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Drug: Romiplostim (AMG 531)
Clinical Study Report: 20050159
Date: 09Mar2007

Protocol Title:	An Open Label, Sequential Cohort, Dose Escalation Study to Evaluate the Safety and Efficacy of AMG 531 in Thrombocytopenic Subjects with Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS)
Investigational Product:	AMG 531
Indication:	Thrombocytopenia associated with MDS
Brief Description:	This ongoing, multicenter, open-label, sequential cohort dose escalation study was designed to evaluate the safety and efficacy of AMG 531 in thrombocytopenic subjects with low or intermediate-1 risk MDS.
Study Sponsor:	Amgen Inc., Thousand Oaks, CA USA
Protocol No.:	20050159
IND No.:	12544
Study Phase:	Phase 1/2
Study Initiation Date:	15 February 2006 (first subject enrolled)
Study Completion Date:	Ongoing; this report presents an interim analysis of data obtained through 15 September 2006
Principal Investigators:	This ongoing multicenter study is being conducted at 10 centers in the United States and European Union. A list of study centers and principal investigators is on file at Amgen.
Good Clinical Practice:	This study was conducted in accordance with the principles of the Food and Drug Administration (FDA) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents will be retained in accordance with ICH GCP.
Report Date:	09 March 2007

Drug: Romiplostim (AMG 531)
Clinical Study Report: 20050159
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1. 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: An Open Label, Sequential Cohort, Dose Escalation Study to Evaluate the Safety and Efficacy of AMG 531 in Thrombocytopenic Subjects with Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS)

Investigator(s) and Study Center(s): This study is being conducted at 10 sites in the United States and European Union. Five sites have enrolled subjects at the time of data cutoff. A list of investigators and study centers is on file at Amgen.

Publication(s): None

Study Period: The first subject enrolled on 15 February 2006, and the study is currently ongoing. Data cutoff for this report occurred on 15 September 2006.

Development Phase: Phase 1/2

Introduction and Objectives: AMG 531 is an Fc fusion protein (peptibody) that stimulates platelet production by a mechanism similar to that of endogenous thrombopoietin (eTPO), but has no sequence homology to eTPO. AMG 531 has been shown to be well tolerated and effective in increasing platelet counts in healthy volunteers and in patients with immune (idiopathic) thrombocytopenic purpura (ITP).

This abbreviated clinical study report provides the interim safety and efficacy data for subjects up to 15 September 2006 based on Amgen Protocol 20050159 dated 15 November 2005. The primary objective of this study was to evaluate the safety and tolerability of AMG 531 in thrombocytopenic subjects with low or intermediate-1 risk MDS. The secondary objective was to evaluate the platelet response of thrombocytopenic subjects with low or intermediate-1 risk MDS who were receiving AMG 531.

Methodology: This is an ongoing, phase 1/2, multicenter, open-label, sequential cohort, dose escalation study designed to evaluate the safety and efficacy of weekly administration of AMG 531 in thrombocytopenic subjects with low or intermediate-1 risk MDS.

Enrollment and Treatment Phases: Subjects were enrolled sequentially into 1 of 4 dose cohorts (minimum of 5 subjects in each cohort) at 300, 700, 1000, and 1500 µg. Subjects received AMG 531 subcutaneously, once weekly for 3 consecutive weeks. Follow-up assessments were conducted on week 4. At this point subjects may elect to continue AMG 531 at the same weekly dose in a treatment extension phase.

At the completion of a cohort, the Safety Review Panel (SRP) recommended whether to proceed to the next dose cohort, add an intermediate dose cohort, or enroll additional subjects into an existing or previous dose cohort.

Dose escalation continued until > 2 out of 5 subjects in a cohort experienced a dose limiting toxicity (DLT [defined as treatment related grade 3 or 4 adverse event per Common Terminology Criteria for Adverse Events]), or when the 1500 µg cohort has been enrolled. In this study, a platelet count ≥ 600 x 10^9/L was considered a DLT. Doses were allowed to be withheld in the treatment period when deemed necessary by the investigator because of adverse events or DLTs. If 2 of 5 subjects experienced a DLT, the cohort was expanded by adding 5 additional subjects to the cohort. Dose escalation continued if < 3 of the 10 subjects in the expanded cohort experienced a DLT.

