17 December 2015
EMA/CHMP/817019/2015 adopted
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nplate

International non-proprietary name: romiplostim

Procedure No. EMEA/H/C/000942/II/0051

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	adverse drug reaction
AMG 531	romiplostim
AE	adverse event
CI	confidence interval
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ITP	immune thrombocytopenic purpura
IV	intravenous(ly)
KM	Kaplan/Meier
MAA	marketing authorization application
MAH	marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
PAM	Post-authorization measure
Q1	25th percentile
Q3	75th percentile
SAE	severe adverse event
SmPC	Summary of Product Characteristics
SMQ	standardized Medical Dictionary for Regulatory Activities query
SOC	standard of care
TAE	treatment related adverse event
TPO	thrombopoietin
WBC	white blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 12 March 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include second line treatment of all non-splenectomised patients (including those without a contraindication to surgery); as a consequence, section 4.1 of the SmPC has been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in Croatia and Italy in the Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Nplate was designated as an orphan medicinal product EU/3/05/283 on 27 May 2005. Nplate was designated as an orphan medicinal product in the following indication: idiopathic thrombocytopenic purpura.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0114/2014 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0114/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Arantxa Sancho-Lopez Co-Rapporteur: Pieter de Graeff

Timetable	Actual dates
Submission date	12 March 2015
Start of procedure	28 March 2015
CHMP Co-Rapporteur Assessment Report	28 May 2015
CHMP Rapporteur Assessment Report	3 June 2015
CHMP members comments	15 June 2015
CHMP Rapporteurs joint Assessment Report	22 June 2015
Request for supplementary information (RSI)	25 June 2015
CHMP Rapporteurs joint response Assessment Report	02 December 2015
CHMP members comments	07 December 2015
CHMP Opinion	17 December 2015

2. Scientific discussion

2.1. Introduction

Immune (idiopathic) thrombocytopenic purpura (ITP) is an autoimmune disease characterized by platelet destruction caused by antiplatelet autoantibodies. In adults, chronic ITP is more common in women than men (approximately 2:1, respectively) and rarely remits spontaneously. It is classified by duration into newly diagnosed, persistent (3-12 months duration) and chronic (≥ 12 months duration). ITP in adults typically has an insidious onset with no preceding viral or other illness and it normally follows a chronic course.

In Europe, adult ITP has an incidence of 1.6 to 3.9 cases per 100,000 per year with increasing incidence with older age and equal for the sexes except in the mid-adult years (30-60 years), when the disease is more prevalent in women. Childhood ITP has an incidence of between 1.9 and 6.4 per 100,000 per year with equal distribution between the sexes.

The diagnosis of ITP can be difficult because of the variety of presentations and lack of specific criteria. The only consistent abnormalities are microangiopathic haemolytic anaemia (with red-cell fragmentation), and thrombocytopenia, features that can also occur in other conditions. Neurologic and renal abnormalities and fever can also occur. The onset of the disease is often insidious because history and physical examination are normal except for symptoms that accompany platelet disorders (purpura, epistaxis, and gingival bleeding are common). In general, ITP is defined by a low platelet count, normal bone marrow, and the absence of other causes of thrombocytopenia.

According to current guidelines the therapeutic goal is to avoid or defer the risks of more toxic treatments (eg splenectomy or immunosuppression), reduce corticosteroid exposure to minimum levels and for the shortest time and achieve long-lasting responses (EMA/CHMP/153191/2013, 2014).

Splenectomy has been utilized to treat immune thrombocytopenia since the early 1900s and remained the 'first-line, gold standard procedure' until the 1950s, when steroids were introduced . Splenectomy has been the standard second-line treatment for adults with ITP since. It remains the treatment option with the highest overall success rate, with approximately two thirds of patients remaining in clinical remission 5-10 years after splenectomy. A systematic review of 135 case-series published between 1966 and 2004 revealed a complete response rate of 66%, with a median duration of follow-up of 28 months (range, 1-153 months) Kojouri et al, 2004. Also, a > 70% probability of maintaining a response after 5 years was found from follow-up of 402 splenectomized patients (Vianelli, et al, 2005). There are near-term and perioperative complications (general anesthesia, bleeding and thrombosis, as well as postoperative pain, pneumonia and atelectasis, wound/other infection and ileus) and longer-term complications, Risk of Infection, Vascular Complications, Mortality and Relapse.

Even though splenectomy remains an appropriate treatment, the frequency of splenectomy as treatment for ITP in adults seems to be decreasing. Older cohorts described in the literature describe the splenectomy rate at 50 to 60% or higher, and in more recent studies it is around 20 to 25% (Rodeghiero and Ruggeri, 2008). The most recent guidelines of ITP (Provan et al, 2010; Neunert et al, 2011) have both recommended splenectomy as a second-line therapy and agree that splenectomy should be delayed at least 6 to 12 months (Provan et al, 2010; Neunert et al, 2011). However, there is no consensus regarding the best sequence of treatments and therapy should be individualized.

Romiplostim (Nplate) is an Fc-peptide fusion protein (peptibody) that increases platelet production via the thrombopoietin (TPO) receptor (also known as cMpl). The peptibody molecule is comprised of human immunoglobulin IgG1 Fc domain, with each single chain subunit covalently linked at the C-terminus to a peptide chain containing 2 TPO receptor-binding domains. Romiplostim has no amino acid sequence homology to endogenous TPO. Romiplostim is produced by recombinant DNA technology in *Escherichia coli* (*E. coli*).

The indication for which it was approved in the EU is as follows:

"Adult chronic immune (idiopathic) thrombocytopenic purpura (ITP): splenectomized patients who are refractory to other treatments (e.g., corticosteroids, immunoglobulins).

Nplate may be considered as second line treatment for adult nonsplenectomized patients where surgery is contra-indicated. "

Following the review of the cumulative evidence presented below, Amgen proposes to revise the currently approved EU Summary of Product Characteristics (SmPC) indication to remove the phrase "where surgery is contra-indicated".

Romiplostim was approved in the European Union (EU) via Centralized Procedure on 04 February 2009. The original marketing authorization application (MAA), submitted in 2008, was based upon 2 pivotal, phase 3 studies of adult subjects with ITP (Studies 20030212 and 20030105) and included supportive data from 7 other clinical studies in subjects with ITP (Studies 20010218, 20000137A, 20000137B, 20050162, 20040209 [ongoing at time of application], 20030213 [ongoing at time of application], and 20050123); a total of 204 subjects with ITP received romiplostim at the time of the MAA submission.

Cumulative evidence is now available from 13 completed clinical studies (including 5 additional studies in adult subjects with ITP [Studies 20060113, 20060131, 20060216, 20080009, and 20080435); data from a total of 1046 subjects [391 splenectomized and 655 nonsplenectomized]) in support of the proposed the use of romiplostim as an effective treatment in increasing and maintaining platelet counts within a therapeutically relevant range in the ITP patient population.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

The applicant justifies the ERA omission in accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 1*, 1 June 2006). Romiplostim meets the criteria for compounds that may be exempted from testing because of their chemical structure and constituents (amino acids and proteins) which should degrade into their amino acid or constitutive elements in the environment. The conclusion of the applicant on environmental risk assessment is accepted. This medicinal product is unlikely to result in significant risk to the environment.

Considering the above data, romiplostim is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

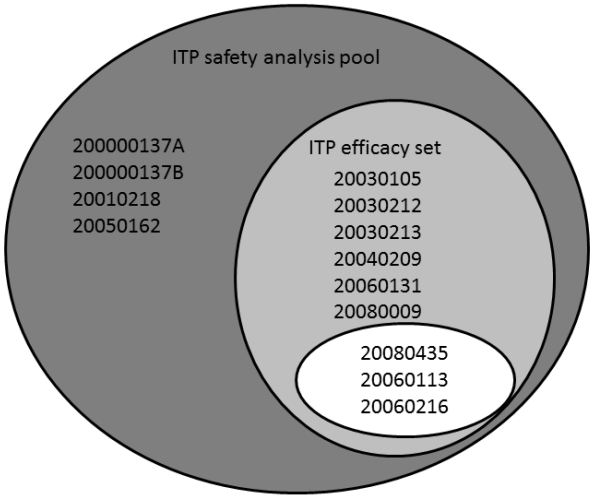
GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

- Tabular overview of clinical studies

In Figure 1 a schematic view is provided of the studies used as the basis of this application. The MAH uses an efficacy set and a safety analysis pool which consist of overlapping studies. Most of the studies have been previously used as part of procedures regarding the MAA of Nplate, type 2 variations, or other procedures regarding romiplostim. Study 20089435, 20060113 and 20060216 have not been previously assessed and are thus included in this assessment in light of the indication extension requested. The safety analysis set consisted of a larger pool of studies due to the addition of Study 20000137A, 20000137B, 20010218 and 20050162 which were not used as part of the efficacy analysis set.

Figure 1. Venn diagram of the studies included in the safety and efficacy analysis pool.



Study numbers of the studies used in the pooled analysis of safety (n=13) and efficacy analysis set (n=9). The white circle indicates studies that have not been assessed as part of a prior procedure.

Table 1. Submission of Final CSRs not included in the Original MAA

Table 1. Submission of Final CSRs not included in the Original MAA

Study Number	CTD Section/ Module CSR Submitted	Sequence Number	Date of Submission
20060113	Submitted with this variation		
20060131	5.3.5.4 final CSR	0078	09 March 2012
20060216	Submitted with this variation		
20080009	5.3.5.2/ cohort 1 report	0074	08 February 2012
	5.3.5.2/ cohort 1 addendum and cohort 2 report	0109	27 June 2013
	5.3.5.2/ final CSR	0131	10 December 2014
20080435	Submitted with this variation		
20030213[a]	5.3.1.2/ subsets A and B only	0000	02 November 2007
	5.3.5.2/ interim CSR	0000	02 November 2007
	5.3.5.2/ final CSR	0078	09 March 2012
20040209[a]	5.3.5.2/ final CSR	0078	09 March 2012

CSR=clinical study report; CTD=common technical document; MAA=marketing authorization application
[a]At the time of the original MAA; Studies 20030213 and 20040209 were ongoing.

2.3.2. Discussion on clinical pharmacology

No new pharmacokinetic/pharmacodynamic studies have been presented. Considering the aim of the current variation, this is considered acceptable (See also clinical efficacy section).

2.4. Clinical efficacy

2.4.1. Main studies

Study 20060216

A Randomized, Double Blind, Placebo Controlled Phase 3 Study Evaluating the Efficacy and Safety of AMG 531 in Thrombocytopenic Japanese Subjects with Immune (Idiopathic) Thrombocytopenic Purpura

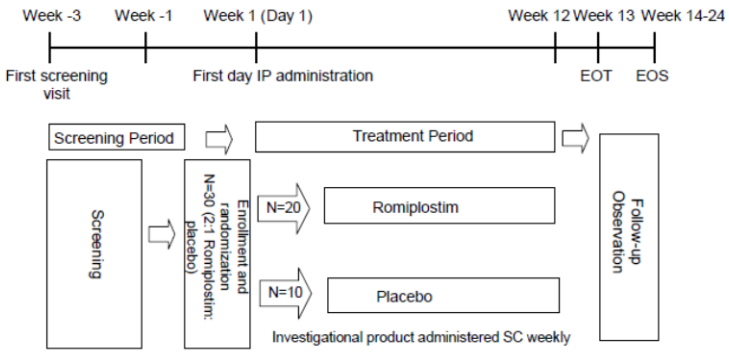
Methods

Study 20060216 was undertaken to evaluate the efficacy and safety of romiplostim in thrombocytopenic Japanese subjects with ITP. This was a phase 3, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of romiplostim in thrombocytopenic Japanese subjects with ITP. The design was similar to that of the 2 pivotal clinical studies that were the basis of the 2007 global marketing applications for romiplostim in adult ITP. Approximately 30 subjects were planned to be enrolled in a 2:1 ratio to romiplostim or placebo (20 subjects for romiplostim and 10 subjects for placebo). Randomization was stratified by splenectomy status (yes or no). Investigational product was administered by SC injection once per week starting at a dose of 3µg/kg. Dose adjustment was allowed throughout the 12-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 10 µg/kg.

After 12 weeks of treatment, a global extension study (Study 20030213) to assess the long-term safety and efficacy of romiplostim is ongoing for subjects who completed another romiplostim ITP study. In Study 20030213, dose adjustment is allowed throughout the treatment period to allow subjects to maintain platelet counts in the targeted therapeutic range. Dose adjustment in the individual subject has resulted in favorable maintenance of the appropriate platelet response.

Eleven sites in Japan participated in this study and each enrolled at least 1 subject.

Figure 7-1. Study Design and Treatment Schema



Study participants

To be eligible for entry into the study, subjects were required to meet the following inclusion criteria during screening:

Inclusion Criteria:

• Japanese patients with diagnosis of ITP according to the diagnostic criteria proposed by Research Committee for Idiopathic Hematopoietic Disorders of the MHLW (revised in 1990) at least 6 months before the first screening visit

• The mean of the 3 scheduled platelet counts taken at the scheduled visits during the screening period was required to be ≤ 30 x 109/L, with no individual count > 35 x 109/L.

• Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

• Subjects were required to be ≥ 20 years of age at the time of providing informed consent

• Subjects must have received at least 1 prior treatment for ITP

• If subjects were known to be *Helicobacter pylori* positive, they must have completed 1 course of *Helicobacter pylori* eradication therapy at least 12 weeks before the first screening visit

• A hemoglobin value taken at scheduled visit during the screening period was required to be ≥ 10 g/dL

• A serum creatinine concentration taken at scheduled visit during the screening period was required to be ≤ 2 mg/dL

• Adequate liver function was required, as evidenced by a total bilirubin taken at scheduled visit during the screening period ≤ 1.5 times of the upper limit of the normal range (except for patients with a confirmed diagnosis of Gilbert's Disease) or an alanine aminotransferase and aspartate aminotransferase taken at the screening visit ≤ 3 times of the upper limit of the normal range.

Exclusion Criteria:

• Any known history of bone marrow stem cell disorder. Any abnormal bone marrow findings other than those typical of ITP

• Any active malignancy. If prior history of cancer other than basal cell carcinoma or cervical carcinoma in situ, no treatment or active disease within 5 years before the first screening visit

• Documented diagnosis of arterial thrombosis (eg, stroke, transient ischemic attack, or myocardial infarction); history of venous thrombosis (eg, deep vein thrombosis, pulmonary embolism) and receiving anticoagulation therapy at the screening visit

• Documented diagnosis of anti-phospholipid antibody syndrome

• Receiving any treatment for ITP except oral corticosteroids, azathioprine, and/or danazol administered at a constant dose and schedule from at least 4 weeks prior to the first screening visit

• Received intravenous immunoglobulin (IV Ig), Anti-D Ig, or any drug administered to increase platelet counts (eg, immunosuppressants except azathioprine) within 2 weeks before the first screening visit

• Had a splenectomy for any reason within 12 weeks before the first screening visit

• Past or present participation in any study evaluating pegacaristim (PEG-rHuMGDF, KRN9000), eltrombopag (SB-497115), recombinant human thrombopoietin (rHuTPO), romiplostim, or other Mpl stimulation product

• Received hematopoietic growth factors (eg, granulocyte colony-stimulating factor, macrophage colony-stimulating factor, erythropoietin, interleukin-11) for any reason within 4 weeks before the first screening visit

• Received any anti-malignancy agents (eg, cyclophosphamide, 6-mercaptopurine, vincristine, vinblastine, Interferon-alfa) for any reason within 8 weeks before the first screening visit

• Received any monoclonal antibody drugs (eg, rituximab) for any reason within 14 weeks before the first screening visit

• Less than 4 weeks before the first screening visit since receipt of any therapeutic drug or device not MHLW-approved for any indication

• Pregnant or breast feeding

• Subjects of reproductive potential not using adequate contraceptive precautions, in the judgment of the investigator

• Known severe drug hypersensitivity

• Concerns for subject's compliance with the protocol

Treatments

Romiplostim was supplied in a 5-mL single-use glass vial as a sterile, white, preservative-free, lyophilized powder. Placebo was supplied as a lyophilized powder in identical 5-mL glass vials to be reconstituted with 1.2 mL of sterile water for injection.

Investigational product was to be administered weekly by SC injection at a starting dose of 3 µg/kg. The maximum permitted dose of investigational product was 10 µg/kg. Dilution was required for injection volumes of ≤ 0.2 mL. Each subject's dose was adjusted based on platelet counts pre- dose.

Table 7-3. Dose Adjustment Rules

Platelet Count ($\times 10^9$/L)	Action
< 10	Dose increased by 1 µg/kg every week when platelet counts are < 10 x 10^9/L. Dose could be increased every week
≥ 10 to < 50	Dose increased by 1 µg/kg after 2 consecutive weeks of platelet counts in this range. Dose could 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 could be reduced every 2 weeks
> 400	Next scheduled dose held, and dose reduced by 1 µg/kg[a] on the next scheduled dose day that the platelet count is ≤ 200 x 10^9/L

[a] If the platelet counts increased to > 400 x 10^9/L with the use of rescue medication, the dose was to remain the same as the previous dose on the next scheduled dose day when the platelet count was ≤ 200 x 10^9/L.

If the current dose was 1 µg/kg and a dose reduction was required, dose administration was to be held until the platelet count fell to < 50 x 109/L. Once the platelet count was < 50 x 109/L, dosing was to resume at a dose of 1 µg/kg using the dose adjustment rules above.

The starting dose of 3 µg/kg was determined based on:

The results of the phase 2 study in Japanese subjects with ITP (Study 20050162). From Study 20050162, the doses tested (1, 3, and 6 µg/kg) were well tolerated and demonstrated dose-dependent effects of increasing platelet counts, and the 6-µg/kg dose was determined to be inappropriate as a starting dose because an excessive increase in platelet counts was observed in 1 subject. The start-up portion of the dose adjustment rules (from initiation of dosing until platelet count is > 50 x 109/L) used in the global phase 3 studies was not used in this study, because the starting dose was 3 µg/kg and thus it was expected that platelet counts > 50 x 109/L could be achieved earlier than in the global phase 3 studies.

Prior and Concomitant Therapy

Treatment of ITP with allowed concurrent oral corticosteroids, azathioprine, and/or danazol was to be continued at a constant dose and schedule throughout the study, except for dose reduction or discontinuation in subjects who experienced intolerable adverse events judged to be related to these drugs.

Throughout the study, rescue medication was permitted for severe bleeding tendency, or if the investigator believed that the subject was at immediate risk of bleeding. Rescue medication was defined as any medication administered for the intended purpose of raising platelet counts. Recommended rescue medications were IV Ig, platelet transfusions, corticosteroids, and an increase in dose or frequency of a concurrent oral corticosteroid, azathioprine, and/or danazol in subjects administered an allowed constant dose. Subjects who required administration of rescue medications during the treatment period were to continue receiving investigational product. Splenectomy therapy was not permitted

Objectives

Primary Objectives: To evaluate the efficacy of romiplostim compared with placebo in thrombocytopenic Japanese subjects with ITP as measured by number of weeks with weekly platelet responses

Secondary Objective: To evaluate the safety of romiplostim

Outcomes / endpoints

The primary endpoint was the number of weeks with weekly platelet response (a platelet count of ≥ 50 x 10^9/L on a weekly scheduled dose day from week 2 to week 13 excluding platelet counts within 4 weeks following the use of rescue medication). For the primary endpoint, a Wilcoxon rank sum test was performed at a 2-sided significance level of 0.05 to compare romiplostim with placebo. In addition, a summary of platelet counts at each timepoint from baseline to week 13 was to be provided by means of numerical summaries and a graph.

Other variables

-Increase in Platelet Count ≥ 20 x 109/L from Baseline

-The proportions of subjects with an increase in platelet count ≥ 20 x 109/L from baseline without the use of rescue medication within 4 weeks before the measurement was to be tested using Fisher's exact test.

-Change from Baseline in Mean of Last 4-week Platelet Counts

The change from baseline in mean of the last 4-week platelet counts of the 2 groups was to be tested with analysis of covariance (ANCOVA) using baseline platelet count as a covariate. The baseline platelet count was the mean of 3 screening and one predose platelet counts. Platelet counts within 4 weeks following the use of rescue medication were to be excluded.

-Rescue Medication

-Weekly Platelet Response Defined as ≥ 50 to ≤ 200 (x 109/L)

In this analysis, a weekly platelet response was defined as a platelet count of ≥ 50 x 109/L to ≤ 200 x 109/L on a weekly scheduled dose day from week 2 to week 13.

The 2 groups were to be tested using Wilcoxon rank sum. Platelet counts within 4 weeks following the use of rescue medication were to be excluded (considered as no response).

Other Efficacy Analyses

The following additional analyses were planned in the protocol and/or the Statistical Analysis Plan:

• Summary statistics exploring the influence of splenectomy status for the primary and the secondary endpoints through subgroup analysis

• Summary statistics exploring the influence of concurrent ITP medication for the primary and the secondary endpoints through subgroup analysis

• Line-connected weekly platelet counts plots with administered doses from baseline to end of study for each individual subject

• Line-connected proportion plots of weekly platelet responses from week 2 to week 13

• Time to first platelet response using Kaplan-Meier estimate and Kaplan-Meier estimates of median, Q1, and Q3

• Summaries of platelet responses defined as a platelet count of ≥ 50 x 109/L and doubling from baseline, ≥ 100 x 109/L, ≥ 200 x 109/L, and ≥ 400 x 109/L

Safety Endpoints

Among others the incidence of adverse events was summarized by system organ class and by preferred term according to the Medical Dictionary for Regulatory activities (MedDRA) (version 12.0) dictionary for each treatment group.

Sample size

The primary endpoint was the number of weeks with weekly platelet responses from week 2 to week 13. The primary endpoint was compared using a Wilcoxon rank sum test at a 2-sided significance level of 0.05. In this study, the sample size was estimated to provide at least 90% power under the above conditions.

To evaluate an appropriate sample size and power for this study, basic statistics regarding the number of weeks with weekly platelet responses were obtained from overseas phase 3 Studies 20030105 and 20030212 using SAS® sample size combination of 16 in the romiplostim group and 8 in the placebo group should provide at least 90% power. To be conservative, the sample sizes for the present study were chosen to be 20 for the romiplostim group and 10 for the placebo group.

Because the use of rescue medications may increase efficacy, in this consideration, 2 statistics were obtained: i) all platelet counts regardless of rescue medication use, and ii) platelet counts within 4 weeks after rescue medication administration was removed.

To be conservative, weekly platelet responses i) for the placebo group and ii) for the romiplostim group were used. Because of the limitation of nQuery® to carry the number of categories in the Wilcoxon rank sum test, the higher categories were collapsed

Randomisation

Participants were randomised in 2:1 ratio (romiplostim vs placebo)

Blinding (masking)

Romiplostim and placebo were labeled and prepared in the same manner. Doses of placebo were volume-matched to romiplostim doses. Per local requirements, the study was unblinded for analysis of romiplostim serum concentrations and for antibody testing. No study personnel were unblinded during the conduct of the study. Antibody results were sent to the study centers after unblinding.

Statistical methods

The study hypothesis was that romiplostim would effectively raise platelet counts to ≥ 50 x 109/L, compared with placebo, over the treatment period. With respect to the primary endpoint (eg, number of weeks with weekly platelet responses), the null hypothesis was that the mean number of weeks with weekly platelet responses was the same in both groups, and the alternative hypothesis was that they were different.

Results

Participant flow

All randomised subjects received their assigned treatment and completed the study.

Recruitment

A total of 34 subjects were randomized to the study, 22 subjects to romiplostim and 12 subjects to placebo. Each center enrolled a total of 1 to 8 subjects.

Conduct of the study

The original protocol, dated 25 July 2007, had 2 superseding versions, 01 April 2008 and 01 September 2008.

The 01 September 2008 superseding version reflects administrative changes due to changes in study organization and contact information and changes in the entire study period due to the extension of the enrollment period.

Minor revisions were made to the Statistical Analysis Plan on 19 May 2009 to clarify the definitions of completion of treatment and completion of study and to update the definitions of concurrent ITP therapy and treatment period to be consistent with the study protocol.

Baseline data

The mean age of subjects in the romiplostim group (58.5 years) was higher than that in the placebo group (47.6 years) and more subjects in the romiplostim group were 65 years or older compared to subjects in the placebo group (32% versus 8%).

Seventy-one percent of the subjects were female (64% for the romiplostim group and 83% for the placebo group) and 44% of the subjects (46% for the romiplostim group and 42% for the placebo group) had undergone splenectomy before entering the study.

Sixty-eight percent of subjects were receiving baseline concurrent ITP therapy (more [83%] in the placebo group than in the romiplostim group [59%]).

Platelet counts at baseline were comparable between the romiplostim (mean 18.4 [SD 8.3] x 109/L) and placebo (mean 15.8 [SD 8.6] x 109/L) groups.

Table 2. ITP Treatment History (Full Analysis Set)

	Placebo (N = 12)	AMG 531 (N = 22)	Total (N = 34)
Years since ITP Diagnosis[a]			
n	12	22	34
Mean	7.6	9.7	9.0
SD	5.9	10.4	9.0
Median	5.6	6.2	5.8
Q1, Q3	3.6, 10.0	2.6, 13.6	2.6, 10.5
Min, Max	1, 22	1, 40	1, 40
Years since Splenectomy[ab]			
n	5	10	15
Mean	10.6	8.1	8.9
SD	6.9	6.8	6.7
Median	10.4	6.8	9.1
Q1, Q3	8.2, 11.1	2.7, 13.4	2.7, 13.4
Min, Max	2, 21	1, 22	1, 22
ITP treatment history at the beginning of this study[c] - n(%)			
Corticosteroid	12 (100.0)	22 (100.0)	34 (100.0)
IV immune gamma globulin	8 (66.7)	11 (50.0)	19 (55.9)
Splenectomy	5 (41.7)	10 (45.5)	15 (44.1)
H pylori eradication therapy	3 (25.0)	11 (50.0)	14 (41.2)
Azathioprine	4 (33.3)	5 (22.7)	9 (26.5)
Danazol	2 (16.7)	3 (13.6)	5 (14.7)
Cyclophosphamide	0 (0.0)	4 (18.2)	4 (11.8)
Rituximab	0 (0.0)	3 (13.6)	3 (8.8)
Vincristine/vinblastine	0 (0.0)	2 (9.1)	2 (5.9)
Other	7 (58.3)	10 (45.5)	17 (50.0)

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The full analysis set (FAS) consisted of all randomized subjects who received at least one dose of investigational product. Subjects were analyzed according to their randomized treatment group.
[a] Years were calculated as (randomization date - ITP diagnosis or splenectomy date) / 365.25. Partial dates of ITP diagnosis or Splenectomy with missing day only were imputed as 15, partial dates with missing month and day were imputed as July 1.
[b] Only applicable to subjects with splenectomy.
[c] Percentages were based on the full analysis set.

