25 July 2024
EMA/369609/2024
Human Medicines Division

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

Doptelet

Avatrombopag

Procedure no: EMEA/H/C/004722/P46/007

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	27 May 2024	27 May 2024	☐
☐	CHMP Rapporteur Assessment Report	1 Jul 2024	9 July 2024	☐
☐	CHMP members comments	15 July 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	18 July 2024	n/a	☐
☒	CHMP adoption of conclusions:	25 July 2024	25 July 2024	☐

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1. Introduction

On May 7th 2024, the MAH submitted a completed paediatric study for Doptelet, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The CSR for AVA-PED-301 that is the basis for this P46 submission is submitted as a stand-alone submission with only the study results. However, the MAH also writes *that a grouped line extension to register a new paediatric formulation and a type II variation to expand the immune thrombocytopenia (ITP) indication to include peadiatric use is planned.*

2. Scientific discussion

2.1. Information on the development program

The MAH stated that AVA-PED-301 is a stand-alone study.

Avatrombopag for paediatric ITP has been evaluated under a PIP (EMEA-001136-PIP01-11). In summary, the PIP required data from juvenile toxicology studies, development of an age-appropriate formulation, and conduct of a clinical trial in subjects with persistent or chronic ITP who have had an insufficient response to a prior therapy, preceded by a PKPD assessment to define starting doses for the clinical trial.

The sponsor submitted a request for a partial compliance check on 28 Nov 2019, and EMA adopted a compliance report on 28 Feb 2020. Table 1 briefly describes the required studies and their status.

Table 1. PIP Studies and Compliance Status

Study No. / Identifier	Compliance status / Conclusion	Procedure No.	Description	Sponsor Notes
Study 1	Compliance confirmed	EMEA-C1-001136-PIP01-11-M01	Development of an age appropriate pharmaceutical for oral use	Information submitted in partial compliance check request; information on final product to be included in Modules 3 and 2.3 in line extension application
Study 2 (AVA-PED-101)	Compliance confirmed	EMEA-C1-001136-PIP01-11-M01	Bioavailability study in healthy adults	Report submitted in partial compliance check request; report will be also be included in Type II variation and line extension application
Study 3 (NCI)	Compliance confirmed	EMEA-C1-001136-PIP01-11-M01	4-week dose range finding oral toxicity study in juvenile rats	
Study 4 (NC2)	Compliance confirmed	EMEA-C1-001136-PIP01-11-M01	10-week oral toxicity study in juvenile rats followed by a 4-week recovery period	

Study No. / Identifier	Compliance status / Conclusion	Procedure No.	Description	Sponsor Notes
Study 5 (AVA-PED-301)	Not checked yet. Completion due by December 2023 (12-week core study) and by December 2025 (2-year open extension)	EMEA-001136-PIP01-11-M03	Randomized, double-blind, placebo-controlled, parallel group trial with open-label extension phase to assess efficacy PK/PD, tolerability and safety of avatrombopag (maleate) in children with chronic idiopathic thrombocytopenic purpura.	PIP modification (positive PDCO opinion 22 March 2024) for completion date of December 2023 based on core phase of study; report will be included in request for a full PIP compliance check and submitted in planned Type II variation and line extension application.
Study 6 (AVA-PKPD-PED-ITP-003)	Compliance of the date of study initiation confirmed; other measures to be confirmed. Completion due by March 2020	EMEA-C1-001136-PIP01-11-M01	Population Pharmacokinetic/ Pharmacodynamic (PopPKD) study to predict initial paediatric doses to be used in further clinical studies	Study report issued 24 Mar 2020, used to define starting doses in Study 5; report to be included in the request for a full PIP compliance check and submitted in planned Type II variation and line extension application.

2.2. Information on the pharmaceutical formulation used in the study<ies>

For patients who cannot swallow the commercial 20 mg Doptelet tablets, avatrombopag has been formulated as a powder for oral suspension that contains 10 mg avatrombopag in a capsule for opening. The capsule is opened, the contents are mixed into a small amount of a compatible liquid or soft food and the resulting suspension is administered as a single dose.