Once the DLT dose had been identified, up to 20 additional confirmatory subjects were enrolled into the lower dose cohort recommended by the SRP, the maximum tolerated dose (MTD) cohort. The MTD was the highest dose where < 34% of subjects experienced grade 3 or 4 adverse event related to AMG 531

and had an acceptable safety profile in the treatment extension phase. Subject enrolled in the MTD cohort were administered the MTD of AMG 531 subcutaneously once weekly for 3 consecutive weeks. At least 5 subjects enrolled into the MTD must have had a baseline platelet count ≤ 20 x 10^9/L.

Treatment Extension Phase: Upon completing treatment (at week 3), subjects from all dose cohorts could continue to receive AMG 531 by enrolling into the treatment extension phase of the study which began at week 4 in their respective dose cohorts. Subjects who did not elect to continue in the extension completed their end of study visit on week 4. Those who continued to receive AMG 531 in the treatment extension phase and did not achieve a complete response (platelet count ≥ 100 x 10^9/L) could have had their dose increased to the next highest dose that had already been tested and approved by the SRP. Subjects in the MTD cohort were not allowed to participate in the treatment extension phase and the extension arm was closed when all subjects in the MTD cohort completed their week 4 visit.

Number of Subjects Planned: A total of 30 subjects (up to a total of 55 if intermediate doses were explored) were planned for this study.

Number of Subjects Enrolled:

Sex: 15 (75%) men, 5 (25%) women

Median (range) Age: 75.5 (48 to 84) years

Ethnicity (Race): 19 (95%) white and 1 (5%) Hispanic

Diagnosis and Main Criteria for Eligibility: Men or women ≥ 18 years diagnosed with MDS (using the World Health Organization classification), with low or intermediate-1 risk MDS (based on IPSS), and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 were eligible for this study. Subjects needed to have adequate liver function (serum bilirubin ≤ 1.5 times the laboratory normal range [except for subjects with confirmed diagnosis of Gilbert's Disease], ALT ≤ 3 times the laboratory normal range, and AST≤ 3 times the laboratory normal range); serum creatinine concentration ≤ 2 mg/dL (≤ 176.8 µmol/L); and the mean of 2 platelet counts taken within 1 week before dosing ≤ 50 x 10^9/L, with no individual count > 55 x 10^9/L (5 patients enrolled in the MTD cohort were to have platelet counts ≤ 20 x 10^9/L).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: AMG 531 was presented as a lyophilized, preservative-free, white powder in a sterile 5mL single use glass vial containing a protein concentration of 500 µg/mL of 10mM histidine, 4.0% mannitol, 2.0% sucrose, 0.004% polysorbate, and pH 5.0 when reconstituted with 1.2 mL of sterile water for injection. AMG 531 was administered subcutaneously once weekly at 300, 700, 1000, and 1500 µg. The manufacturing lots of AMG 531 used in this study is on file at Amgen.

Duration of Treatment: The planned duration of treatment was 3 weeks for the treatment period and up to 1 year for the treatment extension phase.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: No reference therapy was used in this study.

Study Endpoints

Primary Endpoint: The primary endpoint was the incidence of adverse events including evaluation of antibody status. The incidence of treatment related adverse events was used to define the MTD of AMG 531 in thrombocytopenic subjects with low or intermediate-1 risk MDS. The MTD was defined as the dose where < 34% of subjects experienced related grade 3 or 4 toxicity.

Secondary Endpoint: The secondary endpoint was the proportion of subjects who achieved a complete or major platelet response during the treatment period by cohort.

- complete platelet response: increase of platelet count to ≥ 100 x 10^9/L
- major platelet response: increase of absolute platelet count by ≥ 30 x 10^9/L

Statistical Methods: Descriptive statistics for demographic and baseline characteristics, safety and efficacy were summarized for all subjects. For categorical variables, the number and percentage of subjects in each category were summarized. Continuous variables were summarized by n, mean, standard deviation (SD), median, Q1 (25^{th} percentile), Q3 (75^{th} percentile), minimum, and maximum values.