Numbers analysed

No subjects withdrew prematurely from the study.

Important protocol deviations, all related to investigational product administration not being administered at 1 or more visits and missing hematology data at the same visits, occurred in 2 subjects who received placebo and 2 who received romiplostim.

The full analysis set and the safety analysis set consisted of all randomized subjects who received at least 1 dose of investigational product. For the full analysis set, subjects were analyzed according to their randomized treatment group, and for the safety analysis set, subjects were analyzed according to the treatment actually received.

Outcomes and estimation

Romiplostim was statistically significantly superior to placebo for the primary efficacy endpoint, number of weeks with weekly platelet response (platelet count ≥ 50 x 109/L) and for all secondary efficacy endpoints except for rescue medication use.

Table 9-1. Results of Key Efficacy Endpoints (Full Analysis Set)

Endpoint	Placebo (N = 12)	AMG 531 (N = 22)	Treatment group comparison p-value
Primary Endpoint			
Number of Weeks With Weekly Platelet Response			
Median Q1, Q3	0.0 weeks (0.0, 0.0 weeks)	11.0 weeks (9.0, 12.0 weeks)	<0.0001[a]
Secondary Endpoints			
Proportion of Subjects With Increase of Platelet Count by 20 x 10^9/L or Greater from Baseline			
Incidence rate - n (%)	3 (25.0%)	21 (95.5%)	<0.0001[b]
Change from Baseline in Mean of Last 4 Platelet Counts During Week 2 to Week 13			
Mean SD	2.3 x 10^9/L 6.5 x 10^9/L	109.7 x 10^9/L 88.5 x 10^9/L	0.0003[c]
Number of Weeks With Platelet Count Between 50 and 200 (x10^9/L) Inclusive During Week 2 to Week 13			
Mean SD	0.2 weeks 0.4 weeks	6.3 weeks 3.2 weeks	<0.0001[a]
Proportion of Subjects Requiring Rescue Medications			
Incidence Rate - n (%)	2 (16.7%)	2 (9.1%)	0.6015[b]

[a] by Wilcoxon rank sum test
[b] by Fisher's exact test
[c] by ANCOVA, for treatment effect
HT_GRW from: Table 14-4.1.1.1, Table 14-4.2.1, Table 14-4.3.1, Table 14-4.4.1.1, Table 14-4.5.1

Similar results were seen for splenectomized and non-splenectomised subjects in the romiplostim group (median 11 vs 10.5 weeks).

Table 14-4.1.2.1. Summary of Number of Weeks with Weekly Platelet Response by Splenectomy Status (Full Analysis Set)

	Placebo Splenectomy		AMG 531 Splenectomy	
	Yes (N = 5)	No (N = 7)	Yes (N = 10)	No (N = 12)
Weekly Platelet Response[a]: - n(%)				
n	5	7	10	12
Mean	0.0	0.3	9.7	9.3
SD	0.0	0.5	3.4	3.5
Median	0.0	0.0	11.0	10.5
Q1, Q3	0.0, 0.0	0.0, 1.0	10.0, 11.0	8.0, 12.0
Min, Max	0, 0	0, 1	1, 12	0, 12

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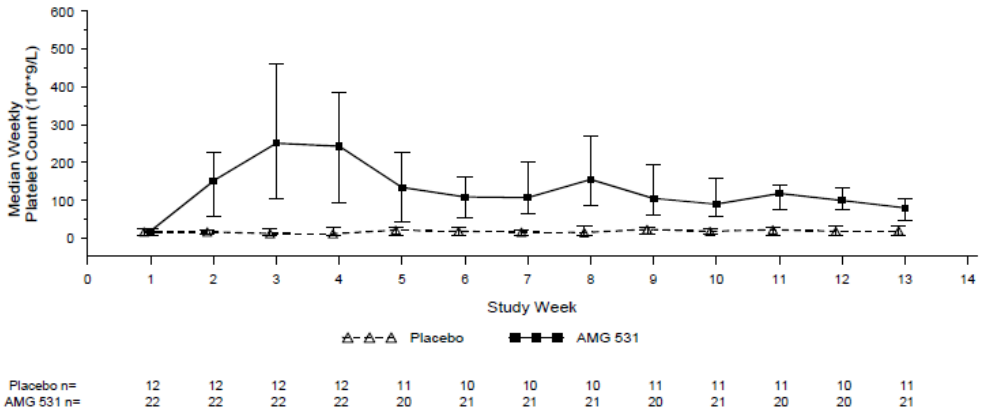
The full analysis set (FAS) consisted of all randomized subjects who received at least one dose of investigational product. Subjects were analyzed according to their randomized treatment group.
Platelet counts within 4 weeks after receiving any rescue medications were considered as no platelet response.
[a] Weekly platelet response was defined as weekly platelet count ≥ 50 x 10^9/L between week 2 and week 13 inclusive. Weeks with missing platelet count were considered no weekly response.

Weekly Platelet Counts

An increase in platelet counts was apparent in the romiplostim group by week 2: mean (SD) of 152.8 (102.0) x 10^9/L for romiplostim compared with 16.8 (9.3)x10^9/L for placebo. The mean platelet count in the romiplostim group increased to a maximum of 303.9 x 109/L at week 3 and remained at an increased mean level ranging from approximately 96 x 10^9/L to 272 x 10^9/L for the remainder of the 13-week treatment period, while levels in the placebo group did not change appreciably during the study.

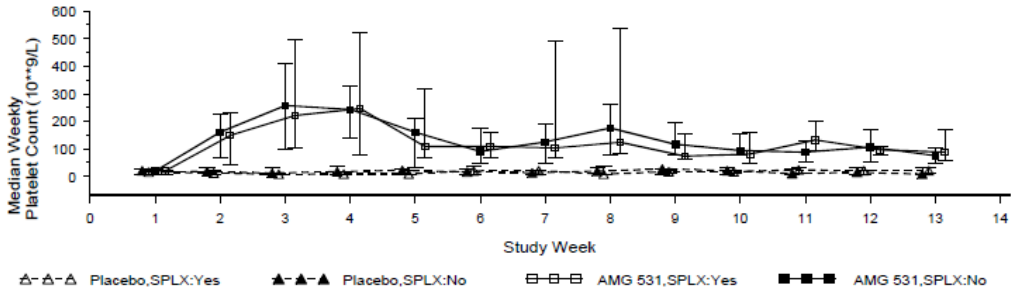
Figure 14-4.4.4.1. Median (Q1, Q3) of Weekly Platelet Count (Full Analysis Set)



Placebo n=	12	12	12	12	11	10	10	10	11	11	11	10	11
AMG 531 n=	22	22	22	22	20	21	21	21	20	21	20	20	21

The full analysis set (FAS) consisted of all randomized subjects who received at least one dose of investigational product.
Subjects were analyzed according to their randomized treatment group.
Platelet counts within 4 weeks after receiving any rescue medications were excluded from the analysis.

Figure 14-4.4.4.2. Median (Q1, Q3) of Weekly Platelet Count by Splenectomy Status (SPLX) by Week (Full Analysis Set)



Placebo, SPLX: Yes n=5	5	5	5	4	3	3	3	4	4	4	3	4
Placebo, SPLX: No n= 7	7	7	7	7	7	7	7	7	7	7	7	7
AMG531, SPLX: Yes n=10	10	10	10	9	9	9	9	8	9	8	8	9
AMG531, SPLX: No n=12	12	12	12	11	12	12	12	12	12	12	12	12

The full analysis set (FAS) consisted of all randomized subjects who received at least one dose of investigational product.
Subjects were analyzed according to their randomized treatment group.
Platelet counts within 4 weeks after receiving any rescue medications were excluded from the analysis.

Table 14-4.4.2.2. Weekly Incidence of Platelet Count Between 50 and 200 ($x10^9$/L) Inclusive During Week 2 to Week 13 by Splenectomy Status (Full Analysis Set)

	Placebo Splenectomy		AMG 531 Splenectomy	
	Yes (N = 5)	No (N = 7)	Yes (N = 10)	No (N = 12)
Weekly Platelet Count Between 50 and 200 ($x10^9$/L) Inclusive: - n/N(%)				
Week 2	0/5 (0.0)	0/7 (0.0)	4/10 (40.0)	7/12 (58.3)
Week 3	0/5 (0.0)	0/7 (0.0)	5/10 (50.0)	4/12 (33.3)
Week 4	0/5 (0.0)	0/7 (0.0)	4/10 (40.0)	3/12 (25.0)
Week 5	0/5 (0.0)	1/7 (14.3)	5/10 (50.0)	4/11 (36.4)
Week 6	0/4 (0.0)	0/7 (0.0)	7/10 (70.0)	7/12 (58.3)
Week 7	0/4 (0.0)	0/7 (0.0)	6/10 (60.0)	6/12 (50.0)
Week 8	0/4 (0.0)	0/7 (0.0)	5/10 (50.0)	4/12 (33.3)
Week 9	0/4 (0.0)	0/7 (0.0)	5/9 (55.6)	7/12 (58.3)
Week 10	0/4 (0.0)	0/7 (0.0)	5/10 (50.0)	9/12 (75.0)
Week 11	0/5 (0.0)	0/7 (0.0)	7/10 (70.0)	9/12 (75.0)
Week 12	0/4 (0.0)	1/7 (14.3)	7/10 (70.0)	7/12 (58.3)
Week 13	0/5 (0.0)	0/7 (0.0)	6/10 (60.0)	6/12 (50.0)

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The full analysis set (FAS) consisted of all randomized subjects who received at least one dose of investigational product. Subjects were analyzed according to their randomized treatment group.
Platelet counts within 4 weeks after receiving any rescue medications were considered as not between 50 and 200 ($x10^9$/L).
n = number of subjects with weekly platelet between 50 and 200 ($x10^9$/L).
N = number of subjects with non-missing weekly platelet count.

Time to Platelet Response

Twenty-one of 22 subjects in the romiplostim group had a platelet response, and the median (Q1, Q3) time to first weekly platelet response for subjects in the romiplostim group was 1.0 week (1.0, 1.3). The median time to platelet response was 1 week regardless of splenectomy status or baseline concurrent ITP therapy.

Thirteen of 14 romiplostim subjects who achieved a platelet response at week 13 had a subsequent platelet count ≤ 50 x 10^9/L or received rescue medication. The median (Q1, Q3) time from week 13 to the first platelet count of 50 x 109/L or less or receiving rescue medication was 1.0 weeks (1.0, 2.0)

Other Platelet Responses

Greater numbers of subjects in the romiplostim group than in the placebo group achieved platelet responses during week 2 to 13 as determined by 4 additional definitions of platelet response. The number of subjects with highest platelet count of ≥ 50 x 109/L and doubling from baseline was 21 of 22 (95.5%) in the

romiplostim group and 1 of 12 (8.3%) in the placebo group. The numbers of romiplostim subjects who had a highest platelet count of ≥ 100 x 109/L, ≥ 200 x 109/L, and ≥ 400 x 109/L were 19 of 22 (86.4%), 16 of 22 (72.7%), and 7 of 22 (31.8%), respectively, while no placebo subjects achieved these platelet responses.

More subjects in romiplostim group than in the placebo group achieved these responses regardless of splenectomy status or baseline concurrent ITP therapy

-Subject Incidence of Bleeding Symptoms

The incidence of bleeding symptoms (subjects who had purpura/petechiae, epistaxis, oral bleeding, menorrhagia, bruising, intra-cranial bleeding, gastrointestinal bleeding, other bleeding symptoms, or any of these symptoms) was analyzed for the safety analysis set. The incidence of any of these bleeding symptoms in the placebo group was 83.3% of subjects at baseline (week 1 predose) and week 5, 100% of subjects at week 9, and 83.3% of subjects at week 13 (end of treatment).

Romiplostim decreased the incidence of bleeding symptoms from 63.6% of subjects at baseline to 31.8% of subjects at weeks 5 and 9 and to 36.4% of subjects at week 13 (end of treatment). In the all postdose period, 100% of placebo subjects and 72.7% of romiplostim subjects had bleeding symptoms.

Pharmacokinetics

In total, 8 serum samples for romiplostim pharmacokinetics analysis were collected from 4 subjects. All 4 subjects who had serum samples collected for romiplostim serum concentration analysis were treated with placebo. All subjects had romiplostim concentrations below the lower limit of quantification (LLOQ = 15 pg/mL) except for one subject, who had measurable romiplostim concentrations of 28.5 pg/mL and 27.5 pg/mL on weeks 8 and 9, respectively. Platelet counts on the dates these measurements were obtained were not increased despite these observed concentrations, suggesting that there were no errors in dose administration.

Ancillary analyses

N/A

Analysis performed across trials (pooled analyses and meta-analysis)

Updated efficacy results from an analysis of pooled data from 9 clinical studies (Studies 20030105, 20030212, 20030213, 20040209, 20060113, 20060131, 20060216, 20080009, and 20080435) are presented in this submission. A total of 1024 subjects (376 subjects had prior splenectomy and 648 had no prior splenectomy) were included in the adult ITP efficacy set. The analyses were based on the treatment the subject actually received and were restricted to romiplostim-treated subjects only; subjects were treated for up to 283 weeks.

Description of Clinical Studies Included in the Pooled Analyses for Efficacy

Study	Phase	Control	Treatment Duration	Study Design	Subject Population Total (splenectomized/ nonsplenectomized)	Key Study Results (Primary Endpoint)
20030105	3	Placebo	24 weeks	Randomized, double-blind study	Adults with ITP refractory to splenectomy 63 (63/0)	Romiplostim was significantly superior to placebo for the primary efficacy endpoint of incidence of durable platelet response.
20030212	3	Placebo	24 weeks	Randomized, double-blind study	Adults with ITP prior to splenectomy 62 (0/62)	Romiplostim demonstrated significant superiority over placebo for all key efficacy endpoints and a tolerable safety profile in subjects with ITP who had not received a splenectomy.
20030213[a,b]	Open-label extension	None	Up to 277 weeks	Open-label extension study (subjects from 20000137A, 20000137B, 20010218, 20030105, 20030212, 20040209, 20060131, 20060195)	Adult and pediatric subjects with ITP 313 (103/210)	Romiplostim was well tolerated in both adult and pediatric populations, and the long-term safety profile was consistent with the safety profiles in the pivotal studies.
20040209[b]	3b	None	Up to 201 weeks	Open-label, expanded access study	Adults with ITP 407 (208/199)	Romiplostim was well tolerated and was able to induce platelet responses within weeks of starting treatment in the majority of subjects enrolled.

Study	Phase	Control	Treatment Duration	Study Design	Subject Population Total (splenectomized/ nonsplenectomized)	Key Study Results (Primary Endpoint)
20060113[b]	Open-label extension	None	Up to 243 weeks	Open-label extension Japanese study (subjects from 20050162 and 20060216)	Japanese adults with ITP 44 (17/27)	Romiplostim was well tolerated; the reported incidence of adverse events did not increase over time during long-term exposure to romiplostim, and no neutralizing antibodies against romiplostim or TPO were detected.
20060131[b]	3b	Standard of care	52 weeks	Randomized, open-label study	Nonsplenectomized adults with ITP 234 (0/234)	Romiplostim administered weekly was well tolerated and significantly reduced the incidences of splenectomy and treatment failure in nonsplenectomized subjects with ITP compared with the standard of care.
20060216[b]	3	Placebo	12-week treatment period	Randomized, double-blind study	Japanese adults with ITP 34 (15/19)	Demonstrated short-term safety of romiplostim compared with placebo in Japanese subjects with ITP and showed evidence for efficacy of romiplostim in raising and sustaining platelet counts in this population.

Study	Phase	Control	Treatment Duration	Study Design	Subject Population Total (splenectomized/ nonsplenectomized)	Key Study Results (Primary Endpoint)
20080009[b]	4	None	3 years	Prospective, open-label study evaluating changes in bone marrow morphology	Adults with ITP 169 (60/109)	Among subjects with evaluable bone marrow results, 0 of 35 subjects in cohort 1, 0 of 39 subjects in cohort 2, and 2 of 58 (3.4%) subjects in cohort 3 developed collagen. One of the 2 subjects who developed collagen had no evidence of collagen at the follow-up bone marrow biopsy 12 weeks after discontinuation of romiplostim.
20080435[b]	2	None	52-week treatment period	Single-arm, interventional study evaluating ITP remission	Adults with ITP who previously received only first-line therapies 75 (0/75)	Treatment with 12 months of romiplostim was associated with a mean of 9.2 months of platelet response during the 12-month treatment period; 93.3% of subjects had a platelet response.

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ITP = immune thrombocytopenic purpura; TPO = thrombopoietin
The adult ITP efficacy set consists of adult subjects who received at least 1 romiplostim dose in 1 of Studies 20030105, 20030212, 20030213, 20040209, 20060113, 20060131, 20060216, 20080009, and 20080435 (N = 1024).
[a] For the 20030213 study, which allowed both adult and pediatric subjects for be enrolled, only subjects over 18 years of age at entry were included in this analysis.
[b] New data that were not included in the original marketing application.

Source "Summary of Clinical Efficacy table 2-1"

Efficacy Endpoints

- platelet values by time
- subject incidence of platelet response
- subject incidence of platelet 50 x 109/L ≤ platelet ≤ 200 x 109/L
- subject incidence of sustained platelet response
- time to first platelet response
- number of months with platelet response
- number of months with 50 x 109/L ≤ platelet ≤ 200 x 109/L
- among subjects with platelet response:
- percent of months on study with platelet response
- percent of months with platelet response during the time between the first platelet response and the end of the study
- maximum number of consecutive weeks a subject has platelet count ≥ 50 x 109/L without use of concomitant ITP medications or romiplostim
- subject incidence of loss of platelet response

Statistical Methodology for Efficacy Analyses of Pooled Data

A subgroup analysis by prior splenectomy status (at the time of enrollment) was conducted on all efficacy endpoints. For subjects who enrolled in an extension study, the splenectomy status at the time of enrollment in the parent study was carried forward.

Platelet counts and platelet response were summarized based on the adult ITP efficacy set, restricted to romiplostim-treated adult subjects only. The earlier phase (phase 1 or 2) dose-finding studies were excluded from this analysis because subjects from those studies were on different and fixed-dose schedules and typically had short study durations. The romiplostim treatment period excluded the washout period that some subjects had between the parent study and the extension study. Platelet counts measured within 4 weeks after use of rescue medication were excluded from all analyses. Median monthly platelet count was summarized. Subjects with missing platelet counts had their values imputed with the last observation carried forward up to the point of study completion/withdrawal. Incidence of platelet response, sustained platelet response, and incidence of platelet count ≥ 50 x 109/L and ≤ 200 x 109/L were summarized using subject incidence and 95% exact confidence intervals (CIs) for the rates by romiplostim treatment period.

Number of months with platelet response and platelet count ≥ 50 x 109/L and ≤ 200 x 109/L were summarized by treatment period using the mean, standard deviation (SD), 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum. The percent of months with platelet response and platelet count ≥ 50 x 109/L and ≤ 200 x 109/L, using the total number of the months with an evaluable platelet count as the denominator, was summarized by treatment period using the mean, SD, Q1, Q3, minimum, and maximum. Time in weeks from the first administration of romiplostim to first platelet response was summarized using the Kaplan-Meier method. Subjects who did not achieve a response were censored at the time of the last platelet count measurement. Among subjects who had a platelet response, the number of months and the percent of weeks with platelet response during the time period between first platelet response and end of the study were summarized using mean, SD, median, Q1, Q3, minimum, and maximum.

The maximum number of consecutive weeks that a subject had a platelet count ≥ 50 x 109/L without use of concomitant ITP medications or romiplostim in the same week was summarized using mean, SD, median, Q1, Q3, minimum, and maximum, by romiplostim treatment period.

Results

Demographics and Baseline Characteristics

A total of 1024 subjects (376 subjects with prior splenectomy and 648 with no prior splenectomy) were included in the adult ITP efficacy set. In the adult ITP efficacy set, 60.2% of the subjects with no prior splenectomy were women, 76.2% were white, the median age was 53.0 years (range 18 to 93 years), and the median (Q1, Q3) time since ITP diagnosis was 1.63 (0.33, 5.41) years . The median baseline platelet count was 19.4 x 109/L.

Among subjects with prior splenectomy, 64.1% were women, 85.4% were white, the median age was 52.0 years (range 18 to 88 years), the median (Q1, Q3) time since ITP diagnosis was 9.03 (3.40, 18.14) years, and the median time since splenectomy was 6.39 years. The median baseline platelet count was 15.0 x 109/L . Thus, in general, the subjects with prior splenectomy represented a more advanced ITP population.

Table 3-1. Demographics and Baseline Disease Characteristics by Prior Splenectomy Status (Adult ITP Efficacy Set)

	Prior Splenectomy Status = No (N = 648)	Prior Splenectomy Status = Yes (N = 376)
Age (years)		
Mean (SD)	52.8 (18.5)	51.9 (15.3)
Median	53.0	52.0
Q1, Q3	38.0, 68.0	40.5, 63.0
Min, Max	18, 93	18, 88
Sex – n (%)		
Female	390 (60.2)	241 (64.1)
Male	258 (39.8)	135 (35.9)
Race – n (%)		
White or Caucasian	494 (76.2)	321 (85.4)
Black or African American	12 (1.9)	11 (2.9)
Hispanic or Latino	26 (4.0)	17 (4.5)
Asian	13 (2.0)	6 (1.6)
Japanese	99 (15.3)	18 (4.8)
American Indian or Alaska Native	1 (0.2)	0 (0.0)
Native Hawaiian or Other Pacific Islander	1 (0.2)	1 (0.3)
Other	1 (0.2)	2 (0.5)
Unknown	1 (0.2)	0 (0.0)
Years since ITP Diagnosis - n (%)		
Mean (SD)	4.15 (6.20)	12.51 (11.56)
Median	1.63	9.03
Q1, Q3	0.33, 5.41	3.40, 18.14
Min, Max	0.0, 45.0	0.0, 57.1
Years since splenectomy		
Mean (SD)	–	10.19 (10.69)
Median	–	6.39
Q1, Q3	–	2.10, 14.49
Min, Max	–	0.0, 53.1

The adult ITP efficacy set consists of adult subjects (age ≥18 years at screening) who received at least 1 romiplostim dose in 1 of studies 20030105, 20030212, 20030213, 20040209, 20060113, 20060131, 20060216, 20080009, and 20080435.
ITP = immune thrombocytopenic purpura; Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation
Percentages are based on N.
If subjects enrolled in multiple studies, the baseline information from the first ITP study was used in the summary.
Source: Modified from Table 14-2.1.4.1, Table 14-2.1.4.2, Table 14-2.2.4.1, and Table 14-2.2.4.2.

Platelet Values by Time

In general, platelet counts over time were similar between subjects with prior splenectomy and subjects with no prior splenectomy.

Figure 3-1. Median and Interquartile Range for Platelet Count Over Time Splenectomy Status = No, Evaluable Without Prior Rescue Medication Use in 4 Weeks (Adult ITP Efficacy Set)

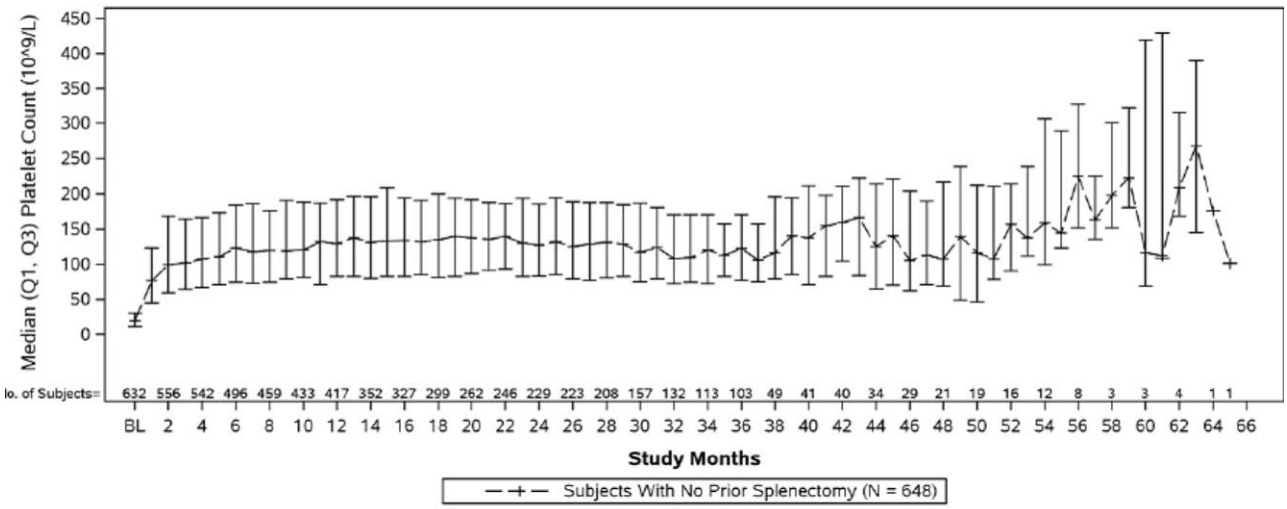
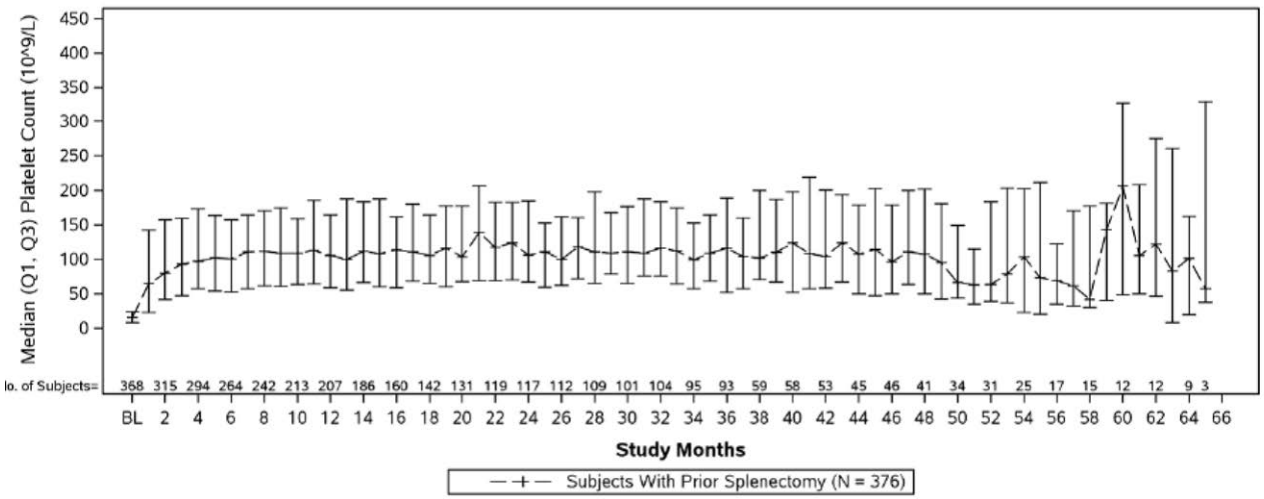


Figure 3-2. Median and Interquartile Range for Platelet Count Over Time
Splenectomy Status = Yes, Evaluable Without Prior Rescue Medication Use in 4 Weeks (Adult ITP Efficacy Set)



Subject Incidence of Platelet Response

- Subject Incidence of Platelet Counts Between 50 x 109/L and 200 x 109/L

During the romiplostim treatment period, most subjects (77.7% of subjects with prior splenectomy and 88.7% of subjects with no prior splenectomy) had at least 1 platelet count during treatment between 50 x 109/L and 200 x 109/L without any use of rescue medication within 4 weeks prior to the date of the platelet measurement (Table 3-6).