Initial work towards a formulation that could be used for preparation of an oral suspension was conducted to develop an age-appropriate formulation for subjects ≥1 to <6 years of age with ITP. As noted above, the PIP activities associated with development of an age-appropriate formulation (Studies 1 and 2) have been determined to be compliant.

The initial potential age-appropriate formulation evaluated was a dispersible tablet that was intended to be administered as an oral suspension after its dispersion in a liquid. In accordance with the PIP, a relative bioavailability study in adults was conducted. The tablet was dispersed in water to create a suspension; after oral administration, the suspension demonstrated a 22% higher C_{max} and a 38% higher AUC compared to the commercial tablets under the fed condition (Doptelet is administered with food to reduce variability of exposure).

Due to its slow dispersion properties in water (>15 minutes) the tablet for oral suspension was not further developed, rather the current powder for oral suspension in a capsule for opening was progressed. These formulations have an identical excipient composition; the only difference is that rather than the granules being compressed into a dispersible tablet, they are provided in a capsule for opening. As both are administered by adding the formulation to an appropriate vehicle to create a suspension, the dispersible tablet and powder for oral suspension are equivalent in all aspects at the time of administration.

The current powder for suspension formulation was used in the Phase 3 paediatric ITP study in the youngest cohort of subjects. Sprinkling and mixing granules or a powder into a liquid or soft food is not an unusual method of administering a medication to young paediatric patients, and there were no reported concerns in the study. In addition, avatrombopag will not be the first treatment for ITP that these patients with a persistent or chronic illness receive; it will be indicated only in patients who are refractory to other treatments. Parents or guardians would be expected to be experienced in administration of medications to young patients in their care.

CHMP's comments:

This is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Phase 3 ITP Study AVA-PED-301

A Phase 3b, Multi-center, Randomized, Double-blind, Placebocontrolled, Parallel-group Trial with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Thrombocytopenia in Pediatric Subjects with Immune Thrombocytopenia for ≥6 Months.

2.3.2. Thrombocytopenia for ≥6 MonthsClinical study<ies>

Clinical study number and title

Phase 3 ITP Study AVA-PED-301

EudraCT Number: 2020-003232-40

NCT Number: 04516967

Description

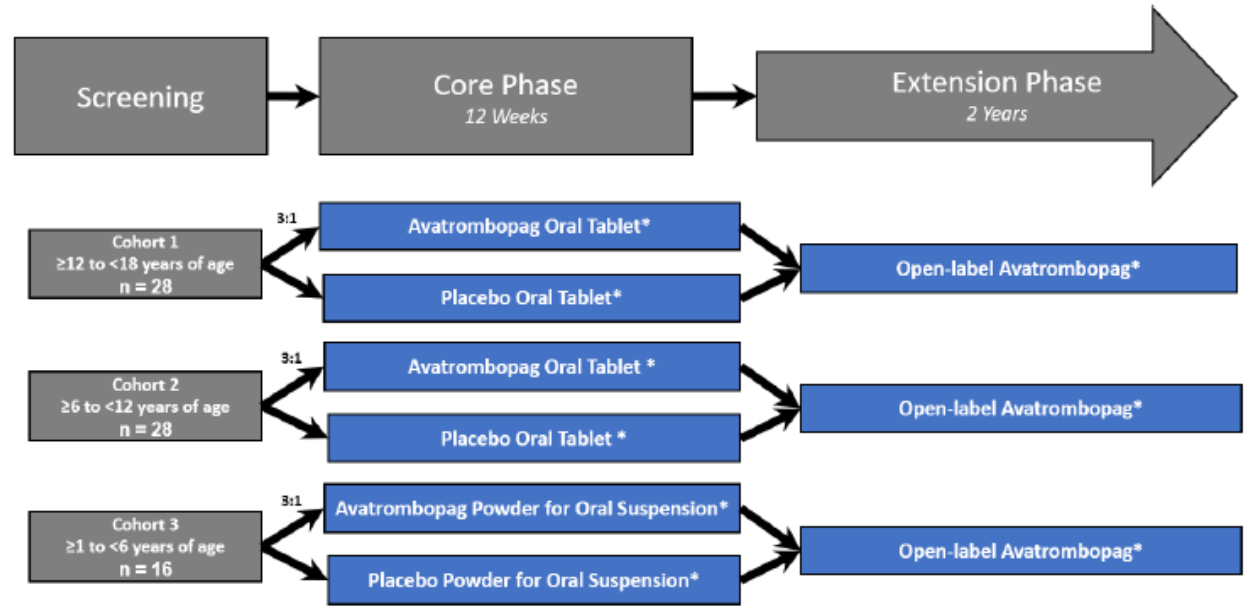
AVA-PED-301 was a multi-center, randomized, double-blind, placebo-controlled, parallel-group study in pediatric subjects with ITP of ≥6 months duration, with a 12-week Core Phase followed by an Open-label Extension Phase to evaluate the efficacy, safety, tolerability, and PK/PD profile of avatrombopag, as well as provide data on palatability/acceptability, dosing parameters, and response to treatment (Figure 1).

