9 November 2017
EMA/302907/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nplate

International non-proprietary name: romiplostim

Procedure No. EMEA/H/C/000942/II/0060/G

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
ANA	antinuclear antibodies
ASH	American Society of Hematology
BCSH	British Committee for Standards in Haematology and General Haematology Task Force
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
EMA	European Medicines Agency
EOI	events of interest
eTPO	endogenous thrombopoietin
EU	European Union
FDA	Food and Drug Administration
IBD	International Birth Date
ICH	International Conference on Harmonisation
ITP	immune thrombocytopenia (also known as idiopathic thrombocytopenic purpura)
IV	intravenous(ly)
IVIg	intravenous immunoglobulin
KHK	Kyowa Hakko Kirin
KIT	Kids ITP Tool
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimal important difference
PBRER	Periodic Benefit-Risk Evaluation Report
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PSUR	Periodic Safety Update Report
Q1	25th percentile
Q3	75th percentile
RI-PMBT	Requests for Post Marketing Blood Tests
RMP	Risk Management Plan
SC	subcutaneous(ly)

SMQ	Standardized MedDRA query
SPA	Special Protocol Assessment
TMP	thrombopoietin-mimetic peptide
TPO	thrombopoietin
TPO-RA	thrombopoietin receptor agonist
RI-PMBT	Requests for Post Marketing Blood Tests
RMP	Risk Management Plan
SC	subcutaneous(ly)
SMQ	Standardized MedDRA query
SPA	Special Protocol Assessment
TGF-β	transforming growth factor-beta
TMP	thrombopoietin-mimetic peptide
TPO	thrombopoietin
TPO-RA	thrombopoietin receptor agonist

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Amgen Europe B.V. submitted to the European Medicines Agency on 5 December 2016 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
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, IIIA and IIIB
B.II.e.5.c	Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products	Type II	I, IIIA and IIIB
B.II.e.5.a.1	Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	Type IAin	I, IIIA and IIIB

C.I.6.a - Extension of Indication to include paediatric population for Nplate: to register Nplate for the use in the paediatric chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients: 1 year of age and older.
As a consequence Product information has been updated accordingly. Furthermore, the PI is brought in line with the latest QRD templare version 10. The RMP version 18 has also been submitted.

B.II.e.5.c – To add a low-dose romiplostim 125 microgram vial presentation for powder for solution for injection (4 vials pack).
B.II.e.5.a.1 – To add a 1 vial pack size of a low-dose romiplostim 125 microgram presentation.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

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: Treatment of 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(s) P/0114/2014 on the agreement of a paediatric investigation plan (PIP).

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: Concepcion Prieto Yerro Co-Rapporteur: Paula Boudewina van Hennik

Timetable	Planned dates	Actual dates
Start of procedure:	24 December 2016	24 December 2016
CHMP Rapporteur Assessment Report	17 February 2017	17 February 2017
CHMP Co-Rapporteur Assessment Report	17 February 2017	17 February 2017
PRAC Rapporteur Assessment Report	24 February 2017	24 February 2017
PRAC members comments	1 March 2017	n/a
Updated PRAC Rapporteur Assessment Report	2 March 2017	n/a
PRAC Outcome	9 March 2017	9 March 2017
CHMP members comments	13 March 2017	13 March 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	16 March 2017	17 March 2017
Request for Supplementary Information	**23 March 2017**	**23 March 2017**
Submission deadline	14 July 2017	14 July 2017
Re-start date	17 July 2017	17 July 2017
CHMP Rapporteur Assessment Report	15 August 2017	16 August 2017
PRAC Rapporteur Assessment Report	18 August 2017	14 August 2017
PRAC members comments	23 August 2017	n/a
Updated PRAC Rapporteur Assessment Report	24 August 2017	n/a
PRAC Outcome	01 September 2017	01 September 2017
CHMP members comments	04 September 2017	04 September 2017
Updated CHMP Rapporteur Assessment Report	07 September 2017	08 September 2017
2nd Request for Supplementary Information	14 September 2017	14 September 2017
Submission deadline	10 October 2017	10 October 2017

Timetable	Planned dates	Actual dates
Re-start date	11 October 2017	11 October 2017
PRAC Rapporteur Assessment Report	16 October 2017	16 October 2017
PRAC members comments	18 October 2017	18 October 2017
Updated PRAC Rapporteur Assessment Report	19 October 2017	n/a
CHMP Rapporteur Assessment Report	25 October 2017	23 october 2017
PRAC Outcome	27 October 2017	27 October 2017
CHMP members comments	30 October 2017	30 October 2017
Updated CHMP Rapporteur Assessment Report	03 November 2017	n/a
Opinion	09 November 2017	09 November 2017

2. Scientific discussion

2.1. Introduction

Immune (idiopathic) thrombocytopenia (ITP) is an autoimmune disorder characterised by a low circulating platelet count (thrombocytopenia), decreased platelet production and increased platelet destruction. Thrombocytopenia places patients at risks for bruising, mucocutaneous bleeding and more seriously intracranial hemorrhage. Although its basic pathophysiology has been elucidated, no clinically apparent cause has been established for ITP.

In the US and EU, paediatric ITP (acute and chronic) occurs at an overall incidence rate of between 4.0 and 5.3 cases per 100,000 per year in otherwise healthy children < 15 years of age, with a peak incidence between ages 2 and 10 and affecting boys and girls equally. Prevalence of pediatric ITP is 7.2 cases per 100,000 per year. Unlike adult ITP in which the majority of cases are chronic in duration, pediatric ITP most commonly occurs in the acute form (platelet count < 150 x 10^9/L for < 6 months from diagnosis), accounting for 70 to 80% of ITP cases in children. Many children with acute ITP require no treatment and in approximately 60% to 75% of cases, the thrombocytopenia resolves within 2 to 4 months regardless of therapy. Twenty to 30% of paediatric ITP cases are considered chronic (platelet count < 150 x $10^{9/}$L for > 6 months from diagnosis) and may become refractory to standard treatments. Chronic ITP in childhood has an estimated incidence of 0.46 per 100,000 children per year. Predictors for chronicity among children include older age (> 10 years) and an insidious presentation. In addition, chronic ITP in children is also associated with higher presenting platelet count (> 20 000/µL), lack of mucosal bleeding at presentation and lack of a previous acute illness.

The risk of intracranial hemorrhage is < 0.5% and increases with age; this risk is proportional to the severity (< 10 x 10^9/L) and duration of severe thrombocytopenia. One review of 332 medical records revealed that 17% of children had major haemorrhage defined as intracranial bleeding, epistaxis requiring cautery or nasal packing, gross haematuria, or other bleeding causing a decline in haemoglobin concentration. Approximately 75% of bleeding episodes in this review occurred in children with platelet counts < 10 x 10^9/L.

The most commonly used therapeutic agents for pediatric ITP include corticosteroids, intravenous immunoglobulin and anti-D immunoglobulin. Repeated treatments may postpone the need for splenectomy, but the responses are generally transient, lasting a median time of 5 weeks. The principal aim of treating children with chronic ITP is to maintain a haemostatically safe platelet count (> 50 x 10^9/L) and thus improve quality of life of the patient, instead of trying to normalise platelet counts. While

these therapies have been shown to result in increased platelet counts, the potential toxicity of these agents compels physicians to weigh the likelihood of clinical efficacy against the likelihood of the occurrence of clinically relevant adverse events.

The American Society of Haematology (ASH) guidelines incorporate both clinical and platelet count data to arrive at specific treatment recommendations; for instance, children either with platelet counts < 20 x 10^9/L and significant mucous membrane bleeding or with platelet counts < 10 x 10^9/L and minor purpura should be treated with specific regimens of immunoglobulin (IVIg) or glucocorticoids. When ITP symptoms persist after primary treatment (glucocorticoid, IVIg) and splenectomy, further treatment is indicated in children with platelet counts < 30 x 10^9/L and who have active bleeding.

The BCSH guidelines (2003) recommend that splenectomy is rarely indicated in childhood, given that the risk of dying from ITP in childhood is extremely low (less than 1 in 500), and that the mortality associated with splenectomy is 1.4 to 2.7%. Moreover, splenectomy is not warranted in younger patients who are at relatively high risk for infection with encapsulated organisms.

The management of children with ITP who either fail to respond after splenectomy or relapse following splenectomy is often challenging. Rituximab has been used in children with severe chronic ITP who are refractory to standard agents, and treatment with 4 weekly doses of 375 mg/m2 resulted in response rates ranging from 31 to 68%. However, rituximab carries warnings with regards to infusion reactions, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy, and 5 to 10% of children with ITP may develop serum sickness. In addition, hepatitis B virus reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients with haematologic malignancies treated with rituximab.

The MAH applied for the following indication which was agreed: "Nplate is indicated for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients one year of age and older who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) (see sections 4.2 and 5.1)."

2.2. Quality aspects

2.2.1. Introduction

The purpose of this extension of indication application is to introduce a new presentation of Nplate finished product with lower-strength to the currently approved range, Nplate 250 µg and 500 µg powder for solution for injection, for the new indication in paediatric chronic ITP patients 1 year of age and older who are refractory to other treatments.

The finished product (Nplate 125 µg) is presented as powder for solution for injection containing 125 µg romiplostim as active substance.

Other ingredients are: Mannitol, Sucrose, L-histidine, Hydrochloric acid (for pH adjustment) and Polysorbate 20.

Nplate 125 µg powder for solution for injection is available only as a vial presentation consisting of a single-dose vial (type 1 clear glass) with a stopper (chlorobutyl rubber), seal (aluminium) and a flip-off cap (polypropylene). These are the same container closure system components of the currently marketed Nplate 250 µg and 500 µg presentations; however Nplate 250 µg and 500 µg strengths also have an additional presentation consisting of a vial and reconstitution kit including solvent. Prior to administration, Nplate 125 µg powder for solution for injection is reconstituted in the vial to give 0.5 mg/mL romiplostim solution, which is the same concentration of the currently approved Nplate presentations of 250 µg and 500 µg. If the calculated individual patient dose is less than 23 µg, the solution is further diluted with

0.9% saline. The final calculated solution volume is drawn into a syringe (not supplied) for subcutaneous injection.

2.2.2. Active Substance

There are no changes declared for the active substance part of Module 3.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Nplate 125 µg is supplied for single use in a glass vial containing 230 µg of romiplostim, providing 125 µg of deliverable romiplostim. The qualitative and quantitative composition for Nplate 125 µg vial is presented in Table 1 below.

Table 1. Composition of Nplate 125 µg vial

Component	Quality Standard	Function
Romiplostim	In-house[a]	Active Substance
Mannitol	Ph. Eur. / USP / JP	Bulking agent, tonicity modifier
Sucrose	Ph. Eur. / N.F./JP	Stabiliser, tonicity modifier
L-Histidine	Ph. Eur. / USP	Buffering agent
Dilute hydrochloric acid	Ph. Eur. / N.F.	pH adjusting agent
Polysorbate 20	Ph. Eur. / N.F.	Stabilising agent

[a] Tested to internal specifications (3.2.S.4, Control of Drug Substance)

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

The buffer formulation used for manufacture of the 125 µg presentation is the same as that used for Nplate 250 µg and 500 µg. In line with Nplate 250 µg and 500 µg, to ensure that the final finished product post-reconstitution is within the protein concentration specified in the label, a manufacturing concentration overage has been applied to the 125 µg presentation, . This is accomplished by diluting the active substance to a target concentration of , as established during process characterization studies, which will result in a of romiplostim vial content.

The primary container closure system consists of a 3 mL Type I borosilicate glass vial with a 13 mm elastomeric stopper (chlorobutyl rubber) and an aluminum seal with flip off dust cover (polypropylene). The material complies with Ph.Eur. and EC requirements. The container closure system was tested for organic extractables. Overall, there was no toxicological concern for the extractable profile generated under the experimental conditions, which was similar to that of the current 5 mL vial used for Nplate 250 µg and 500 µg. The functionality of the vial system was tested according to Ph.Eur 3.2.9 and showed the stopper meets the acceptable limits for functionality and was acceptable for use with the finished product. Container closure integrity was demonstrated by the . The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Prior to use, the lyophilised product is reconstituted with with 0.44 mL water for injection (WFI), forming a solution for injection at 0.5 mg/mL romiplostim in histidine, mannitol, sucrose, and polysorbate 20 at a pH of 5.0. The reconstituted product is a clear, colourless solution practically free from particles.

If the calculated individual patient dose is less than 23 µg, an additional dilution step to 125 µg/mL with preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection is required to ensure accurate volume and that the isotonicity of the dose is maintained. The dose is administered with suitably graduated syringes for subcutaneous administration by a qualified health care professional. The company is recommended to develop a reconstitution and dilution kit for the preparation and administration of paediatric doses by a qualified health care professional.

The stability of these diluted preparations was assessed after storage in a disposable syringe at 25°C (and expulsion from a 27G needle) for 0, 4 or 8 hours to support an upper limit of a 4-hour hold time in the clinical setting. The stability of the 0.5, 0.25, and 0.125 mg/mL samples in disposable syringes was compared to control samples at the same three protein concentrations that were stored in glass vials at 2 to 8°C. Holding diluted material for up to 4 hours was supported by testing to 8 hours.

Nplate 125 µg powder for solution for injection is stable () when reconstituted with WFI and diluted with saline to 0.125 mg/mL and stored in disposable syringes at 25°C for up to four hours followed by expulsion though a 27G needle, or when stored in glass vials at 2 to 8°C for up to four hours.

No other diluents have been tested. Dextrose (5%) in water or WFI should not be used for the dilution of the reconstituted product.

Manufacture of the product and process controls

Nplate 125 µg will be manufactured at the currently approved Nplate finished product manufacturing facility, , using the same equipment used for the approved Nplate 250 µg and 500 µg. The processing steps (active substance thawing, formulation, bioburden reduction filtration, bulk product hold, sterile filtration, aseptic filling, lyophilisation, stoppering and capping) are the same as those for the approved Nplate 250 µg and 500 µg, with minor modifications made to support the 125 µg presentation ().

The in-process controls (IPCs) for Nplate 125 µg are the same as those for the approved Nplate 250 µg and 500 µg with the exception of control at the filtered formulated bulk step, which was has action limits to ensure proper nominal romiplostim concentration upon reconstitution.

Process validation was performed on three consecutive romiplostim finished product batches following a batch size bracketing approach (testing the extremes of the intended batch size range: intermediate, maximum and minimum batch size), using pre-defined acceptance criteria on those process steps that differed from the previously validated 250 µg and 500 µg strengths. Validation data demonstrate consistency and reliability of the Nplate 125 µg formulation, filling, lyophylisation manufacturing process at, showing that the manufacturing process is in a state of control.

Comparability

Comprehensive analytical comparability studies were executed to support the introduction of the 125 µg presentation. The batch analysis results on three commercial batches demonstrate that the molecular size distribution, charge heterogeneity, potency, biological activity, impurity profiles and general product characteristics of post-change product are highly similar to pre-change product. Additional characterization methods were included. The results for the product characterization methods all met comparability assessment criteria. These results provide orthogonal and supplemental evidence to batch analysis results that post-change product is highly similar to pre-change product.

Additionally, pre- and post-change degradation rates under accelerated stability conditions were studied for purity by potency and subvisible particles and forced degradation rates were studied using. For the parameter, pre- and post- change degradation rates were similar and no new peaks were observed. There was no change in results for either the pre-change or post-change material. The statistical evaluation of the main peak and potency by determined that the 125 µg presentation showed degradation at a rate statistically equivalent to the 250 µg and 500 µg presentations. Subvisible particle results

demonstrated consistent results of the particle distribution for the pre-change and post change lots. The levels of , process related impurities for the 125 µg finished product batches are the same after 3 months and fall well within tolerance intervals established to assess comparability. Pre- and post-change chromatographic profiles and degradation rates under forced degradation conditions for the parameter were similar.

All comparability assessment criteria were met. The results demonstrate analytical comparability between the 125 µg presentation and the two commercially approved presentations: 250 µg and 500 µg.

Product specification

The specification for the lyophilised product consist of moisture content (colometric or spectroscopic analysis), appearance and colour . The specification for the reconstituted finished product consist of appearance and colour (), clarity (), identity (enzyme-linked immunosorbent assay (ELISA)), purity (Size Exclusion High Performance Liquid Chromatography (SE-HPLC), Cation Exchange HPLC (CEX-HPLC), Reverse Phase (RP-HPLC)), sterility (), bacterial endotoxin , potency (), protein concentration); pH (); polysorbate 20 (); subvisible particles (); osmolality (). The finished product specification acceptance criteria and test methods for Nplate 125 µg are aligned with the currently approved Nplate 250 µg and 500 µg finished product specifications, with the exception of appearance and colour: for the 125 µg presentation, the appearance, colour, and clarity attributes are tested by individual methods, to align with current Amgen practices, whilst for Nplate 250 µg and 500 µg these attributes are tested with a single method. There is no change to the methodology as a result of this change and the methods are compliant with Ph.Eur. A specification for the extractable volume is not applicable for the reconstituted product as there is a considerable overfill of the product and the volume that needs to be extracted is much smaller than the total volume.

Batch analysis

Batch analysis data have been provided for three production scale batches. The provided batch data comply with the release specifications.

Reference materials

The reference materials are identical to those already approved presentations.

Stability of the product

Based on available stability data, on the fact that the proposed presentation has the same protein concentration and product contact materials and on the comparability study, the proposed shelf-life (60 months) and storage conditions (*"Store in a refrigerator (2°C – 8°C). Do not freeze. Store in the original carton in order to protect from light. May be temporarily removed from the refrigerator for a maximum period of 24 hours at room temperature (up to 25°C"),* which is the same as the registered shelf life for the currently approved 250 µg and 500 µg presentations, is supported.

Real time/real condition (5°C) stability data of three commercial scale batches of finished product for up to 24 months and for up to 6 months under accelerated (37°C) conditions were provided. The batches of Nplate 125 µg are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. The currently available stability data meet the pre-defined acceptance criteria under the recommended storage. The batches will remain in the real time/real condition stability program through the 60 month time point. Any confirmed out of specification results will be reported to the Regulatory Authorities.

Photostability testing for Nplate 125 µg powder for solution for injection is derived from the 250 µg and 500 µg presentations data. This is considered acceptable. The reported stability data are considered sufficient to support the application of a 60 month shelf-life at 5°C with an additional storage allowance for up to 24 hours at room temperature (≤ 25°C). After dilution, chemical and physical in-use stability has been demonstrated for 4 hours at 25°C when the diluted product was held in a disposable syringe, or 4 hours in a refrigerator (2°C – 8°C) when the diluted product was held in the original vial.

The proposed post-approval stability protocol is the same as that for Nplate 250 and 500 µg presentations with the exceptions of some tests A minimum of one lot of drug product from the 125, 250 or 500 µg romiplostim containing vial will be added to the ongoing post-approval stability program annually, as is the current practice. Vial presentations selected will vary from year to year to ensure a balanced program. n view of the similarity of Nplate 125 µg with Nplate 250 µg and 500 µg, this is considered acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality information provided to support this extension of indication has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the new presentation Nplate 125 µg powder for solution for injection is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAH to take due account of technical and scientific progress, the following measures related to quality aspects are recommended for further investigation:

The company is recommended to develop a reconstitution and dilution kit for the preparation and administration of paediatric doses by a qualified health care professional.

2.3. 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.

2.4. Clinical aspects

2.4.1. Introduction

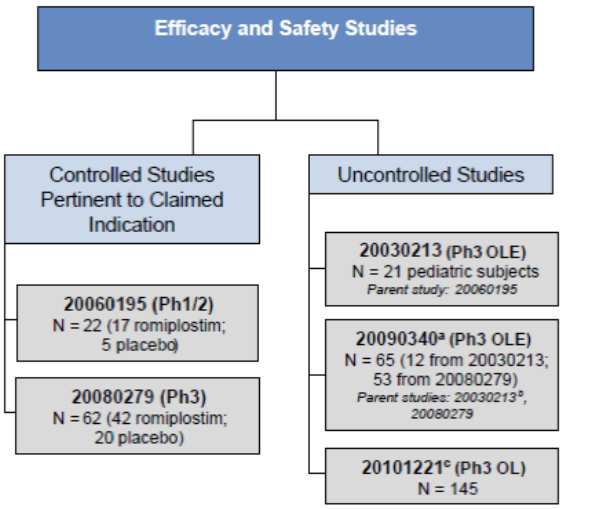
GCP

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

The MAH has conducted a paediatric ITP development program to seek approval for the use of romiplostim in paediatric subjects with chronic ITP. The development program for romiplostim in the setting of paediatric ITP consists of 3 completed studies (Studies 20060195 and 20080279, which were placebo controlled, and Study 20030213, which was a long-term safety and efficacy study) and 2 ongoing studies (Studies 20090340 and 20101221, which are both long term safety and efficacy studies).

•Tabular overview of clinical studies

Figure 1. Romiplostim Pediatric Clinical Program



2.4.2. Pharmacokinetics

Pharmacokinetic characteristics of romiplostim in adults with ITP:

The pharmacokinetics of romiplostim involves target mediated disposition, which is presumably mediated by TPO receptors on platelets and other cells of the thrombopoietic lineage such as megakaryocytes. This may explain the lack of correlation between romiplostim serum concentrations and the dose administered. In adults, romiplostim serum levels appear inversely related to platelet counts.

Pharmacokinetics in paediatric patients:

Data on PK have been collected for the paediatric studies Studies 20060195 and 20090340 and the data from these subjects (subjects providing PK data; N = 17 for Study 20060195 and N = 4 for Study 20090340) are described.

The objectives of the clinical pharmacology evaluation supporting this supplemental marketing application are as follows:

- To characterise PK and pharmacodynamics (platelet count) of romiplostim in paediatric subjects with ITP and examine their consistency with those observed in adults;

• To evaluate paediatric dosing regimen. Paediatric subjects were monitored throughout all studies to characterise the development of anti-romiplostim antibodies and to explore the impact of any positive anti-romiplostim antibodies on the PK of romiplostim.

Study 20060195

Study 20060195 is a multi-center randomized, double-blind, placebo-controlled Phase ½ Study to determine the safety and efficacy of Romiplostim in Thrombocytopenic Pediatric Subjects with Chronic Immune (Idiopathic) Thrombocytopenic Purpura.

This study consisted of a screening period, a 12-week treatment period, a 4-week PK assessment period for responding subjects only (all responding subjects were from the romiplostim group), and an end-of-study visit.

Subjects between the ages of 12 months and below 18 years who had been diagnosed with ITP according to the ASH Guidelines at least 6 months before enrolment were eligible to screen for this study. Eligible subjects must have had severe thrombocytopenia, defined by a mean of 2 platelet counts ≤ 30 x 10^9/L with no single count > 35 x 10^9/L, within 21 days of the enrolment visit. Subjects were allowed entering in the study while receiving concurrent corticosteroid therapy, reductions in which were allowed at any time during the study after a platelet count of > 50 x 10^9/L had been achieved.

A total of 22 subjects were randomized to romiplostim or placebo (3:1); randomization was stratified by age as follows: 12 months to < 3 years, 3 to < 12 years, and 12 to< 18 years to allow for an equal distribution of subjects. Subjects initially entered a 12-week treatment period during which each subject received an initial dose of blinded investigational product SC at 1.0µg/kg with each subsequent weekly dose adjusted based on individual platelet count before dosing to produce platelet responses within the target range of 50 x 10^9/L to 250 x 10^9/L. The maximum permitted dose of investigational product was 10.0µg/kg. At the end of the 12-week treatment period, responding subjects (i.e. subjects achieving platelet count > 20 x 10^9/L above baseline for 2 consecutive weeks in the absence of rescue therapy at any point during the 12-week treatment period) were enrolled into a 4-week PK assessment period.

For PK sample collection, at week 12, samples were obtained from all subjects regardless of platelet counts on day 1 (before investigational product dosing) and day 3. During the PK assessment period, PK samples were drawn weekly at pre-dose (day 1) and 2 days post-dose (day 3).

Disposition

Of the 22 subjects enrolled, 17 subjects were randomized to romiplostim and 5 subjects were randomized to placebo.

Enrolment by age was as follows:

• 12 months to < 3 years: 4 subjects (3 romiplostim, 1 placebo)

• 3 years to < 12 years: 10 subjects (8 romiplostim 2 placebo)

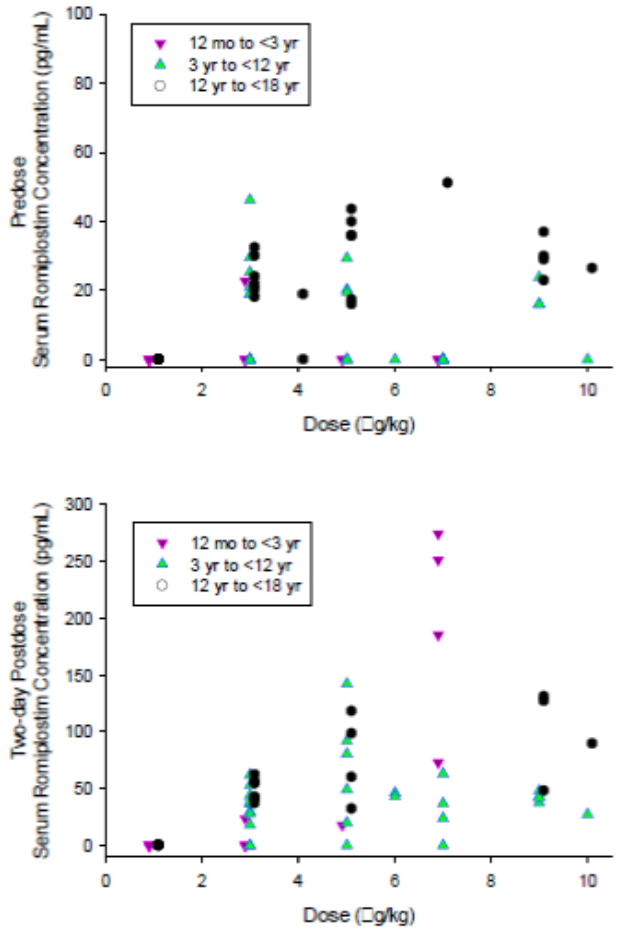
• 12 years to < 18 years: 8 subjects (6 romiplostim, 2 placebo)

All 22 subjects received at least 1 dose of blinded investigational product and completed the study. Blood samples were collected for romiplostim concentration determination at week 12 for all subjects (N = 17 romiplostim treated) and during the 4-week PK assessment period for responding subjects (N = 14, all romiplostim treated). The romiplostim dose ranged from 1 to 7µg/kg, 3 to 10µg/kg, and 1 to 10µg/kg for age cohorts of 12 months to< 3 years, 3 to < 12 years, and 12 to < 18 years, respectively. In total, 8 subjects received the same dose over time for 5 weeks. A total of 136 serum PK samples (including 1 unscheduled sample) from 22 subjects were analysed for romiplostim concentrations.

PK results

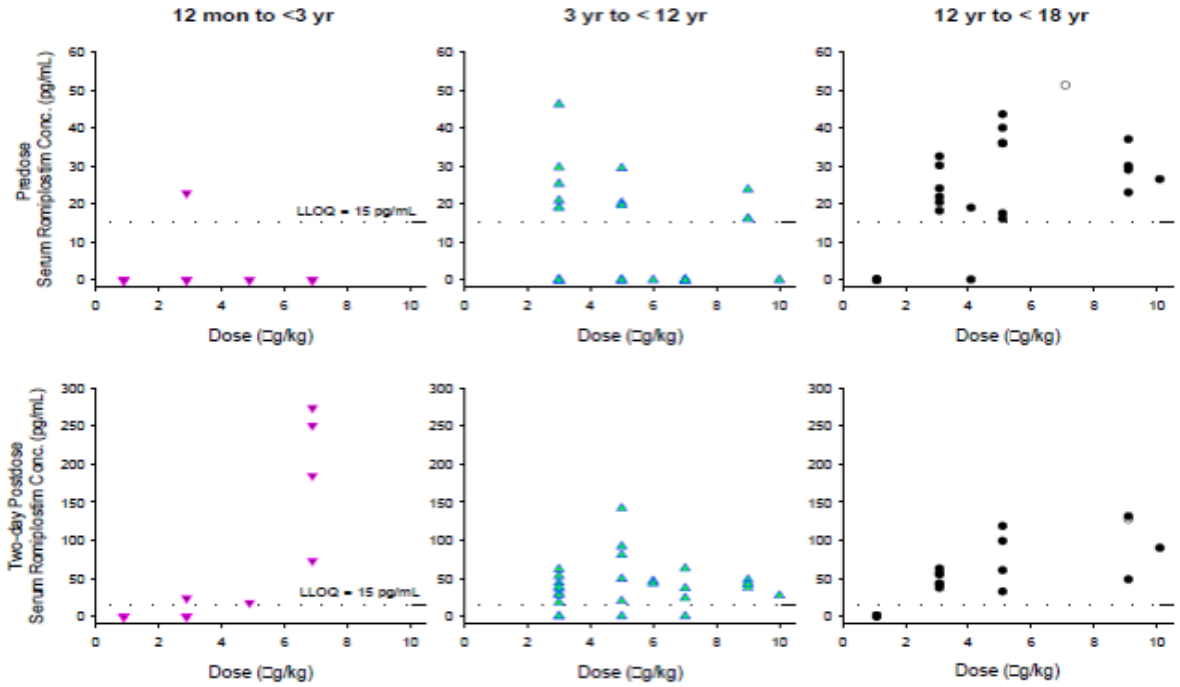
The romiplostim serum concentrations were highly variable both at pre-dose and at 2 days post-dose for each romiplostim dose level and no apparent difference among the 3 age cohorts was observed (Figure 2 and Figure 3). No obvious association between romiplostim dose and serum concentration was observed in all 3 age cohorts (Figure 3), suggesting that factors other than the dose affect the clearance of romiplostim. One of those factors as previously shown in adult subjects is the circulating platelet count, since romiplostim clearance partly is mediated by the TPO receptors on megakaryocytes and platelets. Therefore, higher platelet counts would result in higher romiplostim clearance and lower romiplostim concentration. As shown, for the oldest age cohort (12 to < 18 year), higher platelet counts were associated with lower romiplostim concentrations either at pre-dose or 2 days post-dose (Figure 4); however, this type of relationship was not as apparent for the 2 younger cohorts.

Figure 2. Individual Serum Romiplostim Concentration at Predose or 2 Days Postdose After Multiple Weekly SC Administration of Romiplostim



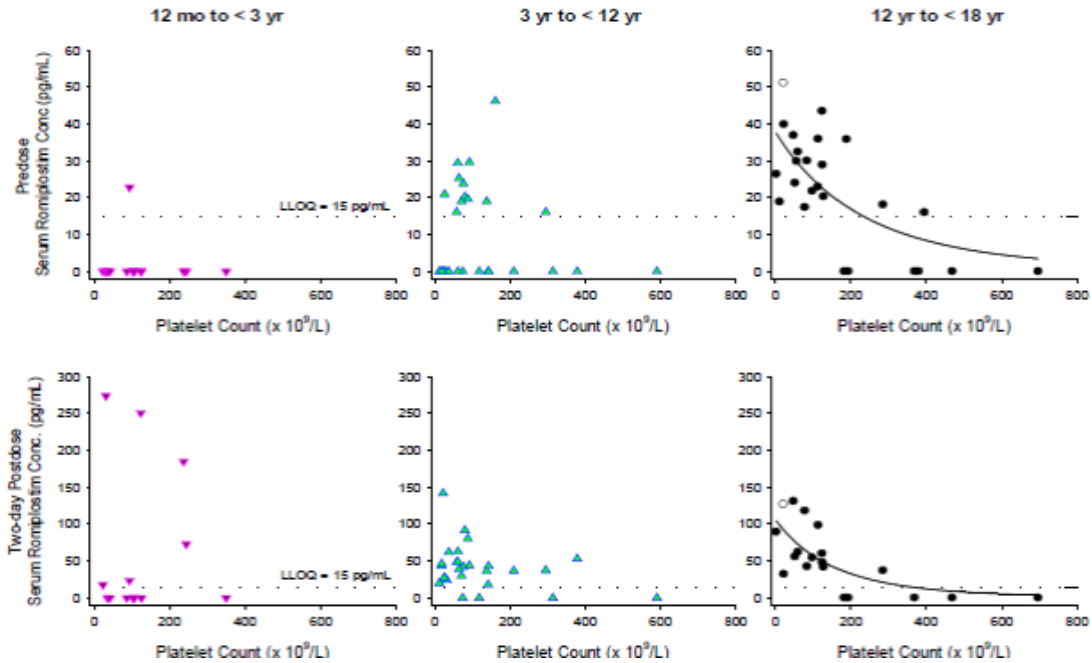
mo = month; SC = subcutaneous
Symbols represents data collected throughout the study, and each subject contributed 1 or more data points on the figure.

Figure 3. Relationship Between Individual Serum Romiplostim Concentration Predose or 2 Days Postdose After Multiple Weekly SC doses of Romiplostim



Conc. = concentration; LLOQ = lower limit of quantification; mon = month; SC = subcutaneous
Symbols represents data collected throughout the study, and each subject contributed 1 or more data points on the figure. These diagnostic plots do not take into
consideration that the platelet count has an impact on serum concentrations of romiplostim.
Source: \\FILESRV01\PCBard-Raw\QPData\Romiplostim\module 2.7.2\Nplate Study 20060195 - All Subjects

Figure 4. Relationship Between Individual Serum Romiplostim Concentration Predose or 2 Days Postdose and Platelet Count After Multiple Weekly SC Doses of Romiplostim



Conc. = concentration; LLOQ = lower limit of quantification; mo = month; SC = subcutaneous
Symbols represents data collected throughout the study, and each subject contributed 1 or more data points on the figure. These diagnostic plots do not take into
consideration that the dose of romiplostim has an impact on serum concentrations of romiplostim.
Source: \\FILESRV01\PCBard-Raw\QPData\Romiplostim\module 2.7.2\Nplate Study 20060195 - All Subjects

Study 20090340

This study was an open label study evaluating the safety and efficacy of long-term dosing of romiplostim in thrombocytopenic pediatric subjects with immune (idiopathic) thrombocytopenia purpura (ITP). This is a long-term extension study for paediatric subjects from Study 20030213 or Study 20080279 (pivotal).

The primary objective of Study 20090340 was to evaluate the safety of romiplostim as a long-term treatment in paediatric thrombocytopenic subjects with ITP.

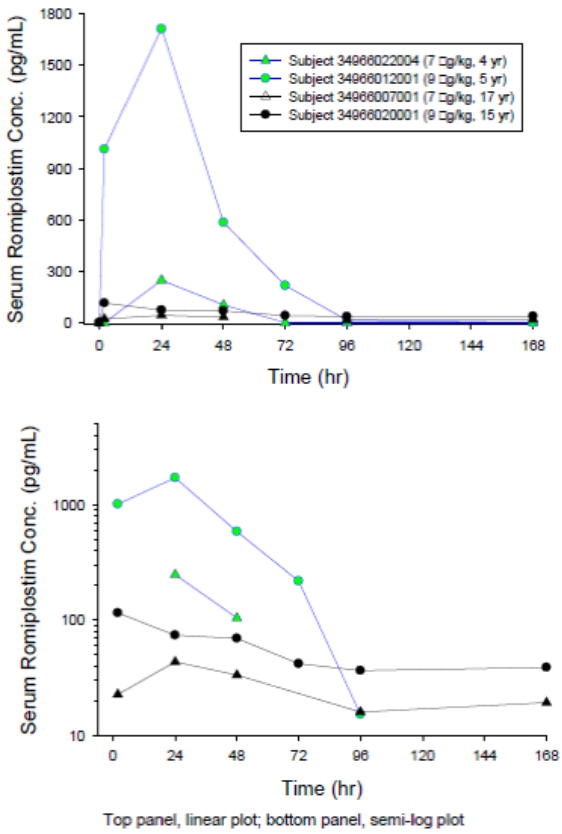
The secondary objectives were to evaluate the long-term platelet response to romiplostim and possible reductions in the dose of concurrent ITP therapies while receiving romiplostim. Subjects enrolled in Study 20090340 were also eligible to participate in an optional PK portion of the study, designed to evaluate the PK profile of romiplostim in paediatric subjects. In this PK portion, serial blood samples were collected from each participating individual during week 1 and week 2 of the study.

Disposition

As of the data cut-off date of 24 February 2016, 66 subjects entered the extension; 12 were from Study 20030213 and 54 were from Study 20080279. A total of 65 subjects received romiplostim for median duration of 100 weeks (range: 5 to 321 weeks); 1 subject withdrew consent before romiplostim treatment.

