30 April 2020
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Nplate

romiplostim

Procedure no: EMEA/H/C/000942/P46/034

Note

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

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Table of Contents

1. Introduction

On 7th February 2020, the MAH submitted a completed paediatric (study 20101221) for romiplostim (Nplate), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of an agreed paediatric investigation plan (EMEA-000653-PIP01-09-M05) for Nplate, approved by the EMA on 11th August 2017 (Decision P/0233/2017).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Romiplostim (Nplate) is currently approved by the European Commission (EC) for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients one year of age and older who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) as powder for solution for injection to be administered subcutaneously once a week.

On 4th February 2009, Nplate was firstly approved by the EC for the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura (ITP).

On 9th November 2017, the CHMP issued a positive opinion on an extension of indication application for Nplate (Procedure No. EMEA/H/C/000942/II/0060/G) to include paediatric chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients: 1 year of age and older. At the time (5 December 2016) of the submission of this variation application, the MAH submitted 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).

The MAH stated that study 20101221 – "A Single Arm, Open-label, Long-term Efficacy and Safety Study of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune Thrombocytopenia (ITP)" is a stand alone study, and is also part of a clinical development program.

The hereby submitted study 20101221 is also part of an EU Paediatric Investigation Plan (PIP) for romiplostim (Nplate) targeted to grant indications for the treatment of chronic immune thrombocytopenia (idiopathic thrombocytopenic purpura; ITP) in paediatric patients who are refractory or intolerant to other treatments (e.g., glucocorticosteroids, immunoglobulins, splenectomy) (EMA Decision number P/0233/2017; PIP number EMEA-000653-PIP01-09-M05). The following table summarizes all clinical studies included in the PIP number EMEA-000653-PIP01-09-M05:

Number and study title	PIP Commitment	Date of Completion*	Submission of Final Study Report
20080279: A Phase 3 Randomized, Double Blind, Placebo Controlled Study to Determine the Safety and Efficacy of Romiplostim in Thrombocytopenic Pediatric Subjects with Immune Thrombocytopenia (ITP)	Study 2	19 February 2015	The final study report was submitted to the EMA under Article 46 (Procedure No. EMEA/H/C/000942/P46/033 submitted on 19th August 2015).
20090340: An Open-label Study Evaluating the Safety and Efficacy of Longterm Dosing of Romiplostim in	Study 3	12 January 2017	Study report submitted as part of procedure EMEA/H/C/942/II/0060/G.

Thrombocytopenic Pediatric Subjects With Immune (Idiopathic) Thrombocytopenia Purpura (ITP)			
20101221: A Single Arm, Open-label, Long-term Efficacy and Safety Study of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune Thrombocytopenia (ITP)	Study 4	15 August 2019	Included in this submission (Procedure No. EMA/H/C/000942/P46/034)

* *Data obtained from: https://www.clinicaltrialsregister.eu*

The outcome date of the compliance report (EMEA-C-000653-PIP01-09-M05) on the agreed PIP was 27th March 2020.

Assessor's comments:

Romiplostim (Nplate) is currently approved by the European Commission (EC) for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients one year of age and older who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) as powder for solution for injection to be administered subcutaneously once a week.

On 4th February 2009, Nplate was firstly approved by the EC for the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura (ITP). At the time (5 December 2016) of the submission of the variation application EMEA/H/C/000942/II/0060/G to grant the extension of indication to include paediatric population (1 year of age and older) for Nplate, the MAH submitted 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).

Studies 20080279, 20090340 and 20101221 are measures of the agreed European Paediatric Investigation Plan (PIP) for Nplate (P/0233/2017; EMEA-000653-PIP01-09-M05). Please, take into account that the outcome date of the compliance report (EMEA-C-000653-PIP01-09-M05) on the agreed PIP was 27th March 2020.

Study 20101221 agrees with Article 46 of Regulation (EC) No1901/2006, as amended, as regards of its submission to the competent authority within six months of completion. Study 20090340 has been submitted to the EMA in procedure EMEA/H/C/942/II/0060/G.

Furthermore, the MAH has not provided information regarding the need for submitting a variation application consisting of the full relevant data package (i.e. containing studies not yet completed at the time of granting the paediatric indication). In order to increase the availability of information on the use of romiplostim in the paediatric ITP population (approx. prevalence of 7.2 cases per 100,000 per year), and considering that the already completed studies 20090340 and 20101221 are also part of an agreed PIP for Nplate, the MAH is requested to apply for a variation to update the summary of product characteristics by reflecting the main results of these studies as soon as possible (please, see Rapporteur's overall conclusion and recommendation).

2.2. Information on the pharmaceutical formulation used in the study

Romiplostim (Nplate) is currently authorised in the European Union to be used in patients one year of age and older as 125 micrograms, 250 micrograms and 500 micrograms powder for solution for injection.

Study 20101221 was performed by administering romiplostim subcutaneously once per week as the authorized formulation developed for use in paediatric population (please, see Assessment Report for Procedure No. EMEA/H/C/000942/II/0060/G).

Nplate 125 micrograms powder for solution for injection is supplied for single use in a 3 mL glass vial containing 230 micrograms of romiplostim, providing 125 micrograms of deliverable romiplostim.

The qualitative and quantitative composition for Nplate 125 micrograms vial is presented in Table 1 below.

Table 1. Composition of Nplate 125 micrograms vial

Component	Quality Standard	Function
Romiplostim	In-housea	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 micrograms presentation is the same as that used for Nplate 250 micrograms and 500 micrograms.

2.3. Clinical aspects

2.3.1. Introduction

Romiplostim (Nplate) is an Fc-peptide fusion protein (peptibody) that signals and activates intracellular transcriptional pathways via the TPO receptor (also known as cMpl) to increase platelet production.

Nplate 125 µg powder for solution for injection is currently approved by the European Commission for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients one year of age and older who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) as powder for solution for injection to be administered subcutaneously once a week.

Nplate 250 µg and 500 µg powder for solution for injection are indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). The initial dose of romiplostim is 1 microgram/kg based on actual body weight.

In children and adults, the initial dose of romiplostim is 1 microgram/kg based on actual body weight. In children, the volume of romiplostim to administer is calculated based on body weight, dose required, and concentration of product. The once weekly dose of romiplostim should be increased by increments of 1 microgram/kg until the patient achieves a platelet count ≥50 x 10^9/L. Platelet counts should be assessed weekly until a stable platelet count (≥50 x 10^9/L for at least 4 weeks without dose

adjustment) has been achieved. Platelet counts should be assessed monthly thereafter. A maximum once weekly dose of 10 micrograms/kg should not be exceeded.

The MAH submitted a final report for:

- Study 20101221: A Single Arm, Open-label, Long-term Efficacy and Safety Study of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune Thrombocytopenia (ITP).

2.3.2. Clinical study

Clinical study 20101221 - "A Single Arm, Open-label, Long-term Efficacy and Safety Study of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune Thrombocytopenia (ITP)"

Description

Study 20101221 was a phase 3b, single-arm, open-label, multicentre study to describe the percentage of time paediatric subjects with ITP had a platelet response while receiving romiplostim. A platelet response was defined as having a platelet count of ≥50 x 10^9L in the absence of ITP rescue medications in the past 4 weeks. This study also includes a protocol supplement to implement bone marrow evaluations. Romiplostim was administered to thrombocytopenic paediatric subjects with ITP diagnosed for at least 6 months and who received at least 1 prior ITP therapy (excluding romiplostim) or were ineligible for other ITP therapies.