Summary of Results:

Subject Disposition: At time of data cutoff, 20 subjects had been enrolled sequentially and all received at least 1 dose of AMG 531. Of these 20 subjects, 6 were enrolled in the 300 µg cohort, 6 in the 700 µg cohort, and 8 in the 1000 µg cohort. Screening continued while dose escalation decisions were made; thus, more than 5 subjects were enrolled per cohort. At the time of data cutoff, all subjects in the 300 and 700 µg cohorts and 7 in the 1000 µg cohort had completed the treatment period and had progressed to the treatment extension phase. Of these 19 subjects, 16 continued into the extension phase and 3 subjects have discontinued during participation in the extension phase. One subject (1590101) in the 300 µg cohort died from an unrelated event of cerebral hemorrhage and 2 subjects (1590108 and 1590109) discontinued from the 700 µg cohort due to disease progression (to AML) and to administrative decision. None of the subjects had completed the study at the time of data cutoff date for this report.

Efficacy Results: Platelet response in this study was defined using a modification of the International Working Group as follows:

- Complete platelet response: increase of platelet count to $\geq 100 \times 10^9$/L
- Major platelet response: increase of absolute platelet count by $\geq 30 \times 10^9$/L

Any subject receiving a platelet transfusion was considered a non-responder. A summary of subjects who had a complete or major response at time of data cutoff is summarized in Section **Error! Reference source not found.**. The number of subjects who had a complete or major platelet response were 3 (50%) for the 300 µg cohort, 3 (50%) for the 700 µg cohort and 2 (29%) for the 1000 µg cohort.

Safety Results: The results from the first 3 cohorts of this study in subjects with IPSS low or intermediate-1 MDS suggested that AMG 531 is well tolerated. Seventeen of 20 (85%) subjects experienced at least 1 adverse event. Most events were mild to moderate in severity and no dose-related trends were observed. Serious adverse events occurred in 3 subjects, but none were considered to be treatment-related by the investigator. Four (20%) subjects experienced one or more treatment-related adverse events of influenza like illness, injection site hematoma, injection site hemorrhage, hypomagnesemia, and dizziness. There were no treatment-related severe, life-threatening, fatal, or serious adverse events. An unrelated fatal event of cerebral hemorrhage occurred in Subject 1590101 of the 300 µg cohort and is discussed in Section **Error! Reference source not found.**. No subjects had withdrawn from the study due to an adverse event as of the data cutoff date (15 September 2006). One DLT (platelet count $\geq 600 \times 10^9$/L) was reported in the 700 µg cohort. The MDT has not been determined and the study is ongoing.

2. SYNOPSIS

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

Name of Finished Product: Romiplostim

Name of Active Ingredient: Romiplostim

Title of Study: An Open Label, Sequential Cohort, Dose Escalation Study to Evaluate the Safety and Efficacy of AMG 531 in Thrombocytopenic Subjects with Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS)

Investigator(s) and Study Center(s): This study was conducted at 19 centers in the United States and European Union. Investigators and study centers are listed in Appendix 2.

Publication(s):

Kantarjian HM, Giles FJ, Fenaux P, Becker PS, Boruchov AM, Bowen DT, Hellström-Lindberg E, Larson RA, Lyons RM, Muus P. Evaluating safety and efficacy of AMG 531 for the treatment of thrombocytopenic patients with myelodysplastic syndrome (MDS): Preliminary results of a phase 1/2 study [abstract]. *J Clin Oncol* 2007;25(18S):7032.

Kantarjian H, Fenaux P, Sekeres MA, Becker P, Boruchov A, Bowen D, Larson R, Lyons R, Muus P, Shammo J, Ehrman M, Hu K, Nichol J. Phase 1/2 study of AMG 531 in thrombocytopenic patients (pts) with low-risk myelodysplastic syndrome (MDS): update including extended treatment [abstract]. *Blood* 2007;110(11):81a.