Four subjects had measurable serum romiplostim concentrations. Two subjects received the romiplostim dose at 7 µg/kg, while the other 2 received at 9 µg/kg. The PK profiles and the PK parameters for these subjects are presented in Figure 5 and Table 3, respectively. The exposure to romiplostim was highly variable. Based on the limited data, after SC administration of romiplostim, the maximum concentration of romiplostim was reached by 24 hours post dose.

Figure 5. Individual Romiplostim Concentration-time Profiles



Top panel, linear plot; bottom panel, semi-log plot

Conc. = concentration

Table 3: PK parameters of Romiplastin in Peadiatric subjects

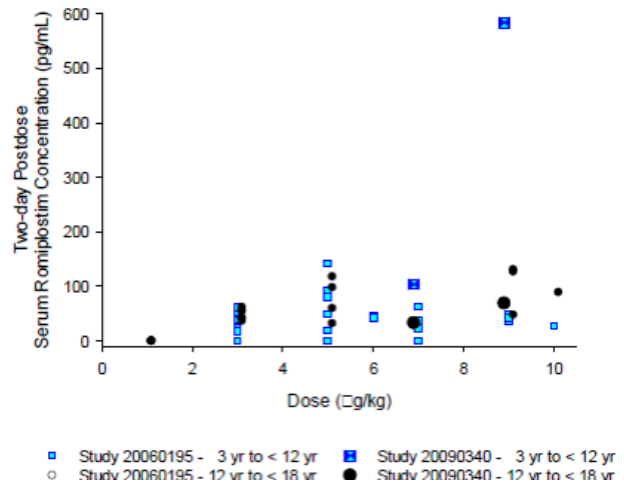
Age (year)	Dose (µg/kg)	C_{max} (pg/mL)	t_{max} (hr)	AUC_{last} (hr·pg/mL)
4	7	247	21	NR
17	7	43.3	25	4090
5	9	1710	24	76400
15	9	115	2.0	9020

AUClast = area under the concentration-time curve from time 0 to the time of the last detectable concentration; Cmax = maximum observed concentration; tmax = time of maximum observed concentration

Comparison and analyses of results across studies

Comparison between Study 20060195 and Study 20090340:

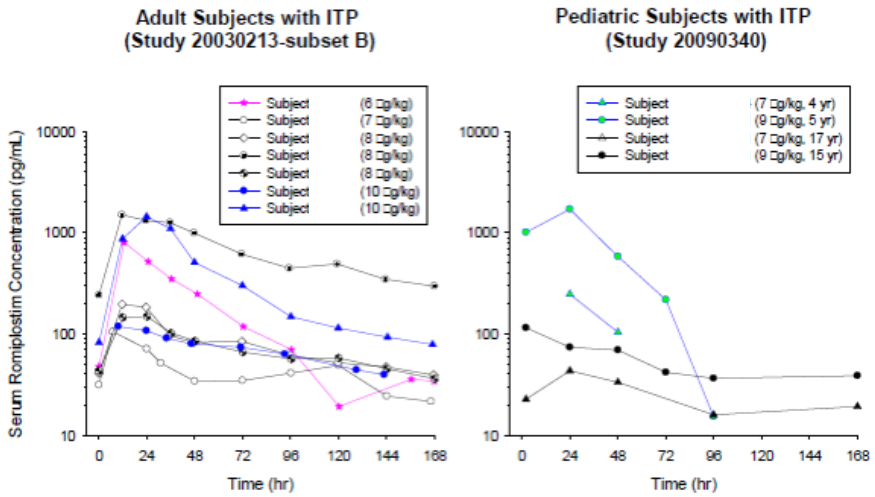
Figure 6. Individual Serum Romiplostim Concentration at 2 Days Postdose After SC Administration of Romiplostim



PK Comparison between Adult Subjects With ITP and Paediatric Subjects With ITP

The PK profiles from paediatric subjects with ITP from Study 20090340 were compared with those from adult subjects with ITP from Study 20030213 in a similar dose range (Figure 7). The adult subjects received at least 3 weekly romiplostim doses before the PK profile was collected, whereas the paediatric subjects received 1 romiplostim dose before the PK profile was collected. High inter-subject variability was observed for both populations. Based on visual inspection, the romiplostim concentrations for pediatric subjects generally fell within the range observed in adult subjects with ITP. Similar to adults with ITP, large variability in romiplostim PK in these pediatric subjects with ITP also suggested that serum romiplostim concentration is not reliable in predicting the platelet responses.

Figure 7. Individual Romiplostim Concentration-time Profiles From Adult and Pediatric Subjects With ITP



ITP = immune thrombocytopenia

2.4.3. Discussion on clinical pharmacology

In adults with ITP, the pharmacokinetics of romiplostim involved target-mediated disposition, which is presumably mediated by TPO receptors on platelets and other cells of the thrombopoietic lineage such as megakaryocytes. There was a correlation between serum exposure (AUC and C_{max}) and pre-dose platelet counts: romiplostim exposure was low when the pre-dose platelet counts were high, and vice versa. Romiplostim, as a protein, is expected to be cleared for a major part by proteolysis.Pharmacokinetics of romiplostim in paediatric subjects was investigated following the first administration in subjects 4-17 years old and by sparse data sampling following repeated dosing in patients with a platelet response aged 1-17 years old. Similar to the pharmacokinetics of romiplostim in adults with ITP, the romiplostim serum concentrations were highly variable in paediatric patients both at pre-dose and at 2 days post-dose ranging from below the limit of quantitation (< 15 pg/mL) to 51.1 pg/mL pre-dose and up to 1710 pg/mL post-dose, respectively. There was no dose-exposure correlation, apparently suggesting that factors other than the dose affect the clearance of romiplostim. One of those factors, as previously shown in adult subjects, is the circulating platelets, since romiplostim clearance partly is mediated by the TPO receptors on megakaryocytes and platelets. Higher platelet counts were associated with lower romiplostim concentrations either at pre-dose or 2 days post-dose for the oldest age cohort (12 to <18 year); however such a relationship was not as apparent for the 2 younger cohorts. There might be a trend for a faster elimination of romiplostim in younger children and younger children had a higher percentage of very low romiplostim trough levels. Insufficient data are available, especially in the group <3 years of age, to draw conclusions regarding the effect of age on pharmacokinetics. This has been reflected in section 5.2 of the SmPC as follows: "Pharmacokinetic data of romiplostim were collected from two studies in 21 paediatric subjects with ITP. In study S5 (195), romiplostim concentrations were available from 17 subjects at doses ranging from 1 to 10 mcg/kg. In Study S6 (340), intensive romiplostim concentrations were available from 4 subjects (2 at 7 mcg/kg and 2 at 9 mcg/kg). Serum concentrations of romiplostim in paediatrics with ITP were within the range observed in adult ITP subjects receiving the same dose range of romiplostim. Similar to adults with ITP, romiplostim pharmacokinetics are highly variable in paediatric subjects with ITP and are not reliable and predictive. However, the data are insufficient to draw any meaningful conclusion relating to the impact of dose and age on the pharmacokinetics of romiplostim."

The starting dose 1 µg/kg and weekly dose increments with 1 µg/kg until the patient achieves a platelet count ≥ 50 x 10^9/L, are similar in paediatric and adult subjects with ITP. At the starting dose of 1 µg/kg, romiplostim serum concentrations were very low (<15 pg/ml) in paediatric patients. Two out of 17 paediatric patients achieved a stable platelet count (≥ 50 x 10^9/L for at least 2 weeks without dose

adjustment) with this starting dose, whereas higher doses were needed for the other patients. The platelet response in paediatric subjects with ITP is in line with that of adult subjects with ITP supporting that the same dosing algorithm as for adults can be applied. These dosing recommendations have been applied in the pivotal paediatric phase 3 Study 20080279.

In addition, there are no data in the literature to support that there are any differences in equilibrium of platelet production/destruction in paediatric ITP patients compared with adult ITP patients.

2.4.4. Conclusions on clinical pharmacology

The limited pharmacokinetic data in paediatric patients with ITP 1-17 years of age preclude conclusions with regards to the effect of age on pharmacokinetics of romiplostim. Similar to adults with ITP, romiplostim pharmacokinetics are highly variable in paediatric subjects with ITP and are not reliable and predictive, this is considered acceptable as the dose for an individual patient is calculated based on body weight, dose required, and concentration of product as reflected in section 4.2 of the SmPC.

Hence no further pharmacokinetic data are requested, this has been reflected in section 5.2 of the SmPC.

2.5. Clinical efficacy

2.5.1. Dose response study

20060195 study

As presented above, this study was a multicenter, randomized, double-blind, placebo-controlled, phase 1/2 study to determine the safety, tolerability, efficacy, and PK of romiplostim among thrombocytopenic paediatric subjects with chronic ITP.

The primary endpoint was the incidence of adverse events, including anti-romiplostim antibody formation and anti-TPO antibody formation, by treatment group during the 12-week treatment period.

Secondary endpoints were as follows:

- Incidence of achieving platelet count ≥ 50 x 10^9/L for 2 consecutive weeks during the 12-week treatment period
- Incidence of achieving an increase in platelet count ≥ 20 x 10^9/L above baseline for 2 consecutive weeks during the 12-week treatment period
- Incidence of requiring rescue therapy during the 12-week treatment period
- Total number of bleeding events (grade 2 or higher) for each subject during weeks 2 to 13
- Pharmacokinetic exposure of romiplostim as measured by drug concentrations taken at specified times during the study
- Number of weeks with platelet count ≥ 50 x 10^9/L during the 12-week treatment period

Efficacy Results

Results

The study was conducted from 19 July 2007 (first subject enrolled) to 03 March 2009(last subject's end-of-study visit). The study was conducted at 10 centers, 8 in the United States, 1 in Spain, and 1 in Australia.

Baseline subject demographics were balanced across the treatment groups. Mean (standard deviation [SD]) age was 9.5 (5.1) years, reflective of most subjects being enrolled into the > 11- to 17-years-old age group. Most subjects (72.7%) were boys, and most (59.1%) were white. Mean (SD) weight was 45.1 (28.5) kg, and mean (SD) BMI was 22.2 (7.4) kg/m2

The mean (SD) baseline platelet count for the romiplostim group was similar to that for the placebo group (13.5 [6.3] x 10^9/L [range: 2 to 27 x 10^9/L] vs 14.3 [8.9] x 10^9/L [range: 8 to 29 x 10^9/L]) Median (range) time since ITP diagnosis was 2.4 (0.8 to 14.0) years in the romiplostim group and 4.1 (0.6 to 8.6) years in the placebo group.

Six subjects (35.3%) in the romiplostim group and 2 subjects (40.0%) in the placebo group had previously undergone splenectomy; median (range) time since splenectomy was 5.4 (0.4 to 12.0) years for the romiplostim group and 3.6 (0.4 to 6.7) years for the placebo group. Sixteen romiplostim-treated subjects (94.1%) and 5 placebo-treated subjects (100%) had received prior ITP treatments with a median (range) number of prior ITP treatments of 5 (0 to 9) for the romiplostim group and 3 (2 to 8 for the placebo group.

Outcomes and estimation

22 subjects were randomised in a 3:1 ratio to receive romiplostim (n = 17) or placebo (n = 5). Doses were increased in increments of 2 mcg/kg every 2 weeks and the target platelet count was ≥ 50 x 10^9/L. Treatment with romiplostim resulted in statistically significantly greater incidence of platelet response compared with placebo (p = 0.0008). Of those 22 subjects, 17 subjects had ITP > 12 months of duration (14 subjects received romiplostim and 3 subjects received placebo). Treatment with romiplostim resulted in statistically significantly greater incidence of platelet response compared with placebo (p = 0.0147).

-Immunogenicity Assessment

One of the 17 subjects from the romiplostim-dosed group tested positive for binding antibodies to the TMP component of romiplostim at week 13 post-dose. No baseline sample was available for this subject. The subject was negative for neutralising antibodies to romiplostim in the bioassay. The sample drawn from the end-of-study time point from this subject was negative for binding antibodies to romiplostim and TMP, indicating a transient antibody response. No subject was positive for binding antibodies to TPO.

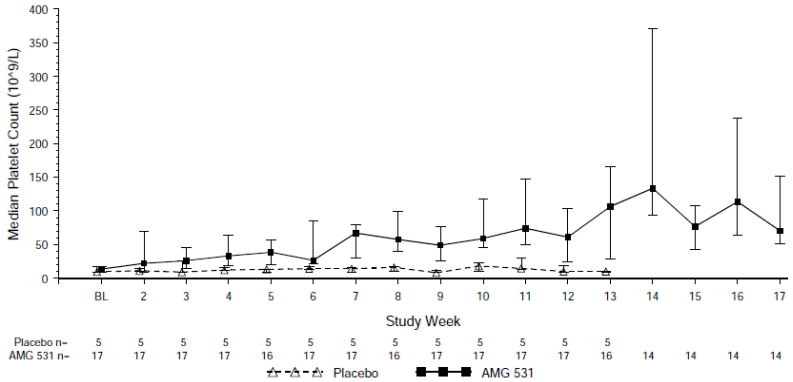
-Subjects Achieving a Platelet Count ≥ 50 x 10^9/L for 2 consecutive weeks during the 12-week treatment period

Of the 17 subjects who received romiplostim, 15 achieved a platelet count ≥ 50 x 10^9/L for 2 consecutive weeks (after excluding platelet counts within 4 weeks following rescue medication use) during the treatment period (88.2%, 95% CI: 63.6%, 98.5%). None of the subjects treated with placebo achieved either endpoint. Treatment with romiplostim resulted in statistically significantly greater incidence of platelet response compared to placebo (p = 0.0008).

Of these 15 subjects, 3 subjects (3/3, 100.0%, exact 97.5% CI: 29.2%, 100.0%) were in the 12-month- to < 3-years-old age group, 7 subjects (7/8,87.5%, 95% CI: 47.3%, 99.7%) were in the 3- to < 12-years-old age group and 5 subjects (5/6, 83.3%, 95% CI: 35.9%, 99.6%) were in the 12- to < 18-years-old age group.

When platelet response for 4 weeks following any administration of rescue medications was included, similar results were observed for the romiplostim group and 1 of the 5 subjects in the placebo group (20.0%, 95% CI: 0.5%, 71.6%) met this endpoint.

Figure 9-1. Median (Q1, Q3) Platelet Count by Visit (Efficacy Analysis Set)



-Subjects achieving an increase in platelet count > 20 x 10^9/L above baseline for 2 consecutive weeks during the 12-week treatment period

The same 15 subjects also achieved an increase in platelet count ≥ 20 x 10^9/L above baseline for 2 consecutive weeks (after excluding platelet counts within 4 weeks following rescue medication use) during the treatment period (88.2%, 95% CI: 63.6%, 98.5%). Two of the 5 subjects (40.0%) in the placebo group (1 in the 12-months- to < 3-years-old age group, 1 in the 12- to < 18-years-old age group) received rescue medication during the treatment period (2 subjects received immunoglobulins and 1 subject received prednisone).

-Subjects requiring rescue therapy during the 12-week treatment period

Two of 17 subjects (11.8%) in the romiplostim group (both in the 3- to < 12-years-old age group) received rescue medication during the treatment period (1 subject received dexamethasone, 1 subject received immunoglobulins).

-Total number of bleeding events (Clinical Grade ≥ 2) for each subject during weeks 2 to 13

Bleeding was the only event of interest observed in this study. During the treatment period, 12 subjects (70.6%) in the romiplostim group and 2 subjects (40.0%) in the placebo group had bleeding adverse events of any grade. These results should be interpreted with caution given the limited subject numbers per group. Events with incidence > 1 subject were (romiplostim, placebo) epistaxis (6 subjects [35.3%], 1 subject [20.0%]), contusion (3 subjects [17.6%], 1 subject [20.0%]), and petechiae (2 subjects [11.8%], 1 subject [20.0%]). Most bleeding adverse events were of CTCAE grade 1 (mild). Twelve (70.6%) romiplostim-treated subjects had events of grade 1; 1 subject in the romiplostim group (5.9%) had bleeding adverse events that were grade 2 (subject: epistaxis, contusion, petechiae). The 2 (40.0%) placebo-treated subjects had events of worst grade 1.

No bleeding adverse events were considered to be serious or treatment related and the majority of the bleeding adverse events for the romiplostim-treated subjects (i.e. those for 10 of the 12 subjects who had an event) occurred in the first 6 weeks of the treatment period.

When adjusted for exposure duration, the rate of bleeding was 7.3 events per 100 subject-weeks in the romiplostim arm and 11.9 events per 100 subject-weeks in the placebo arm. For the placebo group, all bleeding events occurred when the platelet count was < 30 x10^9/L. For the romiplostim group, the majority of the bleeding adverse events occurred in the first 6 weeks of the treatment period and most events (14 of 17) correlated to a platelet count < 30 x10^9/L; no events occurred at a platelet count ≥ 50 x 10^9/L. As most occurred in the first 6 weeks of treatment, these events were observed before the maximum dose allowed on study (10 µg/kg) was reached. The mean (SD) number of bleeding events

(clinical grade ≥ 2) was 0.4 (1.0) for the romiplostim group and 0.0 (0.0) for the placebo groups, with a median (range) number of bleeding events of 0.0 (0, 4) for the romiplostim group and 0.0 (0, 0) for the placebo group. One romiplostim-treated subject and no placebo-treated subjects experienced bleeding events of clinical grade > 2 severity. Subject, a 16-year-old girl, had a moderate (clinical grade 3; "overall" bleeding event after 22 days on treatment with romiplostim; platelet count on the day of the event was 22 x 10^9/L.

Table 14-6.7. Exposure Adjusted Bleeding Adverse Event Incidence Rates by Study Period and by Preferred Term (Safety Analysis Set)

	Placebo		AMG 531	
	Week 1 - 6 (Subj-wk = 30) (N = 5)	Week 7 - 12 (Subj-wk = 30) (N = 5)	Week 1 - 6 (Subj-wk = 96) (N = 17)	Week 7 - 12 (Subj-wk = 96) (N = 17)
PREFERRED TERM	n (r)	n (r)	n (r)	n (r)
Total Number of Bleeding Adverse Events Reported	5 (16.7)	3 (10.0)	15 (15.6)	2 (2.1)
CONTUSION	2 (6.7)	1 (3.3)	3 (3.1)	0 (0)
EPISTAXIS	0 (0)	1 (3.3)	5 (5.2)	2 (2.1)
GENITAL HAEMORRHAGE	0 (0)	0 (0)	1 (1.0)	0 (0)
HAEMATOMA	0 (0)	0 (0)	1 (1.0)	0 (0)
HAEMORRHAGE	0 (0)	0 (0)	1 (1.0)	0 (0)
INJECTION SITE HAEMATOMA	1 (3.3)	0 (0)	0 (0)	0 (0)
MOUTH HAEMORRHAGE	0 (0)	0 (0)	1 (1.0)	0 (0)
PETECHIAE	1 (3.3)	1 (3.3)	3 (3.1)	0 (0)
SKIN LACERATION	1 (3.3)	0 (0)	0 (0)	0 (0)

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Table 14-6.5.1. Baseline Characteristics By Treatment Groups and Bleeding Event Status During the 12 Week Treatment Period (Safety Analysis Set)

	Placebo		AMG531	
	Bleeding=No (N = 3)	Bleeding=Yes (N = 2)	Bleeding=No (N = 5)	Bleeding=Yes (N = 12)
Platelet (10^9/L)				
n	3	2	5	12
Mean	11.8	18.2	11.5	14.3
SD	4.8	14.8	7.3	6.1
Median	9.4	18.2	14.3	13.0
Q1, Q3	8.7, 17.3	7.7, 28.7	5.3, 17.7	10.1, 19.0
Min, Max	9, 17	8, 29	2, 18	6, 27
Time Since ITP Diagnosis (years)				
n	3	2	5	12
Mean	4.60	2.45	1.74	4.71
SD	4.00	2.33	1.44	4.65
Median	4.60	2.45	1.20	2.40
Q1, Q3	0.60, 8.60	0.80, 4.10	1.10, 1.30	1.60, 7.30
Min, Max	0.6, 8.6	0.8, 4.1	0.8, 4.3	0.8, 14.0
Number of Prior ITP Treatments				
n	3	2	5	12
Mean	3.3	5.5	4.4	4.8
SD	1.5	3.5	1.1	2.6
Median	3.0	5.5	4.0	5.0
Q1, Q3	2.0, 5.0	3.0, 8.0	4.0, 5.0	3.5, 6.5
Min, Max	2, 5	3, 8	3, 6	0, 9

Page 1 of 1

Safety analysis set includes all enrolled subjects receiving at least one dose of Investigational Product.

Program: /stat/amp2/itp/amp20060195/analysis/final/tables/t_basechar_by_bleed.sas
Output: t14-06_005_001_basechar_by_bleed.rtf (Date Generated: 04MAY09:07:51:20) Source Data: ae, bleed_v, ds, itpt_v, lb.sas7bdat

Number of Weeks With Platelet Count ≥ 50 x 10^9/L During the 12- week Treatment Period

Table 9-4. Number of Weeks With Platelet Count ≥ 50 x 10^9/L in Treatment Period[a] (Efficacy Analysis Set)

	Placebo (N = 5)	AMG 531 (N = 17)
Number of weeks with Platelet Count ≥ 50x10^9/L		
n	5	17
Mean	0.00	5.65
SD	0.00	3.00
Median	0.00	7.00
Q1, Q3	0.00, 0.00	4.00, 7.00
Min, Max	0.0, 0.0	0.0, 11.0
p-value[b]	0.0019	

2.5.2. Main studies

Study 20080279

A Phase 3 Randomized, Double Blind, Placebo Controlled Study to Determine the Safety and Efficacy of Romiplostimin Thrombocytopenic Pediatric Subjects with Immune Thrombocytopenia (ITP).

Methods

Approximately 60 pediatric subjects ≥ 1 to< 18 years of age diagnosed with ITP according to the ASH guidelines were planned to be enrolled into the study. At a minimum, 12 subjects were stratified into each of the 3 age groups.

Study participants

Main Inclusion Criteria:

- Diagnosis of primary ITP according to the ASH Guidelines at least 6 months prior to screening, regardless of splenectomy status.

- Subject must be refractory to a prior ITP therapy, having relapsed after at least1 prior ITP therapy, or ineligible for other ITP therapies. Prior therapy includes first-line therapies.

-Age ≥ 1 year and < 18 years at the time of providing informed consent.

- The mean of 2 platelet counts taken during the screening period must be≤ 30 x 10^9/L with neither count > 35 x 10^9/L.

-A serum creatinine concentration ≤ 1.5 times the laboratory normal range (for each age category) during the screening period. Adequate liver function

-Hemoglobin > 10.0 g/dL during the screening period.

-Subject and/or subject's legally acceptable representative has provided informed consent prior to any study-specific procedure; subject has provided assent, where required.

Main exclusion criteria:

Main exclusion criteria were known history of a bone marrow stem cell disorder, any abnormal bone marrow findings other than those typical of ITP which should be approved by the MAH before a subject is enrolled in the study, known active or prior malignancy except adequately treated basal cell carcinoma, known history of congenital thrombocytopenia, known history of hepatitis B, hepatitis C, or HIV, known history of H. pylori by urea breath test or stool antigen test within 6 months of enrollment or successfully treated with no evidence of infection, known history of systemic lupus erythematosus, evans syndrome, or autoimmune neutropenia, known history of antiphospholipid antibody syndrome or positive for lupus anticoagulant, known history of disseminated intravascular coagulation, hemolytic uremic syndrome, or thrombotic thrombocytopenic purpura, previous history of venous thromboembolism or thrombotic events, previous use of romiplostim, PEG-rHuMGDF, Eltrombopag, rHuTPO or any platelet producing agent, rituximab (for any indication) or 6-MP within 14 weeks before the screening visit or anticipated use during the time of the proposed study, splenectomy within 4 weeks of the screening visit.

Treatments

Investigational product (romiplostim; placebo) was administered weekly, over a 24-week treatment period, in the clinic by a qualified healthcare provider as a subcutaneous injection. The starting dose of romiplostim was 1 µg/kg; weekly dose increases continued in increments of 1 µg/kg/week to a maximum dose of 10 µg/kg in an attempt to reach a target platelet count of $\geq$50 x 10^9/L.

At any time during the 24-week treatment period, if a subject demonstrated the onset of a sustained platelet response (defined as a continuous platelet count of ≥ 50 x 10^9/L in the absence of romiplostim and all other therapies dosed with the intent to treat ITP) the subject was monitored for a period of up to 6 months beginning with the first platelet count ≥ 50 x 10^9/L. If a subject experienced the onset of a sustained platelet response at the End of Study (EOS) visit they continued platelet count monitoring for 6 months beginning with the first count ≥ 50 x 10^9/L. If at the conclusion of the 6-month follow-up period, a subject required re-initiation of any ITP therapy to raise or maintain their platelet counts ≥ 50 x 10^9/L the subject completed the End of Follow-up visit (EOF) which represented the completion of study participation. A subject who completed the EOF visit was immediately eligible to screen for entry into the romiplostim pediatric open-label extension study (Study 20090340).

At pre-defined time points during the course of the study an independent DMC monitored the ongoing safety. The first DMC was to occur when 10 subjects were enrolled for at least 4 weeks and continued to meet approximately every 6 months as long as there were active subjects on study.

Subjects who weigh < 50 kg may require a decreased concentration of IP to ensure accurate dosing. In such situations, dilution of IP in a 1:2 ratio (a protein concentration of 0.25 mg/mL) or a 1:4 ratio (a protein concentration of 0.125) may be made with 0.9%saline to ensure an appropriate dispensable volume is delivered. Dosing was to be stopped at any time during the study if neutralizing antibodies to romiplostim or to eTPO were detected.

Table 8-1. Dose Adjustment Rules

Platelet count (x 10^9/L)	Investigational Drug Dose Adjustment Rule[a]
< 50[b]	Dose increased by 1 µg/kg each week (to a maximum of 10 ug/kg)
50 to 200[b]	Dose remained constant.
> 200 to < 400[b,c]	After the platelet count remained in this range for 2 consecutive weeks, dose reduced by 1 µg/kg on the next schedule dosing day.
≥ 400 [b,c,d]	Withhold the dose and dose reduce by 1 µg/kg on the next scheduled day of dosing when platelet count falls below 200.

[a] If the platelet count was elevated in response to the initiation or increase in dose of another ITP medication, then the same dose of IP should have been administered when the platelet count was below200 x 10^9/L.

[b] Romiplostim may have been used with other medical ITP therapies. If the subject's platelet count was ≥ 50 x 10^9/L, other medical ITP therapies may have been reduced or discontinued.

[c] If the current dose was 1 µg/kg and a dose reduction was required during the 24-week treatment period, the dose was withheld until the platelet count fell to < 50 x 10^9/L. Once the platelet count was < 50 x 10^9/L, dosing resumed at a dose of 1 µg/kg using the dose adjustment rules above.

[d] If the use of a rescue medication resulted in platelet count > 400 x 10^9/L then at discretion of the investigator, the investigational product dose may have been reduced by 1 µg/kg.

Prior and Concomitant Treatment

Subjects were to enter the study using the same standard of care therapy, administration, dose, and schedule that met the entrance eligibility criteria of 2 platelet counts taken during the screening period that resulted in ≤ 30 × 10^9/L with neither count> 35 × 10^9/L. This medication was not considered excluded medication. Any change to or additional therapy was considered rescue medication. Rescue

medication was defined as any medication that was intended to increase platelet counts or prevent bleeding. Rescue medication was allowed throughout the duration of the study when platelet counts were < 20 × 10^9/L or when a subject had bleeding or wet purpura, or in any situation deemed medically necessary to increase platelet counts in order to treat or prevent bleeding. A reduction or discontinuation of permitted concurrent ITP therapies were permitted once a subject's platelet count increase to ≥ 50 × 10^9/L. Concurrent ITP therapies that were previously reduced may have been increased back to the dose at study start, if the investigator deemed it necessary.

Objectives

Primary Objective:

- To evaluate the efficacy of romiplostim in the treatment of thrombocytopenia in paediatric subjects with ITP as measured by durable platelet response. *Secondary Objectives:*
- To evaluate overall and weekly platelet response (≥ 50 × 10^9/L during weeks 2 through 25 of the treatment period). To evaluate the use of rescue ITP medications*;*
- To evaluate a combined bleeding event and rescue medication use endpoint (composite bleeding episodes).
- To evaluate the overall safety of romiplostim.

Exploratory Objectives:

- To evaluate the discontinuation of ITP medications; the incidence of sustained platelet response; the incidence of splenectomy; the incidence of haematuria and any association with intracranial haemorrhage events; changes in Patient-reported Outcomes (PRO) due to treatment with romiplostim and to estimate the minimal important difference (MID) of the Kids ITP Tool (KIT).

Outcomes/endpoints

Primary Endpoint:

- The primary endpoint is the incidence of durable platelet response. A subject with durable platelet response is defined as achieving at least 6 weekly platelet counts of ≥ 50 x 10^9/L during weeks 18 through 25 of treatment.

Secondary Endpoints:

- Subject incidence of overall platelet response. Overall responders are defined as subjects who achieve a platelet count ≥ 50 x 10^9/L at a minimum of 4 times during weeks 2 to 25 of the treatment period.
- Number of weekly platelet counts ≥ 50 x 10^9/L during weeks 2 to 25 of the treatment period.
- Subject incidence of rescue ITP medications used
- The number of composite bleeding episodes. The composite bleeding episode is defined as clinically significant bleeding events or the use of a rescue medication to prevent a clinically significant bleeding event during weeks 2 to 25 of the treatment period. A clinically significant event is defined as a grade ≥ 2 per the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grading scale.
- Incidence of adverse events, including thromboembolic events and hematologic malignancies, clinically significant changes in laboratory values and the incidence of antibody formation

Sample size

60 subjects will be randomized in a 2:1 ratio to receive IP (40 romiplostim vs. 20 placebo).

The sample size of 60 subjects with a 2:1 randomization ratio (40 romiplostim, 20 placebo) was chosen to provide adequate power to demonstrate that the efficacy, measured by the durable platelet response, of romiplostim is significantly better than placebo. The probability of achieving durable platelet response with romiplostim and placebo is estimated at 60% and 5%, respectively. The sample size will have approximately 99% power to detect the difference in the incidence of durable platelet response between romiplostim and placebo using a 2-sided Mantel-Haenszel test at a significance level of 0.05.

Randomisation

2:1 randomization ratio (40 romiplostim, 20 placebo).

Subjects were stratified into 1 of 3 age categories:

- ≥ 1 - < 6 years (8 subjects [19%] romiplostim; 4 subjects [20%] placebo);
- ≥ 6 - < 12 years (18 subjects [43%] romiplostim; 9 subjects [45%] placebo); and
- ≥ 12 - < 18 years (16 subjects [38%] romiplostim; 7 subjects [35%] placebo).

Blinding (masking)

The study was a double blinded study.

Statistical methods

The incidences of durable and overall platelet responses were compared by the Mantel-Haenszel test stratified by the baseline age group. Exact 95% confidence intervals for the incidence were provided for each treatment group and for the difference between treatment groups. The common odds ratios were estimated along with its 95% confidence interval.

The number of weeks with a platelet response for both treatment groups were summarised and compared by the analysis of variance (ANOVA) model with treatment and age category in the model. To mitigate violation of the model assumptions, Mantel-Haenszel test (row mean score differ) will be performed as a secondary analysis to ensure the robustness of the result.

The number of composite bleeding episodes were summarised and compared by the Mantel-Haenszel test (row mean score differ) stratified by the baseline age group.

A sequential testing scheme will be employed as follows to adjust for multiplicity for the primary and key secondary endpoints in comparing romiplostim vs. placebo.

• Test incidence of durable platelet response, if significant and in the positive direction of romiplostim then

• Test incidence of overall platelet response, if significant and in the positive direction of romiplostim then

• Test number of weeks with platelet response, if significant and in the positive direction of romiplostim then

• Test the subject incidence of rescue ITP medications used, if significant and in the positive direction of romiplostim then

• Test number of composite bleeding episodes

ANALYSIS SUBSETS

Full Analysis Set

The full analysis set will consist of all randomized subjects. Analyses for demographics and baseline characteristics will be based on this analysis set.

Safety Analysis Set

The safety analysis set will consist of all randomized subjects who received at least one dose of investigational product. Safety analysis will utilize this analysis set. Subjects will be analysed based on the actual treatment he/she received. If a subject received at least one dose of romiplostim, that subject's safety data will be included in the romiplostim group.

Efficacy Analysis Set

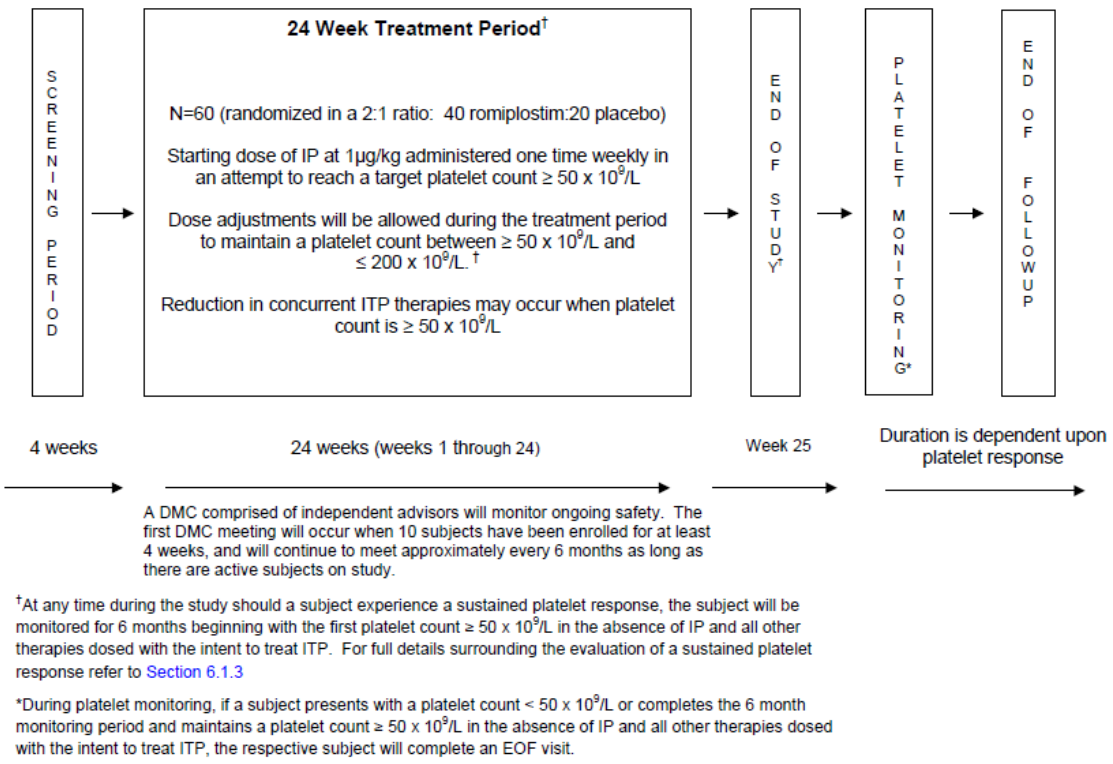
The efficacy analysis set will consist of all randomized subjects. Analyses for efficacy endpoint and PRO will be based on the efficacy analysis set. Subjects will be analyzed according to their randomized treatment group.

Per Protocol Analysis Set

The per protocol analysis set will consist of all subjects who received at least one dose of investigational product and met all eligibility criteria. Subjects will be analyzed according to their randomized treatment group. Sensitivity analysis using the per protocol set will be conducted for the primary efficacy endpoint.

Results

Participant flow



†At any time during the study should a subject experience a sustained platelet response, the subject will be monitored for 6 months beginning with the first platelet count ≥ 50 x 10^9/L in the absence of IP and all other therapies dosed with the intent to treat ITP. For full details surrounding the evaluation of a sustained platelet response refer to Section 6.1.3

*During platelet monitoring, if a subject presents with a platelet count < 50 x 10^9/L or completes the 6 month monitoring period and maintains a platelet count ≥ 50 x 10^9/L in the absence of IP and all other therapies dosed with the intent to treat ITP, the respective subject will complete an EOF visit.

Recruitment

Conduct of the study

The original SAP (Version 1) was amended 3 times (Table 4 below). The changes were instituted before any analyses were performed.