The study was planned to enroll 72 pediatric subjects, aged ≥1 to <18 years (Figure 1). Subjects were assigned to 3 age cohorts in a 2:2:1 ratio, and subjects were randomized within each cohort in a 3:1 ratio to receive either avatrombopag or placebo. Subject age at the time of randomization was used. Cohort 1 and Cohort 2 enrolled more subjects than those enrolled in Cohort 3 to minimize the exposure of the youngest age group to placebo.

Enrollment into the Core Phase was staggered by descending age cohort.

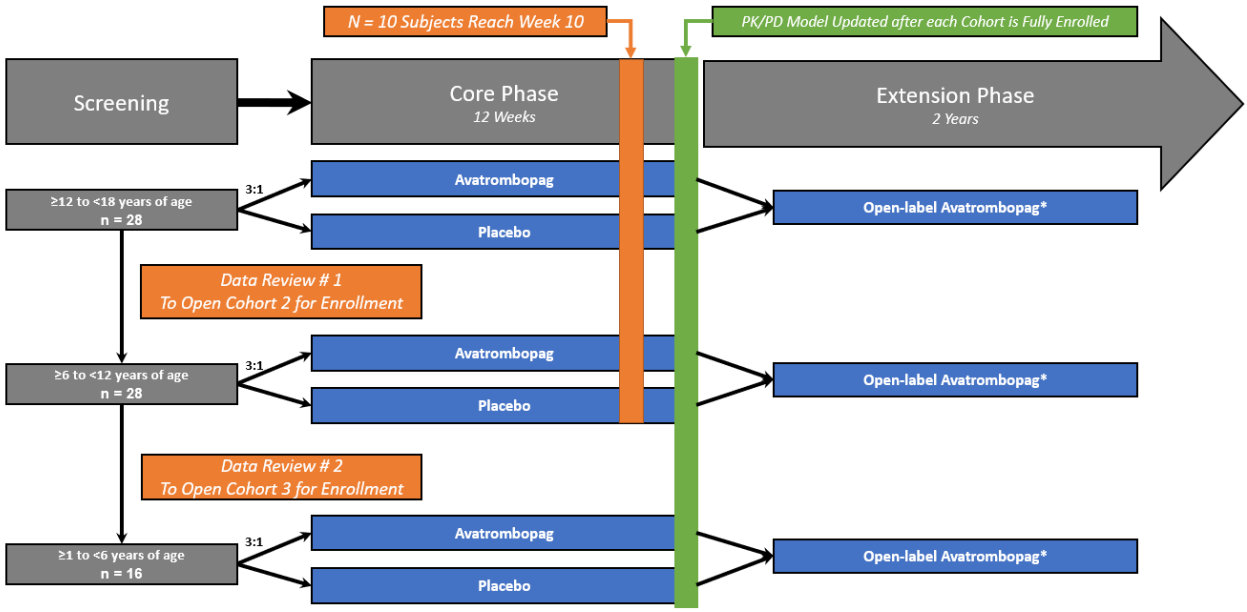
- Cohort 1: ≥12 to <18 years (n=21 avatrombopag; 7 placebo)
- Cohort 2: ≥6 to <12 years (n=21 avatrombopag; 7 placebo)
- Cohort 3: ≥1 to <6 years (n=12 avatrombopag; 4 placebo)

Figure 1. AVA-PED-301 Flow diagram



*Dose titration based on platelet count.

Figure 2 AVA-PED-301 Enrollment and data review plan



Abbreviations: PD, Pharmacodynamic; PK, Pharmacokinetic.

