AMG 531 group. A similar percentage of subjects in each group also experienced serious adverse events (15.0% placebo, 11.9% AMG 531). Adverse events that were graded severe occurred in similar a percentage of subjects in each group (25.0% placebo, 19.0% AMG 531), as did adverse events that were graded life-threatening (5.0% placebo, 4.8% AMG 531). No subjects in the placebo group and 1 subject in the AMG 531 group died; the cause of death was intracranial hemorrhage 2 weeks after discontinuation of AMG 531.

The 5 most common adverse events in both treatment groups were fatigue (35.0% placebo, 35.7% AMG 531), contusion (35.0% placebo, 31.0% AMG 531), headache (30% placebo, 26.2% AMG 531), eptistaxis (15.0% placebo, 26.2% AMG 531), and arthralgia (25.0% placebo, 23.8% AMG 531).

Adverse events that occurred at a ≥ 10% higher incidence in the AMG 531 treatment group than placebo were (placebo, AMG 531) dizziness (0%, 16.7%), abdominal pain (0%, 11.9%), shoulder pain (0%, 11.9%), and epistaxis (15.0%, 26.2%).

Adverse events reported by the investigator as related to investigational product occurred in similar proportions of subjects in the placebo group (20.0%) and the AMG 531 group (26.2%). The most common treatment-related events for AMG 531 were headache (2 [10.0%] placebo,

5 [11.9%] AMG 531), arthralgia (0 placebo, 3 [7.1%] AMG 531), and injection site bruising (1 [5.0%] placebo, 2 [4.8%] AMG 531).

One subject (5%) in the placebo group and 2 subjects (4.8%) in the AMG 531 group withdrew from treatment and from the study because of an adverse event. One subject in the placebo group discontinued due to metastasis to liver of severe severity (subject 351). One subject in the AMG 531 group discontinued due to B-cell lymphoma of life-threatening severity (subject 1958). An additional subject in the AMG 531 group discontinued AMG 531 treatment due to a cerebrovascular accident 3 days after the last (21^{st}) dose of AMG 531 (platelet count was 107 x 10^9/L) (subject 6051). This subject was treated with antiplatelet and antihypertensive therapy for cerebrovascular accident and 10 days later had an intracranial hemorrhage, which ultimately led to death (mentioned above).

Pharmacokinetics Results: Three AMG 531 treated subjects received a dose of 9 to10 µg/kg. These subjects had measurable trough AMG 531 serum concentrations (at 7 days postdose) ranging from 20.9 to 162 pg/mL.