Study Period: The first subject in Part A enrolled on 15 February 2006. The last visit in Part A took place on 23 January 2008. The first subject in Part B enrolled on 13 March 2007. The last visit in Part B took place on 21 May 2008.

Development Phase: Phase 1/2

Introduction and Objectives: AMG 531 (romiplostim) is an Fc fusion protein (peptibody) that stimulates platelet production by a mechanism similar to that of endogenous thrombopoietin (eTPO), but has no amino acid sequence homology to eTPO. Romiplostim has been shown to be well tolerated and effective in increasing platelet counts in healthy volunteers and in patients with immune (idiopathic) thrombocytopenic purpura (ITP).

The primary objective of this study was to evaluate the safety and efficacy of romiplostim in thrombocytopenic subjects with low or intermediate-1 risk MDS. The secondary objectives were (Part A) to evaluate platelet response and (Part B) to assess the pharmacodynamics (PD) and pharmacokinetics (PK) of 3 dosing schedules of romiplostim administered via subcutaneous (SC) or intravenous (IV) administration.

Methodology: The study had 3 parts: Part A (4 weeks), Part B (8 weeks), and a treatment extension phase (up to 1 year). Subjects could participate in either Part A or Part B, and then could choose to enter the treatment extension phase. Subjects participating in Part A were not eligible for participation in Part B.

Part A: Part A was a phase 1/2, multicenter, open-label, sequential-cohort, dose-escalation study designed to assess the safety and efficacy of weekly administrations of romiplostim in thrombocytopenic subjects with IPSS low-risk or intermediate-1 risk MDS not currently receiving treatment for their MDS. Subjects with MDS and an International Prognostic Scoring System (IPSS) rating of low or intermediate-1 receiving only supportive care for their MDS were appropriate to screen for the study. Eligible subjects had to have a mean of 2 platelet counts $\leq 50 \times 10^9$/L.

Subjects were enrolled sequentially into 1 of 4 dose cohorts (minimum of 5 subjects in each cohort) at 300, 700, 1000, and 1500 µg. Subjects received romiplostim SC, once weekly (QW) for 3 consecutive weeks with follow-up assessments at week 4. At this point subjects could elect to continue romiplostim at the same weekly dose in the treatment extension.

At the completion of a cohort, the Safety Review Panel (SRP) recommended whether to proceed to the next dose cohort, add an intermediate dose cohort, or enroll additional subjects into an existing or previous dose cohort.

Dose escalation was to continue until ≥ 2 out of 5 subjects in a cohort experienced dose-limiting toxicity (DLT)—defined as a treatment-related grade 3, 4, or 5 adverse event per Common Terminology Criteria for Adverse Events—or when the 1500-µg cohort was enrolled. A platelet count ≥ 600 x 10^9/L was considered a DLT. Doses could be withheld in the treatment phase when deemed necessary by the investigator because of adverse events or DLTs.

After dose escalation was complete, up to 20 additional confirmatory subjects were to be enrolled at the maximum tolerated dose (MTD). The MTD was the highest dose with treatment-related grade 3 or 4 adverse events in <34% of subjects in the treatment period and an acceptable safety profile in the treatment extension phase. Subjects enrolled in the MTD cohort were to receive the MTD of romiplostim once weekly for 3 consecutive weeks. At least 5 subjects enrolled at the MTD were required to have a baseline platelet count ≤ 20 x 10^9/L.

Part B: Part B was a phase 2, multicenter, open-label study of romiplostim in thrombocytopenic subjects with MDS. After all subjects in Part A completed the 4-week treatment period, the SRP was to review the safety and efficacy data and select a dose (or doses) for use in Part B. Part B explored the PK and PD of 3 schedules of romiplostim administered via SC and IV injection. Subjects with MDS and an IPSS rating of low or intermediate-1 receiving only supportive care for MDS were appropriate to screen. Eligible subjects were required to have a mean platelet count ≤ 50 x 10^9/L at baseline.