Table 4 Summary of Statistical Analysis Plan Amendments

Amendment	Major Changes
2 (dated 02 November 2010)	• Removed the interim analysis when 2 younger cohorts completed enrollment. A final analysis will be done when all three cohorts complete the treatment period. • Regrouped the age category from 1 - 3, 3 - 12, 12 - 17 years old to 1 - 6, 6 - 12, 12 - 17 years old. • Added a sensitivity analysis to the primary end point by imputing the drop outs in the placebo arm as responders and drop outs in the romiplostim arm as nonresponders. • Added a subgroup analysis by age groups, gender, region, and baseline bleeding status. • Added MID analysis to PRO instrument.
3 (dated 05 April 2011)	• Specified analysis method for the composite bleeding endpoint per discussion with FDA. • Updated the imputation method for missing platelet count to be imputing missing data as nonresponse per discussion with FDA. Added a sensitivity analysis by using LOCF. • Specified events of interest.
4 (dated 27 May 2011)	• Exact test of common odds ratio equals 1 stratified by age categories and its exact 95% confidence interval has been added as a sensitivity analysis for the primary endpoint per suggestion from the FDA • Tables for the exact test for the common odds ratio equals 1 and exact confidence interval have been added • Added references for statistical methods

One subject in the romiplostim arm and no subjects in the placebo arm experienced an important protocol deviation. One subject received a box number other than the box number assigned by the IVRS.

Baseline data

In the Full Analysis Set, 35 subjects (57%) were female, 41 subjects (66%) were white, and the median age was 9.5 years (range 3 to 17 years).

Table 5: Baseline Demographics (Full Analysis Set)

	Placebo (N = 20)	Romiplostim (N = 42)	Total (N = 62)
Sex - n (%)			
Male	9 (45.0)	18 (42.9)	27 (43.5)
Female	11 (55.0)	24 (57.1)	35 (56.5)
Race - n (%)			
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian	2 (10.0)	3 (7.1)	5 (8.1)
Black or African American	2 (10.0)	6 (14.3)	8 (12.9)
Multiple	0 (0.0)	1 (2.4)	1 (1.6)
Black or African American, White	0 (0.0)	1 (2.4)	1 (1.6)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (2.4)	1 (1.6)
Other	1 (5.0)	5 (11.9)	6 (9.7)
White	15 (75.0)	26 (61.9)	41 (66.1)
Age (years)			
n	20	42	62
Mean	9.4	9.7	9.6
SD	4.7	4.1	4.3
Median	7.5	10.0	9.5
Q1, Q3	6.5, 13.5	6.0, 14.0	6.0, 14.0
Min, Max	3, 17	3, 16	3, 17
Age group - n (%)			
≥ 1 - < 6 years	4 (20.0)	8 (19.0)	12 (19.4)
≥ 6 - < 12 years	9 (45.0)	18 (42.9)	27 (43.5)
≥ 12 - < 18 years	7 (35.0)	16 (38.1)	23 (37.1)

	Placebo (N = 20)	Romiplostim (N = 42)	Total (N = 62)
Platelet (10^9/L)			
N	20	42	62
Mean	19.9	17.5	18.3
SD	19.3	10.7	13.9
Median	17.7	17.8	17.8
Q1, Q3	9.8, 24.1	7.5, 24.5	8.7, 24.5
Min, Max	1.0, 93.7	1.7, 44.3	1.0, 93.7
Years since ITP Diagnosis[a]			
n	20	42	62
Mean	2.99	2.97	2.98
SD	2.31	2.78	2.62
Median	2.24	1.93	2.05
Q1, Q3	1.52, 3.65	1.04, 4.21	1.08, 4.04
Min, Max	0.5, 8.6	0.5, 10.7	0.5, 10.7
Splenectomized?			
No	19 (95.0)	41 (97.6)	60 (96.8)
Yes	1 (5.0)	1 (2.4)	2 (3.2)
Number of subjects who received any of the following treatments	20 (100.0)	42 (100.0)	62 (100.0)
Number of prior ITP treatments received			
1	6 (30.0)	8 (19.0)	14 (22.6)
2	3 (15.0)	18 (42.9)	21 (33.9)
3	6 (30.0)	8 (19.0)	14 (22.6)
>3	5 (25.0)	8 (19.0)	13 (21.0)
Number of subjects reporting medical or surgical history	18 (90.0)	36 (85.7)	54 (87.1)
Number of subjects reporting bleeding adverse events in 30 days prior to first IP dose	14 (70.0)	31 (73.8)	45 (72.6)

[a] Years are calculated as (randomization date - ITP diagnosis/splenectomy date) / 365.25. Partial dates of ITP diagnosis/splenectomy with missing day only are imputed as 15, partial dates with missing month and day are imputed as July 1

Source: Modified from Table 14-2.1, Table 14-2.2, Table 14-2.3, Table 14-2.4, Table 14-2.5, Table 14-2.6, and Table 14-2.7.

Concomitant diseases at baseline: blood and lymphatic system disorders (23.8% Nplate and 10% placebo), gastrointestinal disorders (23.8% Nplate and 45.0% placebo), immune disorders (16.7% Nplate and 40.0% placebo), infections and infestations (28.6% Nplate and 40% placebo), injury, poisoning and procedural complications (31.0% Nplate and 55.0%placebo), reproductive (11.9% Nplate and 5.0% placebo), skin and subcutaneous tissue disorders (42.9% Nplate and 25.0% placebo) and vascular disorders (4.8% Nplate and 0.0%placebo).

Numbers analysed

Table 6 Subject Disposition (Full Analysis Set)

	Placebo n (%)	Romiplostim n (%)	Total n (%)
Subjects randomized	20	42	62
Investigational Product Accounting			
Subjects who never received investigational product	1 (5.0)	0 (0.0)	1 (1.6)
Subjects who received investigational product	19 (95.0)	42 (100.0)	61 (98.4)
Subjects who completed investigational product	16 (80.0)	41 (97.6)	57 (91.9)
Subjects who discontinued investigational product	3 (15.0)	1 (2.4)	4 (6.5)
Study Completion Accounting			
Subjects who completed study[a]	18 (90.0)	41 (97.6)	59 (95.2)
Subjects who discontinued study prior to Week 25	2 (10.0)	1 (2.4)	3 (4.8)
Prior to Week 18	2 (10.0)	0 (0.0)	2 (3.2)
Week 18 – 25	0 (0.0)	1 (2.4)	1 (1.6)
Follow-up Period			
Subjects who entered follow-up period[b]	1 (5.0)	0 (0.0)	1 (1.6)
Subjects who completed follow-up period[c]	0 (0.0)	0 (0.0)	0 (0.0)

Percentages are based on randomized subjects.
[a] Completed study is defined as completed the 24 week treatment period and week 25 visit (end of study visit).
[b] Subjects who demonstrate sustained platelet response at EOS visit, ie., platelet count ≥ 50 x 10^9/L in the absence of IP and all other ITP therapies, and don't immediately confirm the need for continued treatment, would enter the follow-up for up to 6 month or till the platelet count falls below 50 x 10^9/L, whichever comes first.
[c] Completed follow-up period is defined as platelet count drops to < 50 x 10^9/L, or 6 months after the start of sustained platelet response.
Source: Table 14-1.1

Outcomes and estimation

Primary endpoint: Incidence of durable platelet response

In the Efficacy Analysis Set, a total of 22 subjects (52%) had durable platelet responses in the romiplostim arm compared with 2 subjects (10%) in the placebo arm. The Mantel-Haenszel common odds ratio for achieving durable platelet response was estimated to be 9.1 (romiplostim vs placebo, 95% CI: 1.9, 43.2).

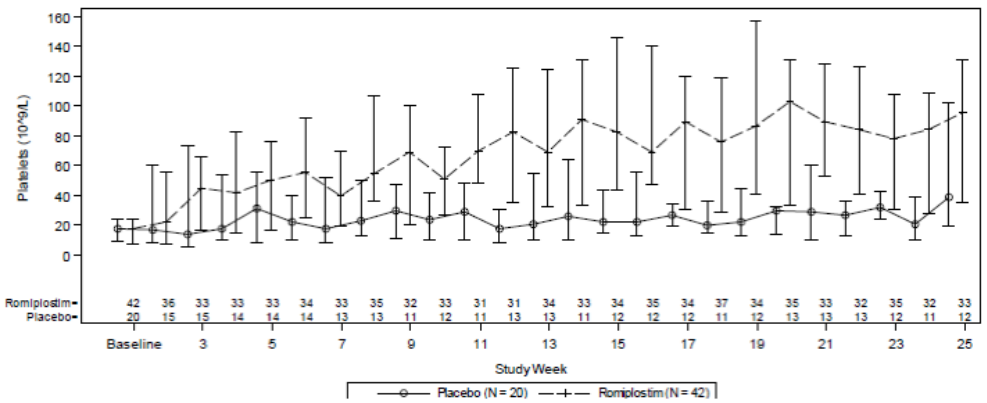
Within each baseline age group, a higher percentage of subjects in the romiplostim arm had durable platelet responses compared with subjects in the placebo arm: ≥ 1 to< 6 years 38% vs 25%; 6 to < 12 years 56% vs 11%; 12 to < 18 years 56% vs 0.

Table 10-1. Subject Incidence of Durable Platelet Response (Efficacy Analysis Set)

Incidence of Durable Platelet Response	Placebo (N = 20)		Romiplostim (N = 42)
By Baseline Age Group			
≥ 1 - < 6 years	1/4 (25.0%)		3/8 (37.5%)
≥ 6 - < 12 years	1/9 (11.1%)		10/18 (55.6%)
≥ 12 - < 18 years	0/7 (0.0%)		9/16 (56.3%)
Overall			
Incidence Rate	2/20 (10.0%)		22/42 (52.4%)
95% exact binomial confidence interval	(1.2%, 31.7%)		(36.4%, 68.0%)
Incidence rate of (Romiplostim - Placebo)		42.4%	
95% normal approximation confidence interval		(22.4%, 62.4%)	
Mantel-Haenszel common odds ratio of (Romiplostim/Placebo)		9.0497	
95% confidence interval		(1.896, 43.199)	
Common odds ratio=1 p-value[a]		0.0018	
Exact 95% confidence interval for common odds ratio of (Romiplostim/Placebo)		(1.841, 89.170)	
Common odds ratio=1 p-value[b]		0.0026	

Efficacy analysis set includes all randomized subjects.
Durable plaelet response was defined as weekly platelet count ≥ 50 x 10^9/L for 6 or more times for Weeks 18-25 measurements. Subject may not have a weekly response within 4 weeks after receiving any rescue medications.
[a]Primary analysis: p-value from Cochran-Mantel-Haenszel test stratified by baseline age group.
[b]Secondary analysis: p-value from exact test stratified by baseline age group.
Source: *Table 14-4.1.1*

Figure 14-4.2. Median(Q1, Q3) of Platelet Count by Week (Efficacy Analysis Set)



Vertical lines represent the first and third quartiles around the median.
Platelet counts measured within 4 weeks following a rescue medication use or after splenectomy were excluded.

Program: /userdata/stat/amp2/itp/amp20080279/analysis/primary/figures/f-plt.sas
Output: f14-04-002-plt-median.rtf (Date Generated: 14MAY15 09:52) Source Data: adam.adplt

A sensitivity analysis using the LOCF for missing platelet count resulted in similar p-values.

In the subset of subjects with ITP > 12 months of duration, the incidence of durable response was also significantly greater in the romiplostim arm compared with the placebo arm (p = 0.0022). A total of 17 subjects (53.1%) had durable platelet response in the romiplostim arm compared with 1 subject (6.3%) in the placebo arm: ≥ 1 to < 6 years 28.6% versus 25%; ≥ 6 to < 12 years 63.6% versus 0%; ≥ 12 to < 18 years 57.1% versus 0%.

The composite bleeding episode was defined as clinically significant bleeding events or the use of a rescue medication to prevent a clinical significant bleeding event during weeks 2 through 25 of the treatment period. A clinically significant bleeding event was defined as a Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grade ≥ 2 bleeding event. The mean (SD) number of composite bleeding episodes was 1.9 (4.2) for the romiplostim arm and 4.0 (6.9) for the placebo arm with a median (Q1, Q3) number of bleeding events of 0.0 (0, 2) for the romiplostim arm and 0.5 (0, 4.5) in the placebo arm. In the subset of subjects with ITP > 12 months of duration, the mean (SD) number of composite bleeding

episodes was 2.1 (4.7) for the romiplostim arm and 4.2 (7.5) for the placebo arm with a median (Q1, Q3) number of bleeding events of 0.0 (0, 2) for the romiplostim arm and 0.0 (0, 4) in the placebo arm. Because the statistical testing for the incidence of rescue medication use was not significant, no statistical test was done for the number of composite bleeding episodes endpoint.

Secondary endpoints

-Subject incidence of overall platelet response

Overall platelet response is defined as either a durable platelet response or transient platelet response. A transient platelet response was defined as weekly platelet count ≥ 50 x 10^9/L for 4 or more times during weeks 2 through 25 measurements, but without durable platelet response. In the Efficacy Analysis Set, a total of 30 subjects (71%) had an overall platelet response in the romiplostim arm compared with 4 subjects (20%) in the placebo arm. The Mantel-Haenszel common odds ratio of romiplostim vs. placebo was estimated to be9.0 (95% CI: 2.5, 32.3).

Within each baseline age group, a higher percentage of subjects in the romiplostim arm had an overall platelet response compared with subjects in the placebo arm: ≥ 1 to< 6 years 63% vs 50%; 6 to < 12 years 83% vs 11%; 12 to < 18 years 63% vs 14%,respectively.

Table 10-3. Subject Incidence of Overall Platelet Response (Efficacy Analysis Set)

Incidence of Overall Platelet Response	Placebo (N = 20)	Romiplostim (N = 42)
By Baseline Age Group		
≥ 1 - < 6 years	2/4 (50.0%)	5/8 (62.5%)
≥ 6 - < 12 years	1/9 (11.1%)	15/18 (83.3%)
≥ 12 - < 18 years	1/7 (14.3%)	10/16 (62.5%)
Overall		
Incidence Rate	4/20 (20.0%)	30/42 (71.4%)
95% exact binomial confidence interval	(5.7%, 43.7%)	(55.4%, 84.3%)
Incidence rate of (Romiplostim - Placebo)	51.4%	
95% normal approximation confidence interval	(29.2%, 73.7%)	
Mantel-Haenszel common odds ratio of (Romiplostim/Placebo)	9.0443	
95% confidence interval	(2.535, 32.265)	
Common odds ratio=1 p-value[ac]	0.0002	
Exact 95% confidence interval for common odds ratio of (Romiplostim/Placebo)	(2.412, 46.527)	
Common odds ratio=1 p-value[bc]	0.0003	

- Number of weekly platelet counts ≥ 50 x 10^9/L during weeks 2 to 25 of the treatment period

The primary statistical test, analysis of variance for treatment difference, resulted in a significant p-value (p = 0.0004) in favor of romiplostim treatment and the secondary statistical test, Cochran-Mantel-Haenszel controlling for baseline age group also resulted in a significant p-value (p = 0.0001) (Table 7).

Table 7: Number of weeks with platelet response (efficacy analysis set)

Number of Weeks With Platelet Response[a]	Placebo (N = 20)	Romiplostim (N = 42)
By Baseline Age Group		
≥ 1 - < 6 years		
n	4	8
Mean	8.8	9.1
SD	10.4	9.2
Median	6.5	8.0
Q1, Q3	0.5, 17.0	0.0, 17.0
Min, Max	0, 22	0, 23
≥ 6 - <12 years		
n	9	18
Mean	2.7	13.4
SD	5.8	7.8
Median	1.0	15.5
Q1, Q3	0.0, 1.0	6.0, 20.0
Min, Max	0, 18	0, 24
≥ 12 - <18 years		
n	7	16
Mean	2.0	11.6
SD	4.0	9.4
Median	0.0	12.5
Q1, Q3	0.0, 2.0	1.5, 21.0
Min, Max	0, 11	0, 22

-Subject incidence of rescue ITP medications used

In the Efficacy Analysis Set, 17 of 42 subjects (41%) in the romiplostim arm and 9 of 20 subjects (45%) in the placebo arm received rescue medication during the treatment period. The Mantel-Haenszel common odds ratio of romiplostim vs. placebo was estimated to be 0.8 (95% CI: 0.3, 2.4).

In the baseline age group of 1 to < 6 years, 4 of 8 subjects in the romiplostim arm used rescue medication compared with 1 of 4 subjects in the placebo arm (50% vs 25%); however, subjects in the baseline age groups of 6 to < 12 years and 12 to < 18 years used more rescue medications in the placebo arm than in the romiplostim arm (romiplostim vs. placebo; 28% vs 44% and 50% vs 57%, respectively). The primary statistical test, Mantel-Haenszel test stratified by age group, did not result in a significant p-value (p = 0.710). The secondary statistical test, exact test stratified by age group, also did not result in a significant p-value (p = 0.9160).

Table 10-6. Subject Incidence of Rescue Medication Use (Efficacy Analysis Set)

Incidence of Rescue Medication Use	Placebo (N = 20)		Romiplostim (N = 42)
By Baseline Age Group			
1 - < 6 years	1/4 (25.0%)		4/8 (50.0%)
6 - < 12 years	4/9 (44.4%)		5/18 (27.8%)
12 - < 18 years	4/7 (57.1%)		8/16 (50.0%)
Overall			
Incidence Rate	9/20 (45.0%)		17/42 (40.5%)
95% exact binomial confidence interval	(23.1%, 68.5%)		(25.6%, 56.7%)
Incidence rate of (Romiplostim - Placebo)		-4.5%	
95% normal approximation confidence interval		(-30.9%, 21.9%)	
Mantel-Haenszel common odds ratio of (Romiplostim/Placebo)		0.813	
95% confidence interval		(0.277, 2.391)	
Treatment group comparison p-value[ac]		0.7103	
Exact 95% confidence interval for common odds ratio of (Romiplostim/placebo)		(0.245, 2.756)	
Common odds ratio=1 p-value[bc]		0.9169	

N = Number of subjects in the analysis set.
Efficacy analysis set includes all randomized subjects.
[a] Primary analysis: p-value from Cochran-Mantel-Haenszel test stratified by baseline age group.
[b] Secondary analysis: p-value from exact test.
[c] Tested since the p-value of the number of weeks with platelet response endpoint is < 0.05.

-Total number of composite bleeding episodes in the 24-week treatment period

In the Efficacy Analysis Set, the mean (SD) number of composite bleeding events (clinical grade ≥ 2) was 1.9 (4.2) for the romiplostim arm and 4.0 (6.9) for the placebo arm with a median (Q1,Q3) number of bleeding events of 0.0 (0, 2) for the romiplostim arm and 0.5 (0, 4.5) in the placebo arm. Because the statistical testing for the incidence of rescue medication use was not significant, no statistical test was done for the number of composite bleeding episodes endpoint according to the pre-specified sequential testing scheme for multiplicity adjustment. The overall duration-adjusted rate per100 subject-years was 80 (8.1) in the romiplostim arm and 79 (18.4) in the placebo arm (p = <0.0001, ad hoc).

The subject incidence of bleeding treatment-emergent adverse events was 35 subjects (83%) in the romiplostim arm and 14 subjects (74%) in the placebo arm. The most frequently reported (≥ 10%) bleeding adverse events were (romiplostim; placebo) epistaxis (20 subjects [48%]; 10 subjects [53%]), contusion (19 subjects [45%];7 subjects [37%]), petechiae (11 subjects [26%]; 6 subjects [32%]); mouth hemorrhage(11 subjects [26%]; 4 subjects [21%]), and gingival bleeding (8 subjects [19%];4 subjects [21%]) (Table 14-6.2.1.25).

Serious adverse events were experienced by 4 subjects in the romiplostim arm; they were epistaxis (2 subjects) and petechiae and contusion (1 subject, each). Two subjects in the placebo arm had serious bleeding adverse events; they were animal bite (1 subject) and hematuria (1 subject). An additional subject in the romiplostim arm had 2 serious adverse events at screening (gingival bleeding and contusion). No subject discontinued romiplostim because of a bleeding adverse event. A summary of the serious bleeding events and associated platelet counts are provided below (Table 12-6).

Table 14-6.2.1.25. Bleeding Treatment-Emergent Adverse Events by Preferred Term in Descending Order of Frequency 24 Week Treatment Period (Safety Analysis Set)

Preferred Term	Placebo (N = 19) n (%)	Romiplostim (N = 42) n (%)
Number of subjects reporting bleeding treatment-emergent adverse events	14 (73.7)	35 (83.3)
Epistaxis	10 (52.6)	20 (47.6)
Contusion	7 (36.8)	19 (45.2)
Petechiae	6 (31.6)	11 (26.2)
Mouth haemorrhage	4 (21.1)	11 (26.2)
Gingival bleeding	4 (21.1)	8 (19.0)
Ecchymosis	2 (10.5)	4 (9.5)
Haematoma	2 (10.5)	4 (9.5)
Injection site bruising	2 (10.5)	4 (9.5)
Purpura	0 (0.0)	4 (9.5)
Haematuria	2 (10.5)	3 (7.1)
Scratch	1 (5.3)	3 (7.1)
Laceration	3 (15.8)	2 (4.8)
Haemorrhage	2 (10.5)	2 (4.8)
Lip haemorrhage	1 (5.3)	2 (4.8)
Metrorrhagia	1 (5.3)	2 (4.8)
Wound haemorrhage	1 (5.3)	2 (4.8)
Haematochezia	0 (0.0)	2 (4.8)
Haemoptysis	0 (0.0)	2 (4.8)
Post procedural haemorrhage	2 (10.5)	1 (2.4)
Tooth socket haemorrhage	2 (10.5)	1 (2.4)
Platelet count decreased	1 (5.3)	1 (2.4)
Acne	0 (0.0)	1 (2.4)

Preferred Term	Placebo (N = 19) n (%)	Romiplostim (N = 42) n (%)
Blood blister	0 (0.0)	1 (2.4)
Cerebral haematoma	0 (0.0)	1 (2.4)
Ear haemorrhage	0 (0.0)	1 (2.4)
Infusion site bruising	0 (0.0)	1 (2.4)
Injection site haemorrhage	0 (0.0)	1 (2.4)
Limb injury	0 (0.0)	1 (2.4)
Muscle haemorrhage	0 (0.0)	1 (2.4)
Rectal haemorrhage	0 (0.0)	1 (2.4)
Tooth loss	0 (0.0)	1 (2.4)
Ulcer haemorrhage	0 (0.0)	1 (2.4)
Lip injury	2 (10.5)	0 (0.0)
Anaemia	1 (5.3)	0 (0.0)
Animal bite	1 (5.3)	0 (0.0)
Conjunctival haemorrhage	1 (5.3)	0 (0.0)
Constipation	1 (5.3)	0 (0.0)
Dry skin	1 (5.3)	0 (0.0)
Gastrointestinal haemorrhage	1 (5.3)	0 (0.0)
Increased tendency to bruise	1 (5.3)	0 (0.0)
Menorrhagia	1 (5.3)	0 (0.0)
Oral disorder	1 (5.3)	0 (0.0)
Vessel puncture site bruise	1 (5.3)	0 (0.0)
Wound	1 (5.3)	0 (0.0)

N=Number of subjects in the analysis set.
AEs from first IP dose till EOS visit were included.
Coded using MedDRA version 17.1.

Table 12-6. Bleeding Serious Adverse Events and Associated Platelet Counts in the Romiplostim Treatment Arm

Subject	Serious Adverse Event (Start Day)	Romiplostim dose (µg/kg) Study Day	Platelet Count 10^9/L (Study Day)	Evaluable Platelet Count[a] (yes/no)
	Epistaxis (11)	2 (7)	6 (7)	Yes
		3 (14)	5 (14)	Yes
	Gingival bleeding[c] (-2) Contusion[c] (-1)	-	15 (-11)	Not applicable
		-	11 (-1)	Not applicable
		1 (1)	33 (1)	Yes
	Petechiae (108)	4 (106)	23 (106)	No
		-	8 (108)	No
		-	37 (109)	No
		0 (113)	910 (113)	No
		0 (120)	449 (120)	No
		3 (127)	140 (127)	No
	Epistaxis (27)	3 (22)	55 (22)	Yes
		3 (28)	53 (28)	Yes
	Contusion (94)	10 (92)	4 (92)	No
		10 (99)	162 (99)	No

[a]Evaluable platelet count was defined as no rescue medication use within 4 weeks prior to platelet measurement.
[b]Subject received immunoglobulins for worsening petechiae on study day 108 and prednisolone for ITP from study day 110 through 134.

Exploratory endpoints:

-Proportion of subjects who reduced or discontinued concurrent ITP therapies

Table 14-4.6. Summary of Reduction or Discontinuation from Baseline in Concurrent ITP Therapy (Efficacy Analysis Set)

	Placebo (N = 20) n (%)	Romiplostim (N = 42) n (%)
Subjects with Baseline Concurrent ITP Therapy[a]	4 (20.0)	5 (11.9)
Number of Baseline Concurrent ITP Therapies[a]		
0	16 (80.0)	37 (88.1)
1	4 (20.0)	5 (11.9)
Week: 13[b]		
Subjects with > 25% reduction[c]	1 (25.0)	1 (20.0)
Subjects discontinued[d]	0 (0.0)	1 (20.0)
Week: 25[b]		
Subjects with > 25% reduction[c]	0 (0.0)	0 (0.0)
Subjects discontinued[d]	2 (50.0)	2 (40.0)

-Incidence of sustained platelet response

This was defined as every platelet count ≥ 50 × 10^9/L for at least 6 months in the absence of the investigational product and all other therapies dosed with the intent-to-treat ITP). No subjects in either treatment arm achieved a sustained platelet response.

-Incidence of splenectomy

No subjects in either treatment arm were splenectomised during the 24-week treatment period. Two subjects, 1 in each treatment arm, were splenectomised before enrolment into this study.

-Change in subjects' quality of life through PRO

Improvement in health-related quality of life as measured in KIT scores (child self-report score, parent-proxy score, and parent impact score) from baseline to the EOS was numerically greater in the romiplostim treatment arm compared with the placebo treatment arm, but the differences were not statistically significant in the descriptive analysis. In the mixed-effects analysis, statistically significant improvement in the romiplostim treatment arm compared with the placebo arm was found for parent impact score, but not for the child self-report score.

Summary of main study

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 8: Summary of Efficacy for trial 20080279

Title: Study 20080279			
Study identifier	Study 20080279		
Design	A Phase 3 Randomized, Double Blind, Placebo Controlled Study to Determine the Safety and Efficacy of Romiplostim in Thrombocytopenic Paediatric Subjects with ITP conducted at 27 centres in the United States, Canada, and Australia.		
	Duration of main phase:		24 weeks
	Duration of Run-in phase:		4 weeks
	Duration of Extension phase:		Dependent on platelet response
Hypothesis	Superiority		
Treatments groups	Romiplostim		Romiplostim 1 ug/kg sc starting dose once weekly N=40
	Placebo		N=20
Endpoints and definitions	Primary endpoint	Durable platelet response	At least 6 weekly platelet counts of ≥ 50 x 10^9/L during weeks 18 through 25 of Treatment
	Secondary endpoint	overall platelet response	Overall responders were defined as subjects who achieved a platelet count ≥ 50 × 10^9/L at a minimum of 4 times during weeks 2 through 25 of the treatment period.
	Secondary endpoint	number of weekly platelet counts	The number of weekly platelet counts ≥ 50 × 10^9/L during weeks 2 through 25 of the treatment period.
	Secondary endpoint	rescue ITP	The subject incidence of rescue ITP medications used

	Secondary endpoint	Composite bleeding episodes	The total number of composite bleeding episodes in the 24-week treatment period. The composite bleeding episode was defined as clinically significant bleeding events or the use of a rescue medication to prevent a clinical significant bleeding event during weeks 2 through 25 of the treatment period. A clinically significant bleeding event was defined as a Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grade ≥ 2 bleeding event.
Database lock	19 February 2015 (last subject completed the last study visit)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Efficacy Analysis Set		
Descriptive statistics and estimate variability	Treatment group	Placebo	Romiplostim
	Number of subject	20	42
	Durable platelet response 95%CI	2/20 (10.0%) (1.2%, 31.7%)	22/42 (52.4%) (36.4%, 68.0%)
	Overall platelet response	4/20 (20.0%)	30/42 (71.4%)
	number of weekly platelet counts; mean (SD)	3.7 (6.6)	11.9 (8.6)
	Median Q1, Q3 p-value	1.0 0.0, 2.5 0.0004	12.0 3.0, 20.0
	Incidence of Rescue Medication	9/20 (45.0%)	17/42 (40.5%)
	95% CI	(23.1%, 68.5%)	(25.6%, 56.7%)

	mean (SD) number of composite bleeding events (grade ≥ 2)	4.0 (6.9)	1.9 (4.2)
	median (Q1,Q3)	0.5 (0, 4.5)	0.0 (0, 2)

Effect estimate per comparison	Primary endpoint	Comparison groups	**Durable Platelet Response (Efficacy Analysis Set)**
		Mantel-Haenszel common odds ratio of (Romiplostim/Placebo)	9.0497
		95% confidence interval	(1.896, 43.199)
		Common odds ratio=1 p-value	0.0018
	Secondary endpoint	Comparison groups	**Overall Platelet Response (Efficacy Analysis Set)**
		Mantel-Haenszel common odds ratio of (Romiplostim/Placebo)	9.0443
		95% confidence interval	(2.535, 32.265)
		Common odds ratio=1 p-value	0.0002
	Secondary endpoint	Comparison groups	**Number of Weeks with Platelet Response (Efficacy Analysis Set)**
		From analysis of variance	0.0004
		From CMH based on rank	0.0001

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

An integrated efficacy analysis evaluated the platelet response to romiplostim, bleeding and rescue medication usage rate, the rate of composite bleeding episodes and the use of concurrent ITP therapies while receiving romiplostim. The paediatric ITP efficacy set was used to summarise efficacy endpoints,

and consists of all paediatric subjects who received at least one dose of romiplostim in an ITP study (20060195, 20080279, 20030213, 20090340 or 20101221). For subjects who received placebo in a parent study and romiplostim in an extension study, only data from the extension study were included. Demographic and baseline characteristics of subjects in the integrated analysis are described in the safety section of this AR.

Platelet count data since the first dose of romiplostim were included in the integrated analysis. To discount the possible effect associated with rescue medications, platelet counts measured within 4 weeks following use of rescue medication or any time after an on-study splenectomy were deemed as non-evaluable.

-Incidence of Platelet Response

A total of 188 of 224 subjects (83.9%; 95% CI: 78.5%, 88.5%) had a platelet response, defined as at least 1 platelet count ≥ 50 x 10^9/L without any use of rescue medication within 4 weeks prior to date of the platelet measurement. Of which a total of 187 of 224 subjects (83.5%; 95% CI: 78.0%, 88.1%) had at least 1 platelet count between 50 x 10^9/L and 200 x 10^9/L, without any use of rescue medication within 4 weeks prior to date of the platelet measurement. The Kaplan-Meier estimate of the time to first platelet response (50th percentile) was 6.0 weeks (95% CI: 5.0, 7.0).

Table 9 Time to First Platelet Response (Paediatric ITP Efficacy Set)

	Romiplostim (N = 224)
Kaplan-Meier Estimated Time to First Platelet Response (Weeks):	
75th percentile (95% CI)	10.0 (9.0, 13.0)
50th percentile (95% CI)	6.0 (5.0, 7.0)
25th percentile (95% CI)	3.0 (2.0, 3.0)
Number of subjects with platelet response	188 (83.9%)
Number of censored subjects	36 (16.1%)

The pediatric ITP efficacy set consists of all pediatric subjects who received at least one dose of romiplostim in an ITP study (20060195, 20080279, 20030213, 20090340, or 20101221).
Platelet response was defined as weekly platelet count ≥ 50 x 10^9/L without any use of rescue medication within 4 weeks prior to date of the platelet measurement. Platelet counts measured after on-study splenectomy were excluded.
Time to first platelet response is calculated as weeks from the first week of administration of Romiplostim until the first week of having platelet response excluding any additional weeks (>1 week) between studies when a subject was enrolled into multiple studies. For subjects who did not have a platelet response during all romiplostim treatment periods, the week of the last platelet count was used as the censoring week.
N = Number of subjects in the analysis set. CI=Confidence Interval. Percentages are based on N.

-Average Weekly Platelet Count Over Time

The mean (SD) platelet count was 19.7 (29.8) x 10^9/L at week 1 and increased to 47.7 (89.1) x 10^9/L at week 2. At week 6, the mean (SD) platelet count was above the platelet response threshold of ≥ 50 x 10^9/L at 55.1 (59.5) x 10^9/L, and with the exception one value of 41.0 (8.5) x 10^9/L at week 392, remained above this threshold for the duration of treatment. The mean (SD) platelet count ranged from 55.1 (59.5) x 10^9/L to 261.6 (157.7) x 10^9/L from week 6 to week 428 (excluding week 392).

-Sustained Platelet Response

A total of 129 of 224 subjects (57.6%; 95% CI: 50.8%, 64.1%) had sustained platelet response, defined as at least 9 weeks with platelet response within a 12-week period. The KM estimate of the time to first sustained platelet response (50th percentile) was 20.0 weeks (95% CI: 15.0, 26.0) (time to first

sustained platelet response was defined as the time from initiation of romiplostim to the start of the 12-week period in which a sustained response was seen).

Table 10: Time to First Sustained Platelet Response (Paediatric ITP Efficacy Set)

	Romiplostim (N = 224)
Kaplan-Meier Estimated Time to First Sustained Platelet Response (Weeks):	
75th percentile (95% CI)	105.0 (47.0, 134.0)
50th percentile (95% CI)	20.0 (15.0, 26.0)
25th percentile (95% CI)	6.0 (4.0, 7.0)
Number of subjects with sustained platelet response	129 (57.6%)
Number of censored subjects	95 (42.4%)

The pediatric ITP efficacy set consists of all pediatric subjects who received at least one dose of romiplostim in an ITP study (20060195, 20080279, 20030213, 20090340, or 20101221).
Sustained platelet response is defined as at least 9 weeks with platelet response within a 12 weeks period. Note that the 12 weeks period must start with a week in which response is seen. Platelet response was defined as weekly platelet count ≥ 50 x 10^9/L without any use of rescue medication within 4 weeks prior to date of the platelet measurement. Platelet counts measured after on-study splenectomy were excluded. Time to first sustained platelet response is calculated as weeks from the first week of administration of Romiplostim until the first week of having sustained platelet response excluding any additional weeks (>1 week) between studies when a subject was enrolled into multiple studies. For subjects who did not have a sustained platelet response during all romiplostim treatment periods, the week of the last platelet count was used as the censoring week.

Program: /userdata/stat/amp2/meta/bla_2016itp_ped/analysis/cse/tables/t-ef-tm-pltresp-sust.sas
Output: t14-04-005-001-ef-tm-pltresp-sust.rtf (Date Generated: 15JUN2016:13:01) Source Data: adam.adsl,adam.adplt,adam.adbase

Platelet Response Over Time

A Month with platelet response was defined as the median (platelet counts measured in the study month) ≥ 50 x 10^9/L. Platelet counts measured within 4 weeks following a rescue medication use or any time after an on-study splenectomy were excluded in this definition. If > 50% of platelet counts within the month were excluded due to rescue medication use then the month was considered as no platelet response regardless of the median value of any platelet counts not excluded for rescue medication. Months without any platelet count measurement were imputed as platelet response if no rescue medication was taken and closest months with platelet counts before and after both showed response. Otherwise, they were imputed as no platelet response.

Based on the evaluation of platelet response by month, the subject incidence of platelet response showed a trend toward increasing over time. The incidence was 25.7% (95% CI: 20.1%, 31.9%) at month 1, 42.5% (95% CI: 35.7%, 49.4%) at month 2, ranged from 58.0% (95% CI: 50.8%, 64.9%) to 65.6% (95% CI: 58.4%, 72.3%) from month 3 to month 6, and was > 70.0% (range 70.7% to 100.0%) from month 7 through month 111.

The incidence of subjects who had at least 1 platelet count between 50 x 10^9/L and 200 x 10^9/L increased from 25.7% (95% CI: 20.1%, 31.9%) at month 1 to > 50% at month 3 and remained ≥ 50% (range 50.0% to 100.0%) from month 3 through month 111.

The median (range) number of months with platelet response (≥ 50 x 10^9/L) was 5.0 months (0,109). The median (range) percentage of months with platelet response was 69.14% (0, 100%).The median (range) number of months with platelet counts between 50 x 10^9/L and 200 x 10^9/L was 4.0 months (0, 100) with a median (range) percentage of 57.19% (0, 100%).