Methods

Objectives

Primary

- To describe the percentage of time that paediatric subjects with ITP have a platelet response in the first 6 months from the start of treatment with romiplostim.
- To evaluate the incidence of changes in bone marrow findings at year 1 or year 2 after initial exposure to romiplostim.

Secondary

- To describe the percentage of time that paediatric subjects with ITP have a platelet response over the study duration.
- To describe the percentage of time that paediatric subjects with ITP have an increase in platelet count ≥ 20 x 10^9/L above baseline over study duration.
- To describe the use of rescue ITP medications.
- To describe the incidence of antibody formation.
- To describe the safety of romiplostim as a long-term treatment in paediatric thrombocytopenic subjects with ITP.
- To evaluate the incidence of increased reticulin as evidenced by silver staining at year 1 or year 2, after initial exposure to romiplostim.

Exploratory

- To describe the incidence of sustained platelet response.
- To describe the incidence of splenectomy.

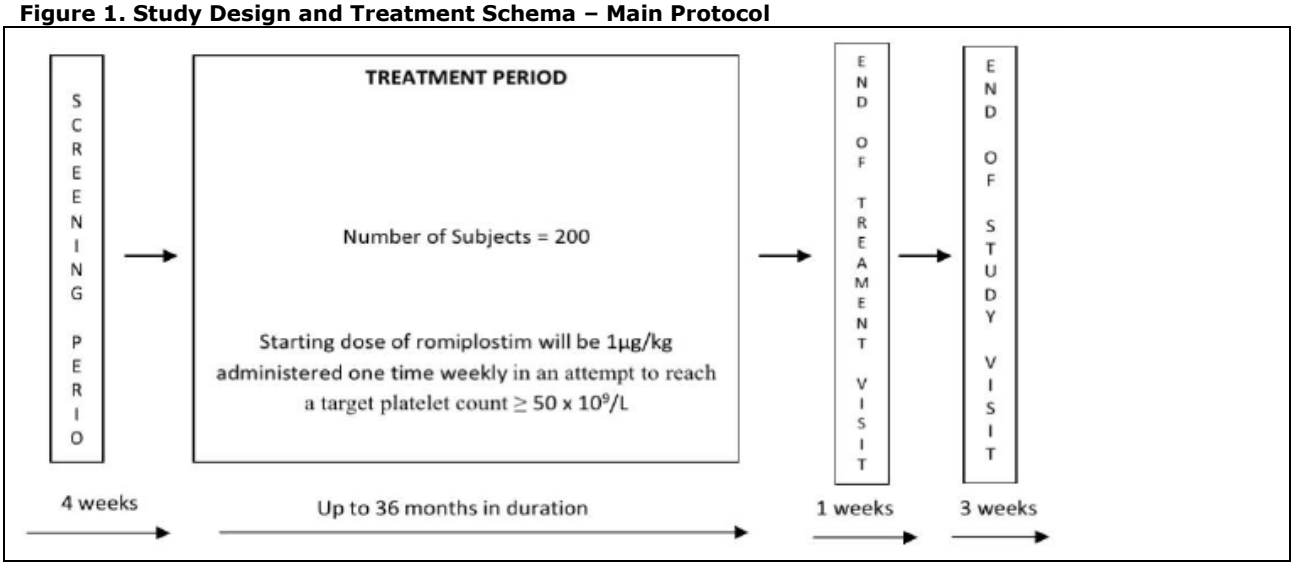
- To describe the subject incidence of romiplostim self-administration.

Study design

This phase 3b, single-arm, open-label, multicentre study was designed to evaluate the percentage of time paediatric subjects with ITP had a response, defined as a platelet count of ≥50 x 10^9/L in the absence of ITP rescue medications in the past 4 weeks, while receiving romiplostim. This study also includes a protocol supplement to implement bone marrow evaluations. Romiplostim was administered to thrombocytopenic paediatric subjects with ITP diagnosed for at least 6 months and who received at least 1 prior ITP therapy (excluding romiplostim) or were ineligible for other ITP therapies.

The study consisted of a 4-week screening period, up to 3-year treatment period, an end-of-treatment (EOT) visit, and an end-of-study (EOS) visit (see Figure 1).

Figure 1. Study Design and Treatment Schema – Main Protocol



Romiplostim was administered weekly by subcutaneous (SC) injection. Dose adjustment rules were based on individual platelet counts. The maximum permitted dose of romiplostim was 10 micrograms/kg.

Subjects who reduced their romiplostim dose, no longer required ITP medications (concomitant or rescue), or had an onset of a sustained platelet response (defined as consecutive platelet counts of ≥50 x 10^9/L) were monitored for at least 6 months beginning with the first platelet count of ≥50 x 10^9/L.

Subjects whose platelet count remained ≥50 x 10^9/L in the absence of any medications for ITP for at least 6 months were followed every 12 weeks for the duration of the 36-month treatment period. If during the 36-month treatment period a subject's platelet count subsequently fell below 50 x 10^9/L, treatment with romiplostim at the initial starting dose could be resumed per the protocol.

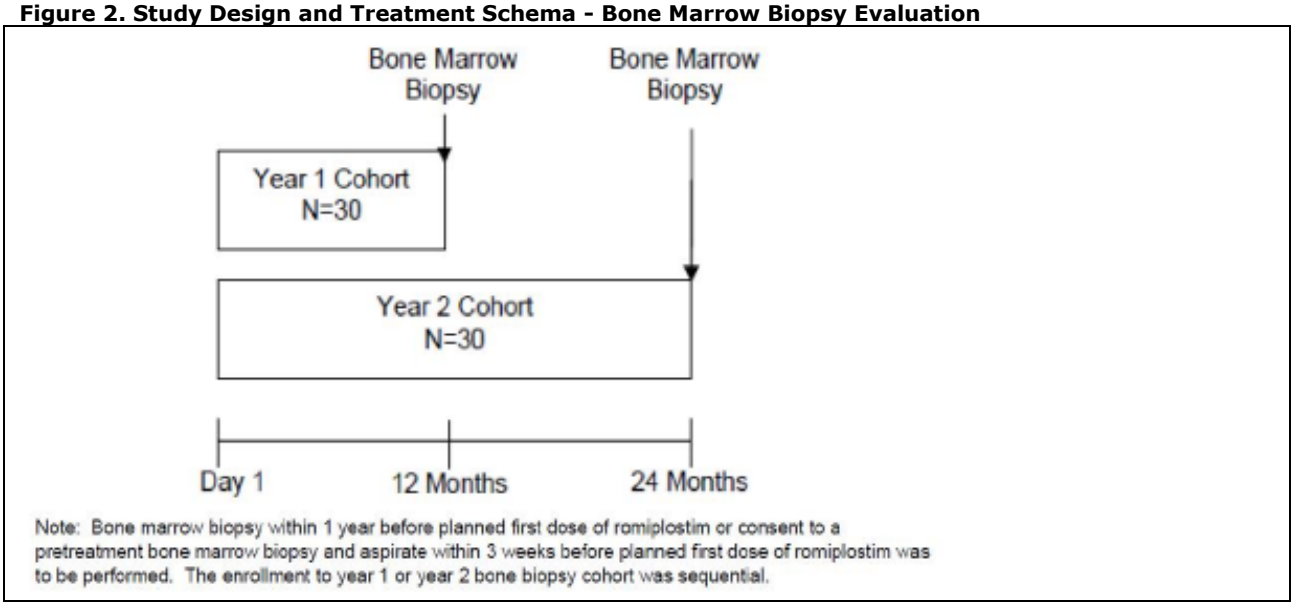
Subjects who had a platelet count of ≤20 x 10^9/L for 4 consecutive weeks at the maximum romiplostim dose of 10 micrograms/kg discontinued romiplostim and were considered non-responders.