Initially 25 subjects were to receive romiplostim injection SC/QW (n=10), SC every 2 weeks (SC/Q2W; n=10), or IV/Q2W (n=5). The dose was 750 µg. After reviewing the data from the initial 3 cohorts, the SRP could expand the IV/Q2W cohort to 10 subjects, and/or add an every-3-week (Q3W) cohort, beginning with 5 subjects and potentially expanded to 10 subjects.

Treatment Extension Phase: Subjects could continue to receive weekly injections of romiplostim in the extension phase for up to 1 year after completing participation in either Part A or Part B. Subjects who did not achieve a complete response (increase of platelet count to ≥ 100 x 10^9/L) in the extension phase could increase their romiplostim dose to a higher dose that had already been tested and approved by the SRP. The end-of-treatment visit was conducted 1 week after the last dose and the end-of-study visit was conducted 4 weeks after the last dose.

Number of Subjects Planned:

Part A: A total of 30 subjects (up to 55 if intermediate doses were explored) were planned.

Part B: Initially 25 subjects were planned; up to 40 subjects could be enrolled depending upon cohort expansion/addition.

Number of Subjects Enrolled:

Part A:

Sex: 32 male, 12 female

Age: Mean (SD), 70.4 (12.2) years

Ethnicity (Race): 89% white, 5% Hispanic, 5% Asian, 2% black

Part B:

Sex: 22 male, 6 female

Age: Mean (SD), 71.0 (7.7) years

Ethnicity (Race): 86% white, 4% black, 11% other

Diagnosis and Main Criteria for Eligibility: For both Part A and Part B, men or women ≥ 18 years of age diagnosed with MDS (using the World Health Organization classification), with low-risk or intermediate-1 risk MDS (based on IPSS), and an Eastern Cooperative Oncology Group

(ECOG) performance status of 0-2 were eligible for this study. Subjects needed to have adequate liver function (serum bilirubin ≤ 1.5 times the laboratory normal range [except for subjects with confirmed diagnosis of Gilbert's Disease], ALT ≤ 3 times the laboratory normal range, and AST≤ 3 times the laboratory normal range); serum creatinine concentration ≤ 2 mg/dL (≤ 176.8 µmol/L); and the mean of 2 platelet counts taken within 1 week before dosing ≤ 50 x 10^9/L, with no individual count > 55 x 10^9/L (5 patients enrolled in the MTD cohort of Part A were to have baseline platelet counts ≤ 20 x 10^9/L).

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number: Romiplostim was presented as a lyophilized, preservative-free, white powder in a sterile 5mL single use glass vial containing a protein concentration of 500 µg/mL [redacted]. In Part A, romiplostim was administered SC/QW at 300, 700, 1000, and 1500 µg. In Part B, romiplostim was administered SC/QW, SC/Q2W, or IV/Q2W at 750 µg. The manufacturing lots of romiplostim used in this study were [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

Duration of Treatment: The planned duration of treatment was 3 weeks of treatment in Part A, 8 weeks of treatment in Part B, and up to 1 year of treatment in the treatment extension phase.

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number: No reference therapy was used in this study.

Study Endpoints

The primary endpoint was the incidence of adverse events, including evaluation of antibody status. The incidence of treatment-related adverse events was used to define the MTD of romiplostim in thrombocytopenic subjects with low-risk or intermediate-1 risk MDS. The MTD was defined as the highest dose with treatment-related grade 3 or 4 adverse events in <34% of subjects in the treatment period and an acceptable safety profile in the treatment extension phase.

A key secondary efficacy endpoint was the proportion of subjects who achieved a complete or major platelet response during the treatment period by cohort:

- *Complete platelet response: increase of platelet count to ≥ 100 x 10^9/L*
- *Major platelet response: increase of platelet count by ≥ 30 x 10^9/L*

Another key secondary endpoint was the proportion of subjects achieving a complete or major platelet response as defined by the modified MDS International Working Group (IWG) Classification (Cheson et al, 2006).

Other secondary efficacy endpoints included assessment of PK parameters of romiplostim in MDS subjects at the recommended dose (Part B only), the time to the first platelet response, the peak platelet count, and the duration of the platelet response will be summarized by treatment cohort.