Table 3. Subject Incidence of Platelet Counts Between 50 x 109/L and 200 x 109/L by Romiplostim Treatment Period and Splenectomy Status, Evaluable Without Prior Rescue Medication Use in 4 Weeks (Adult ITP Efficacy Set)

	Romiplostim		
	Prior Splenectomy (N = 376)	No Prior Splenectomy (N = 648)	Total (N = 1024)
During all romiplostim treatment period:			
Incidence Rate	292/376 (77.7%)	575/648 (88.7%)	867/1024 (84.7%)
95% exact binomial confidence interval	(73.1%, 81.8%)	(86.0%, 91.1%)	(82.3%, 86.8%)
By romiplostim treatment period:			
Month 1 - 6			
Incidence Rate	276/376 (73.4%)	554/648 (85.5%)	830/1024 (81.1%)
95% exact binomial confidence interval	(68.6%, 77.8%)	(82.5%, 88.1%)	(78.5%, 83.4%)
Month 7 - 12			
Incidence Rate	216/290 (74.5%)	438/541 (81.0%)	654/831 (78.7%)
95% exact binomial confidence interval	(69.1%, 79.4%)	(77.4%, 84.2%)	(75.8%, 81.4%)
Year 2			
Incidence Rate	178/231 (77.1%)	343/402 (85.3%)	521/633 (82.3%)
95% exact binomial confidence interval	(71.1%, 82.3%)	(81.5%, 88.6%)	(79.1%, 85.2%)
Year 3			
Incidence Rate	108/139 (77.7%)	212/253 (83.8%)	320/392 (81.6%)
95% exact binomial confidence interval	(69.9%, 84.3%)	(78.7%, 88.1%)	(77.4%, 85.3%)
Year 4			
Incidence Rate	74/109 (67.9%)	86/121 (71.1%)	160/230 (69.6%)
95% exact binomial confidence interval	(58.3%, 76.5%)	(62.1%, 79.0%)	(63.2%, 75.4%)
Year 5			
Incidence Rate	28/41 (68.3%)	14/22 (63.6%)	42/63 (66.7%)
95% exact binomial confidence interval	(51.9%, 81.9%)	(40.7%, 82.8%)	(53.7%, 78.0%)
Year 6			
Incidence Rate	8/14 (57.1%)	2/4 (50.0%)	10/18 (55.6%)
95% exact binomial confidence interval	(28.9%, 82.3%)	(6.8%, 93.2%)	(30.8%, 78.5%)

Footnote of table:The adult ITP efficacy set consists of adult subjects (age ≥18 years at screening) who received at least 1 romiplostim dose in 1 of studies 20030105, 20030212, 20030213, 20040209, 20060113, 20060131, 20060216, 20080009, and 20080435.

ITP = immune thrombocytopenic purpura

All platelet counts recorded within 4 weeks after use of rescue medication are excluded from this analysis. Romiplostim treatment period is counted starting from first dose date of romiplostim, excluding washout period that subjects may have between parent study and extension study. Platelet counts measured on the same day of first dose date were excluded from the analysis. Source: Modified from Table 14-4.1.4.2.1

Table 4: Incidence of platelet response in Romiplostim-treated subjects by Romiplostim treatment period and duration of ITP (Adult ITP Efficacy set) (Table 13, page 442 Response document)

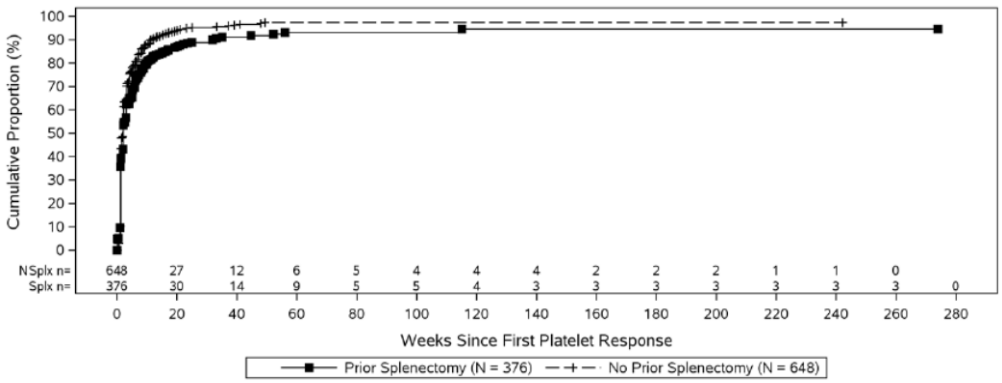
	No Prior Splenectomy			Prior Splenectomy		
	All Subjects (N = 648)	≥ 6 Months Since Diagnosis of ITP (N = 443)	> 12 Months Since Diagnosis of ITP (N = 386)	All Subjects (N= 376)	≥ 6 Months Since Diagnosis of ITP (N = 363)	> 12 Months Since Diagnosis of ITP (N = 351)
During all romiplostim treatment period: Incidence Rate 95% exact binomial confidence interval	592/648 (91.4%) (88.9%, 93.4%)	414/443 (93.5%) (90.7%, 95.6%)	362/386 (93.8%) (90.9%, 96.0%)	310/376 (82.4%) (78.2%, 86.2%)	300/363 (82.6%) (78.3%, 86.4%)	289/351 (82.3%) (77.9%, 86.2%)
By romiplostim treatment period:						
Month 1 - 6 Incidence Rate 95% exact binomial confidence interval	580/648 (89.5%) (86.9%, 91.8%)	406/443 (91.6%) (88.7%, 94.1%)	355/386 (92.0%) (88.8%, 94.5%)	300/376 (79.8%) (75.4%, 83.7%)	290/363 (79.9%) (75.4%, 83.9%)	279/351 (79.5%) (74.9%, 83.6%)
Month 7 - 12 Incidence Rate 95% exact binomial confidence interval	471/541 (87.1%) (83.9%, 89.8%)	336/376 (89.4%) (85.8%, 92.3%)	294/324 (90.7%) (87.0%, 93.7%)	237/290 (81.7%) (76.8%, 86.0%)	228/280 (81.4%) (76.4%, 85.8%)	220/272 (80.9%) (75.7%, 85.4%)
Year 2 Incidence Rate 95% exact binomial confidence interval	366/402 (91.0%) (87.8%, 93.6%)	300/328 (91.5%) (87.9%, 94.3%)	264/286 (92.3%) (88.6%, 95.1%)	187/231 (81.0%) (75.3%, 85.8%)	181/223 (81.2%) (75.4%, 86.1%)	177/219 (80.8%) (75.0%, 85.8%)
Year 3 Incidence Rate 95% exact binomial confidence interval	225/253 (88.9%) (84.4%, 92.5%)	190/211 (90.0%) (85.2%, 93.7%)	165/184 (89.7%) (84.3%, 93.7%)	115/139 (82.7%) (75.4%, 88.6%)	115/139 (82.7%) (75.4%, 88.6%)	113/137 (82.5%) (75.1%, 88.4%)

- Time to First Platelet Response

Table 5. Time to First Platelet Response by Splenectomy Status, Evaluable Without Prior Rescue Medication Use in 4 Weeks (Adult ITP Efficacy Set)

	Romiplostim		
	Prior Splenectomy (N = 376)	No Prior Splenectomy (N = 648)	Total (N = 1024)
Kaplan-Meier Estimated Time to First Platelet Response (Weeks):			
75th percentile (95% CI)	7.3 (6.1, 9.7)	4.1 (3.9, 5.3)	5.3 (5.0, 6.1)
50th percentile (95% CI)	2.1 (2.1, 3.0)	2.0 (1.3, 2.1)	2.1 (2.0, 2.1)
25th percentile (95% CI)	1.1 (NE, NE)	1.1 (NE, NE)	1.1 (NE, NE)
Number of subjects with platelet response	328 (87.2%)	605 (93.4%)	933 (91.1%)
Number of censored subjects	48 (12.8%)	43 (6.6%)	91 (8.9%)

Figure 3-3. Kaplan-Meier Estimates of Time to First Platelet Response by Splenectomy Status, Evaluable Without Prior Rescue Medication Use in 4 Weeks (Adult ITP Efficacy Set)



- Number of Months With Platelet Response

Number of Months With Platelet Count Between 50 x 109/L and 200 x 109/L

The median (Q1, Q3) number of months with platelet count between 50 x 10^9/L and 200 x 10^9/L was 6.0 (1.0, 17.5) in subjects with prior splenectomy and 10.0 (3.0, 19.5) in subjects with no prior splenectomy (Table 3-7). The median (Q1, Q3) percent time (months) with platelet count between 50 x 109/L and 200 x 109/L was 50.0% (11.3%, 77.9%) in subjects with prior splenectomy and 69.0% (40.0%, 88.6%) in subjects with no prior splenectomy.

	Romiplostim		
During all romiplostim treatment period	Prior Splenectomy (N = 376)	No Prior Splenectomy (N = 648)	Total (N = 1024)
Number of Months With Platelet Counts Between 50-200x10^9/L			
Mean (SD)	11.4 (13.2)	12.6 (11.3)	12.2 (12.1)
Median	6.0	10.0	9.0
Q1, Q3	1.0, 17.5	3.0, 19.5	2.0, 19.0
Min, Max	0, 53	0, 52	0, 53
% Time (Months) With Platelet Counts Between 50-200x10^9/L			
Mean (SD)	47.3 (34.3)	61.6 (32.0)	56.4 (33.5)
Median	50.0	69.0	64.1
Q1, Q3	11.3, 77.9	40.0, 88.6	31.5, 84.6
Min, Max	0, 100	0, 100	0, 100

- Sustained Platelet Response

Sustained platelet response was defined as having at least 9 weeks with platelet count ≥ 50 x 109/L in any 9- to12-week interval with no use of rescue medication during the 4 weeks prior to each qualifying platelet count. Among subjects with prior splenectomy, 67.6% (95% CI: 62.6%, 72.3%) had a sustained platelet response (Table 3-5). Among subjects with no prior splenectomy, 79.9% (95% CI: 76.6%, 83.0%) had a sustained platelet response.

Table 6. Subject Incidence of Sustained Platelet Response by Splenectomy Status, Evaluable Without Prior Rescue Medication Use in 4 Weeks (Adult ITP Efficacy Set)

	Romiplostim		
	Prior Splenectomy (N = 376)	No Prior Splenectomy (N = 648)	Total (N = 1024)
During all romiplostim treatment period:			
Incidence Rate	254/376 (67.6%)	518/648 (79.9%)	772/1024 (75.4%)
95% exact binomial confidence interval	(62.6%, 72.3%)	(76.6%, 83.0%)	(72.6%, 78.0%)

- Loss of Platelet Response

Loss of platelet response was defined as having a sustained platelet response followed by platelet counts < 50 x 109/L and romiplostim dose ≥ 10 g/kg for at least 9 weeks during any 9- to 12-week period or at least 3 weeks during the last 3 to 4 weeks of the study for subjects who withdrew early. Of the subjects with sustained platelet response, 7.9% (95% CI: 4.9, 11.9) with prior splenectomy and 6.9% (95% CI: 4.9, 9.5) with no prior splenectomy lost platelet response (Table 3-9).

Table 7. Subject Incidence of Loss of Platelet Response While Being Treated With Romiplostim by Splenectomy Status, Evaluable Without Prior Rescue Medication Use in 4 Weeks (Adult ITP Efficacy Set)

	Romiplostim		
	Prior Splenectomy (N = 376)	No Prior Splenectomy (N = 648)	Total (N = 1024)
Subjects Who Had a Sustained Response – n1	254	518	772
Responders who lost platelet response during subsequent	20/254 (7.9)	36/518 (6.9)	56/772 (7.3)
treatment period – n2/n1 (%)			
95% CI[1] of percent (%)	(4.9, 11.9)	(4.9, 9.5)	(5.5, 9.3)

- Remission

A secondary endpoint of Study 20080435 was subject incidence of ITP remission during the 12-month treatment or tapering period of the study. An ITP remission was defined as maintaining every platelet count ≥ 50 x109/L for at least 6 months in the absence of romiplostim and any medication for ITP (concomitant or rescue) through discontinuation. The study population consisted of adults with primary ITP diagnosed within the last 6 months who had received only first-line therapy for ITP; surgical resection of the spleen was an exclusion criterion, per the protocol. In the safety analysis set for this study, 31 of 75 (41.3%) subjects entered the ITP remission period and 24 of 75 (32.0%) achieved ITP remission during the study. The median (range) time to onset of ITP remission for these subjects was 27 (6 to 57) weeks.

Clinical studies in special populations

N/A

Supportive study(ies)

Studies 131 and 113 are already included in the pooled analysis, however they are of special interest and are presented here individually:

Results of studies compared to standard of care (SOC) in non-splenectomised patients

- **Study 20060131**

The pooled analysis included top line results from study 20060131, which was conducted in non-splenectomised subjects comparing the ability of romiplostim versus medical standard of care (SOC).

Study S3 (131) was an open-label randomised 52 week trial in subjects who received romiplostim or medical standard of care (SOC) treatment. This study evaluated non-splenectomised patients with ITP and platelet counts < 50 x 10^9/l.

The aim was to prevent splenectomy and to provide a durable treatment option to these patients for at least a 52-week period. The study was designed to assess the safety and effectiveness of romiplostin self-administration (N = 109 self-administering adults).

The first primary endpoint was the number of subjects undergoing splenectomy during the 52-week treatment period by randomized treatment group. The second primary endpoint was the number of subjects with a treatment failure during the 52-week treatment period by randomized treatment group.

Subjects were enrolled in a 2:1 randomization.

Results

In total there were 234 subjects, 157 randomized to receive romiplostim and 77 randomized to receive SOC; out of these there were N = 109 self administering adults.

Romiplostim was administered to 157 subjects by subcutaneous (SC) injection once weekly starting at a dose of 3 µg/kg, and adjusted throughout the study within a range of 1-10 µg/kg in order to maintain platelet counts between 50 and 200 x 10^9/l, 77 subjects received SOC treatment according to standard institutional practice or therapeutic guidelines.

The overall subject incidence rate of splenectomy was 8.9% (14 of 157 subjects) in the romiplostim group compared with 36.4% (28 of 77 subjects) in the SOC group, with an odds ratio (romiplostim vs SOC) of 0.17 (95% CI: 0.08, 0.35). The p-value for the treatment difference between groups was < 0.0001.

The overall subject incidence of treatment failure was 11.5% (18 of 157 subjects) in the romiplostim group compared with 29.9% (23 of 77 subjects) in the SOC group, with an odds ratio (romiplostim vs SOC) of 0.31 (95% CI: 0.15, 0.61). The p-value for the treatment difference between groups was 0.0005.

Of the 157 subjects randomised to the romiplostim group, three subjects did not receive romiplostim. Among the 154 subjects who received romiplostim, the total median exposure to romiplostim was 52.0 weeks and ranged from 2 to 53 weeks. The most frequently used weekly dose was between 3-5 µg/kg (25th-75th percentile respectively; median 3 µg/kg).

Of the 77 subjects randomised to the SOC group, two subjects did not receive any SOC. Among the 75 subjects who received at least one dose of SOC, the total median exposure to SOC was 51 weeks and ranged from 0.4 to 52 weeks.

Platelet responses were also consistently achieved by a higher proportion of subjects in the romiplostim group compared with those in the SOC group starting from week 2. Poisson regression analyses indicated that romiplostim subjects were 2.3 times more likely to have a platelet response than subjects in the SOC group (p < 0.0001).

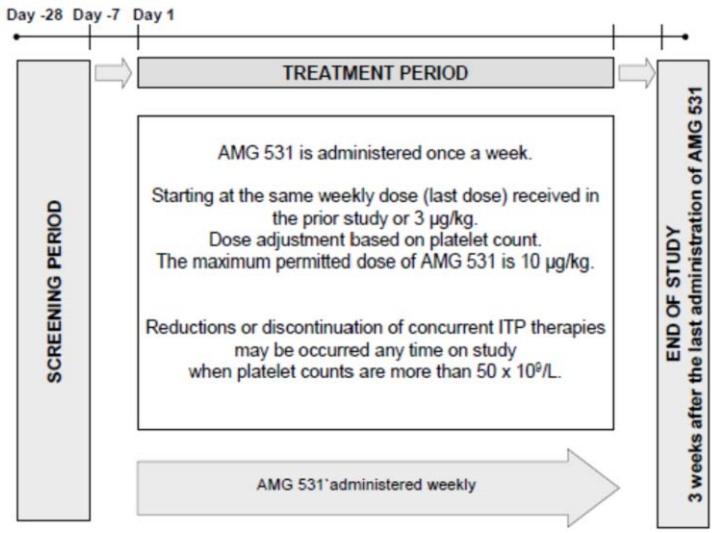
Study 20060113

An Open Label Extension Study Evaluating the Safety and Efficacy of Long-Term Dosing of AMG 531 in Thrombocytopenic Japanese Subjects with Immune (Idiopathic) Thrombocytopenic Purpura

Study 20060113 was designed to provide safety and efficacy data on the long-term use of romiplostim in thrombocytopenic Japanese subjects with ITP.

Based on the results of the phase 2 study in Japanese subjects with ITP (Study 20050162), the default starting dose in Study 20060113 was determined to be 3 µg/kg. For subjects who during their previous study had shown a platelet count increase of ≥ 20 x 109/L over baseline at least once during the 13-week treatment period (except platelet responses that occurred within 4 weeks after rescue therapy), and who were enrolled in Study 20060113 within 12 weeks of receiving their last dose of investigational product in the previous study, the starting dose in Study 20060113 was to be the same as the last dose received in the previous study.

Individual dose adjustments based on platelet counts were permitted. The dose adjustment rules in this study were amended to be consistent with those in the Japan phase 3 study (Study 20060216), and similar to those used in the overseas phase 3 studies (Studies 20030212 and 20030105).



Primary Objectives

The primary objective was to determine the safety of romiplostim as a long-term treatment in thrombocytopenic Japanese subjects with ITP.

Secondary Objectives

- to evaluate the long-term platelet response to romiplostim
- to evaluate possible reductions in the dose of concurrent ITP therapies while receiving romiplostim
- to evaluate changes in Patient-Reported Outcomes (PRO) because of the use of romiplostim

Inclusion Criteria

To be eligible for entry into the study, subjects were required to fulfill all of the following inclusion criteria during screening:

• Subjects must have previously completed a romiplostim ITP study in Japan.

• Platelet count taken at the screening visit must have been < 50 x 109/L.

• Before any study-specific procedure, the appropriate written informed consent must have been obtained.

Exclusion Criteria

• any significant change in medical history since completion of the previous romiplostim ITP study, including bone marrow stem cell disorders or new active malignancies

• known positive result from a test for neutralizing antibodies to romiplostim in the previous romiplostim ITP study

• received any treatment for ITP except oral corticosteroids, azathioprine, and/or danazol administered at a constant dose and schedule from at least 4 weeks prior to the screening visit

• received intravenous immunoglobulin (IV Ig), anti-D immunoglobulin (anti-D Ig), or any drug administered to increase platelet counts within 1 week before the screening visit

• received anti-malignancy agents (eg, cyclophosphamide, 6-mercaptopurine, vincristine, vinblastine, interferon alfa, etc) within 4 weeks before the screening visit

• received any monoclonal antibody drugs (eg, rituximab etc) within 8 weeks before the screening visit

• less than 4 weeks since receipt of any therapeutic drug or device that is not MHLW-approved for any indication before the screening visit (excluding romiplostim)

Treatments Administered

Subjects with a platelet count ≤ 20 x 109/L after receiving a dose of 10 µg/kg were required to return to

the investigational site the following week to obtain a platelet count and for in-clinic dosing. Weekly platelet counts and in-clinic doses were to continue until the subject's platelet count had been > 20 x 109/L for 2 consecutive weeks.

Study Endpoints

The primary endpoint was the incidence of all adverse events, including clinically significant changes in laboratory values.

The secondary endpoints were:

- incidence of anti-romiplostim antibody formation
- incidence of platelet response (platelet response is defined as a doubling of baseline platelet count and ≥ 50 x 109/L; baseline platelet count is that at study entry in the previous study).
- To discount the possible platelet effect associated with rescue medications, subjects were considered to have had no platelet response for 8 weeks after any administration of rescue medication, and those platelet counts were excluded from the efficacy analysis.
- proportion of subjects able to reduce from baseline or discontinue their concurrent ITP therapies (for subjects that are receiving oral corticosteroids, azathioprine, and/or danazol at a constant dose and schedule at the screening visit)

- change from baseline in PRO endpoints at each time point (baseline PRO is obtained at day 1 predose)

The exploratory endpoints were PK parameters such as area under the concentration time curve (AUC) and maximum observed concentration (Cmax).

Subject subsets that may have been addressed in the analysis were defined by the following: splenectomy status (yes, no); concurrent ITP therapy (yes, no); previous study (20050162, 20060216)

Results

-Enrollment and Disposition of Subjects

A total of 44 subjects were enrolled in the study, of whom 42 (95.5%) completed the study. All subjects enrolled received romiplostim and 35 (79.5%) completed romiplostim treatment Forty subjects completed 84 weeks, 23 subjects completed 144 weeks, 9 subjects completed 216 weeks, and 7 subjects completed at least 228 weeks on study

-Investigational Product Discontinuations

All subjects received at least 1 dose of romiplostim. Thirty-five subjects (79.5%) completed romiplostim treatment, while the remainder discontinued treatment because of subject request (6 subjects [13.6%]), administrative decision (2 subjects [4.5%]), or other (1 subject [2.3%] whose platelet count was > 200 x 109/L even after romiplostim was withheld for 3 weeks [Subject 113216083]).

-Demographic and Other Baseline Characteristics

Of the 44 subjects enrolled, 11 (25%) had completed Study 20050162, and 33 (75%) had completed Study 20060216. All subjects were of Japanese ethnicity; 31 subjects (70.5%) were women and 13 (29.5%) were men. Subjects' ages ranged from 25 to 81 years, with an average (SD) age of 54.9 (12.9) years. Eight subjects (18.2%) were ≥ age 65 years, and 3 subjects (6.8%) were ≥ age 75 years. All of the subjects age 65 years or older were previously enrolled in Study 20060216, but with that exception, the subject demographics from the 2 parent studies were similar.

Mean (SD) baseline weight (based on the pretreatment measurement closest to the study's first dose) was 58.5 (11.4) kg. Subjects had received a variety of other therapies for their ITP before this study, including corticosteroids (43 subjects [97.7%]), IV Ig (25 subjects [56.8%]); *H pylori* eradication (21 subjects [47.7%]), splenectomy (17 subjects [38.6%]), azathioprine (11 subjects [25.0%]), danazol (10 subjects [22.7%]), cyclophosphamide (5 subjects [11.4%]), vincristine/vinblastine (3 subjects [6.8%]), rituximab (3 subjects [6.8%]) and other therapies (25 subjects [56.8%]). In the interval between completing the previous romiplostim study and beginning this study, 29 subjects (65.9%) had received corticosteroids and 2 subjects (4.5%) had received azathioprine for their ITP

Efficacy Results

Table 9-1. Platelet Response, Safety Analysis Set

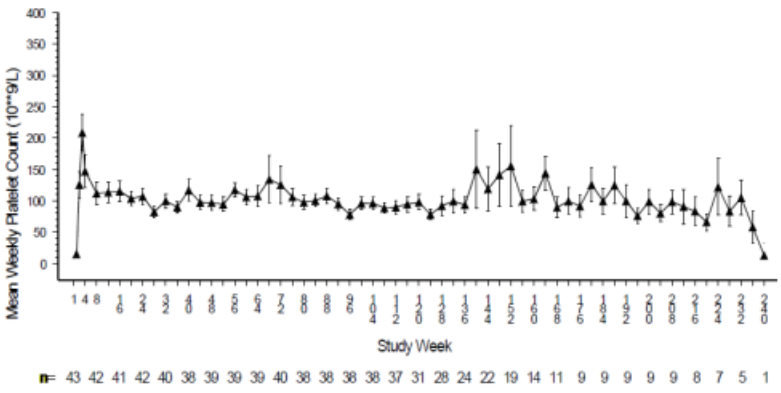
	AMG 531 (N = 44)
Number of Subjects with Peak Platelet Count:	
≥ 50 x 10^9/L and doubling of baseline (Response) 95% exact binomial confidence interval	42 (95.5%) (84.5%, 99.4%)
≥ 20 x 10^9/L increase from baseline 95% exact binomial confidence interval	43 (97.7%) (88.0%, 99.9%)
≥ 50 x 10^9/L 95% exact binomial confidence interval	42 (95.5%) (84.5%, 99.4%)
≥ 100 x 10^9/L 95% exact binomial confidence interval	41 (93.2%) (81.3%, 98.6%)
≥ 150 x 10^9/L 95% exact binomial confidence interval	41 (93.2%) (81.3%, 98.6%)
≥ 400 x 10^9/L 95% exact binomial confidence interval	15 (34.1%) (20.5%, 49.9%)

Page 1 of 1

Safety analysis set included all enrolled subjects receiving at least one dose of AMG 531.
Platelet counts within 8 weeks after receiving any rescue medications were excluded.