Enrollment continued during the data review of a given cohort after Week 10, or the data review after each cohort.

Subjects who did not show a platelet response (see Section 9.3.3.3) at the highest dose of study drug based on the subject's age cohort were to be terminated from the Core Phase and directly enrolled into the Extension Phase.

Subjects participating in the Core Phase entered a Screening Period followed by a 12-week Treatment Period after which they may have either completed the study with an End of Study Visit that occurred 30 days after the last dose of study drug or continued into the Extension Phase. The Core Phase of the study lasted 12 weeks (approximately 84 days), which did not include the 4-week Follow-up Period, with study visits occurring once weekly through the end of Week 12.

Until the last subject completed the Core Phase and the database was locked, the Sponsor (except for required pharmacovigilance reporting), all subjects, and all Investigators were to remain blinded to treatment received in the Core Phase.

Methods

Study participants

Inclusion criteria

Subjects who met all of the following criteria were eligible to participate:

1. Male or female subjects ≥1 and <18 years old at Screening and baseline.
2. Subject and/or subject's LAR providing informed consent and/or assent, as applicable.

3. Had a confirmed diagnosis of primary ITP according to the International Consensus Report on the Investigation and Management of Primary ITP (Provan 2019) for ≥6 months duration and had an insufficient response to a previous treatment, in the opinion of the Investigator.
4. Had an average of 2 platelet counts <30×109/L with no single count >35×109/L. The platelet count obtained at the Screening Visit/Visit 1 and 1 other platelet count taken within 28 days on either side of the Screening Visit (may have used a historical value collected per standard of care if within 28 days of Screening) were to be averaged to obtain the study eligibility platelet count value, which was to be <30×109/L. The 2 samples were to be obtained ≥24 hours and ≤ 28 days apart, and the results were to be available prior to randomization.
5. Subjects treated chronically with corticosteroids or azathioprine/6-mercaptopurine who received a stable dose for at least 30 days prior to Day 1/Visit 2 or who had completed these therapies more than 30 days prior to Day 1/Visit 2.
6. Subjects treated with MMF, CsA, sirolimus, or danazol who received a stable dose for at least 90 days prior to Day 1/Visit 2 or who had completed these therapies more than 30 days prior to Day 1/Visit 2.
7. Previous therapy for ITP with immunoglobulins (IVIG and anti-D) or corticosteroid rescue therapy must have been completed at least 14 days prior to Day 1/Visit 2.
8. Cyclophosphamide and vinca alkaloid regimens must have been completed at least 30 days prior to Day 1/Visit 2.
9. Splenectomy and rituximab must have been completed at least 90 days prior to Day 1/Visit 2.
10. Previous therapy with any other TPO-RAs (e.g., eltrombopag or romiplostim) or recombinant human TPO must have been completed 28 days prior to Day 1/Visit 2.
11. Previous therapy with vitamin K antagonists, antifibrinolytic agents, recombinant activated factor VII, heparin, factor Xa inhibitors, direct thrombin inhibitors, desmopressin, or chronic antiplatelet therapy must have been completed within 7 days of Day 1/Visit 2.
12. Previous therapy with moderate or strong dual inducers or moderate or strong dual inhibitors of cytochrome P450 (CYP)2C9 and CYP3A4 must have been completed within 7 days of Day 1/Visit 2.
13. Platelet transfusion or receipt of blood products containing platelets must have been completed within 7 days of Day 1/Visit 2. Packed RBCs were permitted.
14. Females of childbearing potential must have had a negative urine or serum pregnancy test at Screening and Day 1/Visit 2 and not be breastfeeding.
15. Female subjects of childbearing potential and who were sexually active and male subjects who were sexually active must have agreed to use highly effective methods of contraception.
16. Subject and/or subject's LAR willing to comply with all aspects of the protocol.