-Maximum Number of Consecutive Months With Platelet Response Without Concomitant Medications

The median (range) maximum number of consecutive months with platelet response without any romiplostim or concomitant medication use was 0 months (0, 5). The median (range) maximum number of consecutive months with platelet response without any concomitant ITP medications use other than romiplostim was 4.0 months (0, 108).

-Bleeding Events

Only treatment-emergent bleeding events were included. Overall, the subject incidence of at least one bleeding event was 63.8% (143 of 224 subjects) at any time during treatment (Table 11).

Table 11 Subject Incidence of Bleeding Events by Grade and Time Period (Paediatric ITP Efficacy Set)

Preferred Term	At any Time (N = 224) n (%)	Month 1-6 (N = 224) n (%)	Month 7-12 (N = 144) n (%)	Year 2 (N = 80) n (%)	Year 3 (N = 44) n (%)	Year 4 (N = 24) n (%)	Year 5 (N = 10) n (%)	Year 6 (N = 9) n (%)	Year 7 (N = 8) n (%)	Year 8 (N = 7) n (%)	Year 9 (N = 5) n (%)
Number of subjects with at least one Bleeding event	143 (63.8)	126 (56.3)	58 (40.3)	43 (53.8)	22 (50.0)	9 (37.5)	4 (40.0)	5 (55.6)	4 (50.0)	4 (57.1)	1 (20.0)
Grade 2 or above bleeding event	45 (20.1)	30 (13.4)	14 (9.7)	9 (11.3)	5 (11.4)	3 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3 or above bleeding event	17 (7.6)	11 (4.9)	5 (3.5)	2 (2.5)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4 or above bleeding event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 5 or above bleeding event	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

The pediatric ITP efficacy set consists of all pediatric subjects who received at least one dose of romiplostim in an ITP study (20060195, 20080279, 20030213, 20090340, or 20101221).
Bleeding events are defined using the haemorrhage event of interest (SMQ) definition as specified by the Amgen safety group. Only treatmentemergent bleeding events are included. Bleeding events were graded using the CTCAE grading scale.
Bleeding events are assigned to the time period in which they started. Percentages are based on the number of subjects who start the relevant time period (N).
Coded using MedDRA version
CTCAE = Common Terminology Criteria for Adverse Events; ITP = immune thrombocytopenia; SMQ = Standardised MeDRA Query

Modified from ISE Tables 14-4.14.1.1.1, 14-4.14.1.1.2, 14-4.14.2.1.1, 14-4.14.2.1.2, 14-4.14.3.1.1, 14-4.14.3.1.2, 14-4.14.4.1, 14-4.14.5.1

Bleeding Episodes

A bleeding episode was defined as a group of treatment-emergent bleeding adverse events with overlap or partial overlap so that there was at least 1 bleeding-free day between episodes. The duration-adjusted event rate for all bleeding episodes (per 100 subject-years) at any time during treatment was 874.2. A trend towards a reduction in the duration-adjusted event rate over time was observed for grade 2 or above and grade 3 or above bleeding events; there were no grade 4 or above or grade 5 or above bleeding events.

Table 12 Duration Adjusted Event Rate of Bleeding Episodes by Time Period (Paediatric ITP Efficacy Set)

	At Any Time (N = 224) (Sbj-yr=286.8) e (r)	Month 1-6 (N = 224) (Sbj-yr=96.1) e (r)	Month 6-12 (N = 144) (Sbj-yr=54.8) e (r)	Year 2 (N = 80) (Sbj-yr=56.2) e (r)	Year 3 (N = 44) (Sbj-yr=31.9) e (r)	Year 4 (N = 24) (Sbj-yr=15.4) e (r)	Year 5 (N = 10) (Sbj-yr=9.1) e (r)	Year 6 (N = 9) (Sbj-yr=8.3) e (r)	Year 7 (N = 8) (Sbj-yr=7.5) e (r)	Year 8 (N = 7) (Sbj-yr=5.8) e (r)	Year 9 (N = 5) (Sbj-yr=1.6) e (r)
All Bleeding Episodes	2507 (874.2)	794 (825.8)	452 (824.2)	550 (979.3)	150 (470.6)	244 (1581.0)	238 (2620.5)	47 (563.1)	13 (173.8)	18 (310.6)	1 (61.5)
Grade[a] ≥ 2 Bleeding Episodes	440 (153.4)	103 (107.1)	133 (242.5)	187 (333.0)	14 (43.9)	3 (19.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade[a] ≥ 3 Bleeding Episodes	64 (22.3)	19 (19.8)	41 (74.8)	3 (5.3)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade[a] ≥ 4 Bleeding Episodes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade[a] ≥ 5 Bleeding Episodes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

The pediatric ITP efficacy set consists of all pediatric subjects who received at least one dose of romiplostim in an ITP study (20060195, 20080279, 20030213, 20090340, or 20101221).
Bleeding events were defined using the haemorrhage event of interest (SMQ) definition as specified by the Amgen safety group. Only treatment emergent bleeding events were included.
A bleeding episode was defined as a group of treatment-emergent bleeding adverse events with overlap or partial overlap so that there was at least one bleeding-free day between episodes. If an episode had duration >7 days then it was counted once for each full or partial week of its duration. Bleeding episodes were assigned to the time period in which they started.
Sbj-yr = Total subject years of study duration; e = number of episodes; ITP = immune thrombocytopenia; r=rate of bleeding episodes per 100 subject-years of exposure and calculated as (e/Sbj-yr)*100.
[a]CTCAE=Common Terminology Criteria for Adverse Events Grading Scale
Source: Modified from ISE Tables 14-4.14.6.1.1 and Table 14-4.14.6.1.2

Composite Bleeding Episodes

A composite bleeding episode was defined as a group of clinically significant (CTCAE grade ≥ 2) treatment-emergent bleeding events or the use of a rescue medication with overlap or partial overlap so that there was at least one bleeding-free day between episodes. The incidence of subjects with at least one composite bleeding episode at any time during treatment was 37.9%, which corresponded to a duration-adjusted rate of composite bleeding episodes (per 100 subject-years) at any time of 317.3. The incidence and duration-adjusted rate of composite bleeding episodes showed a trend towards reduction over time. The incidence of composite bleeding episodes decreased from 28.6% during month 1 to 6 to 12.5% with during year 4. There were no composite bleeding episodes recorded in year 5 through year 9.

Concomitant and Rescue Medication Use

The subject prevalence of concurrent ITP therapy use was 39.7% (89 of 224 subjects) at any time during treatment, and there was a trend towards a reduction in concomitant medication use over time. The prevalence of concurrent ITP therapy use was 33.0% from months 1 to 6, 22.9% from months 7 to 12, 23.8% in year 2, 20.5% in year 3, 8.3% in year 4, and 0% from year 5 through year 9 (with the exception of use of concomitant medications reported in 1 subject [12.5%] in year 7).

The subject incidence of rescue medication use was 32.6% (73 of 224 subjects) at any time during treatment, and there was a trend towards a reduction in rescue medication use over time. The incidence of rescue medication use was 26.3% from months 1 to 6, 15.3% from months 7 to 12, 17.5% in year 2, 13.6% in year 3, and 4.2% in year 4. There was no reported rescue medication use in years 5 through 9.

Subgroup analysis

The integrated analyses for efficacy included evaluation of selected efficacy variables by the following subgroups: Age at baseline (≥ 1 to < 6 years, ≥ 6 to < 12 years, ≥ 12 to < 18 years), Sex, Race (Whites, Blacks, Other), Geographic Region, Years since ITP diagnosis (≤ 1, > 1), baseline bleeding status (Yes, No), Prior splenectomy, Number of prior ITP treatments.

- Time to First Platelet Response: The Kaplan-Meier estimate of the time to first response was generally similar across the subgroup comparisons. For all subgroups analysed, the Kaplan-Meier estimate of the time to first response (50th percentile) ranged from 5.0 weeks to 8.5 weeks

- Time to First Sustained Platelet Response: Differences are found with respect to the subgroup analysis of the time to first sustained platelet response (Table 13).

Table 13 Time to First Sustained Platelet Response by Subgroup

Subgroup	Kaplan-Meier Estimated Time to First Sustained Platelet Response (Weeks)		
	25th percentile (95% CI)	50th percentile (95% CI)	75th percentile (95% CI)
Baseline age group (years)			
≥ 1 - <6 (N = 51)	4.0 (2.0, 8.0)	14.0 (7.0, 38.0)	105.0 (24.0, NE)
≥ 6 - <12 (N = 96)	7.0 (3.0, 13.0)	26.0 (16.0, 109.0)	134.0 (47.0, NE)
≥ 12 - < 18 (N = 77)	6.0 (3.0, 7.0)	17.0 (8.0, 28.0)	50.0 (28.0, NE)
Gender			
Male (N = 110)	6.0 (4.0, 8.0)	24.0 (11.0, 47.0)	105.0 (47.0, NE)
Female (N = 114)	5.0 (3.0, 8.0)	17.0 (11.0, 26.0)	50.0 (29.0, NE)
Race			
White (N = 166)	6.0 (4.0, 8.0)	20.0 (15.0, 26.0)	105.0 (33.0, NE)
Black or African American (N = 21)	2.0 (2.0, 7.0)	43.0 (2.0, 119.0)	119.0 (43.0, 119.0)
Other (N = 37)	6.0 (3.0, 10.0)	16.0 (7.0, 50.0)	50.0 (29.0, 126.0)
Geographic region			
North America (N = 100)	3.0 (2.0, 4.0)	8.0 (6.0, 15.0)	33.0 (22.0, 60.0)
European Union (N = 49)	7.0 (5.0, 16.0)	28.0 (11.0, 105.0)	105.0 (50.0, 126.0)
Other (N = 75)	12.0 (4.0, 20.0)	134.0 (21.0, NE)	NE (134.0, NE)
Prior ITP Diagnosis			
≤ 1 Year (N = 51)	6.0 (3.0, 8.0)	17.0 (7.0, 105.0)	134.0 (26.0, 134.0)
> 1 Year (N = 173)	6.0 (3.0, 8.0)	21.0 (15.0, 29.0)	60.0 (43.0, 126.0)
Baseline Bleeding Status			
Yes (N = 116)	4.0 (3.0, 6.0)	15.0 (8.0, 26.0)	47.0 (29.0, 109.0)
No (N = 108)	7.0 (4.0, 12.0)	24.0 (16.0, 134.0)	134.0 (126.0, NE)
Prior Splenectomy			
Yes (N = 16)	24.5 (2.0, 60.0)	53.5 (6.0, 119.0)	114.0 (47.0, 126.0)
No (N = 208)	5.0 (3.0, 7.0)	17.0 (12.0, 26.0)	105.0 (38.0, NE)
Number of Prior ITP Treatments			
< 3 (N = 109)	4.0 (3.0, 7.0)	17.0 (9.0, 26.0)	50.0 (33.0, NE)
≥ 3 (N = 115)	6.0 (4.0, 9.0)	24.0 (16.0, 47.0)	109.0 (47.0, NE)

Incidence of Platelet Response Over Time:

The incidence of platelet response showed a trend towards improvement over time across age groups; gender; race; geographic region; years since ITP diagnosis; baseline bleeding status; prior splenectomy status; and number of prior ITP treatments.

Incidence of Platelet Counts Between 50 x 10^9/L and 200 x 10^9/L Over Time:

The incidence of subjects who had at least 1 platelet count between 50 x 10^9/L and 200 x 10^9/L was generally sustained over time across the tested subgroups.

Number of Months With Platelet Response:

The median (range) number of months with platelet response was per age category:

	median (range) number of months with platelet response	median (range) percentage of months with platelet response
1 to< 6 years	5.0 months (0, 55)	71.36% (0.0, 100.0)
6 to < 12 years	4.0 months (0, 109)	54.55% (0.0, 100.0)
≥ 12 years	6.0 months (0, 45)	75.00% (0.0, 100.0)

Sex: The median (range) number of months with platelet response was 5.0 months (0, 109) in male subjects and 6.0 months (0, 105) in female subjects.

Race: The median (range) number of months with platelet response was 5.0 months (0, 109) in whites; 5.0 months (0, 101) in blacks; and 6.0 months (0, 91) in other race groups.

Region: The median (range) number of months with platelet response was 10.0 months (0, 109) in North America; 4.0 months (0, 49) in the EU; and 3.0 months (0, 29) in other regions.

ITP diagnosis: The median (range) number of months with platelet response was 5.0 months (0, 73) in subjects with ≤ 1 year since ITP diagnosis and 5.0 months (0, 109) in subjects with > 1 year since ITP diagnosis.

Baseline bleeding: The median (range) number of months with platelet response was 7.5 months (0, 109) in subjects with baseline bleeding status "YES" and 4.0 months (0, 39) in subjects with baseline bleeding status "NO."

Splenectomy: The median (range) number of months with platelet response was 10.0 months (0, 101) in subjects with prior splenectomy and 5.0 months (0, 109) in subjects without prior splenectomy.

Prior ITP treatments: The median (range) number of months with platelet response was 6.0 months (0, 105) in subjects with < 3 prior ITP treatments and 4.0 months (0, 109) in subjects with ≥ 3 prior ITP treatments.

Number and Percentage of Months With Platelet Count Between 50 X 10^9/L and 200 X 10^9/L

The median (range) number of months with platelet count between 50 x 10^9/L and 200 x 10^9/L per age category: 4.0 months (0, 42) in the 1 to < 6 years age group; 4.0 months (0, 100) in the 6 to < 12 years of age group; and 6.0 months (0, 42) in the ≥ 12 years of age group. The median (range) percentage of months was 51.19% (0.0, 100.0) in the 1 to < 6 years age group; 50.00% (0.0, 100.0) in the 6 to < 12 years of age group; and 66.67% (0.0, 100.0) in the ≥ 12 years of age group.

Sex: The median (range) number of months with platelet count between 50 X 10^9/L and 200 X 10^9/L was 4.0 months (0, 100) for male subjects and 5.0 months (0, 97) for female subjects.

Race: The median (range) number of months with platelet count between 50 X 10^9/L and 200 X 10^9/L was 4.0 months (0, 100) in whites; 4.0 months (0, 87) in blacks; and 6.0 months (0, 68) in other race groups.

Region: The median (range) number of months with platelet count between 50 x 10^9/L and 200 x 10^9/L was 8.0 months (0, 100) in North America; 4.0 months (0, 42) in the EU; and 2.0 months (0, 27) in other regions.

ITP diagnosis: The median (range) number of months with platelet count between 50 x 10^9/L and 200 x 10^9/L was 4.0 months (0, 67) in subjects with ≤ 1 year since ITP diagnosis and 5.0 months (0, 100) in subjects with > 1 year since ITP diagnosis.

Bleeding status: The median (range) number of months with platelet count between 50 x 10^9/L and 200 x 10^9/L was 7.0 months (0, 100) in subjects with baseline bleeding status "YES" and 3.0 months (0, 34) in subjects with baseline bleeding status "NO."

Splenectomy: The median (range) number of months with platelet count between 50 x 10^9/L and 200 x 10^9/L was 8.5 months (0, 87) in subjects with prior splenectomy and 4.0 months (0, 100) in subjects without prior splenectomy.

Prior ITP treatments: The median (range) number of months with platelet count between 50 x 10^9/L and 200 x 10^9/L was 5.0 months (0, 97) in subjects with < 3 prior ITP treatments and 4.0 months (0, 100) in subjects with ≥ 3 prior ITP treatments.

Bleeding Events by Grade and Age

-All bleeding events by Age:

- 1 to < 6 years age: The subject incidence of bleeding events was 64.7% (33 of 51 subjects) at any time during treatment, and ranged from 25.0% to 56.9% from month 1 through year 4; no bleeding events were reported in this age group from year 5 through year 9.

- 6 to < 12 years age: The subject incidence of bleeding events was 67.7% (65 of 96 subjects) at any time during treatment, and ranged from 20.0% to 71.4% from month 1 through year 9.

- ≥ 12 years age: The subject incidence of bleeding events was 58.4% (45 of 77 subjects) at any time during treatment, and ranged from 33.3% to 63.3% from month 1 through year 4 in the group; no bleeding events were reported in this age group from year 5 through year 9

-Grade 2 or Above Bleeding Events by Age

- 1 to < 6 years age: The subject incidence of bleeding events of grade 2 (CTCAE grading scale) or above was 23.5% (12 of 51 subjects) at any time during treatment, and ranged from 5.6% to 33.3% from month 1 through year 4. No bleeding events of grade 2 or above were reported in this age group from year 5 through year 9.

- 6 to < 12 years age: The subject incidence of bleeding events of grade 2 or above was 18.8% (18 of 96 subjects) at any time during treatment, and ranged from 6.3% to 21.1% from month 1 through year 4. No bleeding events of grade 2 or above were reported in this age group from year 5 through year 9.

- ≥ 12 years age: The subject incidence of bleeding events of grade 2 or above was 19.5% (15 of 77 subjects) at any time during treatment, and ranged from 9.8% to 20.0% from month 1 through year 2 in the ≥ 12 years age group; no bleeding events of grade 2 or above were reported in this age group from year 3 through year 9.

-Grade 3 or Above Bleeding Events by Age

The subject incidence of bleeding events of grade 3 (CTCAE grading scale) or above was 5.9% (3 of 51 subjects) at any time during treatment, and all events occurred from month 1 through month 6 in the 1 to < 6 years age group; no bleeding events of grade 3 or above were reported in this age group from month 7 through year 9. The subject incidence of bleeding events of grade 3 or above was 8.3% (8 of 96 subjects) at any time during treatment, and ranged from 3.1% to 5.3% from month 1 through year 3 in the 6 to < 12 years age group; no bleeding events of grade 3 or above were reported in this age group from year 4 through year 9. The subject incidence of bleeding events of grade 3 or above was 7.8% (6 of 77 subjects) at any time during treatment, and ranged from 3.3% to 6.5% from month 1 through year 2 in the ≥ 12 years age group; no bleeding events of grade 3 or above were reported in this age group from year 3 through year 9. No grade 4 or grade 5 (CTCAE grading scale) bleeding events were reported for any age group.

-Composite Bleeding Episodes by Grade and Age

The subject incidence of composite bleeding episodes at any time during treatment was 41.2%, which corresponded to a duration-adjusted rate of composite bleeding episodes (per 100 subject-years) at any time of 239.5 in the 1 to < 6 years age group. The incidence of composite bleeding episodes decreased from 33.3% to 12.5% from month 1 to 6 to year 3 and was 33.3% at year 4. The duration-adjusted rate of composite bleeding episodes (per 100 subject-years) decreased from 502.7 from month 1 to 6 to 19.1 at year 2, and was 104.5 at year 3, and 44.7 at year 4. There were no reported composite bleeding episodes in this age group from year 5 through year 9.

The subject incidence of composite bleeding episodes at any time during treatment was 39.6%, which corresponded to a duration-adjusted rate of composite bleeding episodes (per 100 subject-years) at any time of 267.1 in the ≥ 6 to < 12 years of age group. The incidence of composite bleeding episodes decreased from 29.2% at month 1 to 6 to 8.3% at year 4, and the duration-adjusted rate of composite bleeding episodes (per 100 subject-years) decreased from 610.2 to 21.4, respectively. There were no reported composite bleeding episodes in this age group from year 5 through year 9 (The subject incidence of composite bleeding episodes at any time during treatment was 33.8%, which corresponded to a duration-adjusted rate of composite bleeding episodes (per 100 subject-years) at any time of 437.3

in the ≥ 12 years of age group. The incidence of composite bleeding episodes decreased from 24.7% at month 1 to 6 to 11.1% in year 4, and the duration-adjusted rate of composite bleeding episodes (per 100 subject-years) decreased from 298.8 to 26.1, respectively. There were no reported composite bleeding episodes in this age group from year 5 through year 9.

Concomitant Medication Use

The subject prevalence of concurrent ITP therapy use while receiving romiplostim at any time during treatment was 41.2% (21 of 51 subjects) in the ≥ 1 to < 6 years age group; 42.7% (41 of 96 subjects in the ≥ 6 to < 12 years of age group); and 35.1% (27 of 77 subjects in the > 12 years of age group). There was a trend towards a reduction in concomitant medication use over time across age groups from months 1 to 6 through year 9.

Rescue Medication Use

The subject incidence of rescue medication use at any time during treatment was 33.3% (17 of 51 subjects) in the ≥ 1 to < 6 years age group, and there was a trend towards a reduction in rescue medication use over time. The incidence of rescue medication use decreased from 27.5% at months 1 to 6 to 12.5% in year 3. There was no reported rescue medication use in years 4 through 9. A similar trend towards a reduction in rescue medication use was observed in the analysis of the duration-adjusted event rate (per 100 subject-years) of rescue medication use over time in the ≥ 1 to < 6 years age group . The subject incidence of rescue medication use at any time during treatment was 36.5% (35 of 96 subjects) in the ≥ 6 to < 12 years age group, and there was a trend towards a reduction in rescue medication use over time. The incidence of rescue medication use decreased from 29.2% at months 1 to 6 to 15.8% in year 3. There was no reported rescue medication use in years 4 through 9. A similar trend towards a reduction in rescue medication use was observed in the analysis of the duration-adjusted event rate (per 100 subject-years) of rescue medication use over time in the ≥ 6 to < 12 years age group.

The subject incidence of rescue medication use at any time during treatment was 27.3% (21 of 77 subjects) in the ≥ 12 years age group, and there was a trend towards a reduction in rescue medication use over time. The incidence of rescue medication use decreased from 22.1% at months 1 to 6 to 11.1% in year 4. There was no reported rescue medication use in years 5 through 9 (ISE Table 14-4.15.1.4.2). A similar trend towards a reduction in rescue medication use was observed in the analysis of the duration-adjusted event rate (per 100 subject-years) of rescue medication use over time in the ≥ 12 years age group.

Supportive studies

- ***Study 20030213***

This was a multicenter, open-label, extension study evaluating the safety and efficacy of long-term dosing of romiplostim in thrombocytopenic subjects with ITP. Subjects who completed a romiplostim ITP study (Study 20060195) were eligible to screen for inclusion in this study. Both adult (n = 292) and paediatric (n = 21) subjects were enrolled.

Romiplostim was administered SC once weekly. Dosing started either at the same dose being received at the end of treatment in the previous study or at a dose of 1 µg/kg (for subjects who had received placebo in a previous study). Subjects for whom the dose of romiplostim was stable (for at least 3 weeks) were allowed to self-administer romiplostim away from the study centre and returned to the study centre for ongoing evaluation at designated study visits. Dose adjustment was allowed throughout the studies

according to predefined rules based on the subject's platelet counts to a maximum permitted dose on 10 g/kg.

Data for paediatric subjects only are presented. The paediatric efficacy analysis set consisted of the 20 paediatric subjects who received at least 1 dose of romiplostim.

Efficacy Results

Platelet Response (platelet count ≥ 50 x 10^9/L at any time on study): Achieved in 100.0% of the paediatric subjects (95% CI: 83.2%, 100.0%).Incidence rates for peak platelet counts were also high. A peak platelet count of ≥ 100 x 10^9/L was reached in 90.0% of subjects and a peak platelet count ≥ 150 x 10^9/L was reached in 85.0% of subjects. A peak platelet count of ≥ 400 x 10^9/L was reached in 45.0% of subjects.

At week 2, the percentage of paediatric subjects with platelet responses was 65.0%. Median platelet count was 16.0 x 10^9/L at baseline and 108.4 x 10^9/L at week 2.

Concurrent ITP Therapy: Approximately 9.5% of the paediatric subjects entered this study on concurrent ITP therapy. One of these subjects discontinued concurrent ITP therapy by the end of the study 20030213. The overall subject incidence of rescue medication use in the paediatric population was 20.0% (4 subjects). The incidence of rescue medication use over time shows a trend towards a reduction in the use of rescue medications.

- **Study 20090340**

This is an open-label extension study evaluating the safety and efficacy of long-term dosing of romiplostim in thrombocytopenic paediatric subjects with ITP. Paediatric subjects who previously completed a romiplostim ITP study (Study 20030213 and Study 20080279) were eligible to screen for inclusion into this study (n=66). Romiplostim was administered weekly by SC injection at the same dose being received at the end of treatment in the previous study or at a dose of 1 µg/kg (for subjects who had received placebo in a previous study). The maximum permitted dose of romiplostim was 10 µg/kg. As of the data cut-off date of 24 February 2016, 66 subjects were enrolled into the study and 65 subjects received at least 1 dose of romiplostim.

Results

Primary Endpoint:

The primary endpoints of this study were the subject incidence and exposure-adjusted incidence of adverse events, including clinically significant changes in laboratory values and incidence of antibody formation. This will be discussed in the safety section.

Secondary Endpoints: Platelet Response and Use of Concurrent ITP Therapies

Across the study, the overall subject incidence of platelet response (platelet count ≥ 50 x 10^9/L in the absence of rescue medication) was 61 subjects (93.8%). The subject incidence of platelet response was similar across age groups and was similar in subjects coming from either previous study. The response rate remained >62% (range: 62.5% to 100%) for the duration of treatment (weeks 2 to 268). The median number of months with platelet response was 20.0 months (range: 0 to 80) and time on study was 25.0 months (range: 2 to 80).

A total of 66 subjects were enrolled in this study, including 54 subjects (82%) who had completed study S4. Of these, 65 subjects (98.5%) received at least 1 dose of romiplostim. The median (Q1, Q3) duration

of treatment was 135.0 weeks (95.0 weeks, 184.0 weeks). The median (Q1, Q3) average weekly dose was 4.82 mcg/kg (1.88 mcg/kg, 8.79 mcg/kg). The median (Q1, Q3) of most frequent dose received by subjects during the treatment period was 5.0 mcg/kg (1.0 mcg/kg, 10.0 mcg/kg). Of the 66 subjects enrolled in the study, 63 subjects had ITP > 12 months of duration. All the 63 subjects received at least 1 dose of romiplostim. The median (Q1, Q3) duration of treatment was 138.0 weeks (91.1 weeks, 186.0 weeks). The median (Q1, Q3) average weekly dose was 4.82 mcg/kg (1.88 mcg/kg, 8.79 mcg/kg). The median (Q1, Q3) of most frequent dose received by subjects during the treatment period was 5.0 mcg/kg (1.0 mcg/kg, 10.0 mcg/kg).

Across the study, the overall subject incidence of platelet response (1 or more platelet count $\geq$ 50 x 10^9/L in the absence of rescue medication) was 93.8% (n = 61) and was similar across age groups. Across all subjects, the median (Q1, Q3) number of months with platelet response was 30.0 months (13.0 months, 43.0 months) and the median (Q1, Q3) time on study was 34.0 months (24.0 months, 46.0 months). Across all subjects, the median (Q1, Q3) percentage of months with platelet response was 93.33% (67.57%, 100.00%) and was similar across age groups.

In the subset of subjects with ITP > 12 months of duration, the overall subject incidence of platelet response was 93.7% (n = 59) and was similar across age groups. Across all subjects, the median (Q1, Q3) number of months with platelet response was 30.0 months (13.0 months, 43.0 months) and the median (Q1, Q3) time on study was 35.0 months (23.0 months, 47.0 months). Across all subjects, the median (Q1, Q3) percentage of months with platelet response was 93.33% (67.57%, 100.00%) and was similar across age groups.

A total of 31 subjects (47.7%) used concurrent ITP therapy during the study including 23 subjects (35.4%) who used rescue medication and 5 subjects (7.7%) who used concurrent ITP medication at baseline. The subject prevalence of concurrent ITP medication use showed a trend towards a reduction over the course of the study: from 30.8% (weeks 1 to 12) to < 20.0% (weeks 13 to 240), and then 0% from week 240 to the end of the study.

In the subset of subjects with ITP > 12 months of duration, 29 subjects (46.0%) used concurrent ITP therapy during the study including 21 subjects (33.3%) who used rescue medication and 5 subjects (7.9%) who used concurrent ITP medication at baseline. The subject prevalence of concurrent ITP medication use showed a trend towards a reduction over the course of the study: from 31.7% (weeks 1 to 12) to < 20.0% (weeks 13 to 240), and then 0% from week 240 to the end of the study.

The subject prevalence of rescue medication use showed a trend towards a reduction over the course of the study: from 24.6% (weeks 1 to 12) to < 13.0% (weeks 13 to 216), then 0% after week 216 until the end of the study. Similar reduction of the subject prevalence of rescue medication over the course of the study was seen in the subset of subjects with ITP > 12 months of duration: from 25.4% (weeks 1 to 12) to $\leq$ 13.1% (weeks 13 to 216), then 0% after week 216 until the end of the study.

- **Study 20101221**

A single-arm, open-label, multicentre study to describe the percentage of time paediatric subjects with ITP (n = 147) have a platelet response while receiving romiplostim. A platelet response was defined as having a platelet count of ≥ 50 x 10^9/L in the absence of ITP rescue medications in the past 4 weeks. Open-label romiplostim was provided to ITP subjects diagnosed for at least 6 months and who received at least 1 prior ITP therapy or were ineligible for ITP therapies.

The study treatment period was up to 3 years. Romiplostim was administered weekly by SC injection. The starting dose of romiplostim was 1 µg/kg; weekly dose increases continued in increments of 1 µg/kg/week to a maximum dose of 10 µg/kg in an attempt to reach a target platelet count of between 50 x 10^9/L and 200 x 10^9/L. Subjects who received their first 8 doses in the clinic and achieved a platelet count ≥ 50 x 10^9/L without romiplostim dose adjustments for 4 consecutive weeks were eligible to self-administer romiplostim or have the injection administered by a caregiver. As of the cut-off date of 15

March 2016, 147 subjects were enrolled in the study and 145 subjects received at least 1 dose of romiplostim.

Results

-Primary endpoint: The percentage of time with a platelet count of ≥ 50 x 10^9/L starting from week 2 in the first 6 months of the treatment period without rescue medication use within the past 4 weeks.

The median percentage of time with a platelet response within the first 6 months of initiation of romiplostim was 50.0%. By baseline age group, the median platelet response was 50.0%, 25.0% and 50.0% for subjects in the < 6 years, 6 to < 12 years, and the 12 to < 18 years age groups, respectively (Study 20121221). The incidence of subjects who had a platelet response from week 2 to end of study was 79.7% (114/143) overall and increased across age groups from < 6 year old (70.6%) age group to 6 to < 12 year old (77.8%) age groups and to the 12 to < 18 year old age groups (89.1%). Analysis of platelet response rate over time showed that the percentage of subjects with platelet response in the first 6 months at week 2 was 19.6%. The total response rate increased over time on study overall and across all age groups. In addition, median platelet counts increased at week 2 and over time on study overall and across all age groups (Study 20121221).

-Secondary endpoints:

The percentage of time with platelet count ≥ 50 x 10^9/L from week 2 through end of treatment without rescue medication use within the past 4 weeks:

The mean (SD) percentage of time with a platelet response (platelet count ≥ 50 x 10^9/L) for all subjects in the efficacy analysis set during the overall treatment period was 45.9% (34.6). The mean (SD) platelet response was similar for the < 6 years and 6 to < 12 years age groups and higher for the 12 to < 18 years group (Study 20121221).

The percentage of time with an increase in platelet count ≥ 20 x 10^9/L above baseline starting from week 2 until the end of the treatment period without rescue medication use in the past 4 weeks:

The mean (SD) percentage of time with a platelet count ≥ 20 x 10^9/L from baseline without rescue medication use for ITP in the past 4 weeks was 53.0% (33.5). The mean (SD) percentage of time with a platelet response was similar for the < 6 years and 6 to < 12 years age groups and higher for the 12 to < 18 years group (Study 20121221).

Subject incidence of rescue ITP medications used: A total of 37/145 subjects (25.5%) overall received rescue medication during the treatment period (week 2 through the data cut-off). The incidence of subjects using rescue medications was similar across the baseline age groups of < 6 years (31.4%, 11/35) and 6 to < 12 years (29.7%, 19/64) and was lower among subjects in the 12 to < 18 years age group (15.2%, 7/46).

2.5.3. Discussion on clinical efficacy

The MAH submitted paediatric data from a pivotal phase 3 placebo controlled study (20080279) and phase 1/2 placebo controlled study (20060195) with supportive data derived from 3 uncontrolled studies (20030213, 20090340, 20101221) as well as a post-hoc integrated efficacy analysis. Of these, two studies are ongoing (uncontrolled studies 20090340 and 20101221). Studies 20080279, 20090340 and 20101221 are conditions of the European Paediatric Investigational Plan (PIP).

Design and conduct of clinical studies

Results from Studies 20060195 (n = 22) and 20080279 (n = 62) provide efficacy data reflecting the claimed indication (second-line treatment of chronic ITP in paediatric patients 1 year of age and older who are refractory to other treatments (e.g., corticosteroids, immunoglobulins). Both studies were randomized, double-blind, placebo-controlled studies and enrolled paediatric subjects (≥ 1 year to < 18 years of age) with thrombocytopenia (defined by a mean of 2 platelet counts ≤ 30 x 10^9/L with neither count > 35 x 10^9/L in both studies) with ITP, regardless of splenectomy status. Platelet study entry criteria were according to the CHMP ITP guideline (EMA/CHMP/153191/2013, dated February 2014). Romiplostim was administered weekly by SC injection in both studies using a starting dose of 1 µg/kg. Individual dose adjustments were employed based on platelet counts to a maximum permitted dose of 10 µg/kg. The target platelet count was ≥ 50 x 10^9/L in both studies.

Study 20060195

The design and conduct of this study was considered appropriate.

Study 20080279

The CHMP guidance "Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia" (EMA/CHMP/153191/2013, dated February 2014) came into effect after the development of the EU PIP and the start of the pivotal Study 20080279. In general, the pivotal Study 20080279 protocol meets the recommendations of the CHMP guidance with some exceptions; patients were not screened for antinuclear antibodies (ANA) prior to entering the study, although patients with a true/clinically significant positive ANA were excluded during screening. Additionally, the inclusion criteria allowed patients with ITP lasting > 6 months since diagnosis to enroll, since this was defined as chronic ITP at the time of study design (ASH guideline 2011). According to the International Working Group Report and the CHMP guideline the term "chronic ITP" is to be reserved for patients with ITP lasting for more than 12 months (Rodegheiro *et al*, 2009). Therefore a proportion of the study subjects do not meet the criteria of chronic disease. The MAH has clarified that Study 20060195 protocol was written before the IWG recommendations on the definition of chronic ITP were published (Rodegheiro *et al*, 2009) and this study was the parent study for several other studies (subjects from Study 20060195 rolled over into Study 20030213 and subjects from Study 20030213 and Study 20080279 rolled over into Study 20090340). Therefore, the inclusion criteria were maintained between these protocols for consistency. A total of 69 of 282 (24.4%) subjects who received at least one dose of romiplostim were 6 months to 12 months since ITP diagnosis at the date of their first dose of romiplostim. Of them, 7 met the criteria for remission (at least 24 weeks with platelet response and no ITP treatment including romiplostim). Information on the actual number of patients with ITP <12 months from diagnosis, including efficacy and safety results from this population have been provided as requested. The data showed that subjects with ITP of 6 to 12 months duration experienced long periods of remission or treatment free periods. Since based on current clinical practice guidelines only patients with >12 months since diagnosis will be treated, the most relevant efficacy results for this subset of patients are reflected in Section 5.1 of the SmPC in addition to the total study results as this is deemed relevant information for prescribers.

In addition, the age limit of 1 year is accepted since a waiver for children under 1 year of age is applicable.

Results from the uncontrolled studies 20030213 (n = 21), 20090340 (n = 66), and 20101221 (n = 147) provided long-term efficacy data with a median (range) duration of treatment of 89 weeks (6, 109 weeks) in Study 20030213, 100 weeks (5, 321 weeks) in Study 20090340 (as of 24 February 2016) and 25.0 weeks (1, 67 weeks) in Study 20101221 (data cutoff 15 March 2016). Subjects in Study 20030213 were enrolled from Study 20060195, and subjects in Study 20090340 were enrolled from Studies 20030213 and 20080279.

A post hoc integrated efficacy analysis was conducted to evaluate the platelet response to romiplostim, bleeding and rescue medication usage rate, the rate of composite bleeding episodes and the use of concurrent ITP therapies while receiving romiplostim. For the integrated analyses, the Paediatric ITP Efficacy Set consisted of all paediatric subjects who received at least 1 dose of romiplostim in an ITP study 20060195, 20080279, 20030213, 20090340 or 20101221. For subjects who received placebo in a parent study and romiplostim in an extension study, only data from the extension study were included.