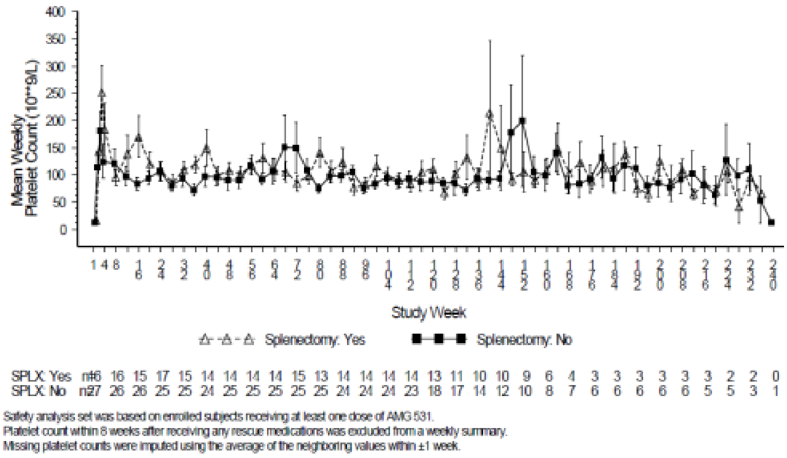
Of the 17 subjects who had received a splenectomy, 17 (100%) had a platelet response, and of the 27 subjects who had not had a splenectomy, 25 (92.6%) had a platelet response

Figure 14-4.4.3.1. Mean(SE) Platelet Count by Week (Safety Analysis Set)



Safety analysis set was based on enrolled subjects receiving at least one dose of AMG 531.
Platelet count within 8 weeks after receiving any rescue medications was excluded from a weekly summary.
Missing platelet counts were imputed using the average of the neighboring values within ±1 week.

Figure 14-4.4.3.2. Mean(SE) Platelet Count by Splenectomy Status (SPLX) by Week (Safety Analysis Set)



Reduction of Concurrent ITP Therapy

Of the 25 subjects (56.8% of the safety analysis set) who were receiving concurrent ITP therapy at baseline 11 (44.0%) had a > 25% reduction in at least 1 concurrent therapy, 6 (24.0%) had a > 50% reduction in at least 1 concurrent therapy, and 9 (36.0%) discontinued all concurrent therapies.

The incidence of > 25% reduction, > 50% reduction, and discontinuation of concurrent ITP therapy was 55.6%, 33.3%, and 22.2% in splenectomized subjects, respectively, and 37.5%, 18.8%, and 43.8% in nonsplenectomized subjects, respectively

-Bleeding Symptoms

During week 1, prior to treatment with romiplostim, 84.1% of subjects reported bleeding symptoms; the most common were purpura/petechiae (81.8%), epistaxis (25.0%), and oral bleeding (22.7%) Bleeding symptoms were reduced during every 4-week period after treatment with romiplostim (after week 1), excluding week 240 in which the single subject still on study reported a bleeding symptom; the maximum and minimum proportion of subjects that reported bleeding symptoms during any 4-week period was 36.6% (as observed at week 40) and 0 (as observed at weeks 164 and weeks 228 through 236), respectively. The incidence of bleeding symptoms at the end of study (3 weeks after the last dose of romiplostim) was

21.4%. The incidence of bleeding symptoms was similar during most 4-week periods in splenectomized subjects and nonsplenectomized subjects.

The incidence of bleeding symptoms was higher during most 4-week periods in subjects who were receiving concurrent ITP therapy at baseline than in those who were not

Rescue Medication Use

Nine subjects (20.5% of the safety analysis set) received rescue medications at some point during the study. The most commonly used rescue mediations were prednisolone (7 subjects [15.9%]), concentrated platelets (4 subjects [9.1%]), platelets (2 subjects [4.5%]), and human normal immunoglobulin (2 subjects [4.5%])

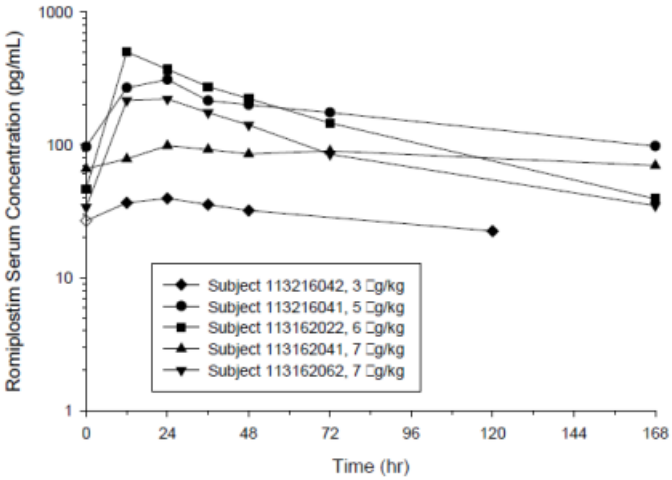
The percentage of subjects using rescue medications was higher among splenectomized subjects than nonsplenectomized subjects (6 subjects [35.3%] and 3 subjects [11.1%], respectively)

Pharmacokinetics Results

In total, 58 serum samples for romiplostim concentration measurement were collected from 15 subjects, of which 5 subjects had serial serum samples collected for PK parameter estimation.

After SC administration, the peak concentrations of romiplostim ranged from 39.5 to 501 pg/mL and were observed at 12 to 24 hours post-dose (See 10-1)

Figure 10-1. Individual Serum Romiplostim Concentration vs Time Profiles After Subcutaneous Administration of Romiplostim



2.4.2. Discussion on clinical efficacy

The efficacy of romiplostim in non-splenectomised patients (second line treatment) was based on the results of the two pivotal double blind and placebo controlled studies. Study 20030212, conducted in non-splenectomised subjects, demonstrated the superiority of romiplostin over placebo in the rate of durable platelet responses (61% vs 4.8% in romiplostin and placebo, respectively), and Study 20030105 did so in patients refractory to splenectomy (38.1% of responders in romiplostim group and 0% in placebo). Interim results from the long term extension Study 20030213, showed sustained platelet responses. However, due to the limited safety database at the time of the initial MAA (62 non-splenectomised and 63 splenectomized subjects), the uncertainties around safety and efficacy of romiplostin in the long term and given the well-established place in therapeutics of splenectomy, with positive results lifelong, the CHMP expressed concerns on the treatment of non-splenectomised patients, which led to a restricted wording of the indication to third line treatment, following splenectomy or, as a second line treatment option only in those cases where splenectomy is not an immediate reasonable option.

Design and conduct of clinical studies

To support broadening of the current indication, a pooled analysis of a total of 9 clinical trials conducted up to date has been provided. This included a total of 1024 subjects (376 subjects with prior splenectomy and 648 with no prior splenectomy).

The data submitted by the MAH provides pooled safety and efficacy data for up to 284 weeks. The pooled analysis provides long term efficacy in chronic ITP patients with and without prior splenectomy, this consists of a heterogeneous population with associated limitations. A comparison of efficacy for romiplostim with other treatments for chronic ITP, including splenectomy, has not been possible. Further information submitted by the Applicant provides detailed data from study 131 supporting reasonably the efficacy of romiplostim in comparison to standard of care in non-splenectomised patients. The weaknesses of comparing pharmaceutical interventions, such as romiplostim with surgical treatment (splenectomy) are acknowledged to some extent.

The pooled studies consisted of a different subgroups of subjects: patients refractory to splenectomy (study 20030105), a heterogeneous group of subjects with ITP (studies 20030213, 20040209, 20060113, 20060216, 200800009, 20080435), non-splenectomised subjects prior to splenectomy (study 20030212), and non-splenectomised subjects (study 20060131). Non-splenectomised patients consist of several subgroups, such as patients eligible for splenectomy awaiting or delaying surgery, patients using romiplostim as maintenance therapy replacing a splenectomy, patients not in need of splenectomy, patients with a contra-indication for surgery. Treatment of patients in these various situations may require different approaches. By pooling within these two groups (non-splenectomised and splenectomized), the MAH assumes that the populations are similar. However within the non-splenectomised patients the group with a contra-indication might differ substantially from patients awaiting splenectomy with respect to disease responsiveness, disease duration and previously received treatment. Moreover, the pooled data differ in follow-up time, baseline characteristics, study-set up, outcome measures etc. There were proportionately more Japanese subjects in the group of non-splenectomised subjects than in the group of splenectomized subjects in the pooled analysis. The additional analysis performed by the MAH has shown that the exclusion of the Japanese subjects did not lead to a different outcome of efficacy and safety between splenectomized and non- splenectomized patients, and therefore regional differences and/or race are not the explanation for the observed difference.

The pool included results from Study 20060131, which was conducted in non-splenectomised subjects comparing the ability of romiplostim versus medical standard of care (SOC) to prevent splenectomy and to provide a durable treatment option to these patients for at least a 52-week period. The first primary endpoint was the number of subjects undergoing splenectomy during the 52-week treatment period by randomized treatment group. The second primary endpoint was the number of subjects with a treatment failure during the 52-week treatment period by randomized treatment group. It should be highlighted that the study was designed to assess the safety and effectiveness of romiplostin self administration.

Patients were classified as chronic ITP patients, however according to the data submitted the 32% of the patients had a disease duration < 6 months. In non-splenectomised subjects, the median number of years since ITP diagnosis was 1.63 years in the overall non-splectomized population, more than 3 prior ITP therapies had been received by 11.4% of all non-splenectomised subjects. 14.9% of those with ITP for > 6 months and 15.3% of those with ITP for > 12 months. In splenectomized subjects, the median number of years since ITP diagnosis was 9.03 years in the overall splenectomized population, more than 3 prior ITP therapies had been received by 35.1% of all splenectomized subjects. 36.4% of those with ITP for > 6 months and 36.5% of those with ITP for > 12 months.

In addition, two new studies completed in the Japanese population were presented as supportive information of the efficacy of romiplostin in non-splenectomised subjects. One small phase III (20060216) double-blind and placebo-controlled study (a total of 34 subjects were randomized, 22 subjects to romiplostim and 12 subjects to placebo) and the open label extension 20060113 Study, where patients were followed in the long-term. In Study 20060216, subjects were stratified according to splenectomy status at baseline and consisted of a double blind 12-week placebo controlled phase which tested a higher than recommended initial starting dose. Study 20060113 was a single arm study aimed to study the safety of romiplostin in the long term. In Study 20060113 a total of 44 subjects were enrolled of whom 42 (95.5%)

completed the study. All subjects enrolled received romiplostim and 35 (79.5%) completed romiplostim treatment. Forty subjects completed 84 weeks, 23 subjects completed 144 weeks, 9 subjects completed 216 weeks, and 7 subjects completed at least 228 weeks on study. Dose adjustments were allowed throughout the treatment period to allow subjects to maintain platelet counts in the targeted therapeutic range, similar to the studies presented in the initial MAA. These studies included cITP subjects that had received at least one previous ITP treatment and continued being thrombocytopenic, i.e. platelet counts ≤ 30 x 109/L was required for study entry.

All studies analysed the efficacy of romiplostin in terms of increments in platelet counts, while assessment of the maintenance of the effect in the long-term, use of rescue and concomitant medication to maintain the response and the proportion of clinical remissions after stopping romiplostin treatment was also performed.

Efficacy data and additional analyses

From the pooled analysis: the median time since ITP diagnosis was 1.63 years in subjects with no prior splenectomy and 9.03 years in subjects with prior splenectomy, and the median baseline platelet count was 19.4 x 109/L in subjects with no prior splenectomy and 15.0 x 109/L in subjects with prior splenectomy. Thus, in general, the subjects with prior splenectomy represented a more advanced ITP population. The non-splenectomised patients are represented by a larger proportion of Japanese patients than the splenectomized patients. This difference can mainly be attributed to study 20060113 and 20060216. It is uncertain what the difference in race or perhaps regional treatment aspects has on the comparability of the studied population as a whole. The MAH was requested to elucidate on whether the Japanese patients are expected to respond differently than Caucasians in the studied population. Excluding Studies 20060113 and 20060216, led to the exclusion of 45 patients on a total of 1024 patients. Japanese patients did not have a discernible impact on the demographics and baseline characteristics of the Adult ITP efficacy set in the splenectomized and non-splenectomised groups. Excluding the Japanese subjects did not have a remarkable effect on the efficacy and the adverse event profile of Romiplostim. There were proportionately more Japanese subjects in the group of non-splenectomised subjects than in the group of splenectomized subjects in the pooled analysis.

There was a high percentage of responders with incidence of platelet count between 50 $x10^9$/L and $200x10^9$/L in the first 6 months (276/376; 73.4% and 554/648; 85.5% in splenectomized and non-splenectomized), while later the percentages decrease over time in parallel to the number of patients accounting for the analysis (28/41; (68.3% and 14/22; 63.6% respectively). Independently of the splenectomy status, the time necessary to reach a first platelet response was two weeks with a 50th percentile similar in both subgroups (2.1 weeks and 2.0 weeks). The median (Q1, Q3) number of months with platelet counts between 50 x 109/L and 200 x 109/L was 6.0 (1.0, 17.5) in subjects with prior splenectomy and 10.0 (3.0, 19.5) in subjects with no prior splenectomy. The median (Q1, Q3) percent time (months) with platelet counts between 50 x 109/L and 200 x 109/L was 50.0% (11.3%, 77.9%) in subjects with prior splenectomy and 69.0% (40.0%, 88.6%) in subjects with no prior splenectomy.

Sustained platelet response was defined as having at least 9 weeks with platelet count ≥ 50 x 109/L in any 9- to12-week interval with no use of rescue medication during the 4 weeks prior to each qualifying platelet count. Among subjects with prior splenectomy, 67.6% (95% CI: 62.6%, 72.3%) had a sustained platelet response. Among subjects with no prior splenectomy, 79.9% (95% CI: 76.6%, 83.0%) had a sustained platelet response. Of the subjects with sustained platelet response, 7.9% (95% CI: 4.9, 11.9) with prior splenectomy and 6.9% (95% CI: 4.9, 9.5) with no prior splenectomy lost platelet response.

During treatment with romiplostim the median values of the total number of months with platelet counts between 50 x 109/L and 200 x 109/L was 6.0 months [subjects with prior splenectomy] and 10.0 months [subjects with no prior splenectomy]). The number of consecutive weeks with positive response was 7 from the non-imputed data vs 21 weeks in splenectomised and 34 in non-splenectomised from the imputed

analyses. Data presented are useful tools to know the maintenance of the response and the effect of romiplostim in the long term, which can be expected despite fluctuations in platelet counts over time.

The rescue medication used is highly variable across the studies, ranging from 9% in study 20060219 to 47% in study 20040209. In general the use seems more frequent in placebo/SOC treated patients compared to romiplostim treated arms, regardless of the splenectomy status. Duration-adjusted use of rescue medications per 100P/Y in non-splenectomised patients at any time was 153.3 in romiplostim and 540.3 in placebo/SOC, and in splenectomized was 263.4 in romiplostim and 850.0 in placebo/SOC. Moreover the rate of rescue medication use in romiplostim-treated (splenectomized and non-splenectomized) subjects declined over time, which is reassuring.

The incidence of platelet response was sufficient (> 87%) among the subgroups of non-splenectomised and splenectomized with subgroups with ⩽ 3 prior ITP therapies or > 3 prior ITP therapies. The incidence of platelet response during different treatment periods was consistent for the first treatment year between subgroups for both non-splenectomised and splenectomized subjects. With longer treatment years the platelet response gradually declined in all subgroups for both non-splenectomised and splenectomized, in the group of splenectomized patients ⩽ 3 prior ITP therapies response declined from 88.9% in the first 6 months to 56,5% after 4 years of treatment. The MAH concludes that this might be due to smaller numbers after longer disease duration. However, the loss of platelet response only occurred in a small portion of the subjects which is reassuring.

In the pooled analysis data regarding the previous lines of therapy was lacking for both splenectomised and non-splenectomised patients. It is therefore not possible to assess the previous lines of therapy and reason not to have undergone splenectomy in this patient group

32% of the patients had a disease duration < 6 months, the short disease duration is likely a reason not to have had a splenectomy (yet). The data presented by the MAH has given no ground for any concern regarding the efficacy, which has shown a platelet response of >87%, in patients with < 3 or > 3 lines of previous therapy or other subgroup analysis based on disease duration

The results of Study 20060131 are of interest. The study demonstrated the superiority of romiplostim over medical SOC in terms of lower rates of splenectomy and treatment failure, but it is uncertain to what extent these medical intervention were standardized to allow firm conclusions. The overall subject incidence of splenectomy was 8.9% (14 of 157 subjects) in the romiplostim group compared with 36.4% (28 of 77 subjects) in the SOC group. The p-value for the treatment difference between groups was < 0.0001, with an odds ratio (romiplostim vs SOC) of 0.17 (95% CI: 0.08, 0.35), indicating that the odds of undergoing a splenectomy was statistically significantly lower in the romiplostim group than the SOC group. For the co-primary endpoint, the overall subject incidence of treatment failure was 11.5% (18 of 157 subjects) in the romiplostim group compared with 29.9% (23 of 77 subjects) in the SOC group. The p-value for the treatment difference between groups was 0.0005, with an odds ratio (romiplostim vs SOC) of 0.31 (95% CI: 0.15, 0.61), indicating that the odds of experiencing treatment failure was statistically significantly lower in the romiplostim group than the SOC group. Platelet responses were also consistently achieved by a higher proportion of subjects in the romiplostim group compared with those in the SOC group starting from week 2. Poisson regression analyses indicated that romiplostim subjects were 2.3 times more likely to have a platelet response than subjects in the SOC group (p < 0.0001).

Results from Studies in the Japanese population: Romiplostim was statistically significantly superior to placebo for the primary efficacy endpoint, number of weeks with weekly platelet response (platelet count ≥ 50 x 109/L), with a median (Q1,Q3) of 0 (0,0) in placebo and 11(9,12) in romiplostim groups, (being 11 weeks and 10.5 weeks in splenectomized and non-splenectomised patients, respectively). All secondary efficacy endpoints support the efficacy of romiplostim. Romiplostim decreased the incidence of bleeding symptoms from 63.6% of subjects at baseline to 31.8% of subjects at weeks 5 and 9 and to 36.4% of subjects at week 13 (end of treatment). In the all postdose period, 100% of placebo subjects and 72.7% of

romiplostim subjects had bleeding symptoms. From the 20060113 study, of the 17 subjects who underwent a splenectomy, 17 (100%) had a platelet response, and of the 27 subjects who had not had a splenectomy, 25 (92.6%) had a platelet response. The incidence of bleeding symptoms was similar during most 4-week periods in splenectomized subjects and nonsplenectomized subjects. Nine subjects (20.5% of the safety analysis set) received rescue medications at some point during the study. The percentage of subjects using rescue medications was higher among splenectomized subjects than nonsplenectomized subjects (6 subjects [35.3%] and 3 subjects [11.1%], respectively)

These results support the efficacy of romiplostim to increase platelet counts above a bleeding risk threshold for an individual patient. The effect appears to be maintained in the long-term, although beyond week 136 data show an important variability, what can be of concern for a treatment intended to be chronic. However, given that few patients were followed beyond week 136 (nearly half of the population enrolled), conclusions should be taken cautiously. No major differences were seen between splenectomized and non splenectomized patients in terms of maintenance of the response in the long-term. It is noted that a higher portion of non-splectomized than splenectomized subjects were able to discontinue concurrent ITP therapy (43.8% vs 22.2%). The magnitude of the response tends to be in general superior in non-splenectomised patients, which is not unexpected given the less advanced status of the disease in these patients while splenectomized patients usually represent a more refractory population.

2.4.3. Conclusions on the clinical efficacy

Romiplostim is efficient in terms of increasing platelet counts above a level, thus decreasing the risk of bleeding events in subjects with chronic ITP after failure to prior first line ITP treatment. The effect is seen regardless of whether patients had undergone prior splenectomy and appears to be maintained in the long-term with appropriate dose adjustments.

2.5. Clinical safety

Introduction

Safety results from an analysis of pooled data from 13 studies (Studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435) are presented in this summary; results are shown by splenectomy status at the time of enrolment. The data from the analysis of pooled data from the 13 clinical studies reported within this submission contain data on exposure to romiplostim for up to 283 weeks.

In addition, 2 integrated long-term safety analyses of romiplostim have been published (Rodeghiero et al, 2013 and Cines et al, 2012 [abstract only]); key results of these analyses are summarized within this document. Available data from 2 postauthorization observational studies (Study 20101323 and 20070225) are also summarized.

Table 1-1. Description of Clinical Studies Included in the Pooled Analyses for Safety

Study	Phase	Control	Treatment Duration	Study Design	Subject Population Total (splenectomized/ nonsplenectomized)	Key Study Results (Primary Endpoint)
20000137A	1/2	None	3 weeks	Open-label, sequential cohort, dose-escalation study	Adults with ITP 24 (19/5)	No safety concerns evident when romiplostim administered at doses up to 10 µg/kg once every other week to subjects with ITP
20000137B	2	Placebo	6 weeks	Randomized, double-blind study	Adults with ITP 21 (14/7)	Romiplostim was well-tolerated; no subject developed anti-romiplostim or anti-eTPO antibodies
20010218	1/2	None	3 weeks	Open-label, sequential cohort, dose-escalation study	Adults with ITP 16 (13/3)	Romiplostim was well-tolerated with adverse events typical of those seen in ITP populations
20030105	3	Placebo	24 weeks	Randomized, double-blind, dose-escalation study	Adults with ITP refractory to splenectomy 63 (63/0)	Romiplostim was significantly superior to placebo for the primary efficacy endpoint of incidence of durable platelet response
20030212	3	Placebo	24 weeks	Randomized, double-blind study	Adults with ITP prior to splenectomy 62 (0/62)	Romiplostim demonstrated significant superiority over placebo for all key efficacy endpoints and a tolerable safety profile in subjects with ITP who had not received a splenectomy

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Study	Phase	Control	Treatment Duration	Study Design	Subject Population Total (splenectomized/ nonsplenectomized)	Key Study Results (Primary Endpoint)
20030213[a,b]	Open-label extension	None	Up to 277 weeks	Open-label extension study (subjects from 20000137A, 20000137B, 20010218, 20030105, 20030212, 20040209, 20060131, 20060195)	Adult and pediatric subjects with ITP 313 (103/210)	Romiplostim was well-tolerated in both adult and pediatric populations and the long-term safety profile was consistent with the safety profiles in the pivotal studies
20040209[b]	3b	None	Up to 201 weeks	Open-label, expanded access study	Adults with ITP 407 (208/199)	Romiplostim was well-tolerated and was able to induce platelet responses within weeks of starting treatment in the majority of subjects enrolled
20050162	2	None	3 weeks for dose escalation phase; up to 1 year for treatment continuation	Open-label, sequential cohort dose-escalation, Japanese study	Japanese adults with ITP 12 (3/9)	Romiplostim was well-tolerated; the majority of adverse events were mild in severity
20060113[b]	Open-label extension	None	Up to 243 weeks	Open-label extension Japanese study (subjects from 20050162 and 20060216)	Japanese adults with ITP 44 (17/27)	Romiplostim was well-tolerated; the reported incidence of adverse events did not increase over time during long-term exposure to romiplostim and no neutralizing antibodies against romiplostim or TPO were detected

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Study	Phase	Control	Treatment Duration	Study Design	Subject Population Total (splenectomized/ nonsplenectomized)	Key Study Results (Primary Endpoint)
20060131[b]	3b	Standard of care	52 weeks	Randomized, open-label study	Nonsplenectomized adults with ITP 234 (0/234)	Romiplostim administered weekly was well-tolerated and significantly reduced the incidences of splenectomy and treatment failure in nonsplenectomized subjects with ITP compared with the standard of care
20060216[b]	3	Placebo	12 weeks treatment period	Randomized, double-blind study	Japanese adults with ITP 34 (15/19)	Demonstrated short-term safety of romiplostim compared with placebo in Japanese subjects with ITP and showed evidence for efficacy of romiplostim in raising and sustaining platelet counts in this population
20080009[b]	4	None	3 years	Prospective, open-label study evaluating changes in bone marrow morphology	Adults with ITP 169 (60/109)	Among subjects with evaluable bone marrow results, 0 of 35 subjects in Cohort 1, 0 of 39 subjects in Cohort 2, and 2 of 58 (3.4%) subjects in Cohort 3 developed collagen. One of the 2 subjects who developed collagen had no evidence of collagen at the follow-up bone marrow biopsy 12 weeks after discontinuation of romiplostim.
20080435[b]	2	None	12 month treatment period	Single-arm, interventional study evaluating ITP remission	Adults with ITP who previously received only first-line therapies 75 (0/75)	Treatment with 12 months of romiplostim was associated with a mean of 9.2 months of platelet response during the 12-month treatment period; 93.3% of subjects had a platelet response

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eTPO = endogenous thrombopoietin; ITP = immune thrombocytopenic purpura; TPO = thrombopoietin
The adult ITP safety set consists of all subjects (≥ 18 years at screening) who received investigational product in Studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435 (N = 1111).
[a] For the 20030213 study, which allowed both adult and pediatric subjects for be enrolled, only subjects over 18 years of age at entry were included in this analysis.
[b] New data that were not included in the original marketing application.

A subgroup analysis of prior splenectomy status (at the time of enrollment) was conducted on all safety endpoints. For subjects who enrolled in an extension study, the splenectomy status at the time of enrollment in the parent study was carried forward.

Patient exposure

A total of 1111 subjects (age ≥ 18 years at screening) received investigational product in studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435 . Of these, 1046 subjects received ≥ 1 dose of romiplostim (391 subjects with prior splenectomy and 655 with no prior splenectomy) The median (25th percentile [Q1], 75th percentile [Q3]) average weekly dose was 3.769 (1.939, 6.538) µg/kg/week in subjects with prior splenectomy and 3.327 (1.969, 5.763) µg/kg/week in subjects with no prior splenectomy. Median duration of exposure was 63.0 weeks in subjects with prior splenectomy and 66.0 weeks in subjects with no prior splenectomy.