Statistical Methods: Descriptive statistics for demographic and baseline characteristics, safety and efficacy were summarized for all subjects. For categorical variables, the number and percentage of subjects in each category were summarized. Continuous variables were summarized by n, mean, standard deviation (SD), median, Q1 (25th percentile), Q3 (75th percentile), minimum, and maximum values. The safety analysis was separate for the treatment phase and the extension phase. The proportion of subjects achieving a complete or major platelet response was summarized for each cohort and a 95% exact binomial confidence interval of the proportion was provided. Descriptive statistics for platelet count change from baseline and the mean of the peak platelet counts were summarized for each cohort. The time to the first platelet response, the peak platelet count, and the duration of response were summarized by treatment cohort. Descriptive statistics were provided for PK observations at each time point and for noncompartmental PK parameters.

Summary of Results:

Subject Disposition:

Part A: A total of 44 subjects were enrolled to study treatment with romiplostim SC/QW 300 µg (n = 6), 700 µg (n = 11), 1000 µg (n = 11), and 1500 µg (n = 16). Two subjects in the 1500-µg cohort discontinued study during the treatment period. A third subject in the 1500-µg cohort completed the treatment period but did not enter the treatment extension. All other subjects, including all subjects in the 300-, 700-, and 1000-µg cohorts and 13 (81%) subjects in the 1500-µg cohort, entered the treatment extension. Thirteen subjects (30%) completed the 1-year treatment extension. Reasons for withdrawal are described in Section 8.4.

Part B: A total of 28 subjects were enrolled to study treatment in the 750 µg SC/QW (n = 11), 750 µg SC/Q2W (n = 12), and 750 µg IV/Q2W (n = 5) cohorts. Six (21%) subjects discontinued the study during the treatment period and 22 (79%) subjects completed the treatment period. Eleven (39%) subjects entered the treatment extension and 6 (21%) subjects completed the extension.

Efficacy Results:

Part A:

Twenty (45%) subjects in Part A had a complete or major platelet response within the initial treatment period, including 50%, 46%, 36%, and 50% of subjects in the 300-, 700-, 1000-, and 1500-µg cohorts, respectively. Observed responses included 14 subjects with complete platelet responses (33%, 27%, 27%, and 38% of subjects in the 300-, 700-, 1000-, and 1500-µg cohorts, respectively) and 6 subjects with major platelet response (17%, 18%, 9%, and 13%, respectively). Overall response rates were 57% (16/28) among subjects with baseline platelet count >20 x 10^9/L and 25% (4/16) among subjects with baseline platelet count ≤20 x 10^9/L.

Platelet response per the modified IWG criteria was maintained for at least 8 weeks in 19 of 41 (46%) subjects overall, including response rates of 50%, 55%, 36%, and 46% in the 300-, 700-, 1000-, and 1500-µg cohorts, respectively. Overall response rates were 43% (6/14) among subjects with baseline platelet count ≤20 x 10^9/L and 48% (13/27) among subjects with baseline platelet count >20 x 10^9/L. Among the subjects who entered the treatment extension, the mean duration of platelet response in the 300-, 700-, 1000-, and 1500-µg cohorts was 31.0, 35.5, 31.8, and 36.0 weeks, respectively.

The overall incidence of platelet transfusion in the treatment period of Part A was 27%, including 33%, 36%, 27%, and 19% of subjects in the 300-, 700-, 1000-, and 1500-µg cohorts, respectively. Platelet transfusion was more common among subjects with baseline platelet count ≤20 x 10^9/L (63%) than among subjects with baseline platelet count >20 x 10^9/L (7%). The total number of platelet transfusions administered was 0, 1-2, 3-4, and 5-10 in 73%, 18%, 7%, and 2% of subjects, respectively.

Platelet counts increased over time in each cohort; there was no evidence of a linear dose-related effect of romiplostim on platelet count. Median peak platelet count in the 300-, 700-, 1000-, and 1500-µg cohorts was 65.5, 73.0, 42.0, and 58.5 x 10^9/L, respectively, for a median change from baseline to the peak platelet count of 38.5, 53.3, 17.3, and 37.7 x 10^9/L, respectively.

