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) Refractory 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 (durable platelet response) of AMG 531 vs placebo
Study Sponsor:	Amgen Inc., Thousand Oaks, CA USA
Study No.:	20030105
IND No.:	10205
Study Phase:	Phase 3
Study Initiation Date:	29 March 2005 (first subject randomized)
Study Completion Date:	05 September 2006 (last subject visit)
Principal Investigators:	Multicenter study conducted in 32 centers in the United States, the United Kingdom, France, the Netherlands, and Spain.
Clinical Study Manager:	Reggie Kelly Amgen Inc., Thousand Oaks, CA USA
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:	13 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) Refractory to Splenectomy

Investigator(s) and Study Center(s): Thirty-five study centers in the United States, the United Kingdom, France, the Netherlands, and Spain participated in the study, 32 of which enrolled subjects.

Publication(s): None

Study Period: 29 March 2005 (first subject randomized) to 05 September 2006 (last subject visit).

Development 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 treating adult thrombocytopenic subjects with ITP refractory to 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 (PK) sample was drawn once a subject reached a dose of $\geq$ 10 µg/kg. The sample was drawn before dosing. Additional PK 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 63 subjects were enrolled: 21 received placebo and 42 received AMG 531.

Sex: placebo: 11 (52.4%) women, 10 (47.6%) men.
AMG 531: 27 (64.3%) women, 15 (35.7%) men.
Age: placebo: median 56.0 years (range 26 to 72 years)
AMG 531: median 50.5 years (range 27 to 88 years)
Ethnicity (Race): placebo: 19 subjects (90.5%) white; AMG 531 34 subjects (81.0%) 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 at al, 1996). Subjects > 60 years of age had to have a documented history of chronic ITP with bone marrow confirmation. All subjects had to have had a splenectomy for the treatment for ITP ≥ 4 weeks before screening. Subjects were required to be refractory to splenectomy as follows: platelet count (mean of 3 counts taken during the screening and pre-treatment periods) was required to be ≤ 30 x 10^9/L, with no individual count > 35 x 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 were excluded. The only concurrent ITP treatments permitted were corticosteroids, azathioprine, and/or danazol administered at a constant dose and schedule. Subjects who received IVIg 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: AMG 531 was provided as a sterile, white, preservative-free, lyophilized powder in 5.0-mL single-use glass vials, to be reconstituted with 1.2 mL sterile water for injection to a concentration of 0.5 mg/mL. 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 (x 10^9/L)	**Action**
Start-up (to a platelet count of > 50 x 10^9/L):	
≤ 10	Dose increase by 2 µg/kg every week 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 ≤ 200 x 10^9/L.

Duration of Treatment: 24 weeks

Reference Therapy, Dose and Mode of Administration: Placebo was 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). A weekly platelet response was defined as a platelet count $\geq 50 \times 10^9$/L on a weekly scheduled dose day during the period from week 2 to week 25. A subject could not have a weekly response within 8 weeks after receiving any 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) subscales and summary scores, Short-form 36 (SF-36) scales and summary scores, EuroQol-5D (EQ-5D), and Patient Global Assessment.

Statistical Methods: The incidences of durable and overall platelet responses, proportion of subjects requiring rescue medication, and incidence of achieving stable dose were 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, the 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: A total of 30 centers randomized 63 subjects: 21 to placebo and 42 to AMG 531. All randomized subjects received at least 1 dose of investigational product. All subjects were included in the full, efficacy, and safety analysis datasets. More than half of the subjects in the placebo group (12 subjects; 57.1%) discontinued treatment, whereas 2 (4.8%) subjects in the AMG 531 group discontinued treatment. Subjects who discontinued

investigational product were asked to remain in the study, and similar proportions of subjects in the 2 treatment groups (19 [90.5%] placebo, 40 [95.2%] AMG 531) 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). No subjects in the placebo group and 16 subjects (38.1%) in the AMG 531 group achieved a durable platelet response ($p = 0.0013$). The analyses of additional secondary efficacy endpoints and descriptive secondary endpoints also demonstrated the efficacy of AMG 531. No subjects in the placebo group and 33 subjects in the AMG 531 group (78.6%) 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 0.2 weeks, SD 0.5 weeks for placebo; mean 12.3 weeks, SD 7.9 for AMG 531 ($p < 0.0001$).

A total of 12 (57.1%) subjects in the placebo group and 11 (26.2%) subjects in the AMG 531 group received rescue medication during the treatment period ($p = 0.0175$). The placebo group had 80 occurrences of rescue medication use (0.17 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 63 occurrences (0.06 per subject*weeks). A total of 13 (31.0%) subjects were able to achieve a durable platelet response at a stable dose of AMG 531 (no subject in the placebo group) ($p = 0.0046$) ("stable dose" was defined as a dose maintained within ± 1 µg/kg during the last 8 weeks of treatment).