Table 1-2. Exposure to Investigational Product, by Prior Splenectomy Status (Adult ITP Safety Set – Subjects Who Received Romiplostim)

	Romiplostim		
	Prior Splenectomy (N = 391)	No Prior Splenectomy (N = 655)	Total (N = 1046)
Duration of exposure (weeks)			
Mean (SD)	87.3 (75.5)	82.2 (60.0)	84.1 (66.2)
Median	63.0	66.0	64.9
Q1, Q3	24.0, 154.0	31.0, 126.0	28.0, 131.0
Minimum, maximum	1, 281	0, 283	0, 283
Average weekly dose (µg/kg/week)			
Mean (SD)	4.420 (3.133)	3.978 (2.556)	4.143 (2.792)
Median	3.769	3.327	3.442
Q1, Q3	1.939, 6.538	1.969, 5.763	1.947, 6.071
Minimum, maximum	0.07, 14.59	0.11, 14.39	0.07, 14.59
Cumulative dose (µg)			
Mean (SD)	35340.4 (54923.3)	27841.1 (34129.4)	30644.4 (43220.0)
Median	15485.0	15704.0	15544.0
Q1, Q3	4770.0, 43530.0	5969.0, 36704.4	5615.0, 39035.0
Minimum, maximum	19, 478866	56, 269750	19, 478866

ITP = immune thrombocytopenic purpura; Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation.
Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009 and 20080435.
Duration of exposure (weeks) = (last dose date – first dose date + 7)/7. If a subject is enrolled in multiple studies, this is the sum of treatment durations of individual studies.
Source: Modified from Table 14-5.1.2.

Disposition

A total of 716 subjects with no prior splenectomy were enrolled in a parent study and 225 in an open-label extension study; 613 and 224 of these subjects, respectively, received at least 1 dose of romiplostim, and 469 (76.5%) and 168 (75.0%) completed romiplostim The most frequent (> 3% of subjects) reasons for discontinuation of romiplostim were adverse event full consent withdrawn, requirement for alternative therapy, and other in the parent study and full consent withdrawn, requirement for alternative therapy, and death in the extension study.

A total of 395 subjects with prior splenectomy were enrolled in a parent study and 111 in an open-label extension study; 368 and 111 of these subjects, respectively, received at least 1 dose of romiplostim, and 266 (72.3%) and 67 (60.4%) completed romiplostim. The most frequent (> 3% of subjects) reasons for discontinuation of romiplostim were adverse event full consent withdrawn, requirement for alternative therapy, and protocol-specified criteria in the parent study and adverse event, full consent withdrawn, requirement for alternative therapy, subject request, and other in the extension study.

Baseline Demographics and Disease Characteristics

In the adult ITP safety set, 60.2% of the subjects with no prior splenectomy were women, 77.1% were white, and the median age was 53.0 years (range 18 to 93 years). The median (25th percentile [Q1], 75th percentile [Q3]) time since ITP diagnosis was 1.62 (0.33, 5.39) years , and the median baseline platelet count was 19.3 x 109/L (Table 1-6). Most (72.3%) of these subjects had prior ITP treatment history; the most frequent (> 20% of subjects with available history) were corticosteroid (96.1%), intravenous (IV) immune gamma globulin (52.1%), rituximab (20.1%), and *Helicobacter pylori* eradication therapy (31.6%).

Among subjects with prior splenectomy, 64.3% were women, 85.6% were white, and the median age was 52.0 years (range 18 to 88 years) . The median (Q1, Q3) time since ITP diagnosis was 8.71 (3.55, 17.91) years , the median baseline platelet count was 14.0 x 109/L , and the median time since splenectomy was 6.38 years . Approximately half (47.3%) of these subjects had prior ITP treatment history; the most

frequent (> 20% of subjects with available history) were corticosteroid (98.9%), anti-D antibody (WinRho) (26.6%), IV immune gamma globulin (80.7%), vincristine/vinblastine (30.5%), cyclophosphamide (20.3%), danazol (45.5%), azathioprine (38.5%), rituximab (48.9%), *H pylori* eradication therapy (53.3%), and other (47.1%) .

Table 1-4. Demographics, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No				Prior Splenectomy Status = Yes			
	Received Placebo/SOC Only (N = 61)	Received Placebo/SOC and Romiplostim (N = 45)	Received Romiplostim Only (N = 610)	Total (N = 716)	Received Placebo/SOC Only (N = 4)	Received Placebo/SOC and Romiplostim (N = 23)	Received Romiplostim Only (N = 368)	Total (N = 395)
Age (years)								
Mean (SD)	54.5 (20.5)	53.7 (17.8)	52.5 (18.7)	52.7 (18.8)	53.0 (12.8)	51.9 (13.7)	51.7 (15.5)	51.7 (15.4)
Median	57.0	52.0	53.0	53.0	51.5	56.0	52.0	52.0
Q1, Q3	37.0, 72.0	42.0, 66.0	37.0, 68.0	38.0, 68.0	45.0, 61.0	42.0, 62.0	40.0, 63.0	40.0, 63.0
Minimum, maximum	18, 86	18, 88	18, 93	18, 93	39, 70	26, 72	18, 88	18, 88
Sex - n (%)								
Female	35 (57.4)	33 (73.3)	363 (59.5)	431 (60.2)	3 (75.0)	14 (60.9)	237 (64.4)	254 (64.3)
Male	26 (42.6)	12 (26.7)	247 (40.5)	285 (39.8)	1 (25.0)	9 (39.1)	131 (35.6)	141 (35.7)
Race - n (%)								
White or Caucasian	53 (86.9)	35 (77.8)	464 (76.1)	552 (77.1)	3 (75.0)	17 (73.9)	318 (86.4)	338 (85.6)
Black or African American	1 (1.6)	0 (0.0)	13 (2.1)	14 (2.0)	1 (25.0)	1 (4.3)	11 (3.0)	13 (3.3)
Hispanic or Latino	6 (9.8)	2 (4.4)	24 (3.9)	32 (4.5)	0 (0.0)	0 (0.0)	17 (4.6)	17 (4.3)
Asian	0 (0.0)	0 (0.0)	13 (2.1)	13 (1.8)	0 (0.0)	0 (0.0)	6 (1.6)	6 (1.5)
Japanese	0 (0.0)	7 (15.6)	93 (15.2)	100 (14.0)	0 (0.0)	5 (21.7)	13 (3.5)	18 (4.6)
American Indian or Alaska Native	0 (0.0)	1 (2.2)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Other	1 (1.6)	0 (0.0)	1 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.5)
Unknown	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
ITP = immune thrombocytopenic purpura; Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation; SOC = standard of care. Percentages are based on N.
If subjects enrolled in multiple studies, the baseline information from the first ITP study was used in the summary.
Source: Modified from Table 14-2.1.3.1 and Table 14-2.1.3.2.

Table 1-5. Baseline Disease Characteristics, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No				Prior Splenectomy Status = Yes			
	Received Placebo/SOC Only (N = 61)	Received Placebo/SOC and Romiplostim (N = 45)	Received Romiplostim Only (N = 610)	Total (N = 716)	Received Placebo/SOC Only (N = 4)	Received Placebo/SOC and Romiplostim (N = 23)	Received Romiplostim Only (N = 368)	Total (N = 395)
Years since ITP Diagnosis - n (%)								
Mean (SD)	3.82 (5.75)	5.36 (4.72)	4.07 (6.27)	4.13 (6.15)	9.65 (7.54)	11.01 (8.58)	12.41 (11.58)	12.30 (11.38)
Median	1.40	4.30	1.52	1.62	7.15	9.60	8.65	8.71
Q1, Q3	0.36, 4.60	1.51, 7.60	0.30, 5.22	0.33, 5.39	4.85, 14.45	2.60, 14.70	3.55, 18.10	3.55, 17.91
Minimum, maximum	0.0, 33.2	0.0, 16.2	0.0, 45.0	0.0, 45.0	3.7, 20.6	1.1, 31.4	0.0, 57.1	0.0, 57.1
Time since ITP Diagnosis - n (%)								
< 6 Months	21 (34.4)	5 (11.1)	201 (33.0)	227 (31.7)	0 (0.0)	0 (0.0)	12 (3.3)	12 (3.0)
6-12 Months	6 (9.8)	3 (6.7)	55 (9.0)	64 (8.9)	0 (0.0)	0 (0.0)	13 (3.5)	13 (3.3)
> 12 Months	34 (55.7)	37 (82.2)	354 (58.0)	425 (59.4)	4 (100.0)	23 (100.0)	342 (92.9)	369 (93.4)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Years since splenectomy								
Mean (SD)	–	–	–	–	8.74 (8.56)	10.14 (8.28)	10.11 (10.71)	10.10 (10.55)
Median	–	–	–	–	7.03	9.05	6.04	6.38
Q1, Q3	–	–	–	–	3.14, 14.34	2.51, 14.26	2.08, 14.44	2.10, 14.38
Minimum, maximum	–	–	–	–	0.3, 20.6	0.9, 31.4	0.0, 53.1	0.0, 53.1

Adult ITP Safety Set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
ITP = immune thrombocytopenic purpura; Q1 = 25th percentile; Q3 = 75th percentile; SD = standard deviation; SOC = standard of care. Percentages are based on N.
If subjects enrolled in multiple studies, the baseline information from the first ITP study was used in the summary.
Source: Modified from Table 14-2.2.3.1 and Table 14-2.2.3.2.

As noted above, the median time since ITP diagnosis was 1.62 years in subjects with no prior splenectomy and 8.71 years in subjects with prior splenectomy, and the median baseline platelet count was 19.3 x 109/L in subjects with no prior splenectomy and 14.0 x 109/L in subjects with prior splenectomy. Thus, in general, the subjects with prior splenectomy represented a more advanced ITP population

Adverse events

Among subjects administered romiplostim, adverse events were reported in 610 (93.1%) subjects with no prior splenectomy and 377 (96.4%) subjects with prior splenectomy; CTCAE grade ≥ 3 adverse events were reported in 251 (38.3%) and 182 (46.5%) subjects, respectively; serious adverse events were reported in 201 (30.7%) and 153 (39.1%) subjects; and fatal adverse events were reported in 31 (4.7%) and 11 (2.8%) subjects

Table 2-1. Overall Summary of Subject Incidence of Adverse Events, by Prior Splenectomy Status (ITP Safety Set)

	Prior Splenectomy Status = No		Prior Splenectomy Status = Yes	
	Placebo/SOC (N = 106)	Romiplostim (N = 655)	Placebo/SOC (N = 27)	Romiplostim (N = 391)
All adverse events - n (%)	99 (93.4)	610 (93.1)	25 (92.6)	377 (96.4)
Grade ≥ 2	75 (70.8)	483 (73.7)	17 (63.0)	296 (75.7)
Grade ≥ 3	43 (40.6)	251 (38.3)	9 (33.3)	182 (46.5)
Grade ≥ 4	14 (13.2)	71 (10.8)	3 (11.1)	52 (13.3)
Grade Unknown	1 (0.9)	2 (0.3)	0 (0.0)	4 (1.0)
Serious adverse events	36 (34.0)	201 (30.7)	6 (22.2)	153 (39.1)
Leading to discontinuation of IP	4 (3.8)	54 (8.2)	1 (3.7)	31 (7.9)
Serious	3 (2.8)	40 (6.1)	0 (0.0)	23 (5.9)
Non-Serious	2 (1.9)	18 (2.7)	1 (3.7)	9 (2.3)
Leading to discontinuation from study	4 (3.8)	47 (7.2)	0 (0.0)	27 (6.9)
Serious	1 (0.9)	39 (6.0)	0 (0.0)	21 (5.4)
Non-Serious	3 (2.8)	8 (1.2)	0 (0.0)	7 (1.8)
Fatal adverse events	5 (4.7)	31 (4.7)	3 (11.1)	11 (2.8)
Treatment related adverse events - n (%)	38 (35.8)	299 (45.6)	8 (29.6)	200 (51.2)
Grade ≥ 2	24 (22.6)	136 (20.8)	3 (11.1)	130 (33.2)
Grade ≥ 3	9 (8.5)	50 (7.6)	0 (0.0)	55 (14.1)
Grade ≥ 4	3 (2.8)	7 (1.1)	0 (0.0)	8 (2.0)
Serious adverse events	6 (5.7)	39 (6.0)	0 (0.0)	37 (9.5)
Leading to discontinuation of IP	1 (0.9)	19 (2.9)	0 (0.0)	20 (5.1)
Serious	1 (0.9)	11 (1.7)	0 (0.0)	13 (3.3)
Non-Serious	1 (0.9)	9 (1.4)	0 (0.0)	7 (1.8)
Leading to discontinuation from study	0 (0.0)	19 (2.9)	0 (0.0)	19 (4.9)
Serious	0 (0.0)	12 (1.8)	0 (0.0)	13 (3.3)
Non-Serious	0 (0.0)	7 (1.1)	0 (0.0)	6 (1.5)
Fatal adverse events	0 (0.0)	3 (0.5)	0 (0.0)	2 (0.5)

Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
IP = investigational product; ITP = immune thrombocytopenic purpura; SOC = standard of care.
Subjects who started on placebo/SOC treatment group and then enrolled to an open-label extension study during which received romiplostim were counted in both treatment groups.
Only adverse events starting after the first dose of investigational product are tabulated.
Severities are based on CTCAE v 3.0.
Source: Modified from Table 14-6.1.1.2 and Table 14-6.1.1.3.

A summary of the subject incidence of adverse events, related adverse events, grade ≥ 3 adverse events, and serious and serious related adverse events by splenectomy status is presented in Table 1 and a summary of these adverse events by duration-adjusted rate is presented in Table 2.

Table 1. Subject Incidence of Adverse Events, Related, Grade ≥ 3, Serious, and Related Serious Adverse Events by Prior Splenectomy Status (ITP Safety Set)

	Prior Splenectomy Status = No		Prior Splenectomy Status = Yes	
	Placebo/SOC (N = 106)	Romiplostim (N = 655)	Placebo/SOC (N = 27)	Romiplostim (N = 391)
All adverse events - n (%)	99 (93.4)	610 (93.1)	25 (92.6)	377 (96.4)
Grade ≥ 3	43 (40.6)	251 (38.3)	9 (33.3)	182 (46.5)
Grade ≥ 4	14 (13.2)	71 (10.8)	3 (11.1)	52 (13.3)
Serious adverse events	36 (34.0)	201 (30.7)	6 (22.2)	153 (39.1)
Fatal adverse events	5 (4.7)	31 (4.7)	3 (11.1)	11 (2.8)
Treatment related adverse events - n (%)	38 (35.8)	299 (45.6)	8 (29.6)	200 (51.2)
Grade ≥ 3	9 (8.5)	50 (7.6)	0 (0.0)	55 (14.1)
Grade ≥ 4	3 (2.8)	7 (1.1)	0 (0.0)	8 (2.0)
Serious adverse events	6 (5.7)	39 (6.0)	0 (0.0)	37 (9.5)
Fatal adverse events	0 (0.0)	3 (0.5)	0 (0.0)	2 (0.5)

Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
IP = investigational product; ITP = immune thrombocytopenic purpura; SOC = standard of care.
Subjects who started on placebo/SOC treatment group and then enrolled to an open-label extension study during which received romiplostim were counted in both treatment groups.
Only adverse events starting after the first dose of investigational product are tabulated.
Severities are based on CTCAE v 3.0.
Source: Modified from Table 14-6.1.1.2 and Table 14-6.1.1.3.

Table 2. Study Duration Adjusted Rate of Related, Grade ≥ 3, Serious, and Related Serious Adverse Events by Splenectomy Status (Adult ITP Safety Set)

	Splenectomy Status = No				Splenectomy Status = Yes			
	Placebo/SOC (Pt-yr=97.7) (N = 106)		Romiplostim (Pt-yr=1129.7) (N = 655)		Placebo/SOC (Pt-yr=11.2) (N = 27)		Romiplostim (Pt-yr=702.0) (N = 391)	
	n	(r)	n	(r)	n	(r)	n	(r)
Total Number of Events Reported								
Related Adverse Events	36	(36.9)	928	(82.1)	15	(134.2)	864	(123.1)
Grade ≥ 3 Adverse Events	118	(120.8)	757	(67.0)	21	(187.9)	751	(107.0)
Serious Adverse Events	92	(94.2)	498	(44.1)	15	(134.2)	478	(68.1)
Related Serious Adverse Events	18	(18.4)	59	(5.2)	0	(0.0)	65	(9.3)

Adult ITP Safety Set consists of all subjects (age >= 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009 and 20080435.
SOC = Standard of Care.
Pt-yr=Total subject-years on study.
n=Number of adverse events. r=duration adjusted event rate per 100 subject-years (n/Pt-yr*100).
Multiple occurrences of the same event for a subject are counted as multiple events.
Only adverse events starting after the first dose of investigational product are tabulated.
Coded using the MedDRA v17.0.
Subjects who started on placebo/SOC treatment group and then received romiplostim were counted in both treatment groups. Data before subjects received first dose of romiplostim was summarized in placebo/SOC group, and all data on or after first dose of romiplostim was summarized in romiplostim group regardless of further treatment switch.
Source: Modified from Tables 14-6.3.4.2, 14-6.3.4.3, 14-6.4.4.2, 14-6.4.4.3, 14-6.7.4.2, 14-6.7.4.3, 14-6.8.4.2, and 14-6.8.4.3

Among subjects administered romiplostim, adverse events were reported in 610 (93.1%) subjects with no prior splenectomy and 377 (96.4%) subjects with prior splenectomy (Table 2-2). The most frequently reported treatment-emergent adverse events (≥ 20% of subjects administered romiplostim, descending order of frequency) were headache, nasopharyngitis, fatigue, and arthralgia in subjects with no prior splenectomy and headache, epistaxis, arthralgia, contusion, nasopharyngitis, fatigue, petechiae, diarrhea, nausea, and upper respiratory tract infection in subjects with prior splenectomy.

Among subjects administered romiplostim, the total number of adverse events reported (duration-adjusted event rate per 100 subject-years) was 9624 (851.9) in subjects with no prior splenectomy and 8609 (1226.3) in subjects with prior splenectomy. The most frequently reported adverse events (duration-adjusted event rate ≥ 20 per 100 subject-years, descending order of frequency) were headache, contusion, nasopharyngitis, fatigue, and epistaxis in subjects with no prior splenectomy; and headache, contusion, epistaxis, nasopharyngitis, fatigue, arthralgia, petechiae, diarrhea, upper respiratory tract infection, and nausea in subjects with prior splenectomy.

Among subjects administered romiplostim, the total number of investigational product-related adverse events reported (duration-adjusted event rate per 100 subject-years) was 928 (82.1) in subjects with no prior splenectomy and 864 (123.1) in subjects with prior splenectomy

The most frequently reported investigational product-related adverse events (duration-adjusted event rate ≥ 5 per 100 subject-years, descending order of frequency) were headache in subjects with no prior splenectomy and headache, fatigue, myalgia, and arthralgia in subjects with prior splenectomy.

Among subjects administered romiplostim, CTCAE grade 3 or higher adverse events were reported in 251 (38.3%) subjects with no prior splenectomy and 182 (46.5%) subjects with prior splenectomy

Table 2-3. Subject Incidence of Investigational Product Related Adverse Events Reported in ≥ 2% of Subjects Administered Romiplostim, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No		Prior Splenectomy Status = Yes	
Preferred Term	Placebo/SOC (N = 106) n (%)	Romiplostim (N = 655) n (%)	Placebo/SOC (N = 27) n (%)	Romiplostim (N = 391) n (%)
Subjects Reporting Adverse Events	8 (7.5)	299 (45.6)	8 (29.6)	200 (51.2)
Headache	3 (2.8)	92 (14.0)	1 (3.7)	67 (17.1)
Arthralgia	0 (0.0)	41 (6.3)	1 (3.7)	29 (7.4)
Fatigue	1 (0.9)	34 (5.2)	0 (0.0)	31 (7.9)
Nausea	0 (0.0)	31 (4.7)	0 (0.0)	14 (3.6)
Pain in extremity	0 (0.0)	22 (3.4)	0 (0.0)	10 (2.6)
Myalgia	0 (0.0)	18 (2.7)	0 (0.0)	22 (5.6)
Musculoskeletal pain	0 (0.0)	13 (2.0)	0 (0.0)	5 (1.3)
Pruritus	0 (0.0)	13 (2.0)	0 (0.0)	11 (2.8)
Paraesthesia	0 (0.0)	12 (1.8)	0 (0.0)	8 (2.0)
Rash	0 (0.0)	11 (1.7)	1 (3.7)	8 (2.0)
Dizziness	1 (0.9)	9 (1.4)	0 (0.0)	11 (2.8)
Pyrexia	1 (0.9)	7 (1.1)	0 (0.0)	8 (2.0)
Pain	0 (0.0)	7 (1.1)	0 (0.0)	10 (2.6)
Thrombocytosis	0 (0.0)	7 (1.1)	0 (0.0)	10 (2.6)
Injection site pain	1 (0.9)	6 (0.9)	1 (3.7)	16 (4.1)
Back pain	0 (0.0)	5 (0.8)	0 (0.0)	9 (2.3)
Insomnia	0 (0.0)	6 (0.9)	0 (0.0)	9 (2.3)
Bone marrow disorder	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.0)

Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
ITP = immune thrombocytopenic purpura; SOC = standard of care.
Coded using the MedDRA v 17.0.
Subjects who started on placebo/SOC treatment group and then enrolled to an open-label extension study during which received romiplostim were counted in both treatment groups.
Only adverse events starting after the first dose of investigational product are tabulated.
Source: Modified from Table 14-6.8.3.2 and Table 14-6.8.3.3.

Table 2-4. Subject Incidence of CTCAE Grade 3 or Higher Adverse Events Reported in ≥ 1% of Subjects Administered Romiplostim, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No		Prior Splenectomy Status = Yes	
Preferred Term	Placebo/SOC (N = 106) n (%)	Romiplostim (N = 655) n (%)	Placebo/SOC (N = 27) n (%)	Romiplostim (N = 391) n (%)
Subjects Reporting Adverse Events	43 (40.6)	251 (38.3)	9 (33.3)	182 (46.5)
Thrombocytopenia	9 (8.5)	49 (7.5)	0 (0.0)	38 (9.7)
Immune thrombocytopenic purpura	2 (1.9)	29 (4.4)	0 (0.0)	20 (5.1)
Headache	1 (0.9)	14 (2.1)	1 (3.7)	25 (6.4)
Fatigue	2 (1.9)	13 (2.0)	0 (0.0)	13 (3.3)
Pneumonia	2 (1.9)	11 (1.7)	2 (7.4)	8 (2.0)
Epistaxis	2 (1.9)	8 (1.2)	1 (3.7)	11 (2.8)
Platelet count decreased	1 (0.9)	8 (1.2)	1 (3.7)	10 (2.6)
Arthralgia	0 (0.0)	8 (1.2)	0 (0.0)	8 (2.0)
Abdominal pain	2 (1.9)	7 (1.1)	0 (0.0)	9 (2.3)
Petechiae	1 (0.9)	6 (0.9)	0 (0.0)	6 (1.5)
Anaemia	0 (0.0)	6 (0.9)	1 (3.7)	9 (2.3)
Back pain	0 (0.0)	6 (0.9)	1 (3.7)	7 (1.8)
Pain in extremity	2 (1.9)	5 (0.8)	0 (0.0)	6 (1.5)
Nausea	1 (0.9)	5 (0.8)	0 (0.0)	7 (1.8)
Gastrointestinal haemorrhage	1 (0.9)	4 (0.6)	2 (7.4)	9 (2.3)
Purpura	0 (0.0)	1 (0.2)	1 (3.7)	7 (1.8)
Dyspnoea	1 (0.9)	2 (0.3)	0 (0.0)	7 (1.8)
Syncope	0 (0.0)	2 (0.3)	0 (0.0)	7 (1.8)
Pulmonary embolism	0 (0.0)	5 (0.8)	1 (3.7)	6 (1.5)
Deep vein thrombosis	0 (0.0)	5 (0.8)	0 (0.0)	6 (1.5)
Vomiting	1 (0.9)	4 (0.6)	0 (0.0)	6 (1.5)
Chest pain	0 (0.0)	2 (0.3)	0 (0.0)	5 (1.3)
Contusion	0 (0.0)	3 (0.5)	0 (0.0)	5 (1.3)
Asthenia	0 (0.0)	3 (0.5)	0 (0.0)	4 (1.0)
Bone marrow disorder	1 (0.9)	1 (0.2)	0 (0.0)	4 (1.0)
Diarrhoea	0 (0.0)	4 (0.6)	0 (0.0)	4 (1.0)
Haematoma	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.0)
Myalgia	0 (0.0)	4 (0.6)	0 (0.0)	4 (1.0)
Neutropenia	1 (0.9)	3 (0.5)	0 (0.0)	4 (1.0)

Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
CTCAE = Common Terminology Criteria for Adverse Events; ITP = immune thrombocytopenic purpura; SOC = standard of care.
Coded using the MedDRA v 17.0. Severities are based on CTCAE v 3.0.
Subjects who started on placebo/SOC treatment group and then enrolled to an open-label extension study during which received romiplostim were counted in both treatment groups.
Only adverse events starting after the first dose of investigational product are tabulated.
Source: Modified from Table 14-6.7.3.2 and Table 14-6.7.3.3.