A subset of at least 60 subjects was enrolled sequentially into the following cohorts of protocol supplement for the EU, Switzerland, and Turkey:

- bone marrow biopsy and aspirate at baseline and year 1
- bone marrow biopsy and aspirate at baseline and year 2

Once the first cohort completed enrolment, the second cohort began enrolling. All subjects in the 2 cohorts were to receive romiplostim for 3 years, unless withdrawn from the study early. Subjects completed an EOT visit at the conclusion of their treatment period and returned for an EOS visit (see Figure 2).

Figure 2. Study Design and Treatment Schema - Bone Marrow Biopsy Evaluation



Note: Bone marrow biopsy within 1 year before planned first dose of romiplostim or consent to a pretreatment bone marrow biopsy and aspirate within 3 weeks before planned first dose of romiplostim was to be performed. The enrollment to year 1 or year 2 bone biopsy cohort was sequential.

A baseline bone marrow biopsy and aspirate were required to determine eligibility; this could either have been a bone marrow biopsy within 1 year before planned first dose of romiplostim (with available bone marrow tissue block or a minimum of 5 unstained, evaluable histological slides to send to a central laboratory) or a pre-treatment bone marrow biopsy and aspirate within 3 weeks before planned first dose of romiplostim. A further bone marrow biopsy and aspirate was required at year 1 (day 365) or year 2 (day 720) (+ 4-week window), depending on cohort in which the subject was enrolled. The study schemas are provided in Figure 1 and Figure 2 above.

Study population /Sample size

Diagnosis and Main Criteria for Eligibility

Eligible paediatric subjects diagnosed with ITP for at least 6 months according to the American Society of Haematology guidelines who had thrombocytopenia (defined as a platelet count of ≤30 x 10^9/L) or bleeding that was uncontrolled with conventional therapy within 4 weeks of enrolment.

Subjects had to meet the following additional inclusion criteria to be included into the bone marrow biopsy analysis:

- Subject must have agreed to a scheduled bone marrow biopsy and aspirate at year 1 or year 2 after romiplostim treatment and any unscheduled biopsies if clinically indicated.
- Subjects must have had a reticulin grade of 0, 1, 2, or 3 according to the modified Bauermeister grading scale, as assessed by central laboratory from a bone marrow biopsy performed within 1 year before planned first dose of romiplostim or consent to a pre-treatment bone marrow biopsy and aspirate before planned first dose of romiplostim.

Number of Subjects Planned

Study 20101221 was planned to include approximately 200 subjects. Of these, at least 30 subjects were to be enrolled into each of the 2 cohorts identified by bone marrow biopsy time points (year 1 or year 2).

Treatments

Dosage, treatment regimen, route of administration

This was a single-arm, open-label study, where romiplostim was administered weekly by subcutaneous (SC) injection at the starting dose of 1.0 micrograms/kg. Dose adjustment rules were based on individual platelet counts.

Intra-individual, weekly dose adjustment by 1 microgram/kg:

- platelets <50 x 10^9/L: increase;
- platelets 50 to 200 x 10^9/L: no change;
- platelets 200 to <400 x10^9/L for two consecutive weeks: reduce;
- platelets >/=400 x 10^9/L: withhold and reduce on next dosing when platelets <200 x 10^9/L.

The maximum permitted dose of romiplostim was 10 micrograms/kg.

Duration of Treatment
The maximum study duration (for a subject completing the study) was approximately 3 years and 2 months: a 4-week screening period, up to 36-month treatment period, an EOT visit, and an EOS visit.

Outcomes/endpoints

<u>Primary</u>

- 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.
- Evaluation of bone marrow changes after year 1 and year 2 for the following:
    - incidence of collagen as evidenced by trichrome staining (using the modified Bauermeister grading scale) after romiplostim exposure,
    - incidence of bone marrow reticulin increases in severity ≥2 grades (ie, grade 0 to 2-4, 1 to 3-4, 2 to 4), compared to baseline, or an increase to grade 3 or grade 4 as evidenced by reticulin silver staining using the modified Bauermeister grading scale after romiplostim exposure,
    - incidence of bone marrow abnormalities (eg, myelodysplastic syndrome, monosomy 7) as evidenced by cytogenetics and fluorescence in situ hybridization (FISH),

<u>Secondary</u>

- The percentage of time with a platelet count of ≥50 x 10^9/L starting from week 2 until the end of the treatment period without rescue medication use within the past 4 weeks.
- 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 subject incidence of rescue ITP medications used.
- The incidence of antiromiplostim neutralizing antibodies and cross-reactive antibodies to TPO at any time during the study.
- The incidence of adverse events, including clinically significant changes in laboratory values.

- The incidence of increased reticulin as evidenced by silver staining at year 1 or year 2, after exposure to romiplostim.

Exploratory

- The subject incidence with a sustained platelet count of ≥50 x 10^9/L for 6 months or greater without the use of any ITP medications (concomitant, rescue, or romiplostim).
- The incidence of splenectomy during the treatment period for subjects entering the study pre-splenectomy.
- The subject incidence of romiplostim self-administration. It was eligible any subject that received its first 8 doses at the clinic and achieved a platelet count of ≥50 x 10^9/L without romiplostim dose adjustments for 4 consecutive weeks.

Statistical Methods

No formal hypothesis was tested. Summary statistics was provided for the primary and secondary endpoints. Categorical data were presented in the form of number and percentage. Continuous data were provided with the descriptive statistics (n, mean, SD, median, Q1 [25th percentile], Q3 [75th percentile], minimum, and maximum).

The analysis of efficacy and safety endpoints was based on the set of subjects receiving at least 1 dose of romiplostim.

Results

Recruitment/ Number analysed

At the time of this final analysis (database snapshot date 23 October 2019), all 203 subjects (100%) enrolled in the study across 3 age groups received at least 1 dose of romiplostim and were included in the Full Analysis Set (see Table 1). Of these, 108 subjects (53.2%) completed romiplostim and 95 subjects (46.8%) discontinued romiplostim. The most frequently reported reason for discontinuation was lack of efficacy (43 subjects [21.2%]).

A total of 109 subjects (53.7%) completed the study; 94 subjects (46.3%) discontinued the study (see Table 1). The most frequently reported reason for discontinuation was protocol-specified criteria (67 subjects [33.0%]).