Subjects for whom the dose of romiplostim was stable (for at least 3 weeks in Study 20030213 and 4 weeks in Studies 20090340 and 20101221) were allowed to self-administer romiplostim (or be administered by a caregiver) away from the study center and returned to the study center for ongoing evaluation at designated study visits.

RESULTS

- Pivotal Study 20080279

In general baseline demographics were well balanced between treatment arms and of which most received > 2 prior treatments, no treatment naïve patients were included and 1 patient in either arm has been splenectomised. Baseline platelet counts were slightly lower in the romiplostim group as compared to the placebo patients (19.9 x 10^9/L for placebo and 17.5 x 10^9/L for romiplostim), this was mainly due to a higher number of subjects in the lower quartile of platelets counts. In the romiplostim group, 76.2% of patients had a bleeding event (of unknown grade) in the 30 days prior to the first IMP versus 73,7% in the placebo group; this together with the low platelet counts indicates the need for a treatment in these patients.

The primary endpoint of the pivotal study is durable platelet response, as a primary endpoint this is acceptable as the platelet blood count is generally used as a valid surrogate endpoint in ITP since it measures treatment activity and is believed to be a reliable predictor of clinical benefit. Romiplostim is intended for long term treatment as such the durability of the response is of interest. The primary objective of durable platelet response was statistically significant (p = 0.0018), a total of 52% (22 subjects) had a durable platelet response in the romiplostim arm compared to 10% (2 subjects) in the placebo arm, this was also reflected in the separate age groups (≥ 1 to< 6 years 38% vs 25%; 6 to < 12 years 56% vs 11%; 12 to < 18 years 56% vs 0), differences among groups are likely due to low subjects numbers per group. The Mantel-Haenszel common odds ratio for achieving durable platelet response was estimated to be 9.1 (romiplostim vs placebo, 95% CI: 1.9, 43.2).

Efficacy was supported in the secondary and supportive endpoints of overall platelet response (p = 0.0002); 30 subjects (71%) in the romiplostim arm compared with 4 of 20 subjects (20%) in the placebo arm; as well as the number of weeks with platelet response (p = 0.0004); the median (minimum; maximum) 12 weeks (0; 24) in the romiplostim arm and 1 week (0; 22) in the placebo arm. Subjects ≥ 1 to < 6 years had a lower rate of durable platelet response with romiplostim (38%) than the older age groups (56% [≥ 6 to < 12 years] and 56% [≥ 12 to < 18 years], respectively. The subject incidence of rescue medication use, a secondary objective, was not statistically significant different between placebo and romiplostim (p = 0.7103), even though platelet counts were low (romiplostim group 41% and placebo 45%). Therefore, the total number of composite bleeding episodes (defined as clinically significant bleeding events or the use of a rescue medication to prevent a clinical significant bleeding

event during weeks 2 through 25) was not tested according to the sequential testing procedure. The mean (SD) number of composite bleeding episodes (clinical grade ≥ 2) was 1.9 (4.2) for the romiplostim arm and 4.0 (6.9) for the placebo arm. The overall duration-adjusted rate per 100 subject-years was 8.1 in the romiplostim arm and 18.4 in the placebo arm (p = < 0.0001, ad hoc). The incidence of bleeding events adjusted by exposure and the timing where these events occurred in relation to the start of treatment have been provided. The graphical presentations of platelet count by duration-adjusted bleeding events and rescue medication over time showed an increase in platelet count over time as well as a decrease in duration-adjusted bleeding events and rescue medication over time for the Pediatric Efficacy Set, this could also be observed for the separate age groups, although at some points the number of subjects was too low to draw conclusions upon. In general, there was a tendency for a decrease in the use of rescue medication and the number of bleeding events with an increase in platelet numbers but this was considered acceptable.

The incidence of rescue ITP medication was rather high in both study arms and overall, no significant differences were observed between treatment arms, (41% in IP and 45% in placebo), resulting in a OR (95% CI) value of 0.8 (0.0, 2.4). Differences are noted by baseline age group: with double use of rescue medication in romiplostim vs placebo (50% vs 25%) in the group 1 to <6 years, 28% vs 44% in the group 6 to <12 years and 50% vs 57% in the group of 12 to <18 years, for romiplostin and placebo respectively. This finding is unexpected and inconsistent with the results seen in the adult population, where a significantly higher proportion in placebo than in romiplostim needed rescue medication (60% in placebo and 23% in romiplostim, section 5.1 of the SmPC). There is not a clear explanation for this difference. One might think that perhaps in children a more cautious approach driven by the higher activity, and thus risk for bleeding events, is taken in this population. On the other hand, the low number of patients in this lower age category makes it difficult to draw any conclusion. The higher use of rescue medication is not concentrated early at the start of treatment as we had previously suggested and that the use decreases consistently over time in the three age groups, which is reassuring.

With regards to the incidence of sustained platelet response (defined as every platelet count ≥ 50 × 10^9/L for at least 6 months in the absence of the investigational product and all other therapies dosed with the intent-to-treat ITP) no subjects in either treatment arm achieved a response.

Given that recommended doses are based on actual body weight, the MAH anticipated problems in younger children or at least those who weighed < 50 Kg, and in such situation a 1:2 dilution or 1:4 dilution is proposed to ensure an appropriate dispensable volume. Although the rationale behind appears adequate, the concern is that this requires additional manipulation that may increase the risk of medication errors and contamination, particularly because the initial reconstitution and dilution are both with clear dissolvent. Considering that self-administration is not permitted for children, the risk is minimised as only health care professionals can administer Nplate. In addition, appropriate instructions are provided in section 4.2 of the SmPC and the educational materials for nurses in order to minimise these risks.

Based on the data presented in these two studies, it is noted that the median time to reach platelet counts above the protective level 50x10^9/L was 6 weeks, and highly variable (25^{th}-75^{th} percentiles: 4 weeks- 10 weeks). This delay in reaching the treatment effect is a matter of concern and questions the proposed dosing regimen for this population. In response to the question raised, the MAH presented additional analysis to investigate whether the observed difference in time to first platelet response between adults and pediatric patients is due to under dosing. The starting dose of 1 ug/kg showed a response in 25.2% of the pediatric patients compared to 26,3% of the adults, as such the starting dose is considered appropriate. Noticeably, the first platelet response of the majority of adults occurs at lower doses (70.4 % in adults versus 46.2% in paediatrics at dosages of 1,2,3 ug/kg). Moreover, adults were permitted a higher maximum dose to reach the first platelet response then pediatric patients (10 ug/kg). Based on the data presented it appeared that a proportion of the pediatric patients required a higher dose and/or have a longer duration before the first platelet response occurs. Even so, after 13 weeks 85,5% of

adults and 84% of the pediatric patients had at least once a platelet response. As such the relevance behind the observed difference in time to first platelet response between adults and paediatric is unknown and requires no further actions at this time.

- Study 20060195

All 22 subjects (17 romiplostim, 5 placebo) received blinded investigational product and were evaluated for efficacy. Of the 17 subjects who received romiplostim, 15 achieved a platelet count ≥ 50 x 10^9/L for 2 consecutive weeks (after excluding platelet counts within 4 weeks following rescue medication use) during the treatment period (88.2%, 95% CI: 63.6%, 98.5%). The same 15 subjects also achieved an increase in platelet count ≥ 20 x 10^9/L above baseline for 2 consecutive weeks (after excluding platelet counts within 4 weeks following rescue medication use) during the treatment period (88.2%, 95% CI: 63.6%, 98.5%). None of the subjects treated with placebo achieved either endpoint. Treatment with romiplostim resulted in statistically significantly greater incidence of platelet responses compared to placebo (p = 0.0008).

Two of 17 subjects (11.8%) in the romiplostim group and 2 of the 5 subjects (40.0%) in the placebo group received rescue medication during the treatment period.

These data supported the pharmacodynamic effect of romiplostim in children (in line with that in adults), with an increase in platelet counts until a protective threshold in a substantial proportion of subjects. However, the benefit for patients in terms of reducing/preventing bleeding events is not that obvious. In fact a higher percentage of patients in romiplostim group (70%) than in placebo (40.0%) had bleeding events of any grade. It is acknowledged that the majority occurred in the first 6 weeks of treatment and that when corrected by time of exposure, no differences are found between treatment arms in this period, whilst a clear reduction is seen from this time point onwards, favouring romiplostin treatment. It is also noted that the vast majority were mild events and that bleeding events occurred with platelet counts below the target of 50 x 10^9/L, which alleviate the concern. Therefore, these events occurred mostly before Nplate reached an effective dose level, which based on the data presented seems to take quite a long time.

- Integrated analysis

The integrated analysis over 5 studies revealed a total of 188 of 224 subjects (83.9%; 95% CI: 78.5%, 88.5%) had platelet response, defined as at least 1 platelet count ≥ 50 x 10^9/L without any use of rescue medication within 4 weeks prior to date of the platelet measurement. The Kaplan-Meier estimate of the time to first platelet response (50st percentile) was 6.0 weeks (95% CI: 5.0, 7.0). A total of 129 of 224 subjects (57.6%; 95% CI: 50.8%, 64.1%) had sustained platelet response, defined as at least 9 weeks with platelet response within a 12-week period. The Kaplan-Meier estimate of the time to first sustained platelet response (50th percentile), defined as the time from initiation of romiplostim to the start of the 12-week period in which a sustained response was seen, was 20.0 weeks (95% CI: 15.0, 26.0). For the integrated analyses, the Kaplan-Meier estimate of the time to first response (50th percentile) was similar across age groups (7.0 weeks, 6.0 weeks, and 6.0 weeks for subjects aged 1 to < 6 years, 6 to < 12 years, and 12 to < 18 years, respectively).

The MAH provided various subgroup analyses in the integrated efficacy analysis set. Several subgroup analyses showed numerical differences with variable results among endpoints. KM estimates of the time first sustained response showed difference in the majority of subgroup analysis, e.g. age, years since diagnosis, baseline bleeding status, prior splenectomy, and number of prior treatments. Given the limited number of patients in most of the relevant subgroups, it is difficult to draw firm conclusions from these data.

- Long-term Efficacy Results

Results from the presented 3 uncontrolled studies provided efficacy data for a median (range) duration of treatment in the long-term studies of 89 weeks (6, 109 weeks) in Study 20030213, 100 weeks (5, 321 weeks) in Study 20090340 (as of 24 February 2016) and 25.0 weeks (1, 67 weeks) in Study 20101221 (data cutoff 15 March 2016).

In long-term safety Study 20090340, paediatric subjects (n = 65) receiving romiplostim for100.0 weeks (median exposure time; range 5 to 321 weeks) maintained platelet responses in the absence of rescue medication in 93.8% of subjects. Across all subjects, the median number of months with platelet response was 20.0 months (range: 0 to 80 months) and the median time on study was 25.0 months (range: 2 to 80 months). The median percentage of months with a platelet response was 95.4% (range 0-100). In the integrated analysis, the subject incidence of platelet response showed a trend toward increasing over time (25.7% at month 1 to >70% from month 7 through month 111). Final results of study 20090340 and 20101221 are pending as data on only a limited number of subjects are present after>3 years of treatment (year 3 n=44 towards year 9, n=5).

In the presented clinical study the efficacy of romiplostim to elevate platelet counts has been clearly demonstrated and is in line with previously reported data in chronic adult ITP patients. Prevention of bleeding is ultimately the clinical benefit of interest for ITP patients, although a direct effect on bleeding has not been clearly demonstrated. The EMA/CHMP "Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia" considers that "The platelet blood count is generally used as a valid surrogate in ITP because it measures treatment activity and is believed to be a reliable predictor of clinical benefit."

It must be noted that a considerable number of subjects do not respond with a durable response to romiplostim treatment (52% responders in study 20080279) and a sustained platelet response in the integrated analysis (57.6% responders). Clinical guidelines issued by haematology societies focus on the platelet count as the key parameter to assess the bleeding risk in patients with ITP and the primary goal of treatment in chronic ITP is to achieve a platelet count sufficient to prevent clinically significant bleeding with the least toxicity. The SmPC contains recommendations to continuously monitor platelet counts over time and stop treatment if the effect is no longer maintained, for the small proportion of patients that spontaneously recover in time the dose of romiplostim will as such be reduced or interrupted when platelet counts increase.

A discussion of the overall experience with self-administration across the different studies has been presented. A total of 194 out of 282 subjects (68.8%) self-administered (or received from a caregiver) at least 1 dose of romiplostim in Studies 20030213, 20090340, and 20101221 (as of 20 March 2017).

Efficacy of romiplostim was demonstrated in subjects on self-administration (SA) with 99.5% showing a platelet response (at least 1 platelet count ≥ 50 x 10^{9}/L without any use of rescue medication within 4 weeks prior to date of the platelet measurement) and 85.1% showing sustained platelet response (at least 9 weeks with platelet response within a 12-week period). The subject incidence of at least 1 composite bleeding at any time during treatment was approximately 38%. The safety profile of romiplostim in this subset of subjects on SA was similar to the safety profile in the integrated pediatric ITP safety set, with similar adverse events reported for both groups.

2.5.4. Conclusions on the clinical efficacy

The clinical package submitted presented is rather extensive and supports the extension of the indication to the paediatric population with ITP. Overall, the data provided are indicative of a clinical benefit in terms of platelet count increase, with a statistically significant greater proportion of romiplostim treated subjects achieving a sustained platelet response compared to placebo in the two main studies presented. Moreover, this effect is maintained in the long term while on treatment as shown by the efficacy data with

a median duration of treatment of >1 year. The observed efficacy was generally consistent among the age cohorts and supported by secondary endpoints. The data obtained is in line with the efficacy in adults, platelet counts are increased significantly a majority of patients.

2.6. Clinical safety

Introduction

The key risks associated with romiplostim in adults include medication errors (dosing/administration), thrombotic/ thromboembolic complications, increased bone marrow reticulin, bone marrow fibrosis, risk of bleeding in ITP patients who have consistently low platelet counts, and reoccurrence of thrombocytopenia after cessation of romiplostim.

Patient exposure

Paediatric ITP Randomized Safety Set (N=59 romiplostim, N=24 placebo)

Weekly dose: In Study 20060195 the mean (SD) average weekly dose of romiplostim was 3.6 (1.7) µg/kg. In Study 20080279 the mean (SD) average weekly dose of romiplostim was 4.5 (2.4) µg/kg. Study 20060195 had a shorter duration of exposure than Study 20080279 (median 16 vs 24 weeks) and also included a PK period.

Maximum dose: The mean (SD) maximum dose (µg/kg) in the romiplostim group was (6.1 [3.1] µg/kg). [In the placebo group this was 9.2 [2.1] µg/kg.]

Duration of treatment: The mean (SD) duration of treatment was 21.5 (4.1) weeks in the romiplostim arm and 19.9 (6.2) weeks in the placebo arm.

Paediatric ITP Safety Set (N=224 romiplostim, N=4 placebo)

This consists of all paediatric subjects who received at least 1 dose of investigational product in an ITP study (Studies 20060195, 20080279, 20030213, 20090340, and 20101221).

Patient numbers: 204 subjects received romiplostim only, 20 subjects received placebo and romiplostim and 4 subjects received placebo only.

Weekly romiplostim dose: The mean average weekly dose was 5.4 (2.7) µg/kg.

Maximum romiplostim dose: The mean (SD) maximum dose was 7.5 (3.2) µg/kg.

Duration of treatment: The mean duration of treatment was 65.5 weeks (range: 1 to 441 weeks).

Table 14 Number of Subjects Exposed to Romiplostim by Treatment Duration (Paediatric ITP Safety Set)

Total Exposure to Romiplostim	Romiplostim (N = 224) n (%)
1 wk to ≤ 12 wks	26 (11.6)
> 12 wks to ≤ 24 wks	53 (23.7)
1 wk to ≤ 24 wks	79 (35.3)
> 24 wks to ≤ 48 wks	55 (24.6)
> 48 wks to ≤ 72 wks	33 (14.7)
> 72 wks to ≤ 96 wks	9 (4.0)
> 96 wks to ≤ 120 wks	12 (5.4)
> 120 wks to ≤ 144 wks	11 (4.9)
> 144 wks to ≤ 168 wks	8 (3.6)
> 168 wks to ≤ 192 wks	7 (3.1)
> 192 wks to ≤ 216 wks	1 (0.4)
> 216 wks to ≤ 240 wks	0 (0.0)
> 240 wks to ≤ 264 wks	0 (0.0)
> 264 wks to ≤ 288 wks	1 (0.4)
> 288 wks to ≤ 312 wks	0 (0.0)
> 312 wks to ≤ 336 wks	1 (0.4)
> 336 wks to ≤ 360 wks	0 (0.0)
> 360 wks to ≤ 384 wks	1 (0.4)
> 384 wks to ≤ 408 wks	1 (0.4)
> 408 wks to ≤ 432 wks	4 (1.8)
> 432 wks to ≤ 456 wks	1 (0.4)

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The pediatric ITP safety set consists of all pediatric subjects who received at least one dose of investigational product in an ITP study (20060195, 20080279, 20030213, 20090340, or 20101221).
If a subject enrolled in multiple studies, total exposure is the summation of treatment durations of individual studies.

In the Paediatric ITP Safety Set (n=224), the mean duration of treatment was approximately 65 ± 82 weeks, median 36 weeks (Q1, Q3: 19, 73; Min 1, Max 441 weeks).

As can be seen in Table 14 which gives the number of subjects exposed to romiplostim by treatment duration, 145/224 (65%) paediatric subjects have received romiplostim for >24 weeks, approximately 17% (n=25) of these subjects for > 3 years.

90/224 subjects (40%) had a treatment duration of >48 weeks, 57/224 (25%) had a treatment duration of >72 weeks, 48/224 subjects (21%) had a treatment duration of >96 weeks and 25/224 subjects (11%) had a treatment duration of >144 weeks (2.8 years).

An update of study 20090340 and 20101221 was provided. The MAH provided an updated dataset in which 40/282 subjects (13,8%) had a treatment duration of >144 weeks, compared to the previous data-cut in which approximately 11% had an exposure duration longer than 144 weeks, unfortunately the increase in number of patients is limited.

The Pediatric Efficacy and Safety set consisted of studies 20060195, 20080279, 20030213, 20090340 and 20101221. Addition of final data from Study 20090340 and study 20101221 resulted in an update with a longer mean duration of treatment 65.5 weeks compared with 84.7 weeks. In study 20101221 all subjects had treatment duration of <144 weeks at the data-cut. The update efficacy data show an increased platelet response (89.4% versus 83.9%), an increased sustained platelet response (68.4% versus 57.6%) compared to the previous data cut. This increase in the efficacy endpoints was consistently shown in the secondary endpoints. As expected, patients with >144 weeks treatment duration all had a platelet response which could be defined as a sustained platelet response in 95% of the cases (38/40), this was also reflected in other efficacy endpoints.

The safety update shows an increased reporting of TEAE (88.8% versus 93.3%). The TEAE with the highest incidence by preferred term remained unchanged even when corrected for duration. Moreover, similar TEAEs were reported in subjects with duration of >144 weeks or <144 weeks. Although the update of efficacy and safety data was minimal with a small increase in patients with exposure >144

weeks, no apparent differences in efficacy and safety analysis are observed with a longer treatment duration and the results are in line with that previously observed. The final results on study 20101221 are expected

Adverse events

Paediatric Randomized ITP Safety Set

During Studies 20060195 and 20080279, most subjects (96.6% romiplostim, 100% placebo) reported 1 or more treatment-emergent adverse event (TEAE), most of these events were mild (grade 1) or moderate (grade 2) in severity.

More subjects receiving romiplostim (20.3%) compared with placebo (4.2%) had serious adverse events but no subjects in either treatment group had adverse events that led to discontinuation from the study or investigational product. There were no fatal adverse events for subjects in either treatment group of either study in Table 15).

Overall the duration–adjusted incidence event rate was 3363.8 per 100 subject-years for romiplostim subjects and 3792.1 per 100 subject-years for placebo subjects (Table 16).

Table 15 Overall Summary of Subject Incidence of Treatment-emergent Adverse Events (Paediatric ITP randomized Safety Set)

	Study 20060195		Study 20080279		Overall	
	Placebo (N = 5) n (%)	Romiplostim (N = 17) n (%)	Placebo (N = 19) n (%)	Romiplostim (N = 42) n (%)	Placebo (N = 24) n (%)	Romiplostim (N = 59) n (%)
All treatment-emergent adverse events - n (%)	5 (100.0)	16 (94.1)	19 (100.0)	41 (97.6)	24 (100.0)	57 (96.6)
Grade ≥ 3	1 (20.0)	3 (17.6)	4 (21.1)	7 (16.7)	5 (20.8)	10 (16.9)
Grade ≥ 4	0 (0.0)	1 (5.9)	1 (5.3)	2 (4.8)	1 (4.2)	3 (5.1)
Serious adverse events	0 (0.0)	2 (11.8)	1 (5.3)	10 (23.8)	1 (4.2)	12 (20.3)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to study discontinuation	0 (0.0)	0 (0.0)	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)
Treatment-related treatment-emergent adverse events - n (%)	1 (20.0)	3 (17.6)	5 (26.3)	11 (26.2)	6 (25.0)	14 (23.7)
Grade ≥ 3	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (1.7)
Grade ≥ 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	1 (1.7)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to study discontinuation	0 (0.0)	0 (0.0)	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)

ITP = immune thrombocytopenia (also known as idiopathic thrombocytopenic purpura).
The pediatric ITP randomized safety set consists of all pediatric subjects who received at least 1 dose of investigational product in an ITP study (20060195 or 20080279).
Events that were reported during the 4-week PK assessment period in Study 20060195 (responders only) and the 6-month platelet monitoring follow up period in Study 20080279 were included in the analysis.
Grade is based on CTCAE v3.0, CTCAE = Common Terminology Criteria for Adverse Events Grading Scale.

Table 16. Overall Summary of Duration Adjusted Incidence Event Rates of Treatment-emergent Adverse Events(Paediatric ITP Randomized Safety Set)

	Study 20060195		Study 20080279		Overall	
	Placebo (Sbj-yr = 1.3) (N = 5) n (r)	Romiplostim (Sbj-yr = 5.3) (N = 17) n (r)	Placebo (Sbj-yr = 8.8) (N = 19) n (r)	Romiplostim (Sbj-yr = 20.3) (N = 42) n (r)	Placebo (Sbj-yr = 10.1) (N = 24) n (r)	Romiplostim (Sbj-yr = 25.6) (N = 59) n (r)
All treatment-emergent adverse events	32 (2529.9)	101 (1923.4)	351 (3972.8)	759 (3736.2)	383 (3792.1)	860 (3363.8)
Grade >= 3	1 (79.1)	3 (57.1)	11 (124.5)	20 (98.5)	12 (118.8)	23 (90.0)
Grade >= 4	0 (0.0)	1 (19.0)	4 (45.3)	6 (29.5)	4 (39.6)	7 (27.4)
Serious adverse events	0 (0.0)	3 (57.1)	2 (22.6)	14 (68.9)	2 (19.8)	17 (66.5)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to study discontinuation	0 (0.0)	0 (0.0)	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)
Treatment-related treatment-emergent adverse events	1 (79.1)	14 (266.6)	14 (158.5)	27 (132.9)	15 (148.5)	41 (160.4)
Grade >= 3	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.9)	0 (0.0)	1 (3.9)
Grade >= 4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.8)	0 (0.0)	2 (7.8)
Leading to discontinuation of investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to study discontinuation	0 (0.0)	0 (0.0)	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)

ITP = immune thrombocytopenia (also known as idiopathic thrombocytopenic purpura).
The pediatric ITP randomized safety set consists of all pediatric subjects who received at least one dose of investigational product in an ITP study (20060195 or 20080279).
Sbj-yr = Total subject years of study duration
n = Number of adverse events r = Duration-adjusted event rate per 100 subject years (n/Sbj-yr*100)
Multiple occurrences of the same event for a subject are counted as multiple events.
Events that were reported during the 4-week PK assessment period in Study 20060195 (responders only) and the 6-month platelet monitoring follow up period in Study 20080279 were included in the analysis.
Grade is based on CTCAE v3.0.

Paediatric ITP Safety Set

In the Paediatric ITP Safety Set most subjects (88.8% romiplostim, 100% placebo) reported 1 or more TEAE, most of which were mild (grade 1) or moderate (grade 2) in severity. (Table 17). More subjects receiving romiplostim (18.3%) compared with placebo (4.2%) had serious adverse events. In these subjects, 4 romiplostim subjects had an adverse event leading to discontinuation of investigational product and 1 romiplostim subject had an adverse event leading to study discontinuation. There were no fatal adverse events for subjects in either treatment group.

Overall the duration–adjusted incidence event rate was 1559.0 per 100 subject-years for romiplostim subjects and 3792.1 per 100 subject-years for placebo subjects.

Table 17. Overall Summary of Subject Incidence of Treatment-emergent Adverse Events (Paediatric ITP Safety Set) Placebo

	Placebo (N = 24) n (%)	Romiplostim (N = 224) n (%)
All treatment-emergent adverse events - n (%)	24 (100.0)	199 (88.8)
Grade ≥ 3	5 (20.8)	47 (21.0)
Grade ≥ 4	1 (4.2)	12 (5.4)
Serious adverse events	1 (4.2)	41 (18.3)
Leading to discontinuation of investigational product	0 (0.0)	4 (1.8)
Leading to study discontinuation	0 (0.0)	1 (0.4)
Fatal adverse events	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events - n (%)	6 (25.0)	55 (24.6)
Grade ≥ 3	0 (0.0)	8 (3.6)
Grade ≥ 4	0 (0.0)	1 (0.4)
Serious adverse events	0 (0.0)	3 (1.3)
Leading to discontinuation of investigational product	0 (0.0)	1 (0.4)
Leading to study discontinuation	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)

ITP = immune thrombocytopenia (also known as idiopathic thrombocytopenic purpura).
The pediatric ITP safety set consists of all pediatric subjects who received at least 1 dose of investigational product in an ITP study (20060195, 20080279, 20030213, 20090340, or 20101221).
For Study 20101221, adverse event is not considered as one of primary reasons leading to study discontinuation.
N = number of subjects who received at least 1 dose of investigational product over the course of all ITP studies.
Subjects who started on placebo and later received romiplostim in an extension study are counted in both treatment groups. Adverse events that occurred before the first dose of romiplostim were counted toward placebo group, otherwise toward romiplostim group.
Grade is based on CTCAE v3.0, CTCAE=Common Terminology Criteria for Adverse Events Grading Scale.

Table 18. Overall Summary of Duration Adjusted Incidence Event Rates of Treatment-emergent Adverse Events (Paediatric ITP Safety Set)

	Placebo (Sbj-yr = 10.1) (N = 24) n (r)	Romiplostim (Sbj-yr = 286.8) (N = 224) n (r)
All treatment-emergent adverse events	383 (3792.1)	4471 (1559.0)
Grade >= 3	12 (118.8)	153 (53.4)
Grade >= 4	4 (39.6)	26 (9.1)
Serious adverse events	2 (19.8)	100 (34.9)
Leading to discontinuation of investigational product	0 (0.0)	9 (3.1)
Leading to study discontinuation	0 (0.0)	1 (0.3)
Fatal adverse events	0 (0.0)	0 (0.0)
Treatment-related treatment-emergent adverse events	15 (148.5)	193 (67.3)
Grade >= 3	0 (0.0)	13 (4.5)
Grade >= 4	0 (0.0)	1 (0.3)
Serious adverse events	0 (0.0)	6 (2.1)
Leading to discontinuation of investigational product	0 (0.0)	3 (1.0)
Leading to study discontinuation	0 (0.0)	0 (0.0)
Fatal adverse events	0 (0.0)	0 (0.0)

ITP = immune thrombocytopenia (also known as idiopathic thrombocytopenic purpura).
The pediatric ITP safety set consists of all pediatric subjects who received at least one dose of investigational product in an ITP study (20060195, 20080279, 20030213, 20090340, or 20101221).
For Study 20101221, adverse event is not considered as one of primary reasons leading to study discontinuation.
N = Number of subjects who received at least one dose of investigational product over the course of all ITP studies. Subjects who started on placebo and later received romiplostim in an extension study are counted in both treatment groups.
Sbj-yr = Total subject years of study duration
n = Number of adverse events r = Duration-adjusted event rate per 100 subject years (n/Sbj-yr*100)
Multiple occurrences of the same event for a subject are counted as multiple events. Events that occurred before the first dose of romiplostim were counted toward placebo group, otherwise toward romiplostim group.
Grade is based on CTCAE v3.0, CTCAE=Common Terminology Criteria for Adverse Events Grading Scale.

TEAEs

Subject incidences of treatment-emergent adverse events occurring in at least 5% of subjects in the romiplostim and placebo treatment groups overall in the Paediatric ITP Safety Set are summarized by MedDRA system organ class. For subjects receiving romiplostim, the highest subject incidences for adverse events were reported in the system organ classes of infections and infestations (69.2%), gastrointestinal disorders (60.3%), and respiratory, thoracic, and mediastinal disorders (56.7%). For subjects receiving placebo, the highest subject incidences of adverse events were reported in the system organ classes of gastrointestinal disorders (66.7%), injury, poisoning, and procedural complications (62.5%), and nervous system disorders (62.5%).

These incidences were very similar in the Paediatric Randomized ITP Safety Set.

Table 19. Subject Incidence of Treatment-emergent Adverse Events Occurring inat least 5% in Either Treatment Group by System Organ Class(Paediatric ITP Safety Set)

System Organ Class	Placebo (N = 24) n (%)	Romiplostim (N = 224) n (%)
Number of subjects reporting treatment-emergent adverse events	24 (100.0)	199 (88.8)
Blood and lymphatic system disorders	4 (16.7)	44 (19.6)
Ear and labyrinth disorders	2 (8.3)	16 (7.1)
Eye disorders	2 (8.3)	23 (10.3)
Gastrointestinal disorders	16 (66.7)	135 (60.3)
General disorders and administration site conditions	14 (58.3)	93 (41.5)
Immune system disorders	1 (4.2)	17 (7.6)
Infections and infestations	14 (58.3)	155 (69.2)
Injury, poisoning and procedural complications	15 (62.5)	95 (42.4)
Investigations	3 (12.5)	23 (10.3)
Metabolism and nutrition disorders	2 (8.3)	19 (8.5)
Musculoskeletal and connective tissue disorders	10 (41.7)	67 (29.9)
Nervous system disorders	15 (62.5)	100 (44.6)
Psychiatric disorders	2 (8.3)	35 (15.6)
Renal and urinary disorders	2 (8.3)	17 (7.6)
Reproductive system and breast disorders	2 (8.3)	18 (8.0)
Respiratory, thoracic and mediastinal disorders	14 (58.3)	127 (56.7)
Skin and subcutaneous tissue disorders	13 (54.2)	97 (43.3)
Vascular disorders	4 (16.7)	37 (16.5)

ITP = immune thrombocytopenia (also known as idiopathic thrombocytopenic purpura).
The pediatric ITP safety set consists of all pediatric subjects who received at least one dose of investigational product in an ITP study (20060195, 20080279, 20030213, 20090340, or 20101221).
N = Number of subjects who received at least one dose of investigational product over the course of all ITP studies. Subjects who started on placebo and later received romiplostim in an extension study are counted in both treatment groups. Adverse events that occurred before the first dose of romiplostim were counted toward placebo group, otherwise toward romiplostim group.
Coded using MedDRA version 19.0.

Subject incidences of treatment-emergent adverse events occurring in at least 5% of subjects in the Paediatric ITP Safety Set in either treatment group by MedDRA preferred term in descending order of frequency are summarized in Table 20.

The treatment-emergent adverse events of highest subject incidence in the Paediatric ITP Safety Set were headache (40.2% romiplostim; 54.2% placebo), epistaxis (34.8% romiplostim; 45.8% placebo), contusion (26.8% romiplostim; 33.3% placebo), and cough (26.3% romiplostim; 12.5% placebo).

These frequencies were very similar to those in the Paediatric Randomized ITP Safety Set in which overall across studies, the treatment-emergent adverse events with the highest subject incidence by preferred term were epistaxis (44.1% romiplostim; 45.8% placebo), contusion (40.7% romiplostim; 33.3% placebo), headache (40.7% romiplostim; 54.2% placebo), and upper respiratory tract infection (30.5% romiplostim; 25.0% placebo).

Apart from the TEAEs occurring most frequently, the frequencies of the other TEAEs by preferred term in the romiplostim group were also very similar to those in the Randomised Paediatric ITP Safety Set.

When the treatment-emergent adverse events were adjusted for duration, adverse events with the highest incidence event rates (number of adverse events per 100 subject-years) in the Paediatric ITP Safety Set overall (with N=224 romiplostim vs 24 placebo patients) were contusion (191.1 romiplostim; 366.3 placebo), headache (105.0 romiplostim; 356.4 placebo), epistaxis (88.6 romiplostim; 198.0 placebo) and petechiae (76.7 romiplostim; 128.7 placebo).

In the Randomised Paediatric ITP Safety Set (with N=59 romiplostim vs 24 placebo patients), the 3 adverse events with the highest duration adjusted incidence event rates overall were also contusion (543.7 romiplostim, 366.3 placebo), headache (281.6 romiplostim, 356.4 placebo), and epistaxis (273.8 romiplostim, 198.0 placebo) *(details can be found in ISS Table 14-6.2.2.3).*

A child (between 4-6-year-old) enrolled in Study 20080279, had 61 events of contusion (affecting the head, body, and limbs) over the span of the 24.3-week treatment period (this case is summarised below). Two ad hoc analyses were performed for duration-adjusted event rates for contusion; 1 with all of the subjects and 1 excluding subject. Including all subjects, the duration-adjusted event rate per 100 subject-years in the romiplostim arm was 664.5 compared with 384.8 in the placebo arm. However, when this subject was excluded from the analysis, the duration adjusted event rate per 100 subject-years event rate was lower in the romiplostim arm (373.1) compared with the placebo group (384.8).

Table 20. *(Part 1)*Subject Incidence of Treatment-emergent Adverse Events Occurring inat least 5% in Either Treatment Group by Preferred Term in Descending Order of Frequency (Paediatric ITP Safety Set)

Preferred Term	Placebo (N = 24) n (%)	Romiplostim (N = 224) n (%)
Number of subjects reporting treatment-emergent adverse events	24 (100.0)	199 (88.8)
Headache	13 (54.2)	90 (40.2)
Epistaxis	11 (45.8)	78 (34.8)
Contusion	8 (33.3)	60 (26.8)
Cough	3 (12.5)	59 (26.3)
Upper respiratory tract infection	6 (25.0)	55 (24.6)
Nasopharyngitis	3 (12.5)	55 (24.6)
Vomiting	6 (25.0)	54 (24.1)
Pyrexia	2 (8.3)	54 (24.1)
Oropharyngeal pain	1 (4.2)	49 (21.9)
Petechiae	7 (29.2)	47 (21.0)
Nausea	7 (29.2)	44 (19.6)
Abdominal pain upper	1 (4.2)	43 (19.2)
Diarrhoea	3 (12.5)	36 (16.1)
Fatigue	5 (20.8)	33 (14.7)
Rhinorrhoea	3 (12.5)	32 (14.3)
Nasal congestion	3 (12.5)	31 (13.8)
Gingival bleeding	4 (16.7)	29 (12.9)
Mouth haemorrhage	4 (16.7)	29 (12.9)
Pain in extremity	4 (16.7)	28 (12.5)
Arthralgia	4 (16.7)	27 (12.1)
Abdominal pain	4 (16.7)	26 (11.6)
Rash	2 (8.3)	26 (11.6)
Ecchymosis	2 (8.3)	22 (9.8)
Haematoma	2 (8.3)	22 (9.8)
Rhinitis	0 (0.0)	22 (9.8)
Constipation	1 (4.2)	19 (8.5)

Table 21. Subject Incidence of Treatment-emergent Adverse Events Occurring in at least 5% in Either Treatment Group by Preferred Term in Descending Order of Frequency (Paediatric ITP Safety Set)*(Part 2)*

Preferred Term	Placebo (N = 24) n (%)	Romiplostim (N = 224) n (%)
Dizziness	4 (16.7)	18 (8.0)
Skin abrasion	1 (4.2)	18 (8.0)
Pharyngitis	0 (0.0)	18 (8.0)
Myalgia	1 (4.2)	15 (6.7)
Pain	1 (4.2)	15 (6.7)
Pharyngitis streptococcal	0 (0.0)	15 (6.7)
Back pain	3 (12.5)	14 (6.3)
Scratch	3 (12.5)	14 (6.3)
Conjunctivitis	0 (0.0)	14 (6.3)
Influenza	0 (0.0)	14 (6.3)
Injection site pain	1 (4.2)	13 (5.8)
Viral infection	1 (4.2)	13 (5.8)
Ear infection	0 (0.0)	13 (5.8)
Decreased appetite	1 (4.2)	12 (5.4)
Fall	0 (0.0)	12 (5.4)
Laceration	7 (29.2)	11 (4.9)
Acne	2 (8.3)	11 (4.9)
Ear pain	2 (8.3)	11 (4.9)
Injection site bruising	3 (12.5)	10 (4.5)
Haemorrhage	2 (8.3)	9 (4.0)
Platelet count decreased	3 (12.5)	8 (3.6)
Head injury	2 (8.3)	8 (3.6)
Haematuria	2 (8.3)	6 (2.7)
Post procedural haemorrhage	2 (8.3)	5 (2.2)
Tooth socket haemorrhage	2 (8.3)	5 (2.2)
Iron deficiency anaemia	2 (8.3)	4 (1.8)
Pneumonia	2 (8.3)	4 (1.8)
Skin mass	2 (8.3)	4 (1.8)
Bone pain	2 (8.3)	2 (0.9)
Lip injury	2 (8.3)	2 (0.9)

Treatment-related TEAEs

In the Paediatric Safety Set the subject incidence of treatment-related adverse events (as reported by the investigator) was similar in the romiplostim (24.6%) and placebo (25.0%) groups in the Paediatric ITP Safety Set.