Serious adverse event / deaths / other significant events

Serious Adverse Events

Among subjects administered romiplostim, serious adverse events were reported in 201 (30.7%) subjects with no prior splenectomy and 153 (39.1%) subjects with prior splenectomy

Table 2-6. Subject Incidence of Serious Adverse Events Reported in > 2 Subjects Administered Romiplostim, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No		Prior Splenectomy Status = Yes	
Preferred Term	Placebo/SOC (N = 106) n (%)	Romiplostim (N = 655) n (%)	Placebo/SOC (N = 27) n (%)	Romiplostim (N = 391) n (%)
Subjects Reporting Serious Adverse Events	36 (34.0)	201 (30.7)	6 (22.2)	153 (39.1)
Thrombocytopenia	9 (8.5)	34 (5.2)	0 (0.0)	25 (6.4)
Pneumonia	2 (1.9)	11 (1.7)	2 (7.4)	11 (2.8)
Immune thrombocytopenic purpura	3 (2.8)	9 (1.4)	0 (0.0)	11 (2.8)
Pyrexia	1 (0.9)	6 (0.9)	0 (0.0)	5 (1.3)
Cerebrovascular accident	0 (0.0)	6 (0.9)	0 (0.0)	1 (0.3)
Epistaxis	0 (0.0)	6 (0.9)	0 (0.0)	11 (2.8)
Myocardial infarction	0 (0.0)	6 (0.9)	0 (0.0)	2 (0.5)
Pulmonary embolism	0 (0.0)	6 (0.9)	1 (3.7)	6 (1.5)
Atrial fibrillation	1 (0.9)	5 (0.8)	0 (0.0)	1 (0.3)
Deep vein thrombosis	1 (0.9)	5 (0.8)	0 (0.0)	6 (1.5)
Platelet count decreased	1 (0.9)	5 (0.8)	1 (3.7)	3 (0.8)
Renal failure	1 (0.9)	5 (0.8)	0 (0.0)	1 (0.3)
Renal failure acute	1 (0.9)	5 (0.8)	0 (0.0)	1 (0.3)
Haemorrhage	0 (0.0)	5 (0.8)	0 (0.0)	3 (0.8)
Abdominal pain	2 (1.9)	4 (0.6)	0 (0.0)	4 (1.0)
Cardiac failure congestive	1 (0.9)	4 (0.6)	0 (0.0)	1 (0.3)
Gastrointestinal haemorrhage	1 (0.9)	4 (0.6)	1 (3.7)	9 (2.3)
Pain in extremity	1 (0.9)	4 (0.6)	0 (0.0)	0 (0.0)
Anaemia	0 (0.0)	4 (0.6)	0 (0.0)	5 (1.3)
Cardiac failure	0 (0.0)	4 (0.6)	0 (0.0)	2 (0.5)
Cellulitis	0 (0.0)	4 (0.6)	0 (0.0)	2 (0.5)
Hyperkalaemia	0 (0.0)	4 (0.6)	0 (0.0)	1 (0.3)
Nausea	0 (0.0)	4 (0.6)	0 (0.0)	4 (1.0)
Rash	0 (0.0)	4 (0.6)	0 (0.0)	0 (0.0)
Rectal haemorrhage	0 (0.0)	4 (0.6)	0 (0.0)	4 (1.0)

	Prior Splenectomy Status = No		Prior Splenectomy Status = Yes	
Preferred Term	Placebo/SOC (N = 106) n (%)	Romiplostim (N = 655) n (%)	Placebo/SOC (N = 27) n (%)	Romiplostim (N = 391) n (%)
Dyspnoea	2 (1.9)	3 (0.5)	0 (0.0)	4 (1.0)
Bronchitis	1 (0.9)	3 (0.5)	0 (0.0)	1 (0.3)
Lobar pneumonia	1 (0.9)	3 (0.5)	0 (0.0)	0 (0.0)
Urinary tract infection	1 (0.9)	3 (0.5)	0 (0.0)	4 (1.0)
Appendicitis	0 (0.0)	3 (0.5)	0 (0.0)	2 (0.5)
Asthenia	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)
Cholecystitis	0 (0.0)	3 (0.5)	0 (0.0)	2 (0.5)
Cholecystitis acute	0 (0.0)	3 (0.5)	0 (0.0)	1 (0.3)
Contusion	0 (0.0)	3 (0.5)	0 (0.0)	3 (0.8)
Dehydration	0 (0.0)	3 (0.5)	0 (0.0)	3 (0.8)
Oedema peripheral	0 (0.0)	3 (0.5)	0 (0.0)	1 (0.3)
Pleural effusion	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)
Respiratory failure	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)
Wound	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)
Headache	1 (0.9)	2 (0.3)	1 (3.7)	6 (1.5)
Petechiae	1 (0.9)	2 (0.3)	0 (0.0)	4 (1.0)
Back pain	0 (0.0)	2 (0.3)	0 (0.0)	3 (0.8)
Bone marrow disorder	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.5)
Chest pain	0 (0.0)	1 (0.2)	0 (0.0)	5 (1.3)
Syncope	0 (0.0)	2 (0.3)	0 (0.0)	5 (1.3)
Vaginal haemorrhage	0 (0.0)	1 (0.2)	0 (0.0)	5 (1.3)
Purpura	0 (0.0)	1 (0.2)	1 (3.7)	4 (1.0)
Mouth haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.0)
Osteoarthritis	0 (0.0)	2 (0.3)	0 (0.0)	4 (1.0)
Lower respiratory tract infection	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.8)
Portal vein thrombosis	0 (0.0)	2 (0.3)	0 (0.0)	3 (0.8)
Transient ischaemic attack	0 (0.0)	2 (0.3)	0 (0.0)	3 (0.8)
Vomiting	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.8)

Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
ITP = immune thrombocytopenic purpura; SOC = standard of care.
Coded using the MedDRA v 17.0.
Subjects who started on placebo/SOC treatment group and then enrolled to an open-label extension study during which received romiplostim were counted in both treatment groups.
Only adverse events starting after the first dose of investigational product are tabulated.
Source: Modified from Table 14-6.3.3.2 and Table 14-6.3.3.3.

Among subjects administered romiplostim, the total number of serious adverse events reported (duration-adjusted event rate per 100 subject-years) was 498 (44.1) in subjects with no prior splenectomy and 478 (68.1) in subjects with prior splenectomy.

Among subjects administered romiplostim, investigational product-related serious adverse events were reported in 39 (6.0%) subjects with no prior splenectomy and 37 (9.5%) subjects with prior splenectomy

Table 2-7. Subject Incidence of Investigational Product-Related Serious Adverse Events Reported in ≥ 2 Subjects Administered Romiplostim, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No		Prior Splenectomy Status = Yes	
Preferred Term	Placebo/SOC (N = 106) n (%)	Romiplostim (N = 655) n (%)	Placebo/SOC (N = 27) n (%)	Romiplostim (N = 391) n (%)
Subjects Reporting Investigational Product Related, Serious Adverse Events	6 (5.7)	39 (6.0)	0 (0.0)	37 (9.5)
Pulmonary embolism	0 (0.0)	6 (0.9)	0 (0.0)	2 (0.5)
Deep vein thrombosis	0 (0.0)	3 (0.5)	0 (0.0)	3 (0.8)
Myocardial infarction	0 (0.0)	3 (0.5)	0 (0.0)	1 (0.3)
Thrombocytopenia	0 (0.0)	3 (0.5)	0 (0.0)	4 (1.0)
Angina unstable	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
Bone marrow reticulin fibrosis	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.3)
Bone marrow disorder	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.5)
Contusion	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Headache	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.5)
Mouth haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Vaginal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)

Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
ITP = immune thrombocytopenic purpura; SOC = standard of care.
Coded using the MedDRA v 17.0.
Subjects who started on placebo/SOC treatment group and then enrolled in an open-label extension study during which they received romiplostim were counted in both treatment groups.
Only adverse events starting after the first dose of investigational product are tabulated.
Source: Modified from Table 14-6.4.3.2 and Table 14-6.4.3.3.

Deaths

Among subjects administered romiplostim, fatal adverse events were reported in 31 (4.7%) subjects with no prior splenectomy and 11 (2.8%) subjects with prior splenectomy The fatal adverse events were deemed related to romiplostim by the investigator in 3 subjects with no prior splenectomy (intestinal ischemia, myocardial infarction, and angina unstable) and 2 subjects with prior splenectomy (hemolysis and aplastic anemia)

The 3 subjects with fatal outcomes due to intestinal ischemia, hemolysis and aplastic anemia were enrolled in Study 20040209. To be eligible for this study, subjects were to have received at least 1 prior therapy for ITP, and had a platelet count of ≤ 30 x 109/L and/or experienced bleeding that was uncontrolled with conventional therapies.

• A death due to intestinal ischemia had hepatopathy (hepatitis B and C) at baseline with portal vein thrombosis prior to experiencing intestinal ischemia; a clinical picture of sepsis, along with a 50% decrease in hematocrit and lower gastrointestinal bleeding; low platelet count; therefore, underlying ITP was a possible contributory factor for the event.

• Death due to hemolysis along with a urinary tract infection and failure of antibiotic therapy in the previous week. The subject was then hospitalized and experienced disseminated intravascular coagulation. Refractory ITP and exposure to antibiotic therapy were possible contributory factors for the reported event.

• Death due to aplastic anemia / macrocytic anemia at baseline and a low platelet count at the time of the reported event.

Fatal outcomes due to myocardial infarction and unstable angina in Study 20030213 (open-label, extension study evaluating the safety and efficacy of long-term dosing of romiplostim).

• Pre-existing risk factors identified for the subject with myocardial infarction included hypertension (not uncontrolled) and type 2 diabetes. No thrombocytosis was reported 3 weeks prior to the event, and romiplostim dosing was stable.

• Pre-existing risk factors identified for the subject with angina unstable included stable angina for several years prior to starting romiplostim, hypercholesterolemia, atrial fibrillation, and familial cardiovascular history. Triple vessel disease (diagnosed during romiplostim therapy) was likely a significant contributory factor for the reported event. Thrombocytosis was not reported on the day of the fatal event, although elevated troponin was. It was not possible following 2 bypasses on that day to wean the patient from an artificial heart.

Table 2-5. Subject Incidence of Fatal Adverse Events by System Organ Class and Preferred Term, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No		Prior Splenectomy Status = Yes	
System Organ Class Preferred Term	Placebo/SOC (N = 106) n (%)	Romiplostim (N = 655) n (%)	Placebo/SOC (N = 27) n (%)	Romiplostim (N = 391) n (%)
Subjects Reporting Fatal Adverse Events	5 (4.7)	31 (4.7)	3 (11.1)	11 (2.8)
Blood and Lymphatic System Disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Aplastic anaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Haemolysis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Cardiac Disorders	2 (1.9)	9 (1.4)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)
Cardiac failure congestive	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
Angina unstable	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Cardiac arrest	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Cardiac failure	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Cardiac tamponade	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Cardio-respiratory arrest	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Left ventricular failure	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)
Intestinal ischaemia	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Intestinal infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
General Disorders and Administration Site Conditions	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
Death	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Sudden death	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Hepatobiliary Disorders	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic failure	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and Infestations	0 (0.0)	5 (0.8)	1 (3.7)	5 (1.3)
Pneumonia	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
Fungal sepsis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Meningitis listeria	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Progressive multifocal leukoencephalopathy	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Cytomegalovirus infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Fungal sepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Osteomyelitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Pneumococcal sepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Pneumonia streptococcal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Atypical pneumonia	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)

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Table 2-5. Subject Incidence of Fatal Adverse Events by System Organ Class and Preferred Term, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No		Prior Splenectomy Status = Yes	
System Organ Class Preferred Term	Placebo/SOC (N = 106) n (%)	Romiplostim (N = 655) n (%)	Placebo/SOC (N = 27) n (%)	Romiplostim (N = 391) n (%)
Injury, Poisoning and Procedural Complications	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Subdural haematoma	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Platelet count decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)	2 (1.9)	1 (0.2)	0 (0.0)	1 (0.3)
Lung neoplasm malignant	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Hepatocellular carcinoma	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.3)
Lung cancer metastatic	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous System Disorders	0 (0.0)	5 (0.8)	1 (3.7)	1 (0.3)
Haemorrhage intracranial	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
Cerebral haemorrhage	0 (0.0)	1 (0.2)	1 (3.7)	0 (0.0)
Intracranial venous sinus thrombosis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Ischaemic stroke	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Brain oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Psychiatric Disorders	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Completed suicide	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Renal and Urinary Disorders	0 (0.0)	4 (0.6)	0 (0.0)	0 (0.0)
Renal failure	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)
Renal failure acute	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders	0 (0.0)	1 (0.2)	1 (3.7)	0 (0.0)
Pulmonary haemorrhage	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Pulmonary embolism	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
Vascular Disorders	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Thrombosis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

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Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
ITP = immune thrombocytopenic purpura; SOC = standard of care.
Coded using the MedDRA v 17.0.
Subjects who started on placebo/SOC treatment group and then enrolled to an open-label extension study during which received romiplostim were counted in both treatment groups.
Only adverse events starting after the first dose of investigational product are tabulated.
Source: Modified from Table 14-6.5.1.2 and Table 14-6.5.1.3.

Safety of Special Interest

Bone Marrow Collagen and Reticulin

Incidence of bone marrow collagen and reticulin in the adult ITP Safety Set (Excluding Study 20080009) is presented in the table below.

Table 2-9. Incidence of Bone Marrow Reticulin/Collagen by Baseline Splenectomy Status (Adult ITP Safety Set Excluding Study 20080009)

	Prior Splenectomy Status = No		Prior Splenectomy Status = Yes	
	Placebo/SOC (N = 106) (Pt-Yr = 97.7)	Romiplostim (N = 546) (Pt-Yr = 866.7)	Placebo/SOC (N = 27) (Pt-Yr = 11.2)	Romiplostim (N = 331) (Pt-Yr = 560.6)
Subject Incidence – n (%)	0 (0)	7 (1.3%)	1 (3.7%)	11 (3.3%)
Adjusted Rate per 100 pt yrs – r	0	0.8	8.9	2.0
95% CI of r	(0, 3.1)	(0.3, 1.7)	(0.2, 49.8)	(1.0, 3.5)

Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
Bone marrow abnormalities were collected differently in Study 20080009 than in other ITP studies; thus, data from this study are excluded in the analysis.
ITP = immune thrombocytopenic purpura; Pt-yr = total subject years on study; SOC = standard of care.
n = number of adverse events. r = duration adjusted event rate per 100 subject-years (n/Pt-yr*100).

Study 20080009

Study 20080009 was a prospective, phase 4, open-label, multi-center study designed to evaluate the changes in bone marrow reticulin and collagen in adult subjects receiving romiplostim once weekly for 3 years for the treatment of thrombocytopenia associated with ITP. Subjects were enrolled in 1 of 3 cohorts, with on-study bone marrow biopsies performed at baseline and at year 1 (Cohort 1), year 2 (Cohort 2), or

year 3 (Cohort 3). Thus, bone marrow abnormalities were collected in a more systematic manner in Study 20080009 compared with the other ITP studies included in the adult ITP safety set. Therefore, data from Study 20080009 were excluded from the analysis and are summarized separately below.

Collagen

Of the 169 subjects enrolled in Study 20080009, 132 (78.1%) had evaluable bone marrow trichrome stain results to assess collagen during the study. Among subjects with evaluable bone marrow results, 0 of 35 subjects developed collagen within 1 year of romiplostim treatment (Cohort 1); 0 of 39 subjects developed collagen within 2 years of romiplostim treatment (Cohort 2), and 2 of 58 subjects (3.4%, 95% confidence interval [CI]: 0.4%, 11.9%) developed collagen within 3 years of romiplostim treatment (Cohort 3). One of the 2 subjects who developed collagen had no evidence of collagen at the follow-up bone marrow biopsy 12 weeks after discontinuation of romiplostim. This subject is not believed to represent a typical ITP patient since this subject showed no response and remained thrombocytopenic after trials of multiple standard ITP therapies; this subject did not have prior splenectomy before enrollment in the study. The biopsy for the other subject was performed after the subject completed 3 years of romiplostim treatment, and the subject refused the follow-up bone marrow biopsy; this subject had prior splenectomy before enrollment in the study.

Reticulin

Nine of 131 subjects showed an increase in modified Bauermeister grade by ≥ 2 severity grades or an increase to grade 4 by silver staining: 0 of 34 subjects within 1 year of romiplostim treatment (Cohort 1); 2 of 39 subjects (5.1%, 95% CI: 0.6%, 17.3%) within 2 years of romiplostim treatment (Cohort 2); and 7 of 58 subjects (12.1%, 95% CI: 5.0%, 23.3%) within 3 years of romiplostim treatment (Cohort 3). Three of the 9 subjects with an increase in modified Bauermeister grade by ≥ 2 severity grades or an increase to grade 4 had prior splenectomy before enrollment in this study. As the presence of collagen defines a modified Bauermeister grade of 4, the 2 subjects who met the primary collagen endpoint also met this secondary endpoint (ie, they comprise 2 of the 9 subjects). Two of the 7 subjects who met this endpoint on reticulin alone had repeat bone marrow biopsies; both subjects showed return to baseline modified Bauermeister grade.

Thrombocytopenia Events After Cessation of Romiplostim Treatment

Table 2-11. Thrombocytopenia Events After Cessation of Romiplostim Treatment by Preferred Term (Adult ITP Safety Set – Subjects Who Received Romiplostim)

	No Prior Splenectomy (N = 655) n (%)	Prior Splenectomy (N = 391) n (%)	Total (N = 1046) n (%)
Number and percent of subjects reported thrombocytopenia events after cessation of romiplostim treatment	24 (3.7)	10 (2.6)	34 (3.3)
Total number of thrombocytopenia events after cessation of romiplostim treatment	25	12	37

Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
ITP = immune thrombocytopenic purpura
Coded using the MedDRA v 17.0.
Percentages are based on N.
Events that started after the last non-zero dose of romiplostim were included in the analysis.
Source: Modified from Table 14-6.6.13.7.

Pulmonary Disorders

Table 2-13. Overall Summary of Pulmonary Disorder Adverse Events of Interest, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No				Prior Splenectomy Status = Yes			
	Placebo/SOC (N = 106) (Pt-yr = 97.7)		Romiplostim (N = 655) (Pt-yr = 1129.7)		Placebo/SOC (N = 27) (Pt-yr = 11.2)		Romiplostim (N = 391) (Pt-yr = 702.0)	
Pulmonary Disorder Adverse Events of Interest	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]
All adverse events	69 (65.1%)	158 (161.8)	426 (65.0%)	1743 (154.3)	13 (48.1%)	42 (375.8)	290 (74.2%)	1548 (220.5)
Serious adverse events	10 (9.4%)	12 (12.3)	41 (6.3%)	61 (5.4)	3 (11.1%)	4 (35.8)	43 (11.0%)	72 (10.3)
Leading to discontinuation of IP	0 (0.0%)	0 (0.0)	8 (1.2%)	8 (0.7)	0 (0.0%)	0 (0.0)	4 (1.0%)	4 (0.6)
Fatal adverse events	2 (1.9%)	2 (2.0)	4 (0.6%)	4 (0.4)	2 (7.4%)	2 (17.9)	1 (0.3%)	1 (0.1)
Treatment-related adverse events	9 (8.5%)	11 (11.3)	28 (4.3%)	33 (2.9)	2 (7.4%)	2 (17.9)	19 (4.9%)	24 (3.4)
Treatment-related serious adverse events	2 (1.9%)	2 (2.0)	10 (1.5%)	10 (0.9)	0 (0.0%)	0 (0.0)	3 (0.8%)	3 (0.4)

IP = investigational product; ITP = immune thrombocytopenic purpura; Pt-yr = total subject years on study; SOC = standard of care.
[a] n (%) = number and percent of subjects reporting predefined adverse events
[b] n (r) = number of adverse events and duration-adjusted event rate per 100 subject-years (n/Pt-yr*100). Multiple occurrences of the same event for a subject are counted as multiple events.
Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
Only adverse events starting after the first dose of investigational product are tabulated. Coded using the MedDRA v 17.0.
Subjects who started on placebo/SOC treatment group and then received romiplostim were counted in both treatment groups. Data before subjects received first dose of romiplostim was summarized in placebo/SOC group, and all data on or after first dose of romiplostim was summarized in romiplostim group regardless of further treatment switch.
Source: Modified from Table 14-6.6.11.1.2, Table 14-6.6.11.1.3, Table 14-6.6.11.2.2, Table 14-6.6.11.2.3, and Table 14-6.6.11.7.1.1 to Table 14-6.6.11.11.2.2.

Haemorrhages

Table 2-15. Overall Summary of Hemorrhage Adverse Events of Interest, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No				Prior Splenectomy Status = Yes			
	Placebo/SOC (N = 106) (Pt-yr = 97.7)		Romiplostim (N = 655) (Pt-yr = 1129.7)		Placebo/SOC (N = 27) (Pt-yr = 11.2)		Romiplostim (N = 391) (Pt-yr = 702.0)	
Hemorrhage Adverse Events of Interest	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]
All adverse events	58 (54.7%)	233 (238.6)	358 (54.7%)	1591 (140.8)	17 (63.0%)	54 (483.2)	257 (65.7%)	1868 (266.1)
Serious adverse events	7 (6.6%)	11 (11.3)	46 (7.0%)	59 (5.2)	4 (14.8%)	7 (62.6)	50 (12.8%)	127 (18.1)
Leading to discontinuation of IP	1 (0.9%)	1 (1.0)	4 (0.6%)	6 (0.5)	0 (0.0%)	0 (0.0)	3 (0.8%)	4 (0.6)
Fatal adverse events	0 (0.0%)	0 (0.0)	5 (0.8%)	5 (0.4)	1 (3.7%)	1 (8.9)	0 (0.0%)	0 (0.0)
Treatment-related adverse events	12 (11.3%)	27 (27.6)	32 (4.9%)	43 (3.8)	2 (7.4%)	4 (35.8)	28 (7.2%)	54 (7.7)
Treatment-related serious adverse events	2 (1.9%)	5 (5.1)	1 (0.2%)	1 (0.1)	0 (0.0%)	0 (0.0)	8 (2.0%)	15 (2.1)

IP = investigational product; ITP = immune thrombocytopenic purpura; Pt-yr = total subject years on study; SOC = standard of care.
[a] n (%) = number and percent of subjects reporting predefined adverse events
[b] n (r) = number of adverse events and duration-adjusted event rate per 100 subject-years (n/Pt-yr*100). Multiple occurrences of the same event for a subject are counted as multiple events.
Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
Only adverse events starting after the first dose of investigational product are tabulated. Coded using the MedDRA v 17.0.
Subjects who started on placebo/SOC treatment group and then received romiplostim were counted in both treatment groups. Data before subjects received first dose of romiplostim was summarized in placebo/SOC group, and all data on or after first dose of romiplostim was summarized in romiplostim group regardless of further treatment switch.
Source: Modified from Table 14-6.6.6.1.2, Table 14-6.6.6.1.3, Table 14-6.6.6.2.2, Table 14-6.6.6.2.3, Table 14-6.6.6.8.2, Table 14-6.6.6.8.3, and Table 14-6.6.6.10.1.1 to Table 14-6.6.6.13.2.2.

Hypersensitivity/Angioedema/Anaphylactic Reactions

Table 2-17. Overall Summary of Preferred Terms From the SMQs for Hypersensitivity/Angioedema/Anaphylactic Reactions, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No				Prior Splenectomy Status = Yes			
	Placebo/SOC (N = 106) (Pt-yr = 97.7)		Romiplostim (N = 655) (Pt-yr = 1129.7)		Placebo/SOC (N = 27) (Pt-yr = 11.2)		Romiplostim (N = 391) (Pt-yr = 702.0)	
Hypersensitivity/Angioedema/Anaphylactic Reaction Adverse Events of Interest	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]
All adverse events	25 (23.6%)	40 (41.0)	176 (26.9%)	325 (28.8)	4 (14.8%)	4 (35.8)	124 (31.7%)	257 (36.6)
Serious adverse events	5 (4.7%)	7 (7.2)	14 (2.1%)	19 (1.7)	0 (0.0%)	0 (0.0)	13 (3.3%)	25 (3.6)
Leading to discontinuation of IP	0 (0.0%)	0 (0.0)	3 (0.5%)	3 (0.3)	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0)
Fatal adverse events	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0)
Treatment-related adverse events	7 (6.6%)	8 (8.2)	29 (4.4%)	37 (3.3)	1 (3.7%)	1 (8.9)	21 (5.4%)	23 (3.3)
Treatment-related serious adverse events	1 (0.9%)	1 (1.0)	1 (0.2%)	1 (0.1)	0 (0.0%)	0 (0.0)	1 (0.3%)	2 (0.3)

IP = investigational product; ITP = immune thrombocytopenic purpura; Pt-y r= total subject years on study; SMQ = standardized MedDRA query; SOC = standard of care.
[a] n (%) = number and percent of subjects reporting predefined adverse events
[b] n (r) = number of adverse events and duration-adjusted event rate per 100 subject-years (n/Pt-yr*100). Multiple occurrences of the same event for a subject are counted as multiple events.
Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
Only adverse events starting after the first dose of investigational product are tabulated. Coded using the MedDRA v 17.0.
Subjects who started on placebo/SOC treatment group and then received romiplostim were counted in both treatment groups. Data before subjects received first dose of romiplostim was summarized in placebo/SOC group, and all data on or after first dose of romiplostim was summarized in romiplostim group regardless of further treatment switch.
Source: Modified from Table 14-6.6.1.1.2, Table 14-6.6.1.1.3, Table 14-6.6.1.2.2, Table 14-6.6.1.2.3, and Table 14-6.6.1.7.1.1 to Table 14-6.6.1.11.2.2.

Renal and urinary Disorders

Table 2-19. Overall Summary of Renal and Urinary Disorder Adverse Events of Interest, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No				Prior Splenectomy Status = Yes			
	Placebo/SOC (N = 106) (Pt-yr = 97.7)		Romiplostim (N = 655) (Pt-yr = 1129.7)		Placebo/SOC (N = 27) (Pt-yr = 11.2)		Romiplostim (N = 391) (Pt-yr = 702.0)	
Renal and Urinary Disorder Adverse Events of Interest	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]
All adverse events	11 (10.4%)	18 (18.4)	75 (11.5%)	118 (10.4)	0 (0.0%)	0 (0.0)	38 (9.7%)	52 (7.4)
Serious adverse events	3 (2.8%)	3 (3.1)	15 (2.3%)	18 (1.6)	0 (0.0%)	0 (0.0)	5 (1.3%)	5 (0.7)
Leading to discontinuation of IP	0 (0.0%)	0 (0.0)	5 (0.8%)	5 (0.4)	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0)
Fatal adverse events	0 (0.0%)	0 (0.0)	4 (0.6%)	4 (0.4)	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0)
Treatment-related adverse events	1 (0.9%)	1 (1.0)	2 (0.3%)	2 (0.2)	0 (0.0%)	0 (0.0)	1 (0.3%)	1 (0.1)
Treatment-related serious adverse events	1 (0.9%)	1 (1.0)	2 (0.3%)	2 (0.2)	0 (0.0%)	0 (0.0)	1 (0.3%)	1 (0.1)

IP = investigational product; ITP = immune thrombocytopenic purpura; Pt-yr = total subject years on study; SOC = standard of care.
[a] n (%) = number and percent of subjects reporting predefined adverse events
[b] n (r) = number of adverse events and duration-adjusted event rate per 100 subject-years (n/Pt-yr*100). Multiple occurrences of the same event for a subject are counted as multiple events.
Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
Only adverse events starting after the first dose of investigational product are tabulated. Coded using the MedDRA v 17.0.
Subjects who started on placebo/SOC treatment group and then received romiplostim were counted in both treatment groups. Data before subjects received first dose of romiplostim was summarized in placebo/SOC group, and all data on or after first dose of romiplostim was summarized in romiplostim group regardless of further treatment switch.
Source: Modified from Table 14-6.6.12.1.2, Table 14-6.6.12.1.3, Table 14-6.6.12.2.2, Table 14-6.6.12.2.3, and Table 14-6.6.12.7.1.1 to Table 14-6.6.12.11.2.2.