Table 1. Subject Disposition With Discontinuation Reason by Age Groups (Full Analysis Set)

	Baseline Age (Years)			
	≥ 1 to < 6 (N = 49) n (%)	≥ 6 to < 12 (N = 81) n (%)	≥ 12 to < 18 (N = 73) n (%)	Overall (N = 203) n (%)
Investigational product accounting				
Subjects who never received investigational product	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects who received investigational product	49 (100.0)	81 (100.0)	73 (100.0)	203 (100.0)
Subjects who completed investigational product	25 (51.0)	44 (54.3)	39 (53.4)	108 (53.2)
Subjects who discontinued investigational product	24 (49.0)	37 (45.7)	34 (46.6)	95 (46.8)
Noncompliance	2 (4.1)	0 (0.0)	4 (5.5)	6 (3.0)
Adverse event	0 (0.0)	2 (2.5)	7 (9.6)	9 (4.4)
Requirement for alternative therapy	0 (0.0)	5 (6.2)	0 (0.0)	5 (2.5)
Lost to follow-up	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.5)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol-specified criteria	0 (0.0)	1 (1.2)	1 (1.4)	2 (1.0)
Splenectomy	0 (0.0)	1 (1.2)	1 (1.4)	2 (1.0)
Development of neutralizing antibodies	4 (8.2)	1 (1.2)	2 (2.7)	7 (3.4)
Lack of efficacy	14 (28.6)	20 (24.7)	9 (12.3)	43 (21.2)
Subject request	3 (6.1)	3 (3.7)	9 (12.3)	15 (7.4)
Other	1 (2.0)	4 (4.9)	2 (2.7)	7 (3.4)
Study completion accounting				
Subjects who completed study	25 (51.0)	45 (55.6)	39 (53.4)	109 (53.7)
Subjects who discontinued study	24 (49.0)	36 (44.4)	34 (46.6)	94 (46.3)
Protocol-specified criteria	17 (34.7)	29 (35.8)	21 (28.8)	67 (33.0)
Withdrawal of consent from the study	5 (10.2)	6 (7.4)	9 (12.3)	20 (9.9)
Decision by sponsor	1 (2.0)	0 (0.0)	3 (4.1)	4 (2.0)
Lost to follow-up	1 (2.0)	1 (1.2)	1 (1.4)	3 (1.5)

N = number of subjects enrolled.
Full Analysis Set includes all enrolled subjects.

A total of 79 subjects were enrolled into the protocol supplement for the EU, Switzerland, and Turkey (see Table 2). Of these, 30 subjects were in cohort 1 (bone marrow samples taken at baseline and year 1) and 49 subjects were in cohort 2 (bone marrow samples taken at baseline and year 2).

Table 2. Subjects With Bone Marrow Biopsy Data (Full Analysis Set - Subjects Recruited Under the EU, Switzerland, and Turkey Supplement)

	Romiplostim		
	Cohort 1 (N = 30)	Cohort 2 (N = 49)	Cohorts 1 and 2 (N = 79)
Subjects with baseline[a] bone marrow biopsy	29 (96.7)	46 (93.9)	75 (94.9)
Subjects with evaluable[b] on-study bone marrow biopsy	27 (90.0)	36 (73.5)	63 (79.7)
Subjects with cohort-defined[c] bone marrow biopsy	18 (60.0)	20 (40.8)	38 (48.1)
Subjects with evaluable follow-up[d] bone marrow biopsy	0 (0.0)	0 (0.0)	0 (0.0)

EOS = end of study; EU = European Union; N = number of subjects in the analysis set.
[a] baseline bone marrow biopsy can be either an evaluable bone marrow biopsy within 1 year before the planned first dose of romiplostim or a pretreatment bone marrow biopsy within 3 weeks before the planned first dose of romiplostim.
[b] An evaluable bone marrow biopsy is defined as a biopsy which has a modified Bauermeister grade of 0-4.
[c] A cohort-defined biopsy is defined as a biopsy which occurred within the window of day 365 (± 4 weeks) or day 730 (± 4 weeks) for cohorts 1 and 2, respectively.
[d] Follow-up bone marrow biopsies were required at the EOS visit, or at 12 weeks (± 2 weeks) after discontinuation of romiplostim for subjects who showed the presence of collagen or had a change to grade 3 reticulin.
Full Analysis Set includes all enrolled subjects.

Baseline data

The distribution of boys (100 subjects; 49.3%) and girls (103 subjects; 50.7%) was similar in the Full Analysis Set.

Most patients (164 subjects; 80.8%) were white, and the mean (SD) age was 9.5 (4.4) years overall. Subjects were stratified into 1 of the 3 age groups as below:

- ≥1 to <6 years (49 subjects [24.1%])
- ≥6 to <12 years (81 subjects [39.9%])
- ≥12 to <18 years (73 subjects [36.0%])

Baseline demographics and disease characteristics were similar between subjects enrolled in cohort 1 and cohort 2 and between subjects enrolled in the protocol supplement and those enrolled in the main protocol. Baseline Bone Marrow characteristics of subjects in the protocol supplement are showed below (see Table 3).

Table 3. Baseline Bone Marrow Biopsy Results (Full Analysis Set - Subjects Recruited Under the EU, Switzerland, and Turkey Supplement)

	Romiplostim		
	Cohort 1 (N = 30) n (%)	Cohort 2 (N = 49) n (%)	Cohort 1 and 2 (N = 79) n (%)
Subjects with baseline bone marrow data	30	49	79
Modified Bauermeister scale score			
0 (no reticulin fibers demonstrable)	5 (16.7)	11 (22.4)	16 (20.3)
1 (occasional fine individual fibers and foci of a fine fiber network)	22 (73.3)	32 (65.3)	54 (68.4)
2 (fine fiber network throughout most of the section; no course fibers)	2 (6.7)	3 (6.1)	5 (6.3)
3 (diffuse fiber network with scattered thick course fibers but no mature collagen a [negative trichrome staining])	0 (0.0)	0 (0.0)	0 (0.0)
4 (diffuse, often course fiber network with a areas of collagenization [positive trichrome staining])	0 (0.0)	0 (0.0)	0 (0.0)
Indeterminate	1 (3.3)	0 (0.0)	1 (1.3)
Missing	0 (0.0)	3 (6.1)	3 (3.8)
Overall bone marrow interpretation[a] at baseline			
Normal within the underlying diagnosis of ITP	30 (100.0)	48 (98.0)	78 (98.7)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)
Indeterminate	0 (0.0)	1 (2.0)	1 (1.3)
Baseline cytogenetic interpretation			
Normal	26 (86.7)	35 (71.4)	61 (77.2)
Abnormal	0 (0.0)	1 (2.0)	1 (1.3)
No or low metaphase cells available	4 (13.3)	10 (20.4)	14 (17.7)
No specimen collected	0 (0.0)	3 (6.1)	3 (3.8)
Baseline FISH panel			
Normal	29 (96.7)	46 (93.9)	75 (94.9)
At least 1 abnormality	0 (0.0)	0 (0.0)	0 (0.0)
No specimen collected	1 (3.3)	3 (6.1)	4 (5.1)

EU = European Union; FISH = fluorescence in situ hybridization; ITP = immune thrombocytopenia; N = number of subjects in the analysis set; n = number of subjects with observed data

[a] An overall interpretation, using bone marrow biopsy and aspirate samples, cytogenetics, and FISH data on whether the subject had bone marrow that was normal within the underlying diagnosis of ITP, or whether it showed any abnormalities that were not consistent with an underlying diagnosis of ITP.