Exclusion criteria

Subjects who met any of the following criteria were not eligible to participate:

1. Known secondary ITP.
2. BMI >30 kg/m2 or >95 % for age.

3. Any history of arterial or venous thrombosis, including partial or complete thrombosis.
4. Subjects with known inherited thrombocytopenia (e.g., MYH-9 disorders).
5. History of myelodysplastic syndrome.
6. Known history of congenital heart abnormalities or arrhythmias.
7. History of hepatitis B, hepatitis C, or human immunodeficiency virus.
8. Known history of disseminated intravascular coagulation, hemolytic uremic syndrome, or thrombotic thrombocytopenic purpura.
9. Subjects with Evans syndrome.
10. Concurrent malignant disease or previous history of myeloid hematologic malignancies.
11. Hemoglobin levels ≤9 g/dL in ages ≥1 to <6 years and ≤8 g/dL in ages ≥6 to <18 years.
12. eGFR <30 mL/min/1.73 m2.
13. Serum total bilirubin >1.5× the ULN for age; ALT and AST >3× the ULN for age.
14. Known allergy to avatrombopag or any of its excipients.
15. Subject unable to take oral medication, had a malabsorption syndrome, or had known hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption or any other uncontrolled gastrointestinal condition.
16. Enrollment in another clinical study with any investigational drug or device within 30 days of Day 1/Visit 2 (or 5 half-lives, whichever was longer); however, participation in observational studies within the previous 30 days was permitted.
17. Any clinically relevant abnormality that made the subject unsuitable for participation in the study, in the opinion of the Investigator.
18. Considered unable or unwilling to comply with the study protocol requirements.

CHMP's comments:

Inclusion and exclusion criteria are considered appropriate.

Treatments

Avatrombopag film-coated oral tablets or matching placebo

Supplies of avatrombopag or placebo oral tablets were provided to the clinical sites.

Avatrombopag was provided as film-coated tablets, with each tablet containing avatrombopag maleate (equivalent to 20 mg of avatrombopag) and excipients. Matching placebo tablets were also provided for the Core Phase.

During the Extension Phase, open-label avatrombopag film-coated oral tablets were provided. The clinical site dispensed the number of tablets required for dosing each subject for a 30-day period (e.g., a monthly supply of thirty 20 mg tablets for a 20 mg daily dose).

Avatrombopag powder for oral suspension in a capsule or matching placebo

Supplies of avatrombopag or placebo powder for oral suspension were provided to the clinical sites in capsules that were opened to sprinkle the powder into an appropriate vehicle to make a suspension. Each avatrombopag capsule contained avatrombopag maleate (equivalent to 10 mg avatrombopag) and excipients. Matching placebo capsules, containing the same excipients as the active capsules, were also provided for the Core Phase.

During the Extension Phase, capsules containing avatrombopag powder for oral suspension were provided.

The clinical site dispensed the number of capsules required for dosing each subject for a 30-day period (e.g., a monthly supply of sixty 10 mg capsules for a 20 mg daily dose).

Avatrombopag dosing and administration

Subjects received avatrombopag or matching placebo as either the film-coated oral tablet or the powder for oral suspension. The powder for oral suspension was contained in a capsule that was to be opened to sprinkle the contents into an appropriate vehicle to prepare the suspension. No partial dosing from the capsule was allowed; the entire contents were to be used to prepare the suspension.

On Day 1/Visit 2, Cohort 1 (≥12 to <18 years old) had a starting dose of avatrombopag of 20 mg once daily, administered as an oral tablet, consistent with the approved adult dosing. The starting dose for Cohort 2 (≥6 to <12 years old) was also 20 mg once daily administered as an oral tablet, and the starting dose for Cohort 3 (≥1 to <6 years old) was 10 mg once daily administered as an oral suspension (**Table 2**). The formulation received was recorded in the eCRF.

Table 2. Study drug starting dose by age cohort in the Core Phase and Extension Phase

Age Range (Years)	Study Drug Starting Dose (mg)	Formulation
Cohort 1		
≥12 to <18	20 mg Once Daily	Oral Tablet
Cohort 2		
≥6 to <12	20 mg Once Daily	Oral Tablet
Cohort 3		
≥1 to <6	10 mg Once Daily	Powder for Oral Suspension (in a Capsule)

Abbreviations: PD, Pharmacodynamic; PK, Pharmacokinetic.
Note: Subject age at the time of randomization was used. The starting dose of study drug could have been revised after scheduled PK/PD and safety reviews.