Cardiac Disorders

Table 2-21. Overall Summary of Cardiac Disorder Adverse Events of Interest, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No				Prior Splenectomy Status = Yes			
	Placebo/SOC (N = 106) (Pt-yr = 97.7)		Romiplostim (N = 655) (Pt-yr = 1129.7)		Placebo/SOC (N = 27) (Pt-yr = 11.2)		Romiplostim (N = 391) (Pt-yr = 702.0)	
Cardiac Disorder Adverse Events of Interest	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]
All adverse events	6 (5.7%)	11 (11.3)	45 (6.9%)	84 (7.4)	0 (0.0%)	0 (0.0)	20 (5.1%)	48 (6.8)
Serious adverse events	3 (2.8%)	8 (8.2)	21 (3.2%)	33 (2.9)	0 (0.0%)	0 (0.0)	7 (1.8%)	17 (2.4)
Leading to discontinuation of IP	0 (0.0%)	0 (0.0)	6 (0.9%)	6 (0.5)	0 (0.0%)	0 (0.0)	1 (0.3%)	1 (0.1)
Fatal adverse events	1 (0.9%)	1 (1.0)	7 (1.1%)	7 (0.6)	0 (0.0%)	0 (0.0)	0 (0.0%)	0 (0.0)
Treatment-related adverse events	2 (1.9%)	3 (3.1)	5 (0.8%)	7 (0.6)	0 (0.0%)	0 (0.0)	3 (0.8%)	4 (0.6)
Treatment-related serious adverse events	2 (1.9%)	3 (3.1)	5 (0.8%)	6 (0.5)	0 (0.0%)	0 (0.0)	2 (0.5%)	3 (0.4)

IP = investigational product; ITP = immune thrombocytopenic purpura; Pt-yr = total subject years on study; SOC = standard of care.
[a] n (%) = number and percent of subjects reporting predefined adverse events
[b] n (r) = number of adverse events and duration-adjusted event rate per 100 subject-years (n/Pt-yr*100). Multiple occurrences of the same event for a subject are counted as multiple events.
Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
Only adverse events starting after the first dose of investigational product are tabulated. Coded using the MedDRA v 17.0.
Subjects who started on placebo/SOC treatment group and then received romiplostim were counted in both treatment groups. Data before subjects received first dose of romiplostim was summarized in placebo/SOC group, and all data on or after first dose of romiplostim was summarized in romiplostim group regardless of further treatment switch.
Source: Modified from Table 14-6.6.2.1.2, Table 14-6.6.2.1.3, Table 14-6.6.2.2.2, Table 14-6.6.2.2.3, and Table 14-6.6.2.7.1.1 to Table 14-6.6.2.11.2.2.

Thrombotic and thromboembolic Events

Table 2-23. Overall Summary of Thrombotic and Thromboembolic Adverse Events of Interest, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No				Prior Splenectomy Status = Yes			
	Placebo/SOC (N = 106) (Pt-yr = 97.7)		Romiplostim (N = 655) (Pt-yr = 1129.7)		Placebo/SOC (N = 27) (Pt-yr = 11.2)		Romiplostim (N = 391) (Pt-yr = 702.0)	
Thrombotic and Thromboembolic Adverse Events of Interest	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]	n (%)[a]	n (r)[b]
All adverse events	4 (3.8%)	5 (5.1)	39 (6.0%)	52 (4.6)	1 (3.7%)	1 (8.9)	30 (7.7%)	44 (6.3)
Serious adverse events	1 (0.9%)	1 (1.0)	29 (4.4%)	36 (3.2)	1 (3.7%)	1 (8.9)	24 (6.1%)	31 (4.4)
Leading to discontinuation of IP	0 (0.0%)	0 (0.0)	11 (1.7%)	11 (1.0)	0 (0.0%)	0 (0.0)	7 (1.8%)	8 (1.1)
Fatal adverse events	0 (0.0%)	0 (0.0)	6 (0.9%)	6 (0.5)	1 (3.7%)	1 (8.9)	1 (0.3%)	1 (0.1)
Treatment-related adverse events	0 (0.0%)	0 (0.0)	17 (2.6%)	24 (2.1)	0 (0.0%)	0 (0.0)	11 (2.8%)	13 (1.9)
Treatment-related serious adverse events	0 (0.0%)	0 (0.0)	15 (2.3%)	18 (1.6)	0 (0.0%)	0 (0.0)	9 (2.3%)	11 (1.6)

IP = investigational product; ITP = immune thrombocytopenic purpura; Pt-yr = total subject years on study; SOC = standard of care.
[a] n (%) = number and percent of subjects reporting predefined adverse events.
[b] n (r) = number of adverse events and duration-adjusted event rate per 100 subject-years (n/Pt-yr*100). Multiple occurrences of the same event for a subject are counted as multiple events.
Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
Only adverse events starting after the first dose of investigational product are tabulated. Coded using the MedDRA v 17.0.
Subjects who started on placebo/SOC treatment group and then received romiplostim were counted in both treatment groups. Data before subjects received first dose of romiplostim was summarized in placebo/SOC group, and all data on or after first dose of romiplostim was summarized in romiplostim group regardless of further treatment switch.
Source: Modified from Table 14-6.6.4.1.2, Table 14-6.6.4.1.3, Table 14-6.6.4.2.2, Table 14-6.6.4.2.3, and Table 14-6.6.4.9.1.1 to Table 14-6.6.4.13.2.2.

Among subjects administered romiplostim, the most frequently reported thrombotic and thromboembolic events (> 1% of subjects, descending order of frequency) were pulmonary embolism in subjects with no prior splenectomy and deep vein thrombosis and pulmonary embolism in subjects with prior splenectomy

Table 2 24. Subject Incidence of Thrombotic and Thromboembolic Event Preferred Terms Reported in > 1 Subject Administered Romiplostim, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No		Prior Splenectomy Status = Yes	
Preferred Term	Placebo/SOC (N = 106) n (%)	Romiplostim (N = 655) n (%)	Placebo/SOC (N = 27) n (%)	Romiplostim (N = 391) n (%)
Subjects Reporting Predefined Adverse Events: Thrombotic and Thromboembolic	4 (3.8)	39 (6.0)	1 (3.7)	30 (7.7)
Pulmonary embolism	0 (0.0)	7 (1.1)	1 (3.7)	6 (1.5)
Deep vein thrombosis	1 (0.9)	6 (0.9)	0 (0.0)	9 (2.3)
Cerebrovascular accident	0 (0.0)	6 (0.9)	0 (0.0)	1 (0.3)
Myocardial infarction	0 (0.0)	6 (0.9)	0 (0.0)	2 (0.5)
Thrombophlebitis	0 (0.0)	4 (0.6)	0 (0.0)	1 (0.3)
Acute myocardial infarction	0 (0.0)	2 (0.3)	0 (0.0)	2 (0.5)
Portal vein thrombosis	0 (0.0)	2 (0.3)	0 (0.0)	3 (0.8)
Pulmonary thrombosis	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
Thrombophlebitis superficial	0 (0.0)	2 (0.3)	0 (0.0)	3 (0.8)
Transient ischaemic attack	0 (0.0)	2 (0.3)	0 (0.0)	3 (0.8)
Thrombosis	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.8)

Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
ITP = immune thrombocytopenic purpura; SOC = standard of care.
Coded using the MedDRA v 17.0.
Subjects who started on placebo/SOC treatment group and then enrolled in an open-label extension study during which they received romiplostim were counted in both treatment groups.
Only adverse events starting after the first dose of investigational product are tabulated.
Source: Modified from Table 14-6.6.4.1.2 and Table 14-6.6.4.1.3.

Hematopoietic Erythropenia and Leukocytosis

Among subjects administered romiplostim, hematopoietic erythropenia and leukocytosis were reported in 39 (6.0%) subjects with no prior splenectomy and 55 (14.1%) subjects with prior splenectomy

Malignancies

Among subjects administered romiplostim, malignancy adverse events of interest were reported in 32 (4.9%) subjects with no prior splenectomy and 18 (4.6%) subjects with prior splenectomy; serious adverse events were reported in 16 (2.4%) and 8 (2.0%) subjects, respectively; adverse events leading to discontinuation of romiplostim were reported in 5 (0.8%) subjects and 2 (0.5%) subjects; and fatal adverse events were reported in 1 (0.2%) subject and 1 (0.3%) subject

Table 2-26. Subject Incidence of Malignancy Preferred Terms Reported in > 1 Subject Administered Romiplostim, by Prior Splenectomy Status (Adult ITP Safety Set)

	Prior Splenectomy Status = No		Prior Splenectomy Status = Yes	
Preferred Term	Placebo/SOC (N = 106) n (%)	Romiplostim (N = 655) n (%)	Placebo/SOC (N = 27) n (%)	Romiplostim (N = 391) n (%)
Subjects Reporting Predefined Adverse Events: Malignancies	8 (7.5)	32 (4.9)	0 (0.0)	18 (4.6)
Basal cell carcinoma	0 (0.0)	6 (0.9)	0 (0.0)	4 (1.0)
Bone marrow reticulin fibrosis	0 (0.0)	3 (0.5)	0 (0.0)	2 (0.5)
Squamous cell carcinoma	0 (0.0)	2 (0.3)	0 (0.0)	1 (0.3)
Plasma cell myeloma	1 (0.9)	0 (0.0)	0 (0.0)	3 (0.8)
Bowen's disease	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)

Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
ITP = immune thrombocytopenic purpura; SOC = standard of care.
Coded using the MedDRA v 17.0.
Subjects who started on placebo/SOC treatment group and then enrolled in an open-label extension study during which they received romiplostim were counted in both treatment groups.
Only adverse events starting after the first dose of investigational product are tabulated.
Source: Modified from Table 14-6.6.9.1.2 and Table 14-6.6.9.1.3.

Drug-related hepatic Disorders

Among subjects administered romiplostim, the total number of drug-related hepatic disorder adverse events

of interest reported (duration-adjusted event rate per 100 subject-years) was 40 (3.5) in subjects with no prior splenectomy and 22 (3.1) in subjects with prior splenectomy

Thrombocytosis

Among subjects administered romiplostim, the total number of thrombocytosis adverse events of interest reported (duration-adjusted event rate per 100 subject-years) was 20 (1.8) in subjects with no prior splenectomy and 18 (2.6) in subjects with prior splenectomy

Hematologic Malignancies/MDS

Among subjects administered romiplostim, the total number of hematologic malignancies/MDS adverse events of interest reported (duration-adjusted event rate per 100 subject-years) was 8 (0.7) in subjects with no prior splenectomy and 6 (0.9) in subjects with prior splenectomy

Myelofibrosis

Among subjects administered romiplostim (excluding those in Study 20080009) myelofibrosis adverse events of interest were reported in 5 (0.9%) subjects with no prior splenectomy and 2 (0.6%) subjects with prior splenectomy; serious adverse events were reported in 3 (0.5%) subjects and 1 (0.3%) subjects, respectively; adverse events leading to discontinuation of romiplostim were reported in 3 (0.5%) and 0 subjects; no fatal adverse events were reported

Table 2-34. Subject Incidence of Myelofibrosis Preferred Terms, by Prior Splenectomy Status (Adult ITP Safety Set Excluding Study 20080009)

	Prior Splenectomy Status = No		Prior Splenectomy Status = Yes	
Preferred Term	Placebo/SOC (N = 106) n (%)	Romiplostim (N = 546) n (%)	Placebo/SOC (N = 27) n (%)	Romiplostim (N = 331) n (%)
Subjects Reporting Predefined Adverse Events: Myelofibrosis	0 (0.0)	5 (0.9)	0 (0.0)	2 (0.6)
Bone marrow reticulin fibrosis	0 (0.0)	3 (0.5)	0 (0.0)	2 (0.6)
Myelofibrosis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Reticulin increased	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

Adult ITP safety set consists of all subjects (age ≥ 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435.
ITP = immune thrombocytopenic purpura; SOC = standard of care.
Coded using the MedDRA v 17.0.
Subjects who started on placebo/SOC treatment group and then enrolled in an open-label extension study during which they received romiplostim were counted in both treatment groups.
Only adverse events starting after the first dose of investigational product are tabulated.
Source: Modified from Table 14-6.6.10.1.2 and Table 14-6.6.10.1.3.

Laboratory findings

A higher percentage of subjects in the romiplostim arm compared with the placebo/ standard of care (SOC) arm experienced predefined adverse events of hematopoietic erythropenia and leukocytosis (13% vs 6%). The median time to first occurrence of hematopoietic erythropenia and leukocytosis was 17 weeks (min: 1; max: 319) in the romiplostim arm and 10.5 weeks (min: 4; max: 55) in the placebo/SOC arm

Table 1 Haematopoietic Erythropenia and Leukocytosis By Splenectomy Status (Adult ITP Safety Set) (Q15-page 683 Response document MAH)

	Splenectomized		Nonsplenectomized	
	Placebo/SOC (N = 27)	Romiplostim (N = 391)	Placebo/SOC (N = 106)	Romiplostim (N = 655)
Subjects Reporting Predefined Adverse Events: Haematopoietic Erythropenia and Leukocytosis[a]	3 (11.1)	74 (18.9)	5 (4.7)	64 (9.8)
Time to First Occurrence of Haematopoietic Erythropenia and Leukocytosis (Weeks)				
N	3	74	5	64
Mean	11.7	36.6	17.2	39.2
SD	2.3	58.8	21.3	43.1
Median	13.0	14.0	9.0	24.5
Q1, Q3	9.0, 13.0	4.0, 34.0	6.0, 12.0	6.0, 52.5
Min, Max	9, 13	1, 319	4, 55	2, 174

Adult ITP Safety Set consists of all subjects (age >= 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009 and 20080435.
Subjects who started on placebo/SOC treatment group and then enrolled to an open label extension study during which received romiplostim were counted in both treatment groups.
[a] Haematopoietic erythropenia is identified by MedDRA terms or lab values (HGB < Lower limit of normal, which is age and gender dependant). Leukocytosis is defined by MedDRA terms or lab values (WBC >11x10^9/L). Concurrent event is defined as both haematopoietic erythropenia and leukocytosis events occurring within a 4-week window.
Only adverse events starting after the first dose of investigational product are tabulated.
SOC = Standard of Care.
Coded using the MedDRA v17.0.
Source: Tables 14-6.4.502 and 14-6.4.503

Table 8. Laboratory Shift Summary for Haematopoietic Erythropenia and Leucocytosis in Non-splenectomised Subjects (Adult ITP Safety Set)

Laboratory Parameter	Direction of Toxicity	Baseline Grade	Maximum Post-baseline Grade	Placebo (N = 106) n (%)	Romiplostim (N = 655) n (%)
Hemoglobin	Decrease	0	1	4 (3.8%)	36 (5.5%)
		0	2	0 (0.0%)	11 (1.7%)
		0	3	0 (0.0%)	2 (0.3%)
		1	2	1 (0.9%)	13 (2.0%)
		1	3	0 (0.0%)	1 (0.2%)
		2	4	0 (0.0%)	1 (0.2%)
Leukocytes	Increase	0	1	4 (3.8%)	38 (5.8%)
		0	2	1 (0.9%)	17 (2.6%)
		1	2	0 (0.0%)	8 (1.2%)

Adult ITP Safety Set consists of all subjects (age >= 18 years at screening) who received investigational product in any of ITP studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009 and 20080435. SOC = Standard of Care.
Subjects who started on placebo/SOC treatment group and then enrolled to an open label extension study during which received romiplostim were counted in both treatment groups.
Haematopoietic erythropenia is identified by MedDRA terms or lab values (HGB < Lower limit of normal, which is age and gender dependant). Leukocytosis is defined by MedDRA terms or lab values (WBC >11x10^9/L). Concurrent event is defined as both haematopoietic erythropenia and leukocytosis events occurring within a 4-week window.

In general, chemistry laboratory results by most severe CTCAE grade were similar among subjects administered romiplostim, regardless of prior splenectomy status.

Anti-Romiplostim Antibody Analysis

Analysis of anti-romiplostim antibodies was not included as part of the analysis of pooled data from 13 studies conducted in support of this variation. However based on a previously conducted analysis with a data cut-off of 31 July 2014, 4 (0.4%) subjects in the ITP safety set were positive for neutralizing antibodies to romiplostim. Anti-romiplostim neutralizing antibodies were detected in samples from 2 subjects in Study 20030213, 1 subject in Study 20080009, and 1 subject in Study 20080435. None of the 4 subjects demonstrated cross-reactivity to TPO. Of these 4 subjects, 3 subjects (1 subject in Study 20030213, 1 subject in Study 20080009, and 1 subject in Study 20080435) had no prior splenectomy and 1 subject (Study 20030213) had prior splenectomy. In the postmarketing immunogenicity registry study (Study

20080091), 2 subjects tested positive for binding and neutralizing antibodies to romiplostim with no cross-reactive antibodies to TPO. Of these 2 subjects, 1 subject had no prior splenectomy 1 subject had prior splenectomy.

Table 1. Total Incidence of Binding Antibodies to Romiplostim and TPO in All Subjects Receiving the Investigational Product and Placebo Control

		Binding Antibodies in Placebo-Dosed Subjects			Binding Antibodies in AMG 531-Dosed Subjects					
Study Number	Study population/Phase	Total Subjects	Subjects with Pre-existing Antibodies to AMG 531 (% Incidence)[a] AMG 531	Subjects with Pre-existing Antibodies to TPO (% Incidence)[a] TPO	Total Subjects	Subjects with Pre-existing Antibodies (% Incidence) AMG 531	Subjects with a Developing Antibody Response (% Incidence) AMG 531	Subjects with Pre-existing Antibodies (% Incidence) TPO	Subjects with a Developing Antibody Response (% Incidence) TPO	Neutralizing Antibodies in AMG 531-Dosed Subjects (% Incidence)
ITP Subjects										
20000137A	ITP Phase 1	–	–	–	24[b]	2 (8.3)	0 (0)	0 (0)	0 (0)	0 (0)
20000137B[c]	ITP Phase 2	4	0 (0)	0 (0)	17	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
20010218	ITP Phase 1	–	–	–	16	0 (0)	0 (0)	1 (6.3)	0 (0)	0 (0)
20030105	ITP Phase 3	21	2 (9.5)	2 (9.5)	42[d]	4 (9.5)	1 (2.4)	3 (7.1)	0 (0)	0 (0)
20030212	ITP Phase 3	20	2 (10.0)	4 (20.0)	42	1 (2.4)	3 (7.1)	2 (4.8)	2 (4.8)	0 (0)
20030213[e]	Open-label extension	–	–	–	56 (234)[f,g]	19 (6.6)[h]	12 (4.1)[h]	16 (5.5)[h]	5 (1.7)[h]	2 (0.7)
20040209	ITP Phase 2	–	–	–	394	13 (3.3)	7 (1.8)	8 (2.0)	11 (2.8)	0 (0)
20050162	ITP Phase 2 Japan	–	–	–	12	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
20060113[i]	Open-label extension Japan	–	–	–	12 (32)[i]	2 (4.5)[h]	4 (9.1)[h]	1 (2.3)[h]	2 (4.5)[h]	0 (0)
20060131	ITP Phase 3b	–	–	–	155	7 (4.5)	7 (4.5)	3 (1.9)	5 (3.2)	0 (0)
20060216	ITP Phase 3 Japan	12	1 (8.3)	1 (8.3)	22	3 (13.6)	0 (0)	0 (0)	0 (0)	0 (0)

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Footnotes defined on the next page.

Table 2. Total Incidence of Binding Antibodies to Romiplostim and TPO in All Subjects Receiving the Investigational Product and Placebo Control (Continued)

		Binding Antibodies in Placebo-Dosed Subjects			Binding Antibodies in AMG 531-Dosed Subjects					
Study Number	Study population/Phase	Total Subjects	Subjects with Pre-existing Antibodies to AMG 531 (% Incidence)[a] AMG 531	Subjects with Pre-existing Antibodies to TPO (% Incidence)[a] TPO	Total Subjects	Subjects with Pre-existing Antibodies (% Incidence) AMG 531	Subjects with a Developing Antibody Response (% Incidence) AMG 531	Subjects with Pre-existing Antibodies (% Incidence) TPO	Subjects with a Developing Antibody Response (% Incidence) TPO	Neutralizing Antibodies in AMG 531-Dosed Subjects (% Incidence)
20080009	Phase 4 Open Label Multi Centre Study	–	–	–	169	1 (0.6)	7 (4.1)[j,k]	5 (3.0)	6 (3.6)[k]	1 (0.6) (AMG 531)
20080435	Phase 2, interventional, single-arm, adult subjects	–	–	–	74	1 (1.4)	2 (3.0)[j]	1 (1.4)	1 (1.4)	1 (1.4) (AMG 531)
Total		23 (39)[l]	5 (8.1)	7 (11.3)	1035[m]	53 (5.1)	43 (4.2)	40 (3.9)	32 (3.1)	4 (0.4)

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ITP = immune thrombocytopenia; TPO = thrombopoietin; - = not applicable. Note: Study 20010218, immunoassay analysis was performed retrospectively.

[a] Placebo subjects were considered positive for pre-existing antibodies if they were antibody positive at the predose or postdose time points.

[b] One additional subject was not part of the original bioassay analysis; however, on retrospective immunoassay analysis, all samples from this subject were analyzed and found to be negative for binding antibodies.

[c] Two subjects did not have samples with sufficient volume available for retrospective immunoassay analysis.

[d] One AMG 531-treated subject was positive for anti-TPO neutralizing antibodies at predose time point only.

[e] Open Label Extension Study 20030213: AMG 531 dosed subjects were rolled over from placebo and dosed groups from earlier studies.

[f] Subjects in parentheses belong to parent studies that were dosed again in the open label extension studies; 234 subjects were dosed with AMG 531 in previous studies and 56 subjects were placebo subjects or subjects on standard of care treatment in previous studies and dosed with AMG 531 for the first time in Study 20030213.

[g] Two AMG 531-treated subjects were positive for anti-AMG 531 neutralizing antibodies postdose. Follow-up samples were found to be positive for binding antibodies but negative for neutralizing antibodies.

[h] Percent incidence based on all subjects in the study, including subjects rolled over from earlier parent studies.

[i] Open Label Extension Study 20060113: Subjects in parenthesis were dosed earlier in parent studies; 11 AMG 531 dosed subjects rolled over from the parent Study 20050162 and 15 subjects rolled over from Study 20060216. These subjects were counted once in the total number. Twelve subjects were dosed earlier with placebo in Study 20060216 and dosed for the first time with AMG 531 in Study 20020113.

[j] One subject positive for neutralizing antibodies to AMG 531

Footnotes continued on the next page.

[k] One subject was positive for anti-AMG 531 and TPO antibodies and the subject has been included as a positive in each group.

[l] Percent incidence based on all placebo subjects in the study, including subjects rolled over into other studies.

Safety in special populations

N/A

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

Among subjects administered romiplostim, adverse events leading to discontinuation of romiplostim were reported in 54 (8.2%) subjects with no prior splenectomy and 31 (7.9%) subjects with prior splenectomy

Among subjects administered romiplostim, the total number of adverse events leading to discontinuation of romiplostim reported (duration-adjusted event rate per 100 subject-years) was 66 (5.8) in subjects with no prior splenectomy and 36 (5.1) in subjects with prior splenectomy. The most frequently reported adverse events leading to discontinuation of romiplostim (duration-adjusted event rate ≥ 0.3 per 100 subject-years, descending order of frequency) were myocardial infarction, pulmonary embolism and renal failure in subjects with no prior splenectomy and bone marrow disorder, arthralgia, deep vein thrombosis, and pulmonary embolism in subjects with prior splenectomy.

Post marketing experience

Study 20101323 (FOCUS) was a retrospective observational postauthorizaton study to evaluate real prescribing conditions (therapeutic indications and prescription patterns) of romiplostim in thrombocytopenic patients in France. During this study, 3/108 (2.8%) subjects (2/44 [4.5%] splenectomized; 1/64 [1.6%] nonsplenectomized) experienced at least 1 concomitant event considered to be related to romiplostim as follows: 1/44 (2.3%) splenectomized subject experienced a concomitant event of antiphospholipid syndrome, 1/44 (2.3%) splenectomized subject experienced a concomitant event of renal vein thrombosis, and 1/64 (1.6%) nonsplenectomized subject experienced a concomitant event of alopecia.

Study 20070225 is an ongoing long-term observational postauthorization study (to be completed in 2015) of romiplostim use in European routine clinical practice. Based on an interim analysis conducted in September 2013, serious ADRs were reported in 4/116 (3%) splenectomized subjects and 9/196 (4%) nonsplenectomized subjects. A total of 2/116 (2%) splenectomized subjects reported thrombotic ADRs (myocardial infarction [1 subject] and transient ischemic attack [1 subject]), and 5/196 (3%) nonsplenectomized subjects reported thrombotic ADRs (deep vein thrombosis [2 subjects], pulmonary embolism [2 subjects], embolism [1 subject], and retinal vein thrombosis [1 subject]). Bone marrow fibrosis ADRs were reported in 1/116 (1%) splenectomized subjects and 1/196 (1%) nonsplenectomized subjects. No fatal ADRs were reported (Papadaki et al, 2014).

2.5.1. Discussion on clinical safety

The main reason to restrict the therapeutic indication of romiplostin at the time of the initial MA to a third line of treatment after failure to splenectomy (unless this were contraindicated) was safety due to the limitations of the safety database and the uncertainties around a novel mechanism of action. In order to solve these gaps the Applicant has submitted a complete safety analysis that includes data from all adult patients who have received romiplostin in the context of any of the 13 clinical studies conducted so far.

In addition, two observational studies, Study 201001323 (a retrospective observational study conducted in France) and a long term observational, Study 20070225, which is ongoing, have been conducted but these data are not included in the main analysis. Study 20101323 included 108 subjects; 44 subjects were splenectomised and 64 subjects were nonsplenectomized. Study 20070225 is ongoing and includes 312 subjects as of September 2013; 116 subjects were splenectomized and 196 subjects were nonsplenectomized. Available data from a postmarketing immunogenicity registry study (Study 20080091) is also included.

A total of 1111 subjects have been included in these studies, 1046 received at least one dose of romiplostim (391 with prior splenectomy and 655 with no prior splenectomy). The duration of exposure was (median;

IQR) 63 weeks (24w, 154w) and 66 weeks (31w, 126w) in splenectomized and non-splenectomized, respectively. Median (IQR) weekly dose (µg/Kg/week) were 3.7 (1.9, 6.5) and 3.3 (1.9, 5.7) in splenectomized and non-splenectomized, respectively.