Treatment-related adverse events occurring in more than 1 subject per treatment group included headache (11.2% romiplostim; 12.5% placebo), nausea (3.1% romiplostim; 4.2% placebo), pain in extremity (2.7% romiplostim; 4.2% placebo), arthralgia (2.2% romiplostim; 0.0% placebo), and dizziness (2.2% romiplostim, 0.0% placebo).

When the treatment-related, treatment-emergent adverse events were adjusted for duration, the adverse events with the highest incidence event rates (number of adverse events per 100 subject-years) overall were headache (16.0 romiplostim; 29.7 placebo), nausea (4.5 romiplostim; 19.8 placebo), arthralgia (2.8 romiplostim; 0.0 placebo), and pain in extremity (2.8 romiplostim; 9.9 placebo).

In the Randomised ITP Paediatric Safety Set, the subject incidence of treatment-related adverse events (as reported by the investigator) was similar in the romiplostim (23.7%) and placebo (25.0%) treatment groups. Treatment-related adverse events occurring in more than 1 subject per treatment group included

headache (8.5% romiplostim; 12.5% placebo), pyrexia (3.4% romiplostim; 4.2% placebo), contusion (3.4% romiplostim; 0.0% placebo), and urticaria (3.4% romiplostim; 0.0% placebo).

When the treatment-related, treatment-emergent adverse events were adjusted for duration, the adverse events with the highest incidence event rates (number of adverse events per 100 subject years) overall were headache (27.4 romiplostim; 29.7 placebo), contusion (19.6 romiplostim; 0.0 placebo), pruritus (15.6 romiplostim; 0.0 placebo).

Grade 3 or Above adverse events

In the Paediatric Randomized ITP Safety Set, the overall subject incidence with grade 3 treatment-emergent adverse events was 13.6% romiplostim subjects and 16.7% placebo subjects.

The preferred term platelet count decreased occurred in 2 (3.4%) romiplostim subjects and no placebo subjects. All other grade 3 treatment emergent adverse events were reported in a single subject each. When the grade 3 treatment-emergent adverse events were adjusted for duration, the adverse events by preferred term with the highest incidence event rates (number of adverse events per 100 subject-years) were platelet count decreased (35.2 romiplostim, 0.0 placebo), and headache (3.9 romiplostim, 19.8 placebo).

The subject incidence of grade 4 treatment emergent adverse events was 5.1% romiplostim subjects *(thrombocytopenia in 3.4%; platelet count decreased in 1.7%)* and 4.2% placebo subjects (only one subject (4.2%), with *platelet count decreased)*.

In the Paediatric ITP Safety Set, the percentage of patients experiencing Grade ≥3 and Grade ≥4 TEAEs was almost the same in both treatment groups: for Grade ≥3 it was 21% in both treatment groups and for Grade ≥4 it was 5.4% for romiplostim and 4.2% for placebo.

In the Paediatric ITP Safety Set, the subject incidence of grade 3 treatment-emergent adverse events was 18.3% romiplostim subjects and 16.7% placebo subjects. The treatment-emergent grade 3 adverse events with the highest subject incidence by preferred term were epistaxis (4.0% romiplostim, 0.0% placebo), headache (3.1% romiplostim, 4.2% placebo), and petechiae (1.3% romiplostim, 4.2% placebo). When the grade 3 treatment emergent adverse events were adjusted for duration, the adverse events by preferred term with the highest incidence event rates (number of adverse events per 100 subject-years) were platelet count decreased (7.3 romiplostim, 0.0 placebo), headache (4.9 romiplostim, 19.8 placebo), and epistaxis (3.5 romiplostim, 0.0 placebo).

The subject incidence of Grade 4 treatment-emergent adverse events was 5.4% romiplostim subjects *(n=8, thrombocytopenia in 3.6%; n=2 platelet count decreased in 0.9%)*.

Treatment-related grade 3 treatment-emergent adverse events were reported in 8/224 (3.6%) of romiplostim subjects only and no placebo subjects . The highest incidences of grade 3 treatment-related, treatment-emergent adverse events by preferred term were headache 3 (1.3%) and abdominal pain 2 (0.9%), both in romiplostim subjects. The duration adjusted incidence rates (number of adverse events per 100 subject years) were reported for romiplostim subjects only and included headache (1.7), abdominal pain (0.7); event rates for ecchymosis, epistaxis, pain in extremity, thrombocytosis and vomiting were all 0.3. One romiplostim subject (0.4%) had a grade 4 treatment-emergent adverse event of thrombocytopenia that was considered treatment-related.

Serious adverse event/deaths/other significant events

Serious adverse events

In the Paediatric Randomized ITP Safety Set, 12 subjects (20.3%) receiving romiplostim and 1 subject (4.2%) receiving placebo had treatment-emergent serious adverse events. Serious adverse events that occurred in > 1 subject receiving romiplostim were epistaxis and headache (2 subjects [3.4%] each). When the serious, treatment emergent adverse events were adjusted for duration (number of adverse events per 100 subject years), the adverse events with the highest incidence event rates overall were epistaxis and headache both at 7.8 events per 100 subject-years and both in the romiplostim group.

For the single placebo treated patient the serious AEs reported were haematuria and an animal bite. Treatment-related serious treatment-emergent adverse events were reported by 1 (1.7%) romiplostim subject and no placebo subjects and included thrombocytosis and headache in a single subject.

In the Paediatric ITP Safety Set 41 subjects (18.3%) receiving romiplostim and 1 subject (4.2%) receiving placebo had treatment-emergent serious adverse events. Serious adverse events that occurred in > 2 (0.9%) subjects receiving romiplostim were epistaxis (4.0%), thrombocytopenia (2.2%), headache, ITP, influenza, petechiae, platelet count decreased, pyrexia (1.3% each). No serious adverse events occurred in > 1 subject receiving placebo.

When the serious, treatment-emergent adverse events were adjusted for duration, the adverse events with the highest incidence event rate were epistaxis (3.8), platelet count decreased (2.8), thrombocytopenia (2.4), and petechiae (1.7) and were reported for romiplostim only.

When the treatment-related, serious, treatment-emergent adverse events were adjusted for duration, adverse events rates were reported for romiplostim subjects only and were 0.3 for abdominal pain, anemia, epistaxis, headache, thrombocytopenia, and thrombocytosis.

The related serious adverse event of thrombocytosis is summarised below.

Deaths
No subjects had a fatal TEAE and no subjects died.

Adverse events of special interest

Thrombocytosis

In the Paediatric Randomized ITP Safety Set the MedDRA preferred terms identified from the EOI searches for thrombocytosis were reported in 2/59 (3.4%) romiplostim subjects (these were in Study 20080279) and 0 (0.0%) placebo subjects.
These thrombocytosis events by preferred term consisted of thrombocytosis (1.7% romiplostim; 0.0% placebo), and platelet count abnormal (1.7% romiplostim; 0.0% placebo). When the treatment-emergent adverse events were adjusted for duration, incidence event rates, the number of adverse events per 100 subject year were platelet count abnormal (1 [3.9] romiplostim; 0 [0.0] placebo), and thrombocytosis (1 [3.9] romiplostim; 0 [0.0] placebo)
In Study 20080279, 1 (1.7%) romiplostim subject had a grade 1 thrombocytosis adverse event, and 1 (1.7%) romiplostim subject had a grade 3 event that was also considered serious and treatment-related.

Search Results by Platelet Counts >450 × 10^9/L in the Paediatric Randomized ITP Safety Set
Overall, in the Paediatric ITP Randomized Safety Set, 20.3% (12/59) (95% CI: 11.0, 32.8) romiplostim subjects and 16.7% (4/24) (95% CI: 4.7, 37.4) placebo subjects had a platelet count >450 × 10^9/L.

In the Paediatric ITP Safety Set the MedDRA preferred terms identified from the EOI searches for thrombocytosis were reported in 2/224 (0.9%) romiplostim subjects and 0 (0.0%) placebo subjects and

concerned the same 2 reports as in the Paediatric Randomized ITP Safety Set.

Search Results by Platelet Counts >450 × 10^9/L in the Paediatric ITP Safety Set

In the Paediatric ITP Safety Set, 25.4% (57/224) (95% CI: 19.9, 31/7) romiplostim subjects and 16.7% (4/24) (95% CI: 4.7, 37.4) placebo subjects had a platelet count >450 x 10^9/L.

The MAH provided an overview and analysis of frequencies of platelet counts above and below 450x10^9/L, confirming that the incidence of laboratory occurrence of platelet count >450x10^9/L in the Pediatric ITP Safety Set at any time was 28.4% in the romiplostim group. In the MAH response, the distinction was made between thrombocytosis as a MedDRA preferred term, as a laboratory value of platelet count >450x10^9/L and as an adverse event reported at the discretion of the investigator based on clinical significance. Although laboratory platelet counts >450x10^9/L were common, in the Pediatric ITP Safety Set there was only one subject incidence of thrombocytosis as an adverse event (serious, Grade 3 platelet count of 1462 x10^9/L) and one subject incidence of increased platelet count (up to a maximum of 872 x10^9/L) reported as an adverse event. The MAH provided the information that the majority of the high platelet counts lasted less than 7 days. Concerning platelet counts >450x10^9/L in the 282 romiplostim treated patients, it can be seen that the median of these counts was 588 x10^9/L with Q1, Q3 approximately 500 and 700 respectively and maximum of 1700. The duration of these counts was ≤7 days in 80.6% of the events, 7 to ≤14 days in 10.6%, 14 to ≤21 days in 1.9% and ≥22 days in 8.8%. It can also be seen that rescue medication had been taken within 7 days before the first count >450x10^9/L in 16.3% of the events and it is conceivable that this may have contributed to some high counts.
From these results, it seems that the potential risk of thromboembolic events (TEEs) was limited as 75% of the counts were <700x10^9/L, which although a high value would not be expected to pose a significant risk in itself in the absence of risk factors for TEEs. Moreover, 80% lasted ≤7 days and a dose was withheld in 90% of the events. The MAH clarified the range and distribution of platelet counts measured in the paediatric population during the clinical trials, the large majority of which did not fall within a range which is usually considered in itself to pose a risk of thrombosis. The possibility of high platelet counts and risk of thromboembolic events are adequately covered in the SmPC and it is not considered necessary to add further information on thrombocytosis in the SmPC.

Haemorrhage

- Paediatric Randomized ITP Safety Set

The MedDRA preferred terms identified from the SMQ searches for hemorrhage were reported in 46/59 (78.0%) romiplostim subjects and 15/24 (62.5%) placebo subjects.

The most frequently reported (by subject incidence) hemorrhage adverse events by preferred term were epistaxis (44.1% romiplostim; 45.8% placebo), contusion (40.7% romiplostim; 33.3% placebo) and petechiae (22.0% romiplostim; 29.2% placebo. When the treatment-emergent adverse events were adjusted for duration, the adverse events with the highest incidence event rates (per 100 subject years) overall were contusion (139 [543.7] romiplostim, 37 [366.3] placebo), epistaxis (70 [273.8] romiplostim, 20 [198.0] placebo), petechiae (66 [258.2] romiplostim; 13 [128.7] placebo), and mouth hemorrhage (19 [74.3] romiplostim; 5 [49.5] placebo)

The overall subject incidence of haemorrhages (SMQ) events by study period (1 to ≤ 12 weeks; 13 to ≤ 24 weeks; 1 to ≤ 24 weeks and > 24 to ≤ 48 weeks) were higher in the romiplostim compared with placebo group and declined over time for both groups (by Study Period) (as summarised below):

	1 to ≤ 12 weeks % (n/N)	13 to ≤ 24 weeks % (n/N)	1 to ≤ 24 weeks % (n/N)	> 24 to ≤ 48 weeks % (n/N)
Romiplostim	74.6% (44/59)	48.3% (28/58)	78.0% (46/59)	18.9% (7/37)
Placebo	54.2% (13/24)	45.5% (10/22)	62.5% (15/24)	12.5% (2/16)

The most frequently reported (by subject incidence) hemorrhage adverse events by preferred term were contusion, epistaxis, petechiae, and mouth haemorrhage summarised below:

	1 to ≤ 12 weeks\ % (n/N)	13 to ≤ 24 weeks % (n/N)	1 to ≤ 24 weeks % (n/N)	> 24 to ≤ 48 weeks % (n/N)
Romiplostim				
contusion	33.9% (20/59)	27.6% (16/58)	40.7% (24/59)	13.5% (5/37)
epistaxis	37.3% (22/59)	19.0% (11/58)	44.1% (26/59)	2.7% (1/37)
petechiae	18.6% (11/59)	10.3 (6/58)	22.0% (13/59)	2.7% (1/37)
mouth haemorrhage	15.3% (9/59)	6.9% (4/58)	18.6% (11/59)	2.7% (1/37)
Placebo				
contusion	29.2% (7/24)	13.6% (3/22)	33.3% (8/24)	0 (0.0)
epistaxis	29.2% (7/24)	27.3% (6/22)	45.8% (11/24)	6.3% (1/16)
petechiae	25.0% (6/24)	13.6% (3/22)	29.2% (7/24)	0 (0.0)
mouth haemorrhage	12.5% (3/24)	4.5% (1/220	16.7% (4/24)	0 (0.0)

Romiplostim

Duration adjusted incidence event rates (number of adverse events per 100 subject years) of haemorrhages (SMQ) events by system organ class and preferred term by Study Period (1 to ≤ 12 weeks; 13 to ≤ 24 weeks; 1 to ≤ 24 weeks and > 24 to ≤ 48 weeks) for subjects who received romiplostim were 1407.6, 1466.1, 1433.8, and 984.5, respectively The treatment-emergent adverse events with the highest duration adjusted incidence event rates (number of adverse events per 100 subject-years) overall by study period for subjects who received romiplostim were:

	1 to ≤ 12 weeks r	13 to ≤ 24 weeks r	1 to ≤ 24 weeks r	> 24 to ≤ 48 weeks r
contusion	442.2	673.9	545.8	492.3
epistaxis	287.4	273.2	281.1	98.5
petechiae	235.8	300.5	264.8	98.5
mouth haemorrhage	103.2	36.4	73.3	98.5

r = duration adjusted event rate per 100 subject-years.

Placebo

Duration adjusted incidence event rates (number of adverse events per 100 subject-years) of haemorrhages (SMQ) events by system organ class and preferred term by study Period (1 to ≤ 12 weeks; 13 to ≤ 24 weeks; 1 to ≤ 24 weeks and > 24 to ≤ 48 weeks) for subjects who received placebo were 1406.2, 869.6, 1169.9, 453.7, respectively (ISS Table 14 6.13.12.2.1.1). The treatment-emergent adverse events with the highest duration adjusted incidence event rates (number of adverse events per 100 subject-years) overall by study period for subjects who received placebo were:

	1 to ≤ 12 weeks r	13 to ≤ 24 weeks r	1 to ≤ 24 weeks r	> 24 to ≤ 48 weeks r
contusion	462.6	282.0	383.1	0.0
epistaxis	203.5	188.0	196.7	226.9
petechiae	166.5	94.0	134.6	0.0
mouth haemorrhage	74.0	23.5	51.8	0.0

r = duration adjusted event rate per 100 subject-years.

The Subject Incidence of Haemorrhages (SMQ) Treatment-emergent Adverse Events by Preferred Term in Descending Order of Frequency in the Paediatric ITP Randomized Safety Set was quite similar to that in the Paediatric ITP Safety Set (please be referred to Table below), with epistaxis, contusion and petechiae being the most common followed by mouth bleeds, haematoma and injection site bruising.

- Paediatric ITP Safety Set

The MedDRA preferred terms identified from the SMQ searches for hemorrhage were reported in 143/224 (63.8%) romiplostim subjects and 15/24 (62.5%) placebo subjects (Table 22).

The most frequently reported (by subject incidence) hemorrhage adverse events by preferred term were epistaxis (34.8% romiplostim; 45.8% placebo), contusion (26.8% romiplostim; 33.3% placebo) and petechiae (21.0% romiplostim; 29.2% placebo (Table 22). When the treatment-emergent adverse events were adjusted for duration, the adverse events with the highest incidence event rates (number of adverse events per 100 subject-years) were contusion (191.1 romiplostim, 366.3 placebo), epistaxis (88.6 romiplostim, 198.0 placebo), petechiae (76.7 romiplostim; 128.7 placebo), and hematoma (18.8 romiplostim; 49.5 placebo)

Table 22. Subject Incidence of Haemorrhages (SMQ) Treatment-emergent AdverseEvents by Preferred Term in Descending Order of Frequency (Paediatric ITP SafetySet)

Preferred Term	Placebo (N = 24) n (%)	Romiplostim (N = 224) n (%)
Number of subjects reporting haemorrhages (SMQ) treatment-emergent adverse events	15 (62.5)	143 (63.8)
Epistaxis	11 (45.8)	78 (34.8)
Contusion	8 (33.3)	60 (26.8)
Petechiae	7 (29.2)	47 (21.0)
Gingival bleeding	4 (16.7)	29 (12.9)
Mouth haemorrhage	4 (16.7)	29 (12.9)
Ecchymosis	2 (8.3)	22 (9.8)
Haematoma	2 (8.3)	22 (9.8)
Injection site bruising	3 (12.5)	10 (4.5)
Purpura	0 (0.0)	10 (4.5)
Haemorrhage	2 (8.3)	9 (4.0)
Injection site haematoma	0 (0.0)	8 (3.6)
Lip haemorrhage	1 (4.2)	7 (3.1)
Immune thrombocytopenic purpura	0 (0.0)	7 (3.1)
Haematuria	2 (8.3)	6 (2.7)
Blood blister	0 (0.0)	6 (2.7)
Injection site haemorrhage	0 (0.0)	6 (2.7)
Post procedural haemorrhage	2 (8.3)	5 (2.2)
Tooth socket haemorrhage	2 (8.3)	5 (2.2)
Menorrhagia	1 (4.2)	5 (2.2)
Haematochezia	0 (0.0)	5 (2.2)
Eye contusion	0 (0.0)	4 (1.8)
Rectal haemorrhage	0 (0.0)	4 (1.8)
Conjunctival haemorrhage	1 (4.2)	3 (1.3)
Wound haemorrhage	1 (4.2)	3 (1.3)
Cerebral haematoma	0 (0.0)	3 (1.3)

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ITP = immune thrombocytopenia (also known as idiopathic thrombocytopenic purpura).
The pediatric ITP safety set consists of all pediatric subjects who received at least one dose of investigational product in an ITP study (20060195, 20080279, 20030213, 20090340, or 20101221).
N = Number of subjects who received at least one dose of investigational product over the course of all ITP studies. Subjects who started on placebo and later received romiplostim in an extension study are counted in both treatment groups. Adverse events that occurred before the first dose of romiplostim were counted toward placebo group, otherwise toward romiplostim group.
Coded using MedDRA version 19.0.

Table 23. Subject Incidence of Haemorrhages (SMQ) Treatment-emergent Adverse Events by Preferred Term in Descending Order of Frequency (Paediatric ITP Safety Set)(Part 2)

Preferred Term	Placebo (N = 24) n (%)	Romiplostim (N = 224) n (%)
Haematemesis	0 (0.0)	3 (1.3)
Haemoptysis	0 (0.0)	3 (1.3)
Vaginal haemorrhage	0 (0.0)	3 (1.3)
Increased tendency to bruise	1 (4.2)	2 (0.9)
Metrorrhagia	1 (4.2)	2 (0.9)
Angina bullosa haemorrhagica	0 (0.0)	2 (0.9)
Traumatic haematoma	0 (0.0)	2 (0.9)
Traumatic haemorrhage	0 (0.0)	2 (0.9)
Ulcer haemorrhage	0 (0.0)	2 (0.9)
Vessel puncture site bruise	1 (4.2)	1 (0.4)
Anal haemorrhage	0 (0.0)	1 (0.4)
Bone contusion	0 (0.0)	1 (0.4)
Ear haemorrhage	0 (0.0)	1 (0.4)
Eye haemorrhage	0 (0.0)	1 (0.4)
Haemarthrosis	0 (0.0)	1 (0.4)
Haemorrhage subcutaneous	0 (0.0)	1 (0.4)
Infusion site bruising	0 (0.0)	1 (0.4)
Muscle haemorrhage	0 (0.0)	1 (0.4)
Periorbital haematoma	0 (0.0)	1 (0.4)
Scleral haemorrhage	0 (0.0)	1 (0.4)
Skin haemorrhage	0 (0.0)	1 (0.4)
Tongue haematoma	0 (0.0)	1 (0.4)
Tongue haemorrhage	0 (0.0)	1 (0.4)
Gastrointestinal haemorrhage	1 (4.2)	0 (0.0)

A high subject incidence of haemorrhagic AEs was seen in the romiplostim group in the Randomized Paediatric ITP Set, where it was not less than in the placebo group and also in the romiplostim group in the Randomized Paediatric ITP Set (approximately 60%). This is in line with the data on bleeding events as presented in the efficacy section.

Incidence of haemorrhage events by study period

The overall subject incidence of haemorrhages (SMQ) events by study period (periods defined as 1 to ≤ 12 weeks and going up to > 360 weeks) are given below.

Table 24. Subject Incidence of Haemorrhages (SMQ) Events referred Term by Study Period in weeks (Paediatric ITP Safety Set - Subjects Who Received Romiplostim)

1 to ≤12 (N = 224) n (%)	13 to ≤24 (N = 200) n (%)	1 to ≤24 (N = 224) n (%)	>24 to ≤48 (N = 153) n (%)	>48 to ≤72 (N = 91) n (%)	>72 to ≤96 (N = 57) n (%)
114 (50.9)	70 (35.0)	124 (55.4)	63 (41.2)	38 (41.8)	21 (36.8)
>96 to ≤120 (N = 48) n (%)	>120 to ≤144 (N = 37) n (%)	>144 to ≤168 (N = 25) n (%)	>168 to ≤192 (N = 20) n (%)	>192 to ≤216 (N = 11) n (%)	>216 to ≤240 (N = 9) n (%)
18 (37.5)	12 (32.4)	11 (44.0)	2 (10.0)	3 (27.3)	3 (33.3)
>240 to ≤264 (N = 9) n (%)	264 to ≤288 (N = 9) n (%)	>288 to ≤312 (N = 8) n (%)	>312 to ≤336 (N = 8) n (%)	>336 to ≤360 (N = 8) n (%)	>360 (N = 7) n (%)

3 (33.3)	4 (44.4)	3 (37.5)	2 (25.0)	3 (37.5)	5 (71.4)

Subjects with Consistently Low Platelet Counts

The MAH has summarised haemorrhages (SMQ) events for subjects who had consistently low platelet counts. Eleven subjects in the romiplostim group and 5 placebo subject had consistently low platelet counts defined as a platelet count of < $20x10^9$/L with dose ≥ 10 µg/kg for 4 consecutive weeks. All of the 5 placebo subjects and 9 of the 11 romiplostim subjects (81.8%) who had consistently low platelet values, reported any haemorrhages events.

Of those 9 subjects, 9 had grade 1 events; 5 had grade 2 events, and 4 had grade 3 events; 2 events were serious.

One of those 9 subjects had haemorrhage events that were considered treatment-related; one event was grade 1, one was grade 2, and one was grade 3; none were serious.

Of those 5 placebo subjects, 5 had grade 1 events; one had a grade 2 event, and one had a grade 3 events; one reported a serious haemorrhages events and one reported a treatment related event.

Subjects with Variable Platelet Counts

The MAH has summarised haemorrhages (SMQ) events for subjects who had variable platelet counts. A total of 77 subjects in the romiplostim group and 2 placebo subjects had variable platelet counts defined as platelet counts increase or decrease by > $100x10^9$/L in 2 consecutive weeks while also crossing 50 $x10^9$/L, and that change in the opposite direction by > 100 $x10^9$/L while crossing 50 $x10^9$/L in the following consecutive week. The incidence of subjects reporting any haemorrhages events was 76.6% (59/77) romiplostim subjects and both placebo subjects. In the romiplostim group 56 (72.7%) subjects had grade 1 events; 21 (27.3%) subjects had grade 2 events, and 9 (11.7%) subjects had grade 3; 10 subjects had haemorrhage events that were serious. Four romiplostim subjects had haemorrhages events that were considered treatment-related; 2 subjects had grade 1 events, 2 subjects had grade 2 events and 1 subject had grade 3 events and 1 subject had a serious treatment-related event.

The 2 placebo subjects had grade 1 events; none were serious or considered treatment-related.

A brief summary is provided for one subject who had a serious adverse event of epistaxis.

Haemorrhages Events by Baseline Age Group

The subject incidence of haemorrhages events reported per age group was:

1. ≥ 1 to < 6 years 64.7% (33/51) romiplostim; 40.0% (2/5) placebo
2. ≥ 6 to < 12 years 67.7% (65/96) romiplostim; 60.0% (6/10) placebo
3. ≥ 12 to < 18 years 58.4% (45/77) romiplostim; 77.8% (7/9) placebo

The haemorrhages (SMQ) treatment-emergent adverse events with the highest subject incidence were epistaxis, contusion, and petechiae (ISS Table 146.13.13.1.2).

	≥ 1 to < 6 years		≥ 6 to < 12 years		≥ 12 to < 18 years)	
	placebo n (%)	romiplostim n (%)	placebo n (%)	romiplostim n (%)	placebo n (%)	romiplostim n (%)
Epistaxis	2 (40.0)	16 (31.4)	4 (40.0)	42 (43.8)	5 (55.6)	20 (26.0)
Contusion	1 (20.0)	15 (29.4)	5 (50.0)	28 (29.2)	2 (22.2)	17 (22.1)
Petechiae	1 (20.0)	10 (19.6)	3 (30.0)	23 (24.0)	3 (33.3)	14 (18.2)

n = number of subjects

Duration adjusted incidence event rates (number of adverse events per 100 subject-years) of haemorrhages (SMQ) events overall by age group were:

4. ≥ 1 to < 6 years 401.1 romiplostim; 235.0 placebo
5. ≥ 6 to < 12 years 670.3 romiplostim; 2072.5 placebo
   ≥ 12 to < 18 years 264.8 romiplostim; 645.8 placebo

The incidence of haemorrhage events is quite similar in all three age categories, varying from approximately 58% to 68%. The numbers of patients per age category in the placebo group are too small to allow comparison per age category.

Haemorrhages Events by Sex Subgroups

The subject incidence of treatment-emergent adverse events was similar for the male and female subjects:

- male subjects 65.5% (72/110) romiplostim; 54.5% (6/11) placebo
- female subjects 62.3% (71/114) romiplostim; 69.2% (9/13) placebo

Haemorrhages Events by Race Subgroups

Most subjects in the Paediatric ITP Safety Set were in the white subgroup. The subject incidence of treatment-emergent adverse events was higher for subjects in the black or African American and Other group compared with the subjects in the white subgroup:

- white subjects 59.6% (99/166) romiplostim; 55.6% (10/18) placebo
- black subjects 71.4% (15/21) romiplostim; 100.0% (2/2) placebo
- other subjects 78.4% (29/37) romiplostim: 75.0% (3/4) placebo

Haemorrhages Events by Time Since ITP Diagnosis

Most subjects (romiplostim and placebo) were in the > 1 year since ITP diagnosis subgroup. The overall subject incidence of treatment-emergent adverse events was similar across time since ITP diagnosis categories.

- ≤ I year since ITP diagnosis 54.9% (28/51) romiplostim; 40.0% (2/5) placebo
- >1 year since ITP diagnosis 66.5% (115/173) romiplostim; 68.4% (13/19) placebo

Haemorrhages Events by Baseline Bleeding Status

The baseline bleeding status was derived based on medical history data and adverse event data prior to first dose. Most subjects (romiplostim and placebo) were in the baseline bleeding status Yes subgroup. The overall subject incidence of haemorrhages (SMQ) treatment-emergent adverse events was similar across both categories of baseline bleeding status.

- Baseline bleeding status Yes 68.1% (79/116) romiplostim; 61.1% (11/18) placebo
- Baseline bleeding status No 59.3% (64/108) romiplostim; 66.7% (4/6) placebo

Haemorrhages Events by Prior Splenectomy

Most subjects (romiplostim and placebo) did not have prior splenectomy. The overall subject incidence of haemorrhages (SMQ) treatment-emergent adverse events was similar across both categories of prior splenectomy.

- Prior splenectomy Yes 75.0% (12/16) romiplostim; 66.7% (2/3) placebo
- Prior splenectomy No 63.0% (131/208) romiplostim; 61.9% (13/21) placebo

Haemorrhages Events by Prior ITP Therapies

The overall subject incidence of haemorrhages (SMQ) treatment-emergent adverse events was similar across both categories of prior ITP therapies.

- < 3 prior ITP treatments 66.1%(72/109) romiplostim; 66.7% (6/9) placebo
- ≥ 3 prior ITP treatments 61.7% (71/115) romiplostim; 60.0% (9/15) placebo

Haemorrhages Events by Baseline Hemoglobin Value

Most subjects (romiplostim and placebo) were included the in the in-range for age category.

- Below-range for age baseline hemoglobin 57.1%(16/28) romiplostim; 100% (3/3) placebo
- Within-range for age baseline hemoglobin 64.8% (125/193) romiplostim; 57.1% (12/21) placebo
- Above-range for age baseline hemoglobin 50.0% (1/2) romiplostim; 0.0 placebo

Haemorrhages Events by Region

The overall subject incidence of haemorrhages (SMQ) treatment emergent adverse events was similar the across categories by region:

- North America 77.0% (77/100) romiplostim; 75.0% (15/20) placebo
- European Union 57.1% (28/49) romiplostim; 0.0% (0/1) placebo
- other 50.7% (38/75) romiplostim; 0.0% (0/3) placebo

Dosing / Administration Errors

As romiplostim is administered in small volumes, and small differences in dose may have large effects on platelet counts, there is the potential for medication errors to occur. Overdose may result in an excessive increase in platelet counts associated with thrombotic/thromboembolic complications; under-dose may result in low platelet counts that can lead to an increased risk of bleeding events.

There have been no reported cases involving an event from the medication error SMQ with an adult subject in the clinical trial setting

There has been 1 reported case (0.4%, 95% CI: 0.0, 2.5) involving a medication error (not serious) with a paediatric subject in the clinical trial setting.

The type of errors reported in the post-marketing setting have included reports of dilution/reconstitution errors and calculation errors (resulting in overdose or under-dose); use of incorrect diluents; and wrong route of administration (ie, IV instead of SC). In brief, in the paediatric post-marketing setting, the search for medication error (SMQ) returned 15 post-marketing cases (with 19 events, 2 of which were serious [accidental overdose and overdose], but not fatal) from 478 paediatric patient-years exposed to romiplostim.

Thrombotic/Thromboembolic Events

MedDRA preferred terms identified from the SMQ searches for thrombotic/thromboembolic events included the preferred term deep vein thrombosis (grade 2) in one (0.4%) romiplostim subject in the Paediatric ITP Safety Set and none in the placebo group. Adjusted for duration, incidence event rates (per 100 subject years) for deep vein thrombosis were 1 (0.3) romiplostim; 0 [0.0] placebo.

In the paediatric post marketing setting, the search for embolic and thrombotic SMQ events returned 6 post marketing cases (with 7 events, all of which were serious). There were no fatal events. The preferred terms for these 7 events were: pulmonary embolism (n = 2), and single events of transient ischaemic attack, transverse sinus thrombosis, jugular vein thrombosis, disseminated intravascular coagulation, and cerebral thrombosis.

Haematological Malignancies

No MedDRA preferred terms identified from the EOI (Event of Interest) searches for haematologic malignancies or myelodysplastic syndrome treatment-emergent events were reported in the Paediatric

ITP Safety Set.(In the Paediatric ITP Safety Set there were also no MedDRA preferred terms identified from the EOI searches for malignancies treatment-emergent events.)
In adult clinical studies of treatment with romiplostim in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to AML were reported.
In the paediatric clinical studies in ITP, in studies 20080279 and 20060195 in the differential counts in peripheral blood, myeloblasts were specifically counted for but none were found.
In the bone marrow examinations in study 20101221, no subject showed any bone marrow abnormalities that were not consistent with an underlying diagnosis of ITP at baseline or on-treatment.
In study 20090340 there is no mention of blast cells in the study report.
In the Integrated Summary of Safety tables there is also no mention of blast cells.
There were no cases of abnormal presence of blast cells in peripheral blood in the paediatric patients in these studies and no evidence for the development of a haematological malignancy, in particular a myeloid malignancy.

Bone marrow fibrosis

Study 20101221 [A Single Arm, Open-label, Long-term Efficacy and Safety Study of Romiplostim in Thrombocytopenic Paediatric Subjects With ITP] included a supplement to evaluate bone marrow changes in the EU, Turkey, and Switzerland. The primary objective defined for the protocol supplement (in addition to those already defined in the main protocol) was to evaluate the incidence of changes in bone marrow findings at year 1 or year 2 after initial exposure to romiplostim. The secondary objective defined for the protocol supplement was to evaluate the incidence of increased reticulin as evidenced by silver staining at year 1 or at year 2, after exposure to romiplostim.
At the time of the data cutoff (16 May 2016), the results were:

- A total of 66 subjects were enrolled into the protocol supplement for the EU, Switzerland, and Turkey. Of these subjects, 30 subjects were in cohort 1 (bone marrow samples taken at baseline and year 1) and 36 subjects were in cohort 2 (bone marrow samples taken at baseline and year 2).
- Twenty-two subjects (73.3%) from cohort 1 and no subjects from cohort 2 had a bone marrow sample collected after the initiation of romiplostim therapy and were included in the bone marrow analysis set. Nine subjects (30.0%) had an end of treatment biopsy or a year 1 biopsy outside the window of day 365 ± 4 weeks and 13 subjects (43.3%) had a year 1 biopsy within the cohort-specified window. Note that for 1 subject, the core biopsy sample at year 1 had not been received by the laboratory in time to be analyzed and as a result the subject did not have an evaluable Bauermeister grade.
- No subjects had a Bauermeister score above 1 at either baseline or on-study. Therefore, no subjects met the primary endpoints for development of collagen or an increase in bone marrow reticulin (Bauermeister score increase of ≥ 2 grades).
- No subject showed any bone marrow abnormalities that were not consistent with an underlying diagnosis of ITP at baseline or on-treatment.
- No subjects had a repeat follow-up bone marrow biopsy at end-of-study as this was only to be performed when subjects were withdrawn due to a presence of collagen or a change to grade 3 reticulin.
- Four subjects (19.0%) were noted as having developed increased reticulin (any increase from baseline in modified Bauermeister grade). However, it is noted that for Subjects 22121001001 and 22121001002, due to an error in data transfer at the time of the snapshot, the baseline values were not properly included in the data. The actual baseline Bauermeister grade for both Subject 22121001001 and 22121001002 was 1 and the Bauermeister grade at week 52 was also 1 for both subjects; therefore, no increase from baseline in Bauermeister grade (and

subsequently no increased reticulin) was observed for these 2 subjects.

- No new safety signals for romiplostim were identified.

With regards to the paediatric population, the search for myelofibrosis EOI (Event of Interest) returned 4 cases of bone marrow reticulin fibrosis as serious adverse events following treatment with romiplostim from spontaneous sources. For all 4 cases, the causal relationship between the event and romiplostim was not provided by the reporter.