Part B:

Fifteen (65%) subjects in Part B had a complete or major platelet response, including 63%, 73%, and 50% of subjects in the 750 µg SC/QW, SC/Q2W, and IV/Q2W cohorts, respectively. Observed responses included 13 subjects with complete platelet responses (50%, 64%, and 50% of subjects in the 750 µg SC/QW, SC/Q2W, and IV/Q2W cohorts, respectively) and 2 subjects with major platelet response (13%, 9%, and 0%, respectively). Overall response rates were 87% (13/15) among subjects with baseline platelet count >20 x 10^9/L and 25% (2/8) among subjects with baseline platelet count ≤20 x 10^9/L.

Platelet response per the IWG criteria was observed in 7 (30%) subjects overall, including response rates of 25%, 36%, and 25% in the 750 µg SC/QW, SC/Q2W, and IV/Q2W cohorts, respectively. Overall IWG response rates were 25% (2/8) among subjects with baseline platelet count ≤20 x 10^9/L and 33% (5/15) among subjects with baseline platelet count >20 x 10^9/L.

Among the subjects who entered the treatment extension, the mean duration of platelet response in the 750 µg SC/QW, SC/Q2W, and IV/Q2W cohorts was 19.5, 9.3, and 9.0 weeks, respectively.

The overall incidence of platelet transfusion in the treatment period was 39%, including 50%, 27%, and 50% in the 750 µg SC/QW, SC/Q2W, and IV/Q2W cohorts, respectively. Platelet transfusion was more common among subjects with baseline platelet count <20 x 10^9/L (63%) than among subjects with baseline platelet count ≥20 x 10^9/L (27%). The total number of platelet transfusions administered was 0, 1-2, 3-4, and 5-10 in 61%, 13%, 9%, and 17% of subjects, respectively.

Median fold change from baseline in platelet count was >1 (ie, platelet count increased) in each cohort at most time points. Median peak platelet count in the 750 µg SC/QW, SC/QW, and IV/Q2W cohorts was 100.0, 111.0, and 83.0 x 10^9/L, respectively, for a median change from baseline to the peak platelet count of 77.5, 84.3, and 57.3 x 10^9/L, respectively.

Pharmacokinetics Results:

Part A:

PK was not assessed in Part A.

Part B:

A total of 327 serum PK samples from 28 subjects were analyzed for romiplostim concentrations. In each of the 2 SC dose cohorts in Part B, the mean (SD) romiplostim concentration-time profiles after the week 1 dose were generally higher than that after the week 7 dose, resulting in mean and median values of C_{max} and AUC_{0-t} that were higher for week 1 than for week 7. Lower trough romiplostim concentrations generally were associated with higher platelet counts.

For the 2 SC dose cohorts in Part B, the mean romiplostim concentration profiles were similar after the dose in week 1 whereas in week 7 the mean romiplostim concentration profile was higher in the SC/QW dosing cohort than in the SC/Q2W dosing cohort. The SC/QW cohort achieved a higher exposure than the SC/Q2W cohort, as indicated by the mean trough concentration profiles. Both cohorts had a median t_{max} of 24 hr after dose in weeks 1 and 7.

When comparing the PK of romiplostim in Q2W dose cohorts, the IV dose cohort had a higher mean concentration profile than the SC dose cohort. Furthermore, the IV dose cohort had higher mean trough concentrations over time than the SC dose cohort.

Safety Results:

Part A:

Of the 44 subjects enrolled in Part A, 43 (98%) had at least one adverse event during the study. Severity of these adverse events was grade 3, 4, and 5 in 36%, 18%, and 9% of subjects, respectively, of which 11%, 7%, and 0% had grade 3, 4, and 5 adverse events that the investigator considered related to romiplostim treatment.