In general, a higher percentage of splenectomized patients discontinued investigational medication than non-splenectomised subjects, either in parent studies (28.9 vs 25.6%) or in open label extension studies (39.6% vs 25.0%). It is remarkable that more subjects discontinued the IP treatment due to death in non-splenectomised patients compared to splenectomized 2.4% vs 1.5% in parent studies and 5.4% vs 2.7% in open-label studies.

Overall, baseline demographic and disease characteristics were rather consistent in the two subset of splectomized and non-splenectomised patients, although patients with prior splenectomy represented a more advanced cITP population, with a median time since ITP diagnosis of 8.71 years longer than that of the non-splenectomised population (1.62 years since diagnosis). At baseline the splenectomized and non-splenectomised group were comparable with respect to age and sex. The non-splenectomised group had a higher percentage of Japanese patients (14%) then the splenectomized group (4.6%). It is uncertain what the difference in race or local treatment guideline has on the comparability of the studied population as a whole.

The median baseline platelet count was 19.3 x 109/L in non-splenectomised subjects and 14.0 x 109/L in splenectomized subjects. The median time since splenectomy was 6.38 years and 47,3% had prior IPT treatment history which consisted of first line therapy.

Of the patients with a prior splenectomy only half of the group had received first line therapy, more details on the group that did not receive first line therapy is requested. Moreover, it is remarkable that the patients with splenectomy had more different types of second line treatment options whereas the non-splenectomized patients only had rituximab and H.pylori eradication therapy as previous treatments.

Not all patients included in the analysis can be classified as chronic ITP patients, with a significant amount of patients having a disease duration of < 6 months. The data provided indicate that romiplostim is well tolerated regardless of whether patients had undergone splenectomy or not . The safety profile does not appear to differ with disease duration or previous treatment lines, but is generally more favourable in non-splenectomised patients. Differences in favour of the non-splenectomised population are not totally unexpected given the generally more advanced status of splenectomised patients which, in addition, are also more at risk of infections.

Therefore, information about adverse events by preferred term reported as duration-adjusted event rate per 100 subjects-years was requested in the following analysis: related adverse events, grade $\geq$3 adverse events, serious adverse events and serious related adverse events with the reporting of all patients.While the incidence of treatment related adverse events is higher in the romiplostim treated patients, the analysis adjusted by exposure (per 100 subjects-years, n/Pt-yr*100) show more favourable results for romiplostim except for the non-splenectomised patients for the rate of drug related adverse events (82.1 vs 36.9 in romiplostim and placebo) and for splenectomized patients with regard to related serious adverse events (9.3 vs 0.0 in romiplostim and placebo). Within splenectomized patients, the small number of subjects in the placebo arm /SOC (only 27) precludes drawing reliable conclusions. For non-splenectomised patients, despite the differences found in the overall incidence of related AE, the incidence of severe AE and >G3 AEs was systematically higher in the placebo/SOC treatment arms, which it is reassuring.

Overall, data available show no major differences in the profile and frequency of adverse events among splenectomized and non-splenectomised subjects, although splenectomized patients showed higher frequencies of CTCAE grade 3 (46.5% **vs** 38.3%), product-related adverse events (123.1 **vs** 82.1 event rate per 100 subject -year), and the total number of serious adverse events reported (68.1 **vs** 44.1 SAE rate adjusted per 100 subject-years). This is not unexpected given the more advanced status of the disease in the splenectomized population. Adverse events leading to discontinuation of romiplostim were reported in

8.2% of subjects with no prior splenectomy and 7.9% of subjects with prior splenectomy. Likewise, when adverse events leading to discontinuation were adjusted for duration of exposure, subjects with no prior splenectomy had a numerically higher duration-adjusted event rate per 100 subject-years compared with subjects with prior splenectomy (5.8 vs 5.1, respectively).

There were no major differences in the incidence of product related adverse events, except for "myalgia", reported in 2.7% vs 5.6% in non-splenectomised and non-splenectomised patients, respectively. Also, for the incidence of product related serious adverse events in bone marrow disorders 0% in non-splenectomised and 1.5% in splenectomized patients, this is not totally unexpected.

However, it is noted that more non-splenectomised patients had fatal adverse events (4.7% vs 2.8%). Nevertheless, the incidence of treatment related fatal adverse events was 0.5% in each group. The fatal adverse events were deemed related to romiplostim by the investigator in 3 subjects with no prior splenectomy (intestinal ischemia, myocardial infarction, and angina unstable) and 2 subjects with prior splenectomy (hemolysis and aplastic anemia). A brief description in each patient has been given. Likewise, when fatal adverse events were adjusted for duration of exposure, subjects with no prior splenectomy had a numerically higher duration-adjusted event rate per 100 subject-years compared with subjects with prior splenectomy (2.7 vs 1.6, respectively)

Serious adverse events were reported in 30.7% subjects with no prior splenectomy and 39.1% subjects with prior splenectomy. Likewise, when serious adverse events were adjusted for duration of exposure, subjects with no prior splenectomy had a numerically lower duration-adjusted event rate per 100 subject-years compared with subjects with prior splenectomy (44.1 vs 68.1, respectively). Thrombocytopenia was the most frequently reported serious adverse event (5.2% and 6.4% of subjects, respectively). Duration-adjusted analyses showed similar results. The most frequently reported serious adverse events (duration-adjusted event rate ≥ 3 per 100 subject-years, descending order of frequency) were thrombocytopenia in subjects with no prior splenectomy and thrombocytopenia and ITP in subjects with prior splenectomy.

With regard to the incidence of bone marrow reticulin/collagen, 7 (1.3%) non-splenectomised subjects and 11(3.3%) splenectomized subjects had bone marrow reticulin/collagen, being the adjusted rate per 100 patients years (95%IC) 2.0 (1.0,3.5) vs 0.8 (0.3, 1.7) in splenectomized and non-splenectomised subjects. Again, this is not totally unexpected given the more advanced status of splenectomized patients.

The number and percentages of subjects reporting thrombocytopenia after cessation of romiplostim treatment was 24 (3.7%) in non-splenectomised and 10 (2.6%) in splenectomized. Overall, 34 subjects (3%) experienced thrombocytopenia after cessation of romiplostim treatment. The total number of thrombocytopenia events after cessation of romiplostim treatment (duration-adjusted event rate per 100 patient-years) was 37 (19.4).

In the non-splenectomised group, 655 subjects with ITP who received romiplostim (128.2 patient-years) were pooled and subject incidence rates and exposure-adjusted event rates (per 100 patient-years) were calculated for the subjects who experienced thrombocytopenia events after cessation of romiplostim treatment. A total of 24 subjects (4%) experienced thrombocytopenia after cessation of romiplostim treatment. The total number of thrombocytopenia events after cessation of romiplostim treatment (duration-adjusted event rate per 100 patient-years) was 25 (19.5).

In the splenectomized group, 391 subjects with ITP who received romiplostim (62.3 patient-years) were pooled and subject incidence rates and exposure-adjusted event rates (per 100 patient-years) were calculated for the subjects who experienced thrombocytopenia events after cessation of romiplostim treatment. A total of 10 subjects (3%) experienced thrombocytopenia after cessation of romiplostim treatment. The total number of thrombocytopenia events after cessation of romiplostim treatment (duration-adjusted event rate per 100 patient-years) was 12 (19.3).

The Applicant has analyzed the subject incidence and study duration-adjusted rate of adverse events of interest, in splenectomized (702.0 pt-y) and non-splenectomised (1129.7 pt-yr) subjects. However in the analysis of myelofibrosis other exposure-adjusted events rate were taken into account 560.0 pt-y and 866.7 pt-year in splenectomized and non-splenectomized. Bone marrow abnormalities were collected differently in Study 20080009 compared with the other 12 clinical studies in adult subjects with immune thrombocytopenia (ITP). More specifically, in Study 20080009, subjects were enrolled in 1 of 3 cohorts, with on-study bone marrow biopsies performed at baseline and at year 1 (cohort 1), year 2 (cohort 2), or year 3 (cohort 3). Thus, bone marrow abnormalities were collected in a more systematic manner in Study 20080009 compared with the other studies. This approach is supported..

In addition, a greater rate of events (duration adjusted event rate per 100 subjects-years) in splenectomized patients than in non-splenectomised was reported for the following AEs: pulmonary disorders (220.5 vs 154.3), hemorrhages (266.1 vs 140.8), hypersensitivity /angioedema/ anaphylactic reactions (36.6 vs 28.8), thombotic/thomboembolic events (6.3 vs 4.6), thombocytosis (2.6 vs 1.8) and hematologic malignancies (0.9 vs 0.7). By contrary the numbers of adverse events (duration adjusted event rate per 100 subjects-years) were greater in non-splenectomised patients than in splenectomized for the following: renal and urinary disorders 118(10.4) vs 52(7.4), cardiac disorders 84(7.4) vs 48(6.8), myelofibrosis 5 (0.6) vs 2(0.4) and immunogenicity (0.1 vs 0.0).

Regardless of splenectomy status, a higher percentage of subjects in the romiplostim arm experienced predefined adverse events of hematopoietic erythropenia and leucocytosis compared with subjects in the placebo/SOC arm. Splenectomised subjects on Romiplostim treatment with at least a 2-grade shift in hematopoietic erythropenia or leucocytosis were investigated to search for a rationale. The majority had a clinical history of at least one risk factor/ possible alternative cause for either the hematopoietic erythropenia or leucocytosis component of the concurrent event. Patients with events of hematopoietic erythropenia experienced previous bleeding manifestations of ITP or a variety of other aetiologies (e.g. anaemia). Regarding the leucocytosis, it is known that a splenectomy can result in increased susceptibility to infection. In section 4.4. of the SmPC it is added: “Concurrent anaemia and leucocytosis (within a 4-week window) may occur in patients regardless of splenectomy status, but have been seen more often in patients who have had a prior splenectomy.”

Although the adjusted rate of bone marrow reticulin/collagen is highest in splenectomized, the adjusted rate of myelofibrosis is greater in non-splenectomized. In any case the incidence is small to draw a firm conclusion about this slight imbalance.

Five (0.8%) subjects with no prior splenectomy who received romiplostim had fatal hemorrhage adverse events (hemorrhage intracranial [2 subjects], cerebral hemorrhage, pulmonary hemorrhage, and subdural hematoma [1 subject, each]). No subject with prior splenectomy who received romiplostim had a fatal hemorrhage adverse event.

Among subjects administered romiplostim, serious adverse events of renal failure (3 events were fatal) and acute renal failure (1 event was fatal) were each reported in 5 subjects with no prior splenectomy. Serious adverse events of acute prerenal failure, anuria, renal colic, renal disorder, renal failure chronic, urinary bladder polyp and urinary retention were reported in 1 subject each with no prior splenectomy. Serious adverse events of calculus urethral, renal colic, renal failure, renal failure acute, and urogenital hemorrhage were reported in 1 subject each with prior splenectomy .

Seven (0.6%) subjects with no prior splenectomy who received romiplostim had fatal cardiac disorder event. No subject with prior splenectomy who received romiplostim had a fatal cardiac event.

Six (0.5%) subjects with no prior splenectomy who received romiplostim had fatal thrombotic events. One (0.1%) subject with prior splenectomy who received romiplostim had a fatal thromboembolic event.

Malignancy adverse events and hematologic /myelodysplastic syndrome (MDS) events occurred similarly in

both subgroups of patients (3.8 and 3.4 event per 100 subjects-years and in 0.7 and 0.9 event per 100 subjects-years in non-splenectomised and splenectomized patients).

Bone marrow reticulin fibrosis was reported in 5(0.6) and 2 (0.4) non-splenectomised and splenectomized subjects, in the study 20080009 BM reticulin fibrosis was reported in 5 non-splenectomised patietns (3 bone marrow reticulin fibrosis, 1 myelofibrosis and 1 reticulin increased) and 2 in splenectomized patietns.

With regard to anti-romiplostim antibody, the incidence of binding antibodies and neutralising antibodies is in line with that reflected in the SmPC, which is reassuring.

In general, both the safety profile and the general incidence of AEs are in line with that currently reflected in Section 4.8 of the SmPC. Further revisions included information on hematopoietic erythropenia and leukocytosis which occurs more often in patients with prior splenectomy. In addition the incidence of “anaemia” has been revised from “uncommon” to “common” under section 4.8 of the SmPC.

The imbalances observed in the description of some AEs of particular interest are taken cautiously given the above mentioned limitations of the pooled analysis and also because differences in favour of the non-splenectomised population would not be totally unexpected given the generally more advanced status of splenectomised patients. In fact, a higher incidence of grade > 3 or serious adverse events had been reported in these patients. However, data provided allow concluding that treatment with romiplostin is generally well tolerated regardless of whether patients had undergone splenectomy or not. With regard to anti-romiplostim antibody formation, the incidence of binding antibodies and neutralising antibodies is in line with that reflected in the SmPC, which is reassuring.

2.5.2. Conclusions on clinical safety

The data presented do not raise any particular concern. The safety profile and the general incidence of AEs from this submission are in line with that reflected in Section 4.8 of the SmPC. Hematopoietic erythropenia and leukocytosis occurs more often in patients with prior splenectomy; the SmPC was amended accordingly.

2.5.3. PSUR cycle

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

CHMP agreed with the MAH that no RMP update is needed. The safety profile of patients treated with romiplostim does not appear to differ based on splenectomy status, providing physicians with more options for treatment. Also the benefit risk remains positive and the indication remains second line for patients refractory to other treatments. RMP submitted within variation II/0049, includes information on all the clinical studies used to support this change to the indication and therefore has not been updated for this submission.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in the Package Leaflet.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

The amended indication for Nplate to include all non-splenectomised patients (including those without a contraindication to surgery) does not have a significant impact on the Package Leaflet. The minor amendments that have been implemented do not require carrying out further consultation with target patients groups.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The MAH has conducted a pooled analysis of the data obtained from 9 clinical trials (phase III, IV and II), which includes a total of 1024 subjects (376 with prior splenectomy and 648 with no prior splenectomy).

The subject incidence of platelet count between 50 $x10^9$/L and $200x10^9$/L show a high percentage of responders in the first 6 months of treatment (276/376; 73.4% and 554/648; 85.5% in splenectomized and non-splenectomized). During treatment with romiplostim the number of months with platelet counts between 50-200 $x10^9$/L was (median values) 6.0 months and 10.0 months in splenectomized and non-splenectomised patients. The subject's incidence of sustained platelet response was 67.6% and 79.9% in splenectomized and non-splenectomised sujects. Of these, few patients lost platelet responses during subsequent treatment (7.9% in splenectomized and 6.9% in non-splenectomized). Responses were maintained in the long term, in some patients beyond fifth year, with a subject incidence of platelet count between 50 $x10^9$/L and $200x10^9$/L which was 68.3% and 63.6%, in splenectomized and non-splenectomized, respectively.

In supportive Study 20060216 (Japanese population) romiplostim was statistically significant superior to placebo for the primary efficacy endpoint, number of weeks with weekly platelet response (platelet count ≥ 50 x 109/L): being median (Q1,Q3) of 0 (0,0) in placebo and 11(9,12) in romiplostim groups (11 weeks and 10.5 weeks in splenectomized and non-splenectomised patietns). Secondary efficacy endpoints support the efficacy of romiplostim.

Eighty six percent (86.4%), 72.7% and 31.8% of the romiplostim treated patients achieved ≥ 100 x 10^9/L, ≥ 200 x 10^9/L, and ≥ 400 x 10^9/L platelet counts. Romiplostim demonstrated an effect in decreasing the incidence of bleeding symptoms from 63.6% at baseline to 36.4% at week 13. The effect appears to be maintained in the long-term, although beyond week 136 data show an important variability. No major differences were seen between splenectomized and non splenectomized patients in terms of maintenance of the response in the long-term. Although it is noted that a higher portion of non-splectomized than splenectomized subjects was able to discontinue concurrent ITP therapy (43.8% vs 22.2%).

In phase II study 20060131 conducted in non-splenectomised patients, the overall subject incidence of splenectomy was 8.9% (14 of 157 subjects) in the romiplostim group compared with 36.4% (28 of 77 subjects) in the SOC (standard of care) group. The p-value for the treatment difference between groups was < 0.0001.

The odd ratio of treatment failure was 0.17 (95% CI: 0.08, 0.35), the overall subject incidence of treatment failure was 11.5% (18 of 157 subjects) in the romiplostim group compared with 29.9% (23 of 77 subjects) in the SOC group.

Uncertainty in the knowledge about the beneficial effects

Uncertainties around the limitations of pooling the controlled studies (with placebo 20030105, 20030212, 20060216, with standard of care 20060131) and non-comparative studies (20030213, 20040209, 20060113, 20080009 and 20080009) with a certain degree of heterogeneity, are acknowledged.

However the results obtained in the key endpoints assessed are robust and clinically relevant regardless the baseline characteristics mentioned, ensuring the efficacy is seen of romiplostim is seen in both non-splenectomised and splenectomised patients.

Risks

Unfavourable effects

The safety profile shown in the pooled analysis does not highlight any new signals or an increase in the occurrence or severity of known adverse events. The description of adverse event and the frequency reported are in line with the safety profile reflected in Section 4.8 of the SmPC. Further, no major differences were observed between splenectomized and non-splenectomised subjects in the safety profile, although splenectomized patients showed a higher incidence of AE grade 3 (46.5% vs 38.3%), product-related adverse events (duration-adjusted event rate per 100 subject -years) (123.1 vs 82.1), and the total number of serious adverse events reported (duration-adjusted event rate per 100 subject-years) (68.1 vs 44.1) compared to non-splenectomised patients.

Treatment with romiplostin appeared to be well tolerated, with an overall low rate of adverse events leading to discontinuation, which was balanced between non-splenectomised (8.2%, 5.8 rate per 100 subject-year) and splenectomized subjects (7.9%, 5.1 rate per 100 subject-year). Although there were more subjects that discontinued the IP treatment due to death in non-splenectomised patients compared with splenectomized 2.4% vs 1.5% in parent studies and 5.4% vs 2.7% in open-label studies, when accounting for romiplostin related deaths no differences were observed between these subsets of patients.

The incidence of bone marrow reticulin/collagen was 7 (1.3%) non-splenectomised subjects and 11(3.3%) splenectomized, being the adjusted rate per 100 patients years (95%IC) 2.0 (1.0,3.5) vs 0.8 (0.3, 1.7) in splenectomized and non-splenectomised subjects.

Some numerical imbalances have been reported in the incidence of adverse event and adverse event of special interest, which were higher in non-splenectomised patients than in splenectomized; renal and urinary disorders 118(10.4) vs 52(7.4), cardiac disorders 84(7.4) vs 48(6.8), myelofibrosis 5 (0.6) vs 2(0.4) and immunogenicity (0.1 vs 0.0). Data was adjusted by exposure time.

Malignancy adverse events and hematologic /MDS events occurred similarly in both subgroups of patients (3.8 and 3.4 event per 100 subjects-years and in 0.7 and 0.9 event per 100 subjects-years in non-splenectomised and splenectomized patients).

Uncertainty in the knowledge about the unfavourable effects

The consequence of a continuous treatment with romiplostin in the bone marrow remains to be established. Until further data become available from ongoing studies, a close monitoring of patients is required in line with current SmPC recommendations.

Effects Table

Effect	Short description	Unit	Treatment Non-splenectomized	Control	Uncertains/Stregth of evidence	Reference
Favourable						
Durable platelet response		%	Non-plenectomized:61 Splenectomized 38	Non-splenectomized: 4 Splenectomized:0	Statistically significantly superior to placebo	Phase III, at MA (20030212 and 20030105)
Month with platelet response		Number	Non-plenectomized: 10.0 Splenectomized: 6.0			Pooled analysis [(1)]
Sustained platelet response	Lost platelet response	%	Non-plenectomized 79.9 Splenectomized: 67.6 Non-plenectomized 6.9 Splentomized:7.9			Pooled analysis [(1)]
Weeks with platelet response	Median (Q1,Q3)	Number	Non-plenectomized: 10.5(8.0,12.0) Splentomized: 11.0(10.0,11.0)	Non-plenectomized :0.0 Splentomized:0.0	Statistically significantly superior to placebo	20060216 study
Incidence of splenectomy		%	8.9		36.4 in SOC arm	20060131 study*
Treatment failure		%	11.5		29.9 in SOC arm	20060131 study*
Unfavourable effects						
AE grade 3		%	Non-splenectomized:38.3 Splenectomized: 46.5 Non-splenectomized:67.0	Non-splenectomized:40.6 Splenectomized:33.3		Pooled analysis [(3)]

Effect	Short description	Unit	Treatment Non-splenectomized	Control	Uncertains/Stregth of evidence	Reference
		Duration adjusted rate over 100P-Y(n/Pt-yr*100)	Splenectomized: 107.0	Non-splenectomized:120.8 Splenectomized:187.9		
Product related AE		Duration-adjusted events rate per 100 Subjects-patient (n/Pt-yr*100) % Duration-adjusted events rate per 100 Subjects-patient(n/Pt-yr*100) %	Non-splenectomized:82.1 Splenectomized: 123.1 Non-splenectomized:45.6 Splenectomized: 51.2	Non-splenectomized:36.9 Splenectomized:134.2 Non-splenectomized:35.8 Splenectomized:29.6		Pooled analysis [3]
SAE		Duration-adjusted events rate per 100 Subjects-patient(n/Pt-yr*100) %	Non-splenetomized:44.1 Splenectomized:68.1 Non-splenetomized:30.7 Splenectomized:39.1	Non-splenetomized:34.0 Splenectomized:22.2		Pooled analysis [3]
Leading to discontinuation		Duration-adjusted events rate per 100 Subjects-patient(n/Pt-yr*100) %	Non-splenectomized:5.8 Splenectomized:5.1 Non-splenectomized:8.2 Splenectomized:7.9	Non-splenectomized:3.8 Splenectomized:3.7		Pooled analysis [3]
Fatal adverse events		% subjects reporting fatal adverse events	Non-splenectomized:4.7 Splenectomized:2.8	Non-splenectomized:4.7 Splenectomized:11.1		Pooled analysis [3]
Bone marrow / reticulin / collagen		%	Non-splenectomized:1.3 Splenectomized:3.3 Non-splenectomized: 0.8(0.3,1.7)	Non-splenectomized:0.0 Splenectomized:3.7 Non-splenectomized:0(0,3.1		Pooled analysis [3]

Effect	Short description	Unit	Treatment Non-splenectomized	Control	Uncertains/Stregth of evidence	Reference
		Rate per 100 S-Y (95%IC)	Splenectomized: 2.0(1.0,3.5)	) Splenectomized8.9(0.2,49.8)		
Haematological / MDS		Rate per 100 S-Y	Non-splenectomized:0.7 Splenectomized:0.9	Non-splenectomized:4.1 Splenectomized:0.0		Pooled analysis [3]
Malignance		Rate per 100 S-Y % (subject incidence in >1 subject administered romiplostim)	Non-splenectomized:3.8 Splenectomized: 3.4 Non-splenectomized:4.9 Splenectomized:4.6	 Non-splenectomized:7.5 Splenectomized:0.0		Pooled analysis [3]

Pooled analysis [1]: controlled studies (with placebo 20030105, 20030212, 20060216, with standard of care 20060131) and studies without comparator (20030213, 20040209, 20060113, 20080009 and 20080009)

Pooled analysis [3] Studies 20000137A, 20000137B, 20010218, 20030105, 20030212, 20030213, 20040209, 20050162, 20060113, 20060131, 20060216, 20080009, and 20080435

20060131 study:a study in nonsplenectomized to compare the ability of romiplostim vesus medical standard of care (SOC) to prevent a splenectomy and to provide a durable treatment option to this patients for 52-week treatment period*

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The benefits of romiplostim in terms of platelet count was initially demonstrated in the pooled analysis of submitted trials and replicated in two independent randomised clinical trials which included both splenectomized and non-splenectomised subjects with chronic ITP. Responses were durable and can be considered clinically relevant for both splenectomized and non-splenectomised patients. Additional evidence generated since the initial MAA provides further support to these results, which is considered a robust evidence for an uncommon orphan condition that may be life threatening and where limited therapeutic alternatives are available. Consistent favourable effects were also observed for the incidence of bleeding events (G1-4) and for the use of rescue medication which was generally low. However data on the reduction of severe bleeding events is lacking, therefore the relevance of the observed effect, though anticipated based on the effect on platelet counts, has not been unequivocally demonstrated.

The main safety concerns, potential and identified, are increased reticulin formation and bone marrow fibrosis, thrombocythemia, thromboembolic events, malignancies, immunogenicity and effects on renal function. In the context of limited treatment options, benefits of the treatment are considered to overweigh the risks for patients with cITP.

Benefit-risk balance

The benefit – risk balance in the indication as worded following the deletion of the restriction in non-splenectomised patients:

Nplate is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins).

- is positive.

Relevant information is included in SmPC sections 5.1 and 4.2.

Discussion on the Benefit-Risk Balance

Romiplostin is regarded as a suitable therapeutic option able to increase platelet counts above a level which reduces the risk of bleeding events in up to 70% of subjects (40% if splenectomised). Responses appear durable and consistent regardless of whether treatment with romiplostin is used in splenectomised or non-splenectomised patients, although responses tend to be lower in splenectomised patients likely due to the more advanced status of the disease. The effect is considered clinically relevant, substantiated by a favourable effect observed in the overall incidence of bleeding events. However, romiplostin does not provide a curative treatment option for cITP but rather a chronic palliative treatment; it is noted that, contrary to other treatment options available, romiplostin does not interfere with the underlying pathophysiological autoimmune disorder of the condition, but rather stimulates platelet production with the aim to compensate peripheral platelet destruction. Thus, remission is unlikely but has been observed in certain patients during romiplostin treatment. Although well tolerated, romiplostin may be associated to the risk of thromboembolic complications, bone marrow fibrosis and progression to haematological malignancies.

Current guidelines indicate that surgery remains as an optimal treatment option for patients refractory to the first line of treatment, however, it can be recognised that surgery may not be suitable and/or an immediate treatment option in all cases. Thus, based on the increased body of safety evidence, a positive benefit/risk balance for the use of Nplate in second line beyond those cases where surgery is contraindicated

could be concluded. In non-splenectomised patients, the option of splenectomy should be regularly re-evaluated on an individual basis by the treating physician according to current treatment guidelines.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include second line treatment of non-splenectomised patients; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in the Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.