Full Analysis Set includes all enrolled subjects.

A baseline bone marrow biopsy can be either an evaluable bone marrow biopsy within 1 year before the planned first dose of romiplostim or a pretreatment bone marrow biopsy within 3 weeks before the planned first dose of romiplostim.

Efficacy and safety results

Efficacy endpoints were assessed using the Efficacy Analysis Set that included all subjects who received at least 1 dose of romiplostim (N=203).

Primary Endpoints

Percentage of time with a platelet response in the first 6 months

All 203 subjects had at least 1 post-baseline platelet count. The mean (SD) and median percentage of time with a platelet response (platelet count of ≥50 x 10^9/L) within the first 6 months of initiation of romiplostim without rescue medication use for the past 4 weeks was 50.57% (37.01) and 50.0%, respectively (see Table 4). The median percentage of time with a platelet response was 50.0%, 33.33%, and 66.67% for subjects in ≥1 to <6 years, ≥6 to <12 years, and ≥12 to <18 years age groups, respectively.

Table 4. Percentage of Time With A Platelet Response in the First 6 Months After Initiation of Romiplostim (Efficacy Analysis Set)

	Baseline Age (Years)			
	≥ 1 to < 6 (N = 49)	≥ 6 to < 12 (N = 81)	≥ 12 to < 18 (N = 73)	Overall (N = 203)
Percentage of time with a platelet response in the first 6 months				
n	49	81	73	203
Mean	47.11	44.55	59.59	50.57
SD	35.50	38.67	34.80	37.01
Median	50.00	33.33	66.67	50.00
Q1, Q3	16.67, 83.33	0.00, 83.33	33.33, 83.33	16.67, 83.33
Min, Max	0.0, 100.0	0.0, 100.0	0.0, 100.0	0.0, 100.0

ITP = immune thrombocytopenia; Min = minimum
Efficacy Analysis Set includes all subjects who received at least 1 dose of romiplostim.
Platelet response is a platelet count of ≥ 50 x 10^9/L without rescue medication use for ITP in the past 4 weeks.
Missing platelet counts are considered as having no platelet response.

Incidence of Changes in Bone Marrow Biopsy: developed collagen, an increased Bauermeister grade by ≥2 grades or an increase to grade 4 and bone marrow abnormalities

- Subjects who developed collagen

Of the subjects with an evaluable on-study bone marrow biopsy, no subjects developed collagen (a grade of 4 on the modified Bauermeister grading scale). No subjects developed collagen at cohort-defined biopsies.

- Subjects who developed an increased Bauermeister grade by ≥2 grades or an increase to grade 4

Of the subjects with an evaluable on-study bone marrow biopsy, 1 of 27 subjects (3.7%) in cohort 1 (no subject in cohort 2) developed an increased modified Bauermeister grade by ≥2 severity grades (from grade 0 baseline value to grade 2 postbaseline value).

- Subjects who developed bone marrow abnormalities (overall interpretation of bone marrow biopsy and aspirate samples, cytogenetics, and FISH data)

No subjects developed a bone marrow abnormality that was not consistent with an underlying diagnosis of ITP.

Secondary Endpoints

Percentage of time with a platelet response over the study duration

The mean (SD) and median percentage of time with a platelet response (platelet count of ≥50 x 10^9/L) without rescue medication use within the past 4 weeks for the overall treatment period (week 2 to EOT) was 60.82% (35.65) and 78.21%, respectively. The mean (SD) percentage of time with a platelet response was similar for ≥1 to <6 years (57.21% [36.46]) and ≥6 to <12 years (55.63% [38.31]) age groups, and was higher in the ≥12 to <18 years (68.99% [30.68]) age group.

Overall, the number of subjects who had at least 1 platelet response from week 2 to EOS was 179 subjects (88.2%) and was similar in ≥1 to <6 years (42 of 49 subjects [85.7%]) and ≥6 to <12 years (68 of 81 subjects [84.0%]) age groups, and was higher in ≥12 to <18 years (69 of 73 subjects [94.5%]) age group. Analysis of platelet response rate over time showed that the overall percentage of subjects with a platelet response at week 2 was 23.2%. The total response rate increased over time on study overall and across all age groups.

Increase in platelet count of ≥20 x 10^9/L above baseline over the study duration

The mean (SD) and median percentage of time with a platelet count of ≥20 x 10^9/L from baseline without rescue medication use for ITP in the past 4 weeks was 64.16% (33.82) and 80.13%, respectively. The mean (SD) percentage of time was similar in ≥1 to <6 years (61.67% [35.54]) and ≥6 to <12 years (59.92% [36.24]) age groups, and was higher in ≥12 to <18 years (70.55% [29.03]) age group.

Use of rescue ITP medications

Sixty subjects (29.6%) overall received rescue medication during the treatment period (week 2 to EOT). The incidence of subjects using rescue medications was higher in ≥1 to <6 years (23 of 49 subjects [46.9%]) age group than in ≥6 to <12 years (23 of 81 subjects [28.4%]) and ≥12 to <18 years (14 of 73 subjects [19.2%]) age groups. The most frequently used rescue medication by category was corticosteroids (19.2%) followed by Ig (17.2%). The incidence of subjects using rescue medication during the sequential 12-week periods (weeks 1 to 12, weeks >12 to 24, weeks >24 to 36) decreased over time in all 3 age groups.

Anti-romiplostim Antibody Assays

Subjects were tested for the presence (at baseline) or development (postbaseline) of romiplostim (including TPO mimetic peptide, the peptide component of romiplostim) and TPO antibodies.

Seventeen subjects (8.4%) had a positive binding non-neutralizing antibody response against romiplostim while on study. Of these, 2 subjects had positive binding antibody status at or before baseline (pre-existing).

Fifteen subjects (7.7%) developed post-baseline binding antibodies to romiplostim with a negative or no result at baseline. Of these, 7 had a transient binding antibody response with a negative result at the subjects' last time point tested within the study period.

Seven subjects (3.4%) had a positive result for neutralizing antibody response against romiplostim while on study. None of these subjects were positive for neutralizing antibodies at or before baseline; all subjects developed neutralizing antibodies post-baseline. Of these, 4 had a transient neutralizing antibody response with a negative result at the subjects' last time point tested within the study period.

Seven subjects (3.4%) had a positive binding, non-neutralizing antibody response against TPO while on study. Of these, 2 subjects had positive binding antibody status at or before baseline (pre-existing).

Five subjects (2.6%) developed post-baseline binding non-neutralizing antibody response with a negative or no result at baseline. Of these 5 subjects, 4 had transient binding antibody response with a negative result at the subjects' last time point tested within the study period.

One subject (0.5%) had a postbaseline positive result for neutralizing antibody response against TPO (negative for antiromiplostim antibodies) while on study with negative or no result at baseline. The subject showed a transient antibody response with a negative result at the subject's last time point tested within the study period.