Table 2-1. Results of Key Efficacy Endpoints

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.
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

Six subjects in the placebo group and 12 subjects in the AMG 531 group were receiving concurrent ITP therapies at baseline. At week 13, 1/6 placebo subject (16.7%) had a > 25% reduction in concurrent ITP treatment, while 5/12 AMG 531 subjects (41.7%) had a > 25% reduction and an additional 5/12 AMG 531 subjects (41.7%) had discontinued all concurrent ITP therapies. At week 25, 1 placebo subject (16.7%) had a > 25% reduction in concurrent ITP treatment, while 4 AMG 531 subjects (33.3%) had a > 25% reduction and an additional 8 AMG 531 subjects (66.7%) had discontinued all concurrent ITP therapies.

Platelet counts increased above their baseline values by ≥ 20 x 10^9/L for 5 (23.8%) subjects in the placebo group and 37 (88.1%) subjects in the AMG 531 group ($p < 0.0001$). The mean change from baseline in platelet counts showed no change for the placebo group and a rapid increase followed by steady maintenance above 50 x 10^9/L for the AMG 531 group when rescue medications were excluded from the analysis.

Several scales of the ITP-PAQ indicated a significant positive effect of AMG 531 on measures of PRO as shown by the mean change from week 1 to week 25. The Physical Health – Symptoms scale showed a difference in means for AMG 531 – placebo of 10.55 ($p = 0.0205$), indicating that subjects receiving AMG 531 perceived an improvement in their physical symptoms. The Physical Health – Bother scale was also significantly improved relative to placebo ($p = 0.0091$), as were Social Quality of Life ($p = 0.0172$) and Women's Reproductive Health ($p = 0.0272$).

Safety Results: Similar proportions of subjects (95.2% placebo, 100% AMG 531) experienced adverse events. Adverse events that were grade 3 (severe) or worse in severity occurred in similar proportions of subjects (38.1% placebo, 35.7% AMG 531), as did serious adverse events (23.8% placebo, 21.4% AMG 531). The most common adverse events in both treatment groups were (placebo, AMG 531) headache (33.3%, 42.9%), epistaxis (33.3%, 38.1%), and fatigue (23.8%, 31.0%).

Adverse events that occurred at a ≥ 10% higher incidence in the AMG 531 treatment group than placebo were (placebo, AMG 531) myalgia (0%, 21.4%), dizziness (0%, 16.7%), pharyngolaryngeal pain (0%, 14.3%), pyrexia (0%, 14.3%), arthralgia (14.3%, 28.6%) insomnia (4.8%, 19%), and diarrhea (9.5%, 21.4%). None of these events were serious. One subject discontinued AMG 531 treatment as a result of arthralgia and myalgia of moderate severity, and another AMG 531 subject experienced arthralgia and myalgia that were severe (both considered treatment-related). Headache occurred in 7 (33.3%) placebo subjects and 18 (42.9%) AMG 531 subjects and was judged treatment-related in 1 (4.8%) placebo subject and 11 (26.2%) AMG 531 subjects. One subject in the placebo group and 5 subjects in the AMG 531 group experienced a headache that was grade 3 (severe) in severity. In 4 of the 5 AMG 531 subjects the severe headache was considered treatment-related. Diarrhea was severe in 1 AMG 531 subject.

Adverse events reported by the investigator as related to investigational product occurred more frequently in the AMG 531 group (54.8%) than the placebo group (33.3%). The most common treatment-related events were headache (1 [4.8%] placebo, 11 [26.2%] AMG 531), and myalgia (0 placebo, 7 [16.7%] AMG 531).

Three subjects (14.3%) in the placebo group and no subjects in the AMG 531 group died. One subject died of pneumonia after the end of the study and ≥ 30 days after the last dose of investigational product (5 weeks after the end of the study and 24 weeks after the last dose of investigational product, following hospitalization due to intracranial hemorrhage). The other deaths were due to pulmonary embolism and cerebral hemorrhage.

Eight subjects had a total of 12 events that met the criteria for a clinically significant bleeding event: 4 subjects in each treatment group (19% placebo, 9.5% AMG 531).

One subject treated with AMG 531 discontinued the study due to an adverse event of bone marrow disorder rated severe. This subject, who entered the study with an observation of reticulin fibrosis of the marrow, experienced an increase of reticulin on study. The subject never responded on study. There was no evidence of increased collagen, and the increase in bone marrow reticulin subsequently improved after AMG 531 was discontinued; no clinical sequelae were associated with this adverse event. One additional AMG 531 subject discontinued treatment due to arthralgia and myalgia of moderate severity (mentioned above). No placebo subjects were withdrawn from treatment or from the study due to an adverse event.

Pharmacokinetics Results:

AMG 531-treated subjects (n=7) who received a dose of 9 to 15 µg/kg had measurable trough AMG 531 serum concentrations (at 7 days postdose), ranging between 20.8 and 92.7 pg/mL.