However, an apparently mild increase in reticulin (not meeting the primary endpoints for development of collagen or an increase in bone marrow reticulin (Bauermeister score increase of ≥ 2 grades) has been seen in 2 subjects in the clinical long term study 20101221 who did not have fibrosis at baseline. This can be concluded on the basis of the 4 subjects having any increase from baseline in modified Bauermeister grade, thus a grade ≤1 on study which in 2 of these 4 subjects was not present at baseline and in 2 subjects it was present at baseline. There were also 4 post-marketing reports relating to bone marrow fibrosis.

The interim results of Study 20101221 showed that 7/31 (22.5%) of subjects (5/27 after 1 year exposure and 2/4 after 2 years exposure) had a low/mild degree of reticulin (thus no mature collagen). The frequencies of increase in bone marrow reticulin in this study are difficult to compare with the findings in the adult study 20080009 (0/34 subjects after one year exposure, 2/39 after 2 years) due to the small numbers. Unfortunately there were no follow-up biopsies to provide information on reversibility of reticulin formation in pediatric patients and there is very little data about reversibility in adults.

Furthermore, results from adult Study 20080009 are suggestive that the incidence of increase in bone marrow reticulin rises with increasing duration of exposure to romiplostim. So far it is not known if the increases of bone marrow reticulin may have clinical consequences or if the incidence of the more severe collagen fibrosis may increase with durations of exposure >1 year.

Laboratory findings

Paediatric ITP Safety Set

In the Paediatric ITP Safety Set there was no evidence of clinically significant changes in mean laboratory values for the hematology other than platelet values and serum chemistry parameters in either treatment group.

Two subjects (1 romiplostim; 1 placebo) had a grade 4 post baseline decrease in neutrophil count. Six subjects in the romiplostim group had grade 3 post baseline decreases for hemoglobin and 2 subjects in the romiplostim group had grade 3 post baseline decreases for leucocytes. No subjects had grade 4 decreases in hemoglobin or leucocytes. Maximum post baseline grade 4 platelet values (decrease) are summarized below for romiplostim and placebo subjects.

Maximum postbaseline grade 4 values for platelets

Baseline Grade	Postbaseline Grade	Romiplostim Subjects N = 228 n (%)	Placebo Subjects N = 24 n (%)
0	4	2 (0.9%)	0 (0.0%)
1	4	0 (0.0%)	1 (4.2%)
2	4	3 (1.3%)	0 (0.0%)
3	4	19 (8.5%)	2 (8.3%)
4	4	158 (70.5%)	19 (79.2%)

Sixteen (7.1%) romiplostim subjects had a shift from grade 4 platelet value at baseline to grade 3 platelet value (decrease) post-baseline.

The incidence of maximum post baseline grade 3 platelet values (decrease) are summarised below for romiplostim and placebo subjects.

Maximum postbaseline grade 3 values for platelets			
Baseline Grade	Postbaseline Grade	Romiplostim Subjects N = 228 n (%)	Placebo Subjects N = 24 n (%)
1	3	3 (1.3%)	0 (0.0%)
2	3	2 (0.9%)	0 (0.0%)
3	3	14 (6.3%)	2 (8.3%)

Two (0.9%) romiplostim subjects had a shift from grade 3 at baseline to grade 2 platelet value (decrease) post baseline.

Two subjects in the romiplostim group had a maximum postbaseline grade 3 value for alanine aminotransferase. No subject had a maximum post-baseline increase or decrease in shift parameters of grade 4 for chemistry parameters.

Apart from the case of Grade 4 neutropenia, the clinical laboratory values are not remarkable in this population of patients with ITP.

The MAH provided a follow up report on this subject with persistent Grade 4 neutropenia including relevant details of any bone marrow evaluations. From the above timeline, it cannot be excluded that there may be a relationship between the treatment with romiplostim and exacerbation of the neutropenia in this subject. However, based on the totality of the cases and the higher incidence of neutropenia observed in the placebo arm vs. romiplostim, a firm conclusion on causality can not be drawn at the present time given that in most cases there were alternative explanations.

Hypersensitivity and/or Angioedema and/or Anaphylactic Reactions (SMQ)

In the Paediatric Randomized ITP Safety Set the MedDRA preferred terms identified from the SMQ searches for hypersensitivity and/or angioedema and/or anaphylactic reactions were reported in 13/59 (22.0%) romiplostim subjects and 5/24 (20.8%) placebo subjects.

The most frequently reported (by subject incidence) hypersensitivity and/or angioedema and/or anaphylactic reactions adverse events by preferred term were rash (15.3% romiplostim; 8.3% placebo), urticaria (5.1% romiplostim; 0.0% placebo), and rhinitis allergic (3.4% romiplostim; 4.2% placebo).

- 11 romiplostim subjects (11/59; 18.6%) and 4 placebo subjects (16.7%) had hypersensitivity and/or angioedema and/or anaphylactic reactions events that were grade 1;
- 3 romiplostim subjects (5%) had events that were grade 2;
- 1 placebo subject had events that were grade 3;
- none were serious.

Three romiplostim subjects and no placebo subjects had hypersensitivity and/or angioedema and/or anaphylactic reactions events that were considered treatment-related.

One romiplostim subject had treatment-related adverse events that were grade 1; 2 romiplostim subjects had events that were grade 2; none were serious.

In the Paediatric ITP Safety Set the preferred terms identified from the SMQ searches for hypersensitivity and/or angioedema and/or anaphylactic reactions were reported in 56/224 (25.0%) romiplostim subjects and 5/24 (20.8%) placebo subjects.

The most frequently reported (by subject incidence) hypersensitivity and/or angioedema and/or anaphylactic reactions adverse events by preferred term were rash (11.6% romiplostim; 8.3% placebo), hypersensitivity (3.1% romiplostim; 4.2% placebo), and immune thrombocytopenic purpura (3.1% romiplostim; 0.0% placebo).

- 45 (20.1%) romiplostim subjects and 4 (16.7%) placebo subjects had hypersensitivity and/or angioedema and/or anaphylactic reactions events that were grade 1;
- 13 romiplostim subjects (5.8%) had events that were grade 2;
- 2 romiplostim subjects and 1 placebo subject had events that were grade 3;
- 3 romiplostim subjects had events that were considered serious.

Eight romiplostim subjects and no placebo subjects had hypersensitivity and/or angioedema and/or anaphylactic reactions events that were considered treatment related.

Six romiplostim subjects had treatment-related adverse events that were grade 1; 3 romiplostim subjects had events that were grade 2; none were serious.

The adverse events reported for the 3 subjects with serious adverse events that were included in the hypersensitivity and/or angioedema and/or anaphylactic reactions (SMQ) were all AEs of immune thrombocytopenic purpura for which no action was taken with romiplostim.

The percentages of subjects treated with romiplostim for whom hypersensitivity / anaphylactic reactions were reported were similar in the romiplostim group and in the placebo group in both the Paediatric Randomized ITP Safety Set and the Paediatric ITP Safety Set. Also the percentages of subjects treated with romiplostim for whom hypersensitivity / anaphylactic reactions were reported were similar in the romiplostim group in both safety data sets.

In the Paediatric ITP Safety Set the proportion of subjects with Grade 2 hypersensitivity events was higher in the romiplostim group (5.8%) compared to none in the placebo group.

There were no discontinuations of romiplostim due to hypersensitivity and it does not seem to have been a significant TEAE in romiplostim treated patients.

Immunogenicity

For the analysis of antibody formation, the ITP Safety Set consists of all paediatric subjects who received at least 1 dose of investigational product in an ITP study (20060195, 20080279, 20090340, or 20101221).

Paediatric Randomized ITP Safety Set

Study 20080279

Subjects in the Safety Analysis Set were tested for the presence (baseline) or development (post-treatment) of romiplostim (including thrombopoietin-mimetic peptide [TMP]) and TPO antibodies.

Antibody samples were obtained from subjects on day 1 (prior to investigational product dosing), at week 12 and end of study (EOS).

Antibodies to romiplostim

None of the 41 subjects in the romiplostim treatment arm or the 17 subjects in the placebo arm tested had a positive pre-existing antibody to the peptide component of romiplostim (TMP) result at baseline. Of the 42 subjects in the romiplostim arm with a post-baseline antibody result, 2 subjects (5%) developed

binding antibodies to the peptide component of romiplostim (TMP) and TMP and whole romiplostim molecule, respectively. No subjects in either treatment arm developed post-dose positive neutralizing antibodies to romiplostim.

No subjects in either treatment arm developed post-dose positive neutralising antibodies to romiplostim.

Antibodies to TPO

Similarly, none of the 41 subjects in the romiplostim treatment arm or the 17 subjects in the placebo arm tested had a positive pre-existing binding antibody to TPO result at baseline. Of the 42 subjects in the romiplostim arm with a post-baseline antibody result, 2 subjects (4%) developed binding antibodies to TPO. Of the 19 subjects in the placebo arm with a post-baseline antibody result, 1 subject (5%) developed binding antibodies to TPO. No subject in the romiplostim or in the placebo arm developed post-dose positive neutralising antibodies to TPO.

Study 20060195

In Study 20060195, 1 of the 17 subjects from the romiplostim-dosed group tested positive for binding antibodies to the TMP component of romiplostim at week 13 post-dose No baseline sample was available for this subject. The subject was negative for neutralising antibodies to romiplostim in the bioassay. The sample drawn from the end-of-study time point from this subject was negative for binding antibodies to romiplostim and TMP, indicating a transient antibody response. No clinical sequelae were associated with this observation.

No subject was positive for binding antibodies to TPO.

Study 20090340

The baseline result could be a pre-existing response or previous positive antibody status from a subject rolled over from the previous parent study (Studies 20030213 or 20080279). Seven subjects out of 65 subjects (7/65; 10.8%) were positive for antibodies to AMG 531 and/or TPO.

Five of the 7 antibody positive subjects (5/65; 7.7%) were positive for binding antibodies to romiplostim at 1 or more time point Two of the subjects that had binding, anti-romiplostim antibodies were transient, seroconverting antibody negative at subsequent time point, including one subject that was positive for neutralising antibodies at EOS and negative at follow-up; three subjects were positive for binding, non-neutralising at the last time point tested.

A girl between 9-11 years old, who had binding antibodies to both romiplostim and TMP, and also developed neutralising antibodies to romiplostim at the EOS, experienced 2 serious adverse events (depression and suicidal ideation, both conditions that predate the study). This subject was on study for 50 weeks, had platelet counts that were non evaluable (i.e., subject had used rescue medication within previous 4 weeks) from week 36 onwards. Of the evaluable platelet counts, 4 out of 12 measurements were ≥ 50 x 10^9/L. Non evaluable platelet counts were recorded and rescue medications were used in many subjects who had not developed neutralizing antibodies, so it is not known whether anti-romiplostim binding antibodies were responsible for the non-evaluable platelet counts in this case.

Study 20101221

Patients included had not been previously exposed to romiplostim.

The study consisted of a 4-week screening period, up to a 3-year treatment period, and end of study (EOS) visit. Antibody samples were obtained from all subjects on day 1 (prior to investigational product dosing), week 12, and week 52, every 24 weeks thereafter and at the end of treatment (EOT). Of the 142 subjects on study at the time of assessment, a total of 9 subjects were antibody positive for AMG 531 and/or TPO.

Antibodies to romiplostim

Seven subjects had a positive binding antibody response against romiplostim at 1 or more time point (7/142; 4.9 %); 2 subjects had positive pre-existing binding, non-neutralizing antibody status at or before baseline with a positive post-baseline binding antibody status.

Three of the five subjects positive for binding antibodies were also neutralizing antibody positive against romiplostim post baseline (3/142; 2.1%). There were no adverse events associated with the three subjects positive for neutralizing antibodies.

Antibodies to TPO

Four of the 142 subjects (4/142; 2.8%) had a positive binding, non-neutralizing antibody response against TPO while on-study; 2 subjects (2/142; 1.4%) had pre-existing positive binding antibody status at or before baseline. One of these 2 subjects also had a positive post-baseline binding antibody status and the other subject had a negative post-baseline binding antibody status (transient). Two subjects were binding antibody positive to TPO post-dose (2/142; 1.4%) with negative or no result at baseline and both subjects had a negative result at the last time point tested (transient).

No subject had a positive result for neutralising antibody against TPO at baseline or post baseline.

Paediatric ITP Safety Set

Subjects were tested for the presence (at baseline) or development (post-baseline) of romiplostim (including TMP, the peptide component of romiplostim) and TPO antibodies. A total of 224 subjects were dosed with romiplostim and 24 were dosed with placebo. Data were available for 207 of 224 romiplostim subjects and 24 placebo subjects for detection of binding antibodies to romiplostim and TPO.

Antibodies to romiplostim

No placebo subjects had a positive romiplostim peptide antibody response during the study. A total of 11/207 (5.3%) romiplostim subjects had a positive binding antibody response for romiplostim while on-study; 2 subjects (1.0%) had positive binding antibody results at baseline (pre-existing) Nine subjects (4.7%) had a binding antibody positive result post-baseline, of which 5 were transient (negative at the last time point tested) and 4 were persistent (positive at the last time point tested). One (0.5%) romiplostim subject had a post-baseline, neutralizing antibody positive result for romiplostim that was persistent while on-study.

Antibodies to TPO

Eight (3.9%) romiplostim subjects and 1 (4.2%) placebo subject were binding antibody positive for TPO at any time during the study. Of those, 2 romiplostim subjects (developed positive binding antibody status at or before baseline (pre-existing) (. Six romiplostim subjects and 1 placebo subject had developing positive binding antibody to TPO result post-baseline. Of these, 4 romiplostim subjects and 1 placebo subject had a transient post-baseline result and 2 romiplostim subjects had a persistent post-baseline result.

No subjects were neutralizing antibody positive for TPO at any time during the study (Table 25).

Table 25. Romiplostim / Romiplostim Peptide Antibody Summary (Paediatric ITP Safety Set)

	Placebo (N = 24) n (%)	Romiplostim (N = 224) n (%)
Subjects with an on-study result	24	207
Total antibody incidence - n (%)		
Binding antibody positive at anytime	0 (0.0)	11 (5.3)
Neutralizing antibody positive at anytime	0 (0.0)	1 (0.5)
Subjects with a result at baseline	21	195
Pre-existing antibody incidence - n (%)		
Binding antibody positive at or before baseline	0 (0.0)	2 (1.0)
Neutralizing antibody positive at or before baseline	0 (0.0)	0 (0.0)
Subjects with a postbaseline result	24	190
Developing antibody incidence - n (%)		
Binding antibody positive[a]	0 (0.0)	9 (4.7)
Transient[b]	0 (0.0)	5 (55.6)
Persistent[c]	0 (0.0)	4 (44.4)
Neutralizing antibody positive[a]	0 (0.0)	1 (0.5)
Transient[b]	0 (0.0)	0 (0.0)
Persistent[c]	0 (0.0)	1 (100.0)

ITP = immune thrombocytopenia (also known as idiopathic thrombocytopenic purpura).
The pediatric ITP safety set consists of all pediatric subjects who received at least one dose of investigational product in an ITP study (20060195, 20080279, 20030213, 20090340, or 20101221).
N = Number of subjects in the analysis set.
[a] First occurrence of positive result
[b] Negative result at the subject's last timepoint tested
[c] Positive result at the subject's last timepoint tested

Table 26. TPO Antibody Summary (Paediatric ITP Safety Set)

	Placebo (N = 24) n (%)	Romiplostim (N = 224) n (%)
Subjects with an on-study result	24	207
Total antibody incidence - n (%)		
Binding antibody positive at anytime	1 (4.2)	8 (3.9)
Neutralizing antibody positive at anytime	0 (0.0)	0 (0.0)
Subjects with a result at baseline	21	195
Pre-existing antibody incidence - n (%)		
Binding antibody positive at or before baseline	0 (0.0)	2 (1.0)
Neutralizing antibody positive at or before baseline	0 (0.0)	0 (0.0)
Subjects with a postbaseline result	24	189
Developing antibody incidence - n (%)		
Binding antibody positive[a]	1 (4.2)	6 (3.2)
Transient[b]	1 (100.0)	4 (66.7)
Persistent[c]	0 (0.0)	2 (33.3)
Neutralizing antibody positive[a]	0 (0.0)	0 (0.0)
Transient[b]	0 (0.0)	0 (0.0)
Persistent[c]	0 (0.0)	0 (0.0)

For footnote see Table on anti-romiplostim antibodies

Updated Summary of Immunogenicity

In paediatric studies, the incidence of binding antibodies to romiplostim at any time was 7.8% (22/282). Of the 22 subjects, 2 subjects had pre-existing binding non-neutralising romiplostim antibodies at baseline. Additionally, 2.5% (7/282) developed neutralising antibodies to romiplostim. A total of 3.2% (9/282) subjects had binding antibodies to TPO at any time during romiplostim treatment. Of these 9 subjects, 2 subjects had pre-existing binding non-neutralising antibodies to TPO. All subjects were negative for neutralising activity to TPO.

Immunogenicity in the Post-marketing Setting

In the post-marketing registry study, 19 confirmed paediatric patients were included. The incidence of binding antibody post treatment was 16% (3/19) to romiplostim, of which 5.3% (1/19) were positive for neutralising antibodies to romiplostim. There were no antibodies detected to TPO. 184 confirmed adult patients were included in this study; for these patients, the incidence of binding antibody post treatment was 3.8% (7/184) to romiplostim, of which 0.5% (1/184) was positive for neutralising antibodies to romiplostim. A total of 2.2% (4/184) adult patients developed binding, non-neutralising antibody against TPO.

Safety related to drug-drug interactions and other interactions

Not applicable.

Discontinuation due to adverse events

No subjects in the Paediatric Randomized ITP Safety Set had treatment-emergent adverse events leading to withdrawal of IP (Investigational product) or study discontinuation.

In the Paediatric ITP Safety Set, 4 (1.8%) romiplostim subjects had adverse events leading to withdrawal of IP:

- Headache and vomiting were each reported in 2 subjects as AEs leading to withdrawal of investigational product.
- Abdominal pain, Anxiety, Asthenia, Dehydration Interstitial lung disease were each reported in one subject as AEs leading to withdrawal of investigational product.

When the treatment-emergent adverse events leading to withdrawal of IP were adjusted for duration, adverse events rates (number of adverse events [per 100 subject years]) were reported for romiplostim subjects only and included 0.7 for headache and vomiting and 0.3 for abdominal pain, anxiety, asthenia, dehydration and interstitial lung disease.

One (0.4%) romiplostim subject had an adverse event of anxiety leading to study discontinuation. No subjects in the placebo group had adverse events leading to withdrawal of IP or discontinuation from study. The above adverse events given as reason for discontinuation do not give rise to concern as they seem unlikely to be directly related to romiplostim.

Post marketing experience

The Post-Marketing Safety Summary for romiplostim (Nplate) covers the reporting period from 31 July 2008 to 31 July 2016 and summarises safety information from Amgen's romiplostim Periodic Safety Update Reports (PSURs) No. 1 through 9, Periodic Benefit-Risk Evaluation Reports (PBRERs) No. 10, 12, 14, and 15, and all cumulative post-marketing safety data since the first worldwide approval of this drug (International Birth Date [IBD]: 31 July 2008).

Cumulative paediatric patient exposure worldwide (not including the Kyowa Hakko Kirin region) through 31 July 2016 amounted to 1165 patient-years.

Overall Summary of Post-marketing Events

Overall, among paediatric patients, the most frequently occurring system organ class (SOCs; ≥ 10%) for serious adverse events were consistent with that reported among adult patients and with the safety

concerns addressed within the risk management plan for romiplostim. Cumulatively, there were 379 serious adverse events received from all post-marketing sources for paediatric patients (< 18 years old). The most common reporting source for paediatric patients was spontaneous sources (309 out of 379 events). For serious adverse events reported for paediatric patients from spontaneous sources the SOCs that contained ≥ 10% of the total serious adverse events were general disorders and administration site conditions (n = 84 serious adverse events), investigations (n = 50 serious adverse events), and blood and lymphatic system disorders (n = 38 serious adverse events). The majority of serious adverse events reported for paediatric patients occurred in those between the ages of 12 years and less than 18 years old.

Among the total 379 serious adverse events received for paediatric patients, there were 15 events (10 cases) reported with a fatal outcome. Individual review of the serious adverse events in all the paediatric patients did not reveal any new safety signals for romiplostim.

Summary of Fatal Adverse Events in Paediatric Patients

This summary is from the above mentioned Post-Marketing Safety Summary up to 31 July 2016:

Among the 379 serious adverse events received for paediatric patients, there were 15 events (10 cases) reported with a fatal outcome. The majority of fatal events were received from spontaneous sources; 2 events were reported from non-Amgen sponsored noninterventional postmarketing studies.

Reported serious adverse events with fatal outcomes (some with limited information) included the following PTs: 2 events each of death, graft versus host disease, and hemorrhage intracranial, and 1 event each of bone marrow necrosis, cerebral hemorrhage, Evans syndrome, hemolytic anemia, pneumonia pseudomonal, renal failure, sepsis, soft tissue infection, and thrombocytopenia. Patient ages ranged from 1 year to 15 years (2 cases of age unknown). Doses ranged from 100 to 125 µg, as well 5 to 12 µg/kg (5 cases of dose unknown). Time to event onset, provided for 2 events, was 33 and 79 days for the 2 events (hemorrhage intracranial and cerebral hemorrhage, respectively). Out of the 15 events, the reported causality assessment was "Not related" for 7 events, "Not Provided" for 7 events, and "Related" to romiplostim by the reporter in a single case (PT of death).

Most of these patients had severe disorders with thrombocytopenia for which Nplate had been given off label as they did not have ITP and the fatal events in these cases seem very unlikely to have been due to romiplostim. Nevertheless, it is of note that in 2 patients (case 2 and case 6 (who may have had a bone marrow disease considering the marked bone marrow reticulin fibrosis and splenomegaly)), cerebral haemorrhage / intracranial haemorrhage occurred some days after stopping romiplostim.

Immunogenicity in the Postmarketing Setting

Please be referred to the separate Immunogenicity Section in this Assessment Report.

2.6.1. Discussion on clinical safety

Safety data for romiplostim in paediatric patients with a diagnosis of ITP at least 6 months prior to screening/enrollment come from 2 randomised double blind placebo controlled studies (Studies 20060195 and 20080279) in children aged from 1 to <18 years, two open label extension (OLE) studies in which patients from these studies could be included (Studies 20030213 and 20090340) and from another open label study (Study 20101221) in subjects aged (≥ 1 year and < 18 years). Studies 20060195, 20030213, 20080279 are completed and Studies 20090340 and 20101221 are ongoing.

These studies provide safety data from 224 patients treated with romiplostim which includes 20 of the 24

placebo treated patients who went on to receive romiplostim in the OLE studies. Considering that Nplate is an orphan medicinal product, 224 patients is an acceptable number for obtaining safety data in paediatric patients with persistent or chronic ITP, also considering that romiplostim has been authorised in the EU since 2008 for adults with chronic ITP. The randomised studies provide useful comparative safety for romiplostim vs. placebo and in both groups other ITP treatments were also allowed reflecting a real life situation. Approximately 40% of the 224 romiplostim treated patients used concurrent ITP treatment at any time with a trend towards a reduction in concomitant medication use over time (Efficacy assessment of this AR).

Patients investigated

Romiplostim was investigated in children aged from 1 to <18 years, with age distribution of patients exposed to romiplostim as follows in the Paediatric ITP Safety Set: ≥ 1 - < 6 years (N = 47 (23%)); ≥ 6 - < 12 years (N = 89 (43%)); ≥ 12 - < 18 years (N = 68 (34%)) and there was also a similar age distribution in each study. These age categories are in line with the recommendation in the above mentioned CHMP ITP guideline. In the Paediatric ITP Safety Set, the median number of years since ITP diagnosis was 2.0 (Q1, Q3: 1.04, 4.15 years; Min 0.5 years, Max 14.0 years). The relevant inclusion criterion for paediatric patients in the studies submitted was ITP diagnosed at least 6 months before enrollment (ASH guidelines) which is less strict than that of the International working Group recommendations (Rodegheiro *et al*, 2009) that define chronic ITP as lasting more than 12 months. However, in view of the fact that the Q1 for years since ITP diagnosis was 1 year and also that subjects from age ≥ 1 year were eligible for inclusion in the studies, the data submitted can be considered as being sufficiently relevant to the claimed indication in paediatric chronic ITP.

Dosage of romiplostim

The mean and median average weekly doses of romiplostim in the Paediatric ITP Safety Set were approximately 5 to 6 µg/kg and fell within the currently approved maximum weekly dose of 10 µg/kg. In most patients the maximum dose received did not exceed 10 µg/kg but a maximum dose of 12 µg/kg and 14 µg/kg were also reported. The proposed posology in the paediatric population is the same as that approved for adults thus safety data in the paediatric population studied are relevant to treatment with romiplostim according to the intended posology.

Duration of treatment with romiplostim

The safety data in terms of years of exposure of more than 1.5 to 2 years are still quite limited considering that treatment may last for an indefinite number of years. The MAH provided an updated dataset in which 40/282 subjects (13.8%) had a treatment duration of >144 weeks, compared to the previous data-cut in which approximately 11% had an exposure duration longer than 144 weeks, unfortunately the increase is number of patients was still limited. Addition of final data from Study 20090340 and study 20101221 resulted in an update with a longer mean duration of treatment 65.5 weeks compared with 84.7 weeks. In study 20101221 all subjects had treatment duration of <144 weeks at the data-cut. The safety update showed an increased reporting of TEAE (88.8% versus 93.3%). The TEAE with the highest incidence by preferred term remained unchanged even when corrected for duration. Moreover, similar TEAEs were reported in subjects with duration of >144 weeks or <144 weeks. Although the update of efficacy and safety data was minimal with a small increase in patients with exposure >144 weeks, no apparent differences in efficacy and safety analysis are observed with a longer treatment duration and the results are in line with that previously observed. Final results on study 20101221 is expected.

Adverse events

Overall, in the Paediatric ITP Safety Set, the percentage of patients experiencing TEAEs was similar in the romiplostim (89%) and placebo treated subjects (100%). The TEAEs reported consisted of both more general AEs and of AEs which may be more specific to a population of ITP patients undergoing treatment.

The most common adverse reactions in paediatric ITP patients 1 year and older were upper respiratory tract infection (30.5% romiplostim; 25.0% placebo), rhinitis, cough, oropharyngeal pain, upper abdominal pain, diarrhoea, rash, pyrexia, contusion (reported very commonly (≥ 1/10)), and pharyngitis, conjunctivitis, ear infection, gastroenteritis, sinusitis, purpura, urticaria and peripheral swelling (reported commonly (≥ 1/100 to < 1/10)).

Oropharyngeal pain, upper abdominal pain, rhinitis, pharyngitis, conjunctivitis, ear infection, sinusitis and peripheral swelling were additional adverse reactions observed in paediatric studies compared to those seen in adult studies (section 4.8 of the SmPC). Some of the adverse reactions seen in adults were reported more frequently in paediatric subjects such as cough, diarrhoea, rash, pyrexia and contusion reported very commonly (≥ 1/10) in paediatric subjects and purpura and urticaria were reported commonly (≥ 1/100 to < 1/10) in paediatric subjects (section 4.8 of the SmPC).

However, it is noticeable that the frequency of haemorrhagic AEs fits into the range of "common" in the paediatric population whereas in the adult population, apart from ecchymosis, any haemorrhagic AEs are mentioned with a frequency "uncommon" in the table in SmPC Section 4.8.

The most frequent AEs in subjects in the Paediatric ITP Safety Set were headache (40.2% romiplostim; 54.2% placebo), epistaxis (34.8% romiplostim; 45.8% placebo), contusion (26.8% romiplostim; 33.3% placebo), and cough (26.3% romiplostim; 12.5% placebo). These frequencies were very similar to those in the Paediatric Randomized ITP Safety Set in which overall across studies, the treatment-emergent adverse events with the highest subject incidence were epistaxis (44.1% romiplostim; 45.8% placebo), contusion (40.7% romiplostim; 33.3% placebo), headache (40.7% romiplostim; 54.2% placebo), and upper respiratory tract infection (30.5% romiplostim; 25.0% placebo). Hemorrhage was reported frequently as an AE. Adverse events falling under the MedDRA preferred terms identified from the SMQ searches for haemorrhage were reported in 143/224 (63.8%) romiplostim subjects and 15/24 (62.5%) placebo subjects. Also of note is that pyrexia was reported more often in the romiplostim group (~24.1% vs ~8.3% in the placebo group) in both the Randomised Paediatric ITP Safety Set and the Paediatric ITP Safety Set which may be associated with the corresponding frequencies of nasopharyngitis although the rate of upper respiratory tract infection was the same in both the romiplostim and placebo treatment groups at approximately 25%. However, in the Randomised ITP Paediatric Safety Set pyrexia was considered to be treatment related in a similar proportion of patients in each treatment group (3.4% romiplostim vs 4.2% placebo. It is not clear why there is such a difference in subject incidence of the TEAE pyrexia between the romiplostim and placebo groups whereas the incidence of pyrexia as treatment related TEAE was almost the same in both groups. Updated data showed an increased number of subjects in the romiplostim arm of the study experienced an event of pyrexia (31.6% romiplostim versus 8.3% placebo-updated data), when corrected for the duration of exposure the increase in pyrexia in the romiplostim treated patients remains present (19.8 per 100 subject years for placebo versus 42,3 per 100 subject years for romiplostim). The majority of the events was a grade 1-2 and was resolved within a median duration of 2 days. As noted by the MAH there was an increase in the reporting of pyrexia in the younger age groups, an increase in pyrexia is more likely in younger patients (as supported by the CPRD analysis). Four patients experienced a serious event of pyrexia (0.9%), the MAH provided short case summaries and in all subjects the pyrexia resolved within 2 days of hospitalisation and was not related to a positive post-baseline result for TPO or romiplostim. Additionally, a number of patients had positive antibodies while experiencing pyrexia but an association between the occurrence of positive antibody findings and pyrexia is not likely. The MAH has listed pyrexia in SmPC section 4.8 as a common AE, however this is not a new ADR. The frequency of injection site pain was fairly similar in both the romiplostim group (5.8%) and the placebo group (4.2%) suggesting that the romiplostim injections do not pose a major tolerability problem. Lastly, iron deficiency anaemia was more frequent in the placebo group (8.3% vs 1.8% in the romiplostim arm) which could be indicative of an increased bleeding tendency but the actual numbers of placebo patients for which it was reported is small at 2 patients.

The extent of serious or higher grade reported AEs in patients treated with romiplostim, seems to have been limited. There were no deaths during the clinical studies and it is reassuring that there were very few discontinuations due to adverse events with only 4 (1.8%) romiplostim subjects having adverse events which led to withdrawal.

Adverse events of special interest

Bleeding events:

A high subject incidence of haemorrhagic AEs was seen in the romiplostim group in the Randomized Paediatric ITP Set, where it was not less than in the placebo group, and also in the romiplostim group in the Paediatric ITP Set (approximately 60%). The subject incidence of haemorrhage AEs was higher in weeks 1 to ≤ 12 at 50.9% and thereafter it ranged approximately between 35% and 44% in the periods up to >144 to ≤ 168 weeks. From then on, numbers of patients are too small to allow conclusions to be made. A similar pattern was seen in the first 24 weeks in the Paediatric Randomized ITP Safety Set in which the frequency was 74.6% in weeks 1 to ≤ 12 and 48.3% in weeks 13 to ≤ 24. It seems likely that the higher rate of haemorrhage in the first 12 weeks of a study is due to the delay before patients' platelet count responds to romiplostim. The median time to First Platelet Response in the Paediatric ITP Efficacy Set was 6 weeks which would be in keeping with this.

The incidence of haemorrhage events in the Paediatric ITP Set is quite similar in all three age categories in patients treated with romiplostim, varying from approximately 58% to 68%. The numbers of patients per age category in the placebo group are too small to allow comparison per age category. Although the subject incidence of haemorrhage adverse events in the Paediatric ITP Set was high, with overall 63.8% in romiplostim treated patients, the incidence of severe bleeds was low with a subject incidence of 20% Grade ≥ 2, 7.6% Grade ≥ 3 and none Grade ≥ 4.

The MAH also analysed the incidence of haemorrhage events according to various other subject categories including sex, race, time since ITP diagnosis, baseline bleeding status, prior splenectomy, prior ITP therapies, baseline haemoglobin value and region. There were no major differences in the incidence of haemorrhage events between the subgroups within each of the categories, notably for example in patients who had a baseline bleeding status of "yes" or "no", patients with or without prior splenectomy (although only 12 romiplostim patients had prior splenectomy), patients with <3 prior ITP treatments or ≥ 3 prior ITP treatments.

Thrombocytosis

Thrombocytosis was reported infrequently as an adverse event with romiplostim both in in the Paediatric Randomized ITP Safety Set (2/59 patients (3.4%)) and in the Paediatric ITP Safety Set (2/224 (0.9%) patients, the same 2 patients) and no cases in the placebo group. The large majority of platelet counts did not fall within a range which is usually considered in itself to pose a risk of thrombosis. The possibility of high platelet counts and risk of thromboembolic events are adequately covered in section 4.8 of the SmPC and it is not considered necessary to add further information on thrombocytosis in the SmPC.

Thrombotic/Thromboembolic Events

MedDRA preferred terms searches for thrombotic/thromboembolic events identified the preferred term deep vein thrombosis (grade 2) in one (0.4%) romiplostim subject in the Paediatric ITP Safety Set and none in the placebo group. However, it turned that this patient had clinical signs of phlebitis and the Doppler ultrasound did not show a thrombus.

In the paediatric post-marketing setting 7 cases were identified, with 7 events, all of which were serious. There were no fatal events. The preferred terms for these 7 events were: pulmonary embolism (n = 2), and single events of transient ischaemic attack, transverse sinus thrombosis, jugular vein thrombosis, disseminated intravascular coagulation, and cerebral thrombosis. These reports of 7 thrombotic events,

which appear to have been very serious, are of concern and highlight the thrombotic potential of TPO agonists and the necessity of continuing vigilance.

Increased bone marrow reticulin

In an ongoing paediatric clinical trial, of the subjects with an evaluable on-study bone marrow biopsy, 5 out of 27 subjects (18.5%) developed increased reticulin in cohort 1 and 2 out of 4 subjects (50.0%) developed increased reticulin in cohort 2. However, no subject showed any bone marrow abnormalities that were inconsistent with an underlying diagnosis of ITP at baseline or on-treatment.

The interim results of Study 20101221 showed that 7/31 (22.5%) of subjects (5/27 after 1 year exposure and 2/4 after 2 years exposure) had a low/mild degree of reticulin (thus no mature collagen). The frequencies of increase in bone marrow reticulin in this study are difficult to compare with the findings in the adult study 20080009 (0/34 subjects after one year exposure, 2/39 after 2 years) due to the small numbers. Unfortunately there were no follow-up biopsies to provide information on reversibility of reticulin formation in paediatric patients and there is very little data about reversibility in adults. Furthermore, results from adult Study 20080009 are suggestive that the incidence of increase in bone marrow reticulin rises with increasing duration of exposure to romiplostim. So far it is not known if the increases of bone marrow reticulin may have clinical consequences or if the incidence of the more severe collagen fibrosis may increase with durations of exposure >1 year.

Data on reversibility of abnormal bone marrow findings are considered essential but it is not clear from protocol 20101221 if provision has been made to obtain post treatment bone marrow biopsies to evaluate reversibility of findings of increases of reticulin or collagen formation. The MAH confirmed that provision is made to obtain post treatment bone marrow biopsies from subjects in Study 20101221 to evaluate reversibility of findings of increases of reticulin or collagen formation. The MAH has confirmed that the results of Study 20101221 will be submitted. Section 4.8.of the SmPC with regards to bone marrow reticulin has been updated with pediatric data.

Immunogenicity

Binding antibodies were measured in 4.7% (N=9) subjects in the Paediatric Safety Set, persistent in 4 patients and one patient had a post-baseline neutralising antibody positive result for romiplostim that was persistent while on-study. In the post marketing registry (Study 20080091) one paediatric patient and one adult patient tested positive for neutralising antibodies to Nplate, and for both of these reduced efficacy was reported. In the Paediatric Safety Set, binding antibodies to TPO were measured in 3.2 % of subjects (n=6), transient in 4 subjects and persistent in 2 subjects and no patients had a neutralising antibody to TPO. In the post marketing registry no patients had a neutralising antibody to TPO. Although the occurrence of antibodies to romiplostim, to the peptide component of romiplostim and to TPO has been described, it is difficult to get a clear picture per patient of which antibodies they had and whether or not there were clinical consequences. It was not clear if the occurrence of antibodies to romiplostim might be associated with the occurrence of antibodies to TPO.