Subjects who developed increased reticulin

Of the subjects with an evaluable on-study bone marrow biopsy, 5 of 27 subjects (18.5%) in cohort 1 (95% exact binomial CI: 6.3, 38.1) and 17 of 36 subjects (47.2%) in cohort 2 (95% exact binomial CI: 30.4, 64.5) developed increased reticulin (any increase from baseline in the modified Bauermeister grade).

Subjects without an evaluable baseline result were assumed to have a baseline modified Bauermeister score of 0.

Exploratory Endpoints

Sustained platelet response

Eleven subjects (5.4%) had a sustained platelet response (consecutive platelet counts of ≥50 x 10^9/L in the absence of any ITP medications for at least 24 weeks). The incidence of sustained platelet response was 10.2% (5 of 49 subjects) for ≥1 to <6 years, 2.5% (2 of 81 subjects) for ≥6 to <12 years, and 5.5% (4 of 73 subjects) for ≥12 to <18 years age groups. Overall, the mean (SD) time to onset of sustained platelet response was 57.1 (36.0) weeks.

Incidence of splenectomy

A total of 193 subjects entered the study as non-splenectomized. Three of 193 subjects (1.6%) underwent splenectomy during the study. The incidence of splenectomy during the study was 0% (0 of 47 subjects) for ≥1 to <6 years, 2.6% (2 of 77 subjects) for ≥6 to <12 years, and 1.4% (1 of 69 subjects) for ≥12 to <18 years age groups.

Incidence of romiplostim self-administration

A total of 138 subjects (68.0%) started self-administration of romiplostim during the overall treatment period and 101 subjects (49.8%) ended the study on self-administration of romiplostim.

Safety endpoints

Analysis of safety endpoints was done using the Safety Analysis Set that included all subjects who received at least 1 dose of romiplostim (N=203).

Extent of exposure

All 203 subjects enrolled in the study received at least 1 dose of romiplostim and were included in the Safety Analysis Set. Overall, the median (range) duration of treatment was 155.9 (8.0, 163.0) weeks, total number of non-zero doses was 123.0 (8.0, 158.0) micrograms/kg, and the most frequent dose received by subjects during the treatment period was 10.0 (0, 11.0) micrograms/kg. The median (range) cumulative dose received by subjects during the treatment period was 22 655 (400, 185 335) micrograms and the average weekly dose was 6.92 (0.1, 9.7) micrograms/kg.

Treatment-emergent adverse events

A total of 193 subjects (95.1%) overall had at least 1 treatment-emergent adverse event (unless specified otherwise, the term adverse events refers to treatment-emergent adverse events). Adverse events by preferred term reported for ≥20% of subjects were epistaxis (80 subjects [39.4%]),

headache (78 subjects [38.4%]), nasopharyngitis (75 subjects [36.9%]), pyrexia (65 subjects [32.0%]), cough (52 subjects [25.6%]), petechiae (48 subjects [23.6%]), vomiting (47 subjects [23.2%]), and hematoma (42 subjects [20.7%]).

The subject incidence of adverse events for ≥1 to <6 years, ≥6 to <12 years, and ≥12 to <18 years age groups was 93.9% (46 of 49 subjects), 95.1% (77 of 81 subjects), and 95.9% (70 of 73 subjects), respectively. Adverse events with the highest subject incidence in ≥1 to <6 years age group were pyrexia (25 of 49 subjects [51.0%]) followed by cough (23 of 49 subjects [46.9%]). Adverse events with the highest subject incidence in ≥6 to <12 years age group were epistaxis (36 of 81 subjects [44.4%]) followed by headache (31 of 81 subjects [38.3%]). Adverse events with the highest subject incidence in ≥12 to <18 years age group were headache (33 of 73 subjects [45.2%]) followed by nasopharyngitis (30 of 73 subjects [41.1%]).

Subject incidence of individual preferred terms for adverse events was variable across age groups, with preferred terms reported overall at ≥5% subject incidence generally occurring at a higher subject incidence in the younger (≥1 to <6 and ≥6 to <12 years) age groups.

- Contusion, cough, decreased platelet count, diarrhoea, ear infection, ecchymosis, fall, gastroenteritis, mouth haemorrhage, nasal congestion, petechiae, pyrexia, rash, rhinitis, rhinorrhoea, upper respiratory tract infection, and vomiting occurred at a higher subject incidence in ≥1 to <6 years age group than in ≥6 to <12 and ≥12 to <18 years age groups.
- Tonsillitis occurred at a similar incidence in ≥1 to <6 and ≥12 to <18 years age groups.
- Abdominal pain, anaemia, conjunctivitis, ear pain, epistaxis, hematoma, limb injury, nausea, upper abdominal pain, and viral infection occurred at a higher subject incidence in ≥6 to <12 years age group than in ≥1 to <6 and ≥12 to <18 years age groups.
- Gingival bleeding occurred at a similar incidence in ≥6 to <12 and ≥12 to <18 years age groups.
- Arthralgia, dizziness, fatigue, headache, hypersensitivity, influenza, nasopharyngitis, oropharyngeal pain, pain in extremity, pharyngitis, sinusitis, and skin laceration occurred at a higher subject incidence in ≥12 to <18 years age group than in ≥1 to <6 and ≥6 to <12 years age groups.

Adverse events by severity

Most subjects (127 [62.6%]) had mild or moderate adverse events. A total of 57 subjects (28.1%) had grade 3 adverse events and 19 subjects (9.4%) had grade 4 adverse events.

The grade 3 adverse events by preferred term reported for ≥3 subjects were epistaxis (9 subjects [4.4%]); decreased platelet count (7 subjects [3.4%]); headache (6 subjects [3.0%]); thrombocytopenia (4 subjects [2.0%]); and abdominal pain, pain in extremity, and upper respiratory tract infection (3 subjects [1.5%] each).

The grade 4 adverse events by preferred term reported for >1 subject were decreased platelet count (9 subjects [4.4%]) and thrombocytopenia (5 subjects [2.5%]).

Treatment-related adverse events

Adverse events considered by the site investigator to be related to romiplostim were reported for 56 subjects (27.6%).

Treatment-related adverse events by preferred term reported for >2 subjects were headache (20 subjects [9.9%]); nausea (7 subjects [3.4%]); neutralizing antibody positive (6 subjects [3.0%]);

arthralgia, pain in extremity, and petechiae (5 subjects [2.5%] each); abdominal pain and injection site reaction (4 subjects [2.0%] each); and myalgia and rash (3 subjects [1.5%] each).

Exposure-adjusted adverse events

When adverse events were adjusted for duration, the total number of adverse events and the duration-adjusted event rate was 4.433 (1017.8 per 100 subject-years).

Adverse events with the highest duration-adjusted event rate (per 100 subject-years) overall were: contusion (84.0), epistaxis (77.1), and headache (77.1).

The duration-adjusted event rate (per 100 subject-years) for adverse events by preferred term was higher in ≥1 to <6 years age group (1175.4) than in ≥6 to <12 (1073.8) and ≥12 to <18 (866.4) years age groups.