The dose of study drug was to be titrated up or down based on the subject's platelet count to maintain a platelet count between ≥50 and ≤150×109/L during the 12-week Core Phase (Table 3).

Table 3. Study drug dose level titration (core and extension)

Dose	Dose Level
Cohort 1 (≥12 to <18 Years) and Cohort 2 (≥6 to <12 Years) Dosed with Oral Tablet	
40 mg Once Daily	6
40 mg Three Times a Week AND 20 mg on the Four Remaining Days of Each Week	5
20 mg Once Daily[a]	**4**
20 mg Three Times a Week	3
20 mg Twice a Week	2
20 mg Once Weekly	1

Dose	Dose Level
Cohort 3 (≥1 to <6 Years) Dosed with Powder for Oral Suspension	
20 mg Once Daily	6
20 mg Three Times a Week AND 10 mg on the Four Remaining Days of Each Week	5
10 mg Once Daily[a]	**4**
10 mg Three Times a Week	3
10 mg Twice a Week	2
10 mg Once Weekly	1

[a] Subject age at the time of randomization was used. Initial dose regimen based on modeling and simulation. Actual initial dose in Cohort 2 and Cohort 3 could have been modified after modeling was completed using data from the previous cohort.

Rescue therapies

Subjects may have received rescue therapy at the discretion of the Investigator if there was an urgent need to increase platelet count, such as in the case of life-threatening thrombocytopenia, in the opinion of the Investigator, or there were clinical signs and symptoms suggesting a potential bleed (e.g., wet purpura) or a major bleed. All rescue medications, including dose and frequency, were recorded in the eCRF.

Rescue therapy included the following:

- The addition of any new ITP medication or medication to treat thrombocytopenia, such as:
  - Corticosteroids
  - IVIg
  - Anti-D
  - Platelet transfusion
- Any increase in the Day 1/Visit 2 dose of a concomitant ITP medication.

TPO-RAs were not allowed as rescue therapy.

CHMP's comments:

This is considered appropriate.

Objectives and endpoints

The study objectives and endpoints are provided in Table 4 below.

Table 4. Objectives and endpoints for the study

Tier	Objectives	Endpoints
Primary	To demonstrate that the efficacy of avatrombopag is superior to placebo for the treatment of pediatric subjects with ITP of ≥6 months duration who have had an insufficient response to a previous treatment	**Primary Efficacy** • Durable platelet response as defined by the proportion of subjects achieving at least 6 out of 8 weekly platelet counts $\geq 50\times10^9$/L during the last 8 weeks of the 12-week Treatment Period in the Core Phase in the absence of rescue medication. **Alternative Primary Efficacy (per EU PIP)** • Platelet response as defined by the proportion of subjects for whom at least 2 consecutive platelet assessments are $\geq 50\times10^9$/L over the 12-week Treatment Period in the Core Phase in the absence of rescue medication.
Secondary		**Secondary Efficacy** • The percentage of weeks subjects have a platelet count $\geq 50\times10^9$/L during 12 weeks of treatment in the Core Phase, in the absence of rescue therapy. • Platelet response at Day 8 (defined by the proportion of subjects with a platelet count $\geq 50\times10^9$/L at Day 8, in the absence of rescue therapy). • The percentage of weeks subjects have a platelet count between $\geq 50\times10^9$/L and $\leq 150\times10^9$/L, during 12 weeks of treatment in the Core Phase, in the absence of rescue therapy. • The proportion of subjects who require rescue medications during 12 weeks of treatment in the Core Phase of the study. • Incidence and severity of bleeding symptoms associated

Tier	Objectives	Endpoints
		with ITP measured using the WHO Bleeding Scale.
Safety	To evaluate the safety and tolerability of avatrombopag	**Safety** • Incidence of AEs, SAEs, and AESIs during the study. • Measurement of clinical laboratory tests during the study. • Measurement of vital signs during the study.
Pharmacokinetic and Pharmacodynamic	To evaluate the PK and PD of avatrombopag	**PKPD** • Individual PK parameters will be derived from the final population PK model. Effects of intrinsic factors, including age and weight, and extrinsic factors, including formulation, on the PK parameters may be evaluated. • Effects of covariates on PD parameters may be evaluated.
Exploratory	To provide data on the palatability and parent/caregiver-reported acceptability of the avatrombopag powder for oral suspension.	**Exploratory** • Platelet count assessments and platelet response during the Extension Phase. • An exploratory efficacy endpoint was predefined in the SAP but not included in the protocol: Month 3 durable platelet response defined as the proportion of subjects achieving at least 3 out of 4 weekly platelet counts $\geq 50 \times 10^9$/L during the last 4 weeks of the 12-week Treatment Period in the Core Phase in the absence of rescue medication. • Subject-reported palatability and parent/caregiver-reported acceptability assessed by a palatability/acceptability questionnaire administered after the first dose of the powder for oral suspension.