In the updated Pediatric ITP Safety Set, the incidence of binding antibodies to romiplostim was 7.8% (22 of 282) overall and 0.7% were considered pre-existing. Of the 20 post-baseline results, 11 (3.9%) were considered persistent. Seven subjects (2.5%) developed neutralising antibodies to romiplostim; 5 of 7 subjects had results that were considered persistent. A total of 3.2% (9 of 282) subjects had binding antibodies to TPO at any time during romiplostim treatment; 1 subject had binding antibodies to TPO considered persistent and all subjects were negative for neutralising activity to TPO. 1 subject in Study 20101221 had a persistent, neutralising antibody result for romiplostim at week 52 and week 100 and a transient, non-neutralising positive antibody result for TPO at week 52.

Most subjects who had binding antibodies to romiplostim or TPO had a positive binding antibody result at a single visit, 13 of 20 and 4 of 9, respectively. Five subjects had binding antibodies to romiplostim at a single time point considered persistent because the result occurred at the final assessment.

Binding and neutralising antibodies to romiplostim and binding antibodies to TPO have been observed in children. In some cases adverse bleeding events were preceding or at the same time as positive antibody results. Therefore an association between the presence of antibodies and bleeding events cannot be excluded. The SmPC mentions the possible loss of response in section 4.2 of the SmPC and the possible immunogenicity in section 4.4 and 4.8 of the SmPC. This adequately covers the possible risk associated with the presence of binding or neutralising antibodies.

Hematological Malignancies

No MedDRA preferred terms searches for hematologic malignancies or myelodysplastic syndrome treatment-emergent events were reported in the Paediatric ITP Safety Set. It is not clear if the search using preferred terms for hematologic malignancies or myelodysplastic syndrome would identify cases of abnormal presence of blast cells in peripheral blood. However, in the paediatric clinical studies in ITP, in studies 20080279 and 20060195 in the differential counts in peripheral blood, myeloblasts were specifically counted for but none were found. In study 20090340 there is no mention of blast cells in the study report. In the bone marrow examinations in study 20101221, no subject showed any bone marrow abnormalities that were not consistent with an underlying diagnosis of ITP at baseline or on-treatment.

Thus from the available data it can be concluded that there is no evidence so far of an increase in blast cells or suggestion of haematological malignancy in paediatric patients treated with romiplopstim.

Hypersensitivity

There were no discontinuations of romiplostim due to hypersensitivity and it does not seem to have been a significant TEAE in romiplostim treated patients. Hypersensitivity is mentioned with a frequency of "very common" in section 4.8 of the SmPC which is in line with findings in the paediatric patients investigated.

Dosing / Administration Errors

There are complicated instructions and calculations for reconstituting and diluting romiplostim before administration. Dose (re-) calculation, the reconstitution step, administration of small amounts to the patients, as well as the optional additional dilution step are considered important risk factors contributing to medication errors for all presentations of Nplate. This, combined with very small amounts to be administered, may present a problem. Several presentations of Nplate exist, but not all of these contain the WFI and devices for reconstitution and administration.

There have been no reported cases involving an event from the medication error SMQ with an adult subject in the clinical trial setting and one case (0.4%, 95% CI: 0.0, 2.5) involving a medication error (non-serious) with a paediatric subject in the clinical trial setting. In the paediatric post-marketing setting, the search for medication error (SMQ) returned 15 post-marketing cases (with 19 events, 2 of which were serious [accidental overdose and overdose], but not fatal) from 478 paediatric patient-years exposed to romiplostim.

There are educational materials for Nplate with key elements which include the provision of a dosing calculator to simplify the calculation of the correct dose and assist in correct reconstitution and administration. In addition, as risk minimisation measure Nplate cannot be used in a home treatment setting for the paedatric population.

2.6.2. Conclusions on clinical safety

Overall, the safety profile of Nplate in the paediatric population appears similar to that described in adults.

Oropharyngeal pain, upper abdominal pain, rhinitis, pharyngitis, conjunctivitis, ear infection, sinusitis and peripheral swelling were additional adverse reactions observed in paediatric studies compared to those seen in adult studies (section 4.8 of the SmPC). Some of the adverse reactions seen in adults were reported more frequently in paediatric subjects such as cough, diarrhoea, rash, pyrexia and contusion reported very commonly (≥ 1/10) in paediatric subjects and purpura and urticaria were reported commonly (≥ 1/100 to < 1/10) in paediatric subjects (section 4.8 of the SmPC).

The AEs experienced in the paediatric population in the clinical studies seem to have been almost all not serious and well tolerated. Adverse events of special interest are considered to remain antibody formation, bone marrow fibrosis, thrombocytosis and thrombo-embolic events. Also, the risk of haemorrhage remains during romiplostim treatment and especially within the first days after stopping treatment with romiplostim.

Dosing and administration errors due to complicated reconstitution and dilution instructions and calculations are considered a source of dosing errors. An update of the educational materials with the new presentation has been done and Nplate can not be used in a home treatment setting for the paediatric population to minimise this risk.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 18.2 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 18.2 with the following content:

Safety concerns

Table 27: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Reoccurrence of thrombocytopenia after cessation of romiplostim • Increased bone marrow reticulin • Thrombocytosis • Risk of bleeding in ITP patients who have consistently low platelet counts • Risk of bleeding during the period of low platelet counts in patients with variable platelet counts • Progression of existing MDS[a,b] • Thrombotic/thromboembolic complications • Romiplostim medication errors (dosing/administration) • Hypersensitivity reactions
Important potential risks	• Neutralising antibodies that cross-react with eTPO • Bone marrow fibrosis • Concurrent leukocytosis and anemia • Renal impairment
Missing information	• Risks during pregnancy and lactation • Use in pediatric patients (< 1 year of age) • Use in patients of different racial and/or ethnic origins • Use in patients with renal, hepatic, cardiac, or pulmonary impairment • Use in patients with bone marrow stem cell disorder and/or any active malignancy • Use in patients concurrently receiving rituximab or alkylating agents

a Appropriately diagnosed ITP patients are not expected to have existing hematological malignancies including MDS.
b Solid tumors are not applicable.

Pharmacovigilance plan

Table 28: On-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study/Activity, Type, Title, and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Date for Submission of Interim or Final Reports**
Study 20070797 Postmarketing surveillance study Population based prospective annual assessment of safety of romiplostim treatment in adult patients with chronic idiopathic (immune) thrombocytopenic purpura (ITP) based on national health registry systems in Denmark, Sweden, and Norway Category 3	• To estimate the incidence rate of increased bone marrow reticulin and/or bone marrow fibrosis with associated clinical signs, confirmed by bone marrow biopsy findings of adults with chronic ITP receiving romiplostim • To describe the phenomenon of worsened thrombocytopenia (platelet count significantly reduced to, or below, baseline platelet count levels) after romiplostim cessation among adult chronic ITP subjects • To study the incidence	Reoccurrence of thrombocytopenia after cessation of romiplostim; increased bone marrow reticulin; thrombocytosis; progression of existing MDS; thrombotic/ thromboembolic complications; bone marrow fibrosis; concurrent leukocytosis and anemia; renal impairment	Agreed

Study/Activity, Type, Title, and Category (1-3)	Objectives	Safety Concerns Addressed	Date for Submission of Interim or Final Reports
	rate of thrombocytosis (platelet count > 450 x 10^9/L) among romiplostim-treated adult chronic ITP subjects with or without adverse events • To describe the incidence rate of thrombotic / thromboembolic events and the distribution of specific diagnoses of these thrombotic / thromboembolic events for a romiplostim-exposed cohort and an unexposed cohort • To assess the incidence rate of hematological malignancies and premalignant states (focused on AML and MDS) for a romiplostim-exposed cohort and an unexposed cohort • To describe clinically significant bleeding and/or receipt of rescue medication (any new ITP medication prescribed to a chronic ITP subject during romiplostim therapy) in predefined romiplostim therapy periods • To describe the incidence rate of concurrent leukocytosis and anemia (measured by laboratory test results taken within 4 weeks of each other) • To describe subject safety profiles, including the incidence rate of renal failure among adult chronic ITP subjects with renal		

Study/Activity, Type, Title, and Category (1-3)	Objectives	Safety Concerns Addressed	Date for Submission of Interim or Final Reports
	impairment medical condition at the time romiplostim therapy is initiated • To measure the impact of the EU dosing rule in the cohort of romiplostim exposed subjects • To describe the prevalence of reticulin and collagen fiber content in the first bone marrow biopsy of adult chronic ITP subjects prior to romiplostim exposure, by splenectomy status • To assess the incidence of collagen fibrosis with associated clinical signs confirmed by findings in bone marrow biopsies of adults with chronic ITP either receiving or not receiving romiplostim • To study the incidence of CIMF (primary myelofibrosis) to the WHO diagnostic criteria in adults with chronic ITP either receiving or not receiving romiplostim • To assess overall and specific incidence of bone marrow fibrosis, including reticulin and collagen fiber content formation, and CIMF among adult chronic ITP subjects with bone marrow data prior to and following romiplostim therapy,		

Study/Activity, Type, Title, and Category (1-3)	Objectives	Safety Concerns Addressed	Date for Submission of Interim or Final Reports
	regardless of clinical signs and symptoms in adults with chronic ITP either receiving or not receiving romiplostim • To describe the romiplostim utilization pattern in subjects without adult chronic ITP (romiplostim off-label use)		
Study 20101221 A single-arm, open-label, long-term efficacy and safety study of romiplostim in thrombocytopenic pediatric subjects with immune thrombocytopenia (ITP) Category 3	• To describe the percentage of time that pediatric subjects with ITP have a platelet response in the first 6 months from the start of treatment with romiplostim • To evaluate incidence of changes in bone marrow findings at year 1 and year 2 after initial exposure to romiplostim	Use in pediatric subjects	Agreed
Study 20140195 Country-specific monitoring protocol for patients in France receiving Nplate (romiplostim) 250 µg powder and solvent for solution for injection 500 µg powder and solvent for solution for injection for the treatment of primary chronic immune thrombocytopenic purpura refractory to other treatments in children > 1 year old Category 3	• To allow access to romiplostim outside of the scope of the marketing authorization • To confirm the relevance of the off-label use of romiplostim • To monitor the safety of patients treated in this setting	Use in pediatric subjects	Agreed

Risk minimisation measures

Table 29: Summary of Risk Minimisation Measures

Safety concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Reoccurrence of thrombocytopenia after cessation of romiplostim	Relevant text is provided in the following sections of the SmPC: Sections 4.2, 4.4 and 4.8	None
Increased bone marrow reticulin	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects • Section 5.3, Preclinical safety data	None
Thrombocytosis	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.5, Interaction with other medicinal products and other forms of interaction • Section 4.8, Undesirable effects • Section 4.9, Overdose	None
Risk of bleeding in ITP patients who have consistently low platelet counts	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects • Section 5.1, Pharmacodynamic properties	None
Risk of bleeding during the period of low platelet counts in patients with variable platelet counts	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects	None

Safety concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	• Section 5.1, Pharmacodynamic properties	
Progression of existing MDS	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects	None
Thrombotic/ thromboembolic complications	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects • Section 4.9, Overdose	None
Romiplostim medication errors (dosing/ administration)	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects • Section 4.9, Overdose • Section 6.6, Special precautions for disposal and other handling (in the SmPC for the reconstitution pack only [containing Nplate powder and solvent])	Provision of a dosing calculator to physicians involved in the prescribing of romiplostim to adults and children > 1 year of age to simplify the calculation of the correct dose and guide to the correct reconstitution, dilution (if required) and administration procedures (including information on the 125, 250 and 500 µg presentations of romiplostim powder for solution for injection). Physicians who express an interest in initiating self-administration for specific adult subjects will receive a HAT pack for those subjects. The HAT pack will include the following materials for HCPs: • A guide for physicians on how to select and train subjects for self-administration

Safety concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
		of Nplate, titled "Selecting and training subjects for home administration of Nplate" • Checklist for Nplate self-administration: A list of items for physicians to complete in order to initiate self-administration for a given subject The HAT pack will include the following materials for subjects: • Quick guide booklet - a pictogram-style brochure to help subjects visualize major steps during the reconstitution process in a simplified manner and identify points of common mistakes based on the FMEA • Self-administration diary - a simple booklet to track a subject's prescribed dose(s) and product volumes; the HCP would calculate the dose and injection volume and write this down for the subject; the HCP would then demonstrate what this looks like when drawn up in to the syringe to give the subject a visual record of the amount of drug in

Safety concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
		the syringe, and the HCP could mark the correct volume on the syringe for the subject; the booklet also contains space for recording training dates, dates of drug administration, and any questions the subject might have for the HCP • Nplate preparation mat - a table placemat presenting the reconstitution process, including diagrams of kit components to aid identification; the table placemat will become the place, after sterilization with an alcohol swab, where the subject can lay out all of the kit components and verify that they have everything before starting the reconstitution and administration process • Step-by-step guide • Self-administration DVD to explain how to self-administer Nplate
Hypersensitivity reactions	Relevant text is provided in the following sections of the SmPC: • Section 4.3, Contraindications • Section 4.8, Undesirable effects	None

Safety concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Potential Risks		
Neutralizing antibodies that cross-react with eTPO	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects • Section 5.3, Preclinical safety data	None
Bone marrow fibrosis	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects • Section 5.3, Preclinical safety data	None
Concurrent Leukocytosis and anemia	Relevant text is provided in the following sections of the SmPC: • Section 4.4, Special warnings and precautions for use • Section 4.8, Undesirable effects • Section 5.3, Preclinical safety data	None
Renal impairment	None	None
Missing information		
Risks during pregnancy and lactation	Relevant text is provided in the following sections of the SmPC: • Section 4.6, Fertility, pregnancy and lactation • Section 5.3, Preclinical safety data	None
Use in paediatric patients (<1 year of age)	Relevant text is provided in the following sections of the SmPC: • Section 4.1, Therapeutic indications • Section 4.2, Posology and method of administration	None
Use in patients of different racial and/or ethnic	None	None

Safety concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
origins		
Use in patients with renal, hepatic, cardiac, or pulmonary impairment	Relevant text is provided in the following sections of the SmPC: • Section 4.2, Posology and method of administration • Section 5.2, Pharmacokinetic properties	None
Use in patients with bone marrow stem cell disorder and/or any active malignancy	None	None
Use in patients concurrently receiving rituximab or alkylating agents	Relevant text is provided in the following sections of the SmPC: • Section 4.5, Interaction with other medicinal products and other forms of interaction	None

2.8. Update of the Product information

As a consequence of this new indication, sections 1, 2, 4.1, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 6.3, 6.4, 6.5 and 6.6 of the SmPC have been updated. Particularly, a new warning with regards to the adequate reconstitution of Nplate has been added to the product information. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current QRD template which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Slovakia.

C.I.6.a - Extension of Indication to include paediatric population for Nplate: to register Nplate for the use in the paediatric chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients: 1 year of age and older.
As a consequence Product information has been updated accordingly. Furthermore, the PI is brought in line with the latest QRD template version 10. The RMP version 18 has also been submitted.

B.II.e.5.c – To add a low-dose romiplostim 125 microgram vial presentation for powder for solution for injection (4 vials pack).
B.II.e.5.a.1 – To add a 1 vial pack size of a low-dose romiplostim 125 microgram presentation.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

2.8.1. User consultation

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

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Nplate 500 mcg and 250mcg strengths. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Immune (idiopathic) thrombocytopenia (ITP) is an autoimmune disorder characterised by a low circulating platelet count (thrombocytopenia), decreased platelet production and increased platelet destruction. Thrombocytopenia places patients at risks for bruising, mucocutaneous bleeding and more seriously intracranial hemorrhage. Although its basic pathophysiology has been elucidated, no clinically apparent cause has been established for ITP.

In the US and EU, paediatric ITP (acute and chronic) occurs at an overall incidence rate of between 4.0 and 5.3 cases per 100,000 per year in otherwise healthy children < 15 years of age, with a peak incidence between ages 2 and 10 and affecting boys and girls equally. Prevalence of pediatric ITP is 7.2 cases per 100,000 per year. Unlike adult ITP in which the majority of cases are chronic in duration, pediatric ITP most commonly occurs in the acute form (platelet count < 150 x 10^9/L for < 6 months from diagnosis), accounting for 70 to 80% of ITP cases in children. Many children with acute ITP require no treatment and in approximately 60% to 75% of cases, the thrombocytopenia resolves within 2 to 4 months regardless of therapy. Twenty to 30% of paediatric ITP cases are considered chronic (platelet count < 150 x 10^9/L for > 6 months from diagnosis) and may become refractory to standard treatments. Chronic ITP in childhood has an estimated incidence of 0.46 per 100,000 children per year. Predictors for chronicity among children include older age (> 10 years) and an insidious presentation. In addition, chronic ITP in children is also associated with higher presenting platelet count (> 20 000/µL), lack of mucosal bleeding at presentation and lack of a previous acute illness.

The risk of intracranial hemorrhage is < 0.5% and increases with age; this risk is proportional to the severity (< 10 x 10^9/L) and duration of severe thrombocytopenia. One review of 332 medical records revealed that 17% of children had major haemorrhage defined as intracranial bleeding, epistaxis requiring cautery or nasal packing, gross haematuria, or other bleeding causing a decline in haemoglobin concentration. Approximately 75% of bleeding episodes in this review occurred in children with platelet counts < 10 x 10^9/L.

3.1.2. Available therapies and unmet medical need

The most commonly used therapeutic agents for pediatric ITP include corticosteroids, intravenous immunoglobulin and anti-D immunoglobulin. Repeated treatments may postpone the need for splenectomy, but the responses are generally transient, lasting a median time of 5 weeks. The principal aim of treating children with chronic ITP is to maintain a haemostatically safe platelet count (> 50 x 10^9/L) and thus improve quality of life of the patient, instead of trying to normalise platelet counts. While these therapies have been shown to result in increased platelet counts, the potential toxicity of these

agents compels physicians to weigh the likelihood of clinical efficacy against the likelihood of the occurrence of clinically relevant adverse events.

The American Society of Haematology (ASH) guidelines incorporate both clinical and platelet count data to arrive at specific treatment recommendations; for instance, children either with platelet counts < 20 x 10^9/L and significant mucous membrane bleeding or with platelet counts < 10 x 10^9/L and minor purpura should be treated with specific regimens of immunoglobulin (IVIg) or glucocorticoids. When ITP symptoms persist after primary treatment (glucocorticoid, IVIg) and splenectomy, further treatment is indicated in children with platelet counts < 30 x 10^9/L and who have active bleeding.

The BCSH guidelines (2003) recommend that splenectomy is rarely indicated in childhood, given that the risk of dying from ITP in childhood is extremely low (less than 1 in 500), and that the mortality associated with splenectomy is 1.4 to 2.7%. Moreover, splenectomy is not warranted in younger patients who are at relatively high risk for infection with encapsulated organisms.

The management of children with ITP who either fail to respond after splenectomy or relapse following splenectomy is often challenging. Rituximab has been used in children with severe chronic ITP who are refractory to standard agents, and treatment with 4 weekly doses of 375 mg/m2 resulted in response rates ranging from 31 to 68%. However, rituximab carries warnings with regards to infusion reactions, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy, and 5 to 10% of children with ITP may develop serum sickness. In addition, hepatitis B virus reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients with haematologic malignancies treated with rituximab.

3.1.3. Main clinical studies

3.2. Favourable effects

In the pivotal study, the primary objective of durable platelet response was statistically significant (p = 0.0018), a total of 52% (22 subjects) had a durable platelet response in the romiplostim arm compared to 10% (2 subjects) in the placebo arm. The Mantel-Haenszel common odds ratio for achieving durable platelet response was estimated to be 9.1 (romiplostim vs placebo, 95% CI: 1.9, 43.2). Consistent results were observed among the different cohorts of patient, resulting romiplostim vs placebo: ≥ 1 to<6 years 38% vs 25%; ≥ 6 to <12 years 56% vs 11%; ≥ 12 to <18 years 56% vs 0.

In the pivotal study, the efficacy was supported in the secondary and supportive endpoints of overall platelet response (p = 0.0002); 30 subjects (71%) in the romiplostim arm compared with 4 of 20 subjects (20%) in the placebo arm; as well as the number of weeks with platelet response (p = 0.0004); the median (minimum; maximum) 12 weeks (0; 24) in the romiplostim arm and 1 week (0; 22) in the placebo arm.

The efficacy in terms of platelet counts increments has been demonstrated at short and long term. In long-term safety Study 20090340, paediatric subjects (n = 65) receiving romiplostim for100.0 weeks (median exposure time; range 5 to 321 weeks) maintained platelet responses in the absence of rescue medication in 93.8% of subjects. Across all subjects, the median number of months with platelet response was 20.0 months (range: 0 to 80 months) and the median time on study was 25.0 months (range: 2 to 80 months). The median percentage of months with a platelet response was 95,4% (range 0-100). In the integrated analysis, the subject incidence of platelet response showed a trend toward increasing over time (25.7% at month 1 to >70% from month 7 through month 111).

The integrated analysis over 5 studies revealed a total of 188 of 224 subjects (83.9%; 95% CI: 78.5%, 88.5%) had platelet response, There was no comparator arm. A total of 129 of 224 subjects (57.6%;

95% CI: 50.8%, 64.1%) had sustained platelet response, The Kaplan-Meier estimate of the time to first sustained platelet response (50th percentile), was 20.0 weeks (95% CI: 15.0, 26.0). For the integrated analyses, the Kaplan-Meier estimate of the time to first response (50st percentile) was similar across age groups.

3.3. Uncertainties and limitations about favourable effects

The starting doses and the dose adjustment proposed are based on body weight. When the calculated volume is less than 0.05 mL, dilution 1:2 or dilution 1:4 are proposed to ensure an appropriate dispensable dose, a situation foreseen for subjects < 50Kg body weight. This is a matter of concern due to the added complexity in the preparation of the medication and thus, the risk for contamination and for medication errors. Hence, the educational materials were updated. In addition, the MAH is recommended to develop a reconstitution and dilution kit for the preparation and administration of paediatric doses by a qualified health care professional.

In the pivotal study the results of platelet response by baseline age group are in favour of romiplostim, however in the group of ≥1-<6 years the data are less prominent being the rate of responders 37.5% of the patients in romiplostim arm. Further, the high use of rescue medication in this group, substantially higher in romiplostin vs. placebo, questions the consistency of efficacy results in this group. However, the very low number of patients in the lowest age category precludes drawing firm conclusions on the actual efficacy and/or safety results in this population. At the same time, this subset of patient might represent a more severe form of the disease, which further complicates reaching conclusions. Nevertheless, data indicated that some of these patients can benefit from treatment with romiplostin in a setting where options available are limited. Thus, no additional age restrictions are deemed appropriate and relevant information for the different age categories are reflected in the SmPC.

Final results of study 20101221 are pending as data on only a limited number of subjects are present after>3 years of treatment (year 3 n=44 towards year 9, n=5). As such the long-term efficacy in children has not been clearly demonstrated. Loss of efficacy is possible for example due to antibody formation or the development of bone marrow fibrosis. Additional data from Study 20090340 and study 20101221 resulted in an update with a longer mean duration of treatment 65.5 weeks compared with 84.7 weeks. In study 20101221 all subjects had treatment duration of <144 weeks at the data-cut. Although the update of efficacy and safety data was minimal with a small increase in patients with exposure >144 weeks, no apparent differences in efficacy analysis are observed with a longer treatment duration and the results are in line with that previously observed. Final results on study 20101221 are expected as reflected in the RMP.

3.4. Unfavourable effects

The most frequent AEs in subjects in the Paediatric ITP Safety Set were headache (40.2% romiplostim; 54.2% placebo), epistaxis (34.8% romiplostim; 45.8% placebo), contusion (26.8% romiplostim; 33.3% placebo), and cough (26.3% romiplostim; 12.5% placebo).

Most subjects (88.8% romiplostim, 100% placebo) reported 1 or more TEAE, most of which were mild (grade 1) or moderate (grade 2) in severity. More subjects receiving romiplostim (18.3%) compared with placebo (4.2%) had serious adverse events. In general, there were no major differences in the frequency of subject incidences of the different AEs between the romiplostim and placebo groups.

The most common adverse reactions in paediatric ITP patients 1 year and older were upper respiratory tract infection, rhinitis, cough, oropharyngeal pain, upper abdominal pain, diarrhoea, rash, pyrexia, contusion (reported very commonly (≥ 1/10)), and pharyngitis, conjunctivitis, ear infection,

gastroenteritis, sinusitis, purpura, urticaria and peripheral swelling (reported commonly (≥ 1/100 to < 1/10)).

Oropharyngeal pain, upper abdominal pain, rhinitis, pharyngitis, conjunctivitis, ear infection, sinusitis and peripheral swelling were additional adverse reactions observed in paediatric studies compared to those seen in adult studies.

Some of the adverse reactions seen in adults were reported more frequently in paediatric subjects such as cough, diarrhoea, rash, pyrexia and contusion reported very commonly (≥ 1/10) in paediatric subjects and purpura and urticaria were reported commonly (≥ 1/100 to < 1/10) in paediatric subjects.

In an ongoing paediatric clinical trial, of the subjects with an evaluable on-study bone marrow biopsy, 5 out of 27 subjects (18.5%) developed increased reticulin in cohort 1 and 2 out of 4 subjects (50.0%) developed increased reticulin in cohort 2. However, no subject showed any bone marrow abnormalities that were inconsistent with an underlying diagnosis of ITP at baseline or on-treatment. So far it is not known if the increases of bone marrow reticulin may have clinical consequences or if the incidence of the more severe collagen fibrosis may increase with durations of exposure >1 year. Data on reversibility of abnormal bone marrow findings are considered essential. Therefore, protocol 20101221 was amended to obtain post treatment bone marrow biopsies to evaluate reversibility of findings of increases of reticulin or collagen formation. The MAH has confirmed that the results of Study 20101221 will be submitted in line with the RMP.

3.5. Uncertainties and limitations about unfavourable effects

Safety and data in terms of years of exposure of more than 1.5 to 2 years are still quite limited. Addition of final data from Study 20090340 and study 20101221 resulted in an update with a longer mean duration of treatment 65.5 weeks compared with 84.7 weeks. Although the update of efficacy and safety data was minimal with a small increase in patients with exposure >144 weeks (40/282 subjects (13.8%) compared to the previous data-cut in which approximately 11% had such an exposure), no apparent differences in safety analysis are observed with a longer treatment duration and the results are in line with that previously observed. Final results on study 20101221 are expected in line with the RMP.

In the clinical trials apart from was one case of phlebitis, there were no reports of thrombotic / thromboembolic Events. However, there were reports of 7 serious events post-marketing which are of concern and highlight the thrombotic potential of TPO agonists and the necessity of continuing vigilance. Study 20101221 will provide more data on this issue and the MAH will submit the final results.

In paediatric studies, the incidence of binding antibodies to romiplostim at any time was 7.8% (22/282). Of the 22 subjects, 2 subjects had pre-existing binding non-neutralising romiplostim antibodies at baseline. Additionally, 2.5% (7/282) developed neutralising antibodies to romiplostim. A total of 3.2% (9/282) subjects had binding antibodies to TPO at any time during romiplostim treatment, of which 2 subjects had pre-existing antibodies to TPO. All subjects were negative for neutralising activity to TPO. In the post-marketing registry study, 19 confirmed paediatric patients were included. The incidence of binding antibody post treatment was 16% (3/19) to romiplostim, of which 5.3% (1/19) were positive for neutralising antibodies to romiplostim. There were no antibodies detected to TPO. 184 confirmed adult patients were included in this study; for these patients, the incidence of binding antibody post treatment was 3.8% (7/184) to romiplostim, of which 0.5% (1/184) was positive for neutralising antibodies to romiplostim. A total of 2.2% (4/184) adult patients developed binding, non-neutralising antibody against TPO. An association between the presence of antibodies and bleeding events cannot be excluded.

More paediatric data will be available from Study 20101221 in order to further assess this risk.

3.6. Effects Table

Table 30. Effects Table for Nplate in the treatment of ITP in the paediatric population:

Effect	Short Description	Unit	Romiplostim	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Sustained platelet response	proportion of patients with at least 6 weekly platelet count of >50x10^9/L during weeks 18 through 25 of treatment	%	52%	10%	ORR (romiplostim/placebo) 9.1 (1.9,43.2) Consistent results among the three cohorts of patients Uncertainties on the maintenance of the effect over time	20080279 study
Number of weeks with platelet response		Median (minimum, maximum)	12(0,24)	1(0,22)	Analysis of the variance (ANOVA), p=0.0004	20080279 study
Composite bleeding episodes	Incidence of any bleeding events grade ≥ 2	Mean(SD)	1.9(4.2)	4.0(6.9)	No statistical test was done	20080279 study (1)
Rescue medication use		%	41	45	ORR 0.8(0.3,2.4)	
Unfavourable Effects						
SAE	Serious adverse events	%	23.8	5.3		Paediatric randomized ITP safety set (2)
		%	18.3	4.2		Paediatric ITP safety population (3)
Treatment related AE		%	25.0	23.7		Paediatric randomized ITP safety set
		%	24.6	25.0		Paediatric ITP safety population

Effect	Short Description	Unit	Romiplostim	Placebo	Uncertainties/ Strength of evidence	References
Inmunogenicity	Binding antibody for romiplostim TPO antibody	N (%)	11/207 (5.3) 8/207(3.9)	0 1/24(4.2 %)	4 subjects de novo and persistent	Paediatric ITP safety population
	Neutralising antibodies	N (%)	1(0.5%)	0	De novo and persistent	Paediatric ITP safety population
Bone marrow biopsy	Increased reticulin (no subjects Bauermeister score >1)	N (%)	4/22(19.0)	No studied	Two patients reticuline =1 at baseline	20101221 study (4)
Haemorrhages (SMQ)	Period 1 to ≤12 weeks Period 23 to ≤ 24 weeks	Event per 100 subjets-years	1407.6 1466.1	1406.2 869.6		Paediatric randomized ITP safety set
Haemorrhages (SMQ)			46/59(78.0)	15/24(62.5)		Paediatric randomized ITP safety set
			143/224 (63.8)	15/24(62.5)		Paediatric ITP safety population
Thrombocytosis			1(0.4%)	0		Paediatric ITP safety population

Notes:

(1) Phase 3, multicenter, randomized, double-blind, placebo controlled study

(2). Paediatric randomized safety set, all pediatric subjects who were randomized in a randomzed ITP study (20060195 and 20080279)

(3). Paediatric ITP safety population; comprises all pediatric subjects in studies 20060195, 20080279, 20030213, 20090340 and 20101221 who received at least one dose of romiplostim

(4) A single-arm, open-label, long-term efficacy and safety.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A statistically significant difference in the proportion of patients who reach a sustained platelet response was seen in patients treated with romiplostim compared to those on placebo. The efficacy of romiplostim to elevate platelet counts has been clearly demonstrated and is in line with that previously reported in chronic adult ITP patients, moreover consistent results are observed among the age groups.

The observed results are considered clinically relevant, particularly in the context of patients not responding to current first line standard of care.

Prevention of bleeding is ultimately the clinical benefit of interest for ITP patients, a decline in bleeding events and rescue medication use was observed with longer time on study.
The benefit in terms of prevention of bleeding events and use of rescue medication are more apparent in the long-term. Data of longer term follow up (beyond 144 weeks) are still limited. However, long term efficacy and safety study of romiplostim in thrombocytopenic pediatric subjects with immune thrombocytopenia (ITP) will be provided with the submission of the results of study 20101221.

Overall, the types of AEs commonly reported in the paediatric population are within the distribution of types of AE seen in the adult population as mentioned in the Nplate SmPC and do not represent new safety concerns. Apart from bleeding type AEs and decreased platelet count, most are compatible with what might be expected to be reported as AEs in this young population. Although long term follow up was limited, the durations of treatment reached so far do imply that treatment with romiplostim, including the weekly injections, was well tolerated. There were minimal discontinuations due to adverse events and the relationship between the AEs concerned and treatment with romiplostim is unclear. However, there was not a pattern of AEs leading to discontinuation of treatment or to study discontinuation.

3.7.2. Balance of benefits and risks

Overall, the data presented are indicative of an increase in platelet counts in the subjects treated with romiplostim compared to placebo. The observed efficacy was generally consistent among the age cohorts and supported by secondary endpoints. The data obtained is in line with the efficacy in adults, platelet counts are increased significantly in a majority of patients.

Nplate is considered well tolerated and the risks are well known and manageable.

Overall, the efficacy in increasing the platelet count in patients with ITP failing to prior treatment options is considered to balance favourably against the adverse events.

3.7.3. Discussion on the Benefit-Risk balance

The clinical development of romiplostim follows an agreed PIP and results of these studies support the efficacy of romiplostin to increase platelet counts both temporarily and in the long term. Supportive benefits have been observed in the risk of bleeding events and use of rescue medication, which are both reduced in the long-term treatment.

Treatment with romiplostim also carries risks and there are limited data on long term treatment for longer than 1.5 to 2 years. With the available data there have been only a few cases of bone marrow reticulin fibrosis (2 mild cases seen after one year of treatment in the paediatric clinical trial (Study 20101221 designed to monitor fibrosis) apparently not clinically significant. However, data are still limited and results of Study 20101221 which will examine bone marrow in 2 cohorts of paediatric patients after one year and after 2 years of treatment with romiplostim are awaited. The current advice in the SmPC

concerning increased bone marrow reticulin is to perform regular examinations for cellular morphological abnormalities using peripheral blood smear and complete blood count (CBC) prior to and during treatment with romiplostim. Further, if a loss of efficacy and abnormal peripheral blood smear is observed in patients, administration of romiplostim should be discontinued, a physical examination should be performed, and a bone marrow biopsy with appropriate staining for reticulin should be considered. If available, comparison to a prior bone marrow biopsy should be made. If efficacy is maintained and abnormal peripheral blood smear is observed in patients, the physician should follow appropriate clinical judgment, including consideration of a bone marrow biopsy, and the risk-benefit of romiplostim and alternative ITP treatment options should be re-assessed.

These recommendations will not detect early bone marrow (reticulin) fibrosis, however, the magnitude and seriousness of this risk is not yet known. The full results of the bone marrow examinations after one year and after 2 year exposures to romiplostim can be awaited before considering if more pro-active assessments for bone marrow fibrosis are considered necessary. In this regard, the MAH has confirmed that provisions to generate information on reversibility of any detected bone marrow (reticulin) fibrosis after stopping treatment have been included and results of study 20101221 will be submitted

This is a matter of concern due to the added complexity in the preparation of the medication and thus, the risk for contamination and for medication errors. Hence, the educational materials were updated and self-administration of Nplate is not allowed for the paediatric population. In addition, the MAH is recommended to develop a reconstitution and dilution kit for the preparation and administration of paediatric doses by a qualified health care professional.

3.7.4. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Nplate is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends by a majority, the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
B.II.e.5.c	B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products	Type II	I, IIIA and IIIB
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, IIIA and IIIB
B.II.e.5.a.1	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules,	Type IAin	I, IIIA and IIIB

	etc.) in a pack - Change within the range of the currently approved pack sizes		

Extension of Indication to include paediatric population for Nplate: to register Nplate for the use in the paediatric chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients: 1 year of age and older.

As a consequence sections 2, 4.2, 4.4, 4.8, 4.9, 5.1, 5.2, 6.3, 6.5, 6.6 and 8 of the SmPC have been updated accordingly. The Package Leaflet and Labelling are updated in accordance.
Furthermore, the PI is brought in line with the latest QRD template version 10.
The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

The MAH shall agree the details of the following educational tools with the National Competent Authorities and must implement such programme nationally.

Dose calculator

- Physicians involved in the prescribing of romiplostim are provided with a dosing calculator to simplify the calculation of the correct dose and as a guide to the correct reconstitution, dilution (if required) and administration procedures.

Home Administration Training (HAT) pack

- Physicians who express an interest in initiating self-administration for specific patients are provided with a HAT pack for those patients. The HAT pack includes materials for HCPs on how to select and train patients for self-administration of romiplostim; and for patients, in order to help them with the process of preparation and self-administration of the correct dose of romiplostim.
- As self-administration of Nplate is not allowed for paediatric patients, the HAT pack is intended for use with adult patients and not with paediatric patients.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0114/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.