Withdrawals from investigational product due to adverse events

Fifteen subjects (7.4%) had adverse events leading to withdrawal of romiplostim. Of these:

- 4 subjects had treatment-related neutralizing antibodies positive that were serious for 3 subjects (grade 3 [1 subject], grade 1 [2 subjects]) and nonserious for 1 subject (grade 1).
- 3 subjects had systematic lupus erythematosus that was not considered treatment related and was serious in 1 subject (grade 3) and nonserious in 2 subjects (grade 2 [1 subject], grade 3 [1 subject]).
- 2 subjects had neutralizing antibodies that were nonserious (grade 2 [1 subject], grade 1 [1 subject]) and was considered treatment related in 1 subject.
- 1 subject had nonserious (grade 3) adverse events of abdominal pain, headache, and vomiting that were considered treatment related.
- 1 subject had headache (serious, grade 3) that was considered treatment related.
- 1 subject had B-cell lymphoma (serious, grade 4).
- 1 subject had dizziness (nonserious, grade 1) that was considered treatment related.
- 1 subject had interstitial lung disease (serious, grade 2).
- 1 subject had mixed connective tissue disease (serious, grade 1).

Serious adverse events

Serious adverse events were reported for 60 subjects (29.6%). The serious adverse events by preferred term reported for >1 subject were:

- epistaxis (12 subjects [5.9%]);
- decreased platelet count (10 subjects [4.9%]);
- neutralizing antibody positive and thrombocytopenia (4 subjects [2.0%] each);
- immune thrombocytopenic purpura (3 subjects [1.5%]); and
- abdominal pain, anaemia, headache, influenza, petechiae, and pre-syncope (2 subjects [1.0%] each).

Deaths

No fatal adverse events occurred during the study.

Events of interest

For adverse events of interest, reported preferred terms were compared against a list of predefined preferred terms. The most frequently reported adverse events of interest were pulmonary disorders

(Amgen Medical Dictionary for Regulatory Activities [MedDRA] query [AMQ]) (168 subjects [82.8%]), events from the haemorrhages standardized MedDRA query (SMQ) (141 subjects [69.5%]), and events from the hypersensitivity/angioedema/anaphylactic reactions/anaphylactic-anaphylactoid shock conditions SMQs (69 subjects [34.0%]). No events of angioedema or anaphylaxis were reported.

The most frequently reported (>10 subjects) haemorrhage adverse events were epistaxis (80 subjects [39.4%]), petechiae (48 subjects [23.6%]), hematoma (42 subjects [20.7%]), contusion (40 subjects [19.7%]), gingival bleeding (21 subjects [10.3%]), ecchymosis (20 subjects [9.9%]), and mouth haemorrhage (17 subjects [8.4%]). The grade ≥3 adverse events identified by the SMQ search for haemorrhage were reported for 20 subjects (9.9%). The grade ≥3 adverse events reported for >1 subject were epistaxis (9 subjects [4.4%]); immune thrombocytopenic purpura (3 subjects [1.5%]); and contusion and ecchymosis (2 subjects [1.0%] each).

Concurrent hematopoietic erythropenia (SMQ) and leukocytosis (AMQ) events were reported for 24 subjects (11.8%) (Hematopoietic erythropenia and leukocytosis was defined by MedDRA terms or laboratory values. Hematopoietic erythropenia was identified when haemoglobin level was lower limit of normal, which was age- and sex-dependent, and leukocytosis was identified when white blood cell count was >11 x 10^9/L. A concurrent event was defined as both hematopoietic erythropenia and leukocytosis events that occurred within a 4-week window).

Immunogenicity events (AMQ) were reported for 9 subjects (4.4%), renal and urinary disorders system organ class (AMQ) events were reported for 8 subjects (3.9%), cardiac disorders (SMQs) were reported 4 subjects (2.0%), malignancies (SMQ) were reported for 2 subjects (1.0%), drug-related hepatic disorders (SMQ) were reported for 1 subject (0.5%), haematological malignant tumors/haematological tumors of unspecified malignancy/myelodysplastic syndrome (SMQs) were reported for 1 subject (0.5%), thrombocytosis (AMQ) was reported for 1 subject (0.5%), and thrombotic/thromboembolic events (SMQs) were reported for 1 subject (0.5%).

Anti-romiplostim antibodies

Seventeen subjects (8.4%) had a positive binding non-neutralizing antibody response against romiplostim while on study. Of these, 15 subjects (7.7%) developed postbaseline binding antibodies to romiplostim with a negative or no result at baseline.

Seven of 15 subjects had a transient binding antibody response with a negative result at the subjects' last time point tested within the study period.

Seven subjects (3.4%) had a positive result for neutralizing antibody response against romiplostim while on study. None of these subjects were positive for neutralizing antibodies at or before baseline; all subjects developed neutralizing antibodies postbaseline. Of these, 4 had a transient neutralizing antibody response with a negative result at the subjects' last time point tested within the study period.

Seven subjects (3.4%) had a positive binding, non-neutralizing antibody response against TPO while on study. Of these, 5 subjects (2.6%) developed postbaseline binding non-neutralizing antibody response with a negative or no result at baseline.

Four of 5 subjects had transient binding antibody response with a negative result at the subjects' last time point tested within the study period.

One subject (0.5%) had a postbaseline positive result for neutralizing antibody response against TPO while on study (negative for anti-romiplostim antibodies) with negative or no result at baseline. The subject showed a transient antibody response with a negative result at the subject's last time point tested within the study period.

Clinical laboratory

Maximum postbaseline grade ≥3 decreases were reported for haemoglobin (5 subjects), neutrophils (4 subjects), platelets (199 subjects), and leukocytes (3 subjects). No postbaseline grade ≥3 increase in bilirubin or creatinine were reported.

2.3.3. Discussion on clinical aspects

Nplate is currently approved by the European Commission (EC) for chronic immune (idiopathic) thrombocytopenic purpura (ITP) patients one year of age and older who are refractory to other treatments (e.g. corticosteroids, immunoglobulins) as powder for solution for injection to be administered subcutaneously once a week.

On 4th February 2009, Nplate was firstly approved by the EC for the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura (ITP). On 9th November 2017, the CHMP issued a positive opinion on an extension of indication for Nplate (EMEA/H/C/000942/II/0060/G) to include paediatric population (1 year of age and older). At the time (5 December 2016) of the submission of that variation application, the MAH submitted 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).

The hereby submitted study (20101221) is also part of an EU Paediatric Investigation Plan (PIP) for Nplate (P/0233/2017; EMEA-000653-PIP01-09-M05). Agreed PIP includes a total of three clinical studies: 20080279, 20090340 and 20101221.