Abbreviations: AE, Adverse event; AESI, Adverse event of special interest; ITP, Immune thrombocytopenia; PD, Pharmacodynamic; PK, Pharmacokinetic; SAE, Serious adverse event; SAP, Statistical Analysis Plan; WHO, World Health Organization.

CHMP's comments:

Endpoints are considered acceptable in this setting.

Sample size

The sample size was based on the anticipated response rates for avatrombopag and placebo for the primary endpoint (durable platelet response) and the alternative primary endpoint (platelet response for at least 2 consecutive weeks).

Based on the eltrombopag PETIT2 study conducted in pediatric patients with chronic ITP, the durable response rates were 41.3 % and 3.4 % for eltrombopag and placebo, respectively (Grainger 2015). It was reasonable to assume that the treatment effect of avatrombopag would be very similar to that of eltrombopag due to both drugs being in the same class, having similar mechanisms of action, and treating similar patient populations (e.g., patients ≥1 to <18 years old with relapsed or refractory disease after 1 or more previous treatments for ITP and a baseline platelet count <30×109/L). With the 3:1 ratio of avatrombopag to placebo, a total of 72 subjects (54 avatrombopag and 18 placebo) would provide at least 90 % power to detect a treatment difference of 37.9 % in durable response at α =0.05, based on the Fisher's exact test.

In addition, a 12-week study of romiplostim in treating pediatric ITP patients showed that 88% of romiplostim-treated subjects achieved a platelet count ≥50×109/L for 2 consecutive weeks (alternative primary endpoint for this study), whereas none of the placebo-treated subjects achieved the same endpoint (Bussel 2011). With the 3:1 ratio of avatrombopag to placebo, a total of 72 subjects (54 avatrombopag and 18 placebo) would provide ≥99 % power to detect a treatment difference of 80 % in the proportion of subjects achieving a platelet count ≥50×109/L for 2 consecutive weeks at α =0.05, based on the Fisher's exact test.

Randomisation and blinding (masking)

Treatment allocation

During the 12-week Core Phase of the study, the subjects were randomized in a 3:1 ratio to receive either avatrombopag or matching placebo.

The Extension Phase of this study is open-label, in which all subjects receive avatrombopag.

Randomization strategy

During Day 1/Visit 2 of the Core Phase, after study eligibility had been confirmed, randomization assignment was performed using interactive response technology.

Stratification

Randomization was stratified by age cohort. Subjects were also stratified by a baseline platelet count of ≤15×109/L or >15×109/L to <30×109/L to ensure treatment groups were approximately balanced.

Extent and maintenance of blinding

Following randomization, study drug was dispensed in a double-blind manner. The Sponsor, the subject, and the clinical site personnel were blinded to the treatment assignment.

The Sponsor and the project team remained blinded during the ongoing safety data review.

Interim PK/PD analyses were conducted by an unblinded designee.

No randomization or blinding was necessary for the Extension Phase as it is open-label and all subjects receive avatrombopag.

Planned unblinding

At the initiation of the study, the Investigator was instructed on the method for breaking the blind during the Core Phase. The blind was not to be broken during the study unless considered necessary by the Investigator for emergency situations and/or for reasons of subject safety.

Unplanned or unintentional unblinding

Unblinding at the clinical site for any other reason was considered a major protocol deviation.

The Investigator was to contact the Medical Monitor before breaking the blind, if possible. The reason for breaking the blind had to be fully documented.

Statistical Methods

Unless otherwise stated, all primary and secondary efficacy endpoints were analyzed for the FAS and PPS.