Serious adverse events were reported for 17 (39%) subjects overall, and investigators considered these serious adverse events related to romiplostim in 5 (11%) subjects, all of whom were in the 1500-µg cohort. One (2%) subject in the 1500-µg cohort withdrew from the treatment period due to an adverse event (grade 2, non-serious increase in blast cell count) and 2 (5%) subjects withdrew from the treatment extension due to adverse events (grade 2 granulocytic sarcoma and grade 2 diarrhea; neither was considered related to romiplostim).

Four subjects died during Part A (cerebral hemorrhage, fall, general health deterioration, and MDS disease progression); none of the deaths was considered related to romiplostim.

The most commonly reported adverse events (≥15% overall) were as follows (300, 700, 1000, 1500 µg): fatigue (67%, 46%, 0%, 19%), diarrhea (50%, 9%, 18%, 31%), headache (17%, 27%, 18%, 19%), peripheral edema (50%, 18%, 9%, 13%), hematoma (0%, 18%, 18%, 25%), nausea (0%, 9%, 9%, 31%), back pain (17%, 27%, 27%, 6%), and contusion (33%, 9%, 9%, 19%).

Up to 17% subjects at each visit had positive binding antibodies to romiplostim peptide and up to 11% of subjects had positive binding antibodies to TPO, but no subject had neutralizing antibodies to romiplostim or TPO at any visit.

Part B:

Of the 28 subjects enrolled in Part B, 26 (93%) had at least one adverse event during the study. Severity of these adverse events was grade 3, 4, and 5 in 25%, 7%, and 4% of subjects, respectively, but none of the grade 3, 4, and 5 adverse events were considered related to romiplostim treatment.

Serious adverse events were reported for 5 (18%) subjects overall and investigators considered 1 of these adverse events to be related to romiplostim treatment (hypersensitivity in a subject in the IV/Q2W cohort). The overall incidence of treatment-related adverse events was 18%, none of which were reported during the treatment extension. One subject withdrew from the treatment period due to an adverse event. No subject withdrew due to an adverse event during the treatment extension.

One subject in Part B died (subarachnoid hemorrhage); the death was not considered related to romiplostim.

The most commonly reported adverse events (≥15% overall) were (750 µg SC/QW, 750 µg SC/Q2W, 750 µg IV/Q2W) fatigue (36%, 8%, 0%) and headache (36%, 8%, 0%).

Up to 25% subjects at each visit had positive antibodies to romiplostim peptide and up to 25% had antibodies to TPO, but no subject had neutralizing antibodies to romiplostim or TPO at any assessment.

As evaluated by WHO criteria (bone marrow or peripheral blast cells ≥ 20% [Vardiman et al, 2002] and persisting for at least 4 weeks after withdrawal of study drug, or evidence of chloroma), 3 subjects were identified as having progressed to AML (2 in Part A [[redacted], [redacted]] and 1 in Part B [[redacted]]). In addition, 4 subjects (all in Part A) had transient increases in blast cells to ≥ 20% that subsequently fell to below 20% ([redacted], [redacted], [redacted], [redacted]), and 1 subject from Part A (with monocytosis at baseline) developed CMML ([redacted]).

Conclusions:

Romiplostim administered by SC or IV injection generally was well tolerated, with few DLTs, withdrawals due to adverse events, or treatment-related serious adverse events.

The overall rate of complete or major platelet responses during the initial treatment period was 45% with QW dosing for 3 weeks and 65% with QW or Q2W dosing for 8 weeks. Response rates were similar across dosing cohorts in Part A and they appeared to be greater with SC dosing than with IV dosing in Part B. However, comparisons of response rates across dosing cohorts or across phases of the study were limited by the small sample size. Additionally, many subjects received platelet transfusions, potentially confounding the study findings. Ultimately, the absence of a control group limits the ability to reach conclusions about efficacy.

The PK analyses suggested that IV dosing achieved a higher exposure than SC dosing at Q2W schedule. Subcutaneous dosing of romiplostim QW resulted in a higher exposure than Q2W dosing.

The results of this study suggest romiplostim 750 µg weekly SC is an appropriate starting dose for further clinical study in patients with MDS and thrombocytopenia.