Study 20101221 was a phase 3b, single-arm, open-label, multicentre study where romiplostim was administered weekly by subcutaneous (SC) injection to thrombocytopenic paediatric subjects with ITP diagnosed for at least 6 months and who received at least 1 prior ITP therapy (excluding romiplostim) or were ineligible for other ITP therapies. Dose adjustment rules were based on individual platelet counts, being 10 micrograms/kg the maximum permitted dose of romiplostim. The study consisted of a 4-week screening period, up to 3-year treatment period, an end-of-treatment (EOT) visit, and an end-of-study (EOS) visit. The primary objectives of study 20101221 were to describe the percentage of time that paediatric subjects with ITP have a platelet response in the first 6 months from the start of treatment with romiplostim as well as evaluating the incidence of changes in bone marrow findings at year 1 or year 2 after initial exposure to 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. Secondary objectives were to describe the percentage of time that paediatric subjects with ITP have a platelet response over the study duration, the percentage of time that paediatric subjects with ITP have an increase in platelet count ≥20 x 10^9/L above baseline over study duration, the use of rescue ITP medications, the incidence of antibody formation, the safety of romiplostim as a long-term treatment in paediatric thrombocytopenic subjects with ITP and to evaluate the incidence of increased reticulin as evidenced by silver staining at year 1 or year 2, after initial exposure to romiplostim. In addition, it was proposed as exploratory objectives to describe the incidence of sustained platelet response, the incidence of splenectomy and the subject incidence of romiplostim self-administration.

A total of 203 subjects were enrolled in the study across 3 age groups (≥1 to <6 years: 49 subjects [24.1%]; ≥6 to <12 years: 81 subjects [39.9%]; ≥12 to <18 years: 73 subjects [36.0%]). For evaluating the incidence of changes in bone marrow, a total of 79 subjects were enrolled sequentially into the protocol supplement for the EU, Switzerland, and Turkey. Of these, 30 subjects were in cohort

1 (bone marrow samples [biopsy and aspirate] taken at baseline and year 1) and 49 subjects were in cohort 2 (bone marrow samples [biopsy and aspirate] taken at baseline and year 2).

With respect to the primary endpoints, the mean (SD) and median percentage of time with a platelet response within the first 6 months of initiation of romiplostim was 50.57% (37.01) and 50.0%, respectively. The median percentage of time with a platelet response was 50.0% for ≥1 to <6 age group, 33.33% for ≥6 to <12 age group, and 66.67% for ≥12 to <18 years age group. When the subjects with an evaluable on-study bone marrow biopsy (cohort 1: 27/30 subjects [90.0%] and cohort 2: 36/49 subjects [73.5%]) were evaluate, no subjects developed collagen (a grade of 4 on the modified Bauermeister grading scale), 1/27 subjects (3.7%) in cohort 1 developed an increased modified Bauermeister grade by ≥2 severity grades (from grade 0 baseline value to grade 2 post-baseline value) and no subjects developed a bone marrow abnormality. Moreover, 5/27 subjects (18.5%) in cohort 1 (95% exact binomial CI: 6.3, 38.1) and 17/36 subjects (47.2%) in cohort 2 (95% exact binomial CI: 30.4, 64.5) developed increased reticulin (any increase from baseline in the modified Bauermeister grade).

Regarding the safety results, a total of 193 subjects (95.1%) overall had at least 1 treatment-emergent adverse event. Adverse events reported for ≥20% of subjects were epistaxis (39.4%), headache (38.4%), nasopharyngitis (36.9%), pyrexia (32.0%), cough (25.6%), petechiae (23.6%), vomiting (23.2%), and hematoma (20.7%). Fifteen subjects (7.4%) had adverse events leading to withdrawal of romiplostim. Serious adverse events were reported for 60 subjects (29.6%). No fatal adverse events were reported in the study. The most frequently reported adverse events of interest were pulmonary disorders (Amgen MedDRA query) (82.8%), events from the haemorrhages standardized MedDRA query (SMQ) (69.5%), and events from the hypersensitivity/ angioedema/ anaphylactic reactions/ anaphylactic-anaphylactoid shock conditions SMQs (34.0%). Fifteen subjects (7.7%) developed postbaseline binding antibodies to romiplostim with a negative or no result at baseline. Five subjects (2.6%) developed postbaseline binding non-neutralizing antibody response against TPO with a negative or no result at baseline.

Study 20101221 agrees with Article 46 of Regulation (EC) No1901/2006, as amended, as regards of its submission to the competent authority within six months of completion. Study 20090340 has been submitted as part of procedure EMEA/H/C/942/II/0060/G .

In summary, study 20101221 has been adequately designed and completed in accordance (EMEA-C-000653-PIP01-09-M05) to the agreed PIP. Regarding the submitted data on the primary endpoints, although results of percentage of time with a platelet response within the first 6 months of initiation of treatment were generally consistent with the known efficacy profile of romiplostim, study 20101221 appears to be of particular interest since it provides information regarding long-term bone marrow effects in paediatric ITP subjects which has not been yet included in the EU summary product characteristics (SmPC). In view of the safety results, the overall safety profile of the paediatric subjects who received romiplostim in study 20101221 was similar to the known safety profile of romiplostim.

The main limitation of the submitted study is the limited sample size, which makes challenging drawing any conclusion for the overall and, in particular, for the different age cohorts. Due to the difficulties to recruit paediatric ITP subjects (approx. prevalence 7.2 cases per 100,000 per year), this limitation is not posed as an objection. In this regard, it should be taken into account that Nplate was designated as an orphan medicinal product EU/3/05/283 from 27 May 2005 to February 2019 (at the end of the 10-year period of market exclusivity) in the following indication: Treatment of idiopathic thrombocytopenic purpura.

In order to increase the availability of information on the use of romiplostim in the paediatric population suffering from this rare condition (ITP), the SmPC should be updated to also reflect the main results of the completed study 20101221.

3. Rapporteur's overall conclusion and recommendation

Study 20101221 has been submitted within six months of its completion and is part of the PIP EMEA-000653-PIP01-09-M05 (P/0233/2017). The study has been adequately designed and completed in accordance (EMEA-C-000653-PIP01-09-M05) to the agreed PIP. On the light of the obtained results, it is considered of interest to conduct a formal benefit/risk evaluation in order to increase the availability of information on the use of romiplostim in the paediatric ITP population.

Study 20090340 (also included in the agreed PIP) has been submitted as part of procedure EMEA/H/C/942/II/0060/G to the EMA.

☒ Fulfilled:

In view of the available data regarding study 20101221, the MAH is requested to submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 to update the summary of product characteristics by reflecting the main results not only from study 20101221 but also from study 20090340, or provide a justification for not doing so.

This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.

Annex. Line listing of all the studies included in the development program

Clinical studies

Product Name: Nplate.

Active substance: romiplostim.

Number and study title	PIP Commitment	Date of Completion*	Submission of Final Study Report
20080279: A Phase 3 Randomized, Double Blind, Placebo Controlled Study to Determine the Safety and Efficacy of Romiplostim in Thrombocytopenic Pediatric Subjects with Immune Thrombocytopenia (ITP)	Study 2	19 February 2015	The final study report was submitted to the EMA under Article 46 (Procedure No. EMEA/H/C/000942/P46/033 submitted on 19th August 2015).
20090340: An Open-label Study Evaluating the Safety and Efficacy of Longterm Dosing of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune (Idiopathic) Thrombocytopenia Purpura (ITP)	Study 3	12 January 2017	The final study report has been submitted to the EMA in procedure EMEA/H/C/942/II/0060/G under Article 46.
20101221: A Single Arm, Open-label, Long-term Efficacy and Safety Study of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune Thrombocytopenia (ITP)	Study 4	15 August 2019	Included in this submission (Procedure No. EMA/H/C/000942/P46/034)