For the efficacy evaluation of platelet count responses, platelet counts assessed by local laboratories were used. Platelet counts collected via the central laboratory were used in the safety assessments of clinical laboratory tests.

The methods used for efficacy analysis for the Core Phase are summarized in Table 5 below. All CMH tests at α =0.05 within each age cohort were performed adjusting for baseline platelet count category ($\leq 15 \times 10^9$/L vs. $>15 \times 10^9$/L). For the CMH test in the overall group, the test was performed adjusting for age cohort and baseline platelet count category. Fisher's exact test was used if the number of durable platelet responders was sparse in the strata (less than 3 in a specific subgroup). Durable platelet response with 2-sided 95 % exact binomial (Clopper-Pearson) CI was provided. The difference in response rate (avatrombopag – placebo) with 2-sided 95 % CI (Wald) was also provided.

Subjects without sufficient data for the determination of response status (i.e., responder vs. non-responder) were treated as non-responders in the analysis.

For the primary efficacy endpoint determination, a subject must have remained in the Core Phase through at least Week 10 (to have at least 6 weeks of platelet count data starting from Week 5 to either Week 12 if the subject completed the Core Phase or the last week if the subject prematurely terminated the Core Phase). If a subject terminated the Core Phase prior to Week 10, they would be considered a non-responder for the primary efficacy endpoint.

Table 5. Efficacy analysis methods for Core Phase

Endpoint	Analysis Method
Primary Efficacy Endpoint	
Durable platelet response defined as proportion of subjects achieving at least 6 out of 8 weekly platelet counts $\geq 50\times10^9$/L during the last 8 weeks of the 12-week Treatment Period in the Core Phase in the absence of rescue medication. In the case of rescue medication being used, platelet count assessments from the start date of rescue medication up until 4 weeks after the end date of rescue medication will be excluded from analysis.	CMH test
Alternative Primary Efficacy Endpoint (per EU PIP)	
• Platelet response defined as proportion of subjects for whom at least 2 consecutive platelet assessments are $\geq 50\times10^9$/L during last 8 weeks of the 12-week treatment in the Core Phase in the absence of rescue medication.	CMH test
Additional Secondary Efficacy Endpoints	
• Percentage of weeks subjects have a platelet count $\geq 50\times10^9$/L during 12 weeks of treatment in the Core Phase in the absence of rescue therapy. Denominator for this calculation is based on the number of weeks the subject was on treatment (up to 12 weeks).	Nonparametric Wilcoxon Rank Sum tests
• Platelet response at Day 8 (defined by the proportion of subjects with a platelet count $\geq 50\times10^9$/L at Day 8, in the absence of rescue therapy).	CMH test
• Percentage of weeks subjects have a platelet count between $\geq 50\times10^9$/L and $\leq 150\times10^9$/L during 12 weeks of treatment in the Core Phase in the absence of rescue therapy. Denominator for this calculation is based on the number of weeks the subject was on treatment (up to 12 weeks).	Nonparametric Wilcoxon Rank Sum tests
• Proportion of subjects who require rescue medications during 12 weeks of treatment in the Core Phase of the study.	CMH test
• Overall incidence and incidence of severe bleeding symptoms (scales 3 and 4) associated with ITP measured using the WHO Bleeding Scale.	CMH test

Abbreviations: CMH, Cochran-Mantel-Haenzel; EU, European Union; ITP, Immune thrombocytopenia; PIP, Pediatric investigation plan; WHO, World Health Organization.
Note: Fisher's exact test was to be used if CMH test failed.

If the test of the treatment effect on the primary efficacy endpoint was statistically significant, the statistical tests on the secondary efficacy endpoints were considered inferential; otherwise, the tests were considered descriptive, and no statistical inference could be drawn with regard to the secondary efficacy endpoints.

To control the family-wise Type I error rate at a significance level of α=0.05 (2-sided), a stepdown closed testing procedure was used when testing the secondary efficacy endpoints. The alternative primary efficacy endpoint was tested as the first (key) secondary endpoint. Starting with the first secondary efficacy endpoint, if the test was significant at α=0.05, then the test on the next endpoint was considered inferential; otherwise, the tests on the subsequent endpoints were considered descriptive only. This process was repeated from the top of the hierarchy for the remaining endpoints.

The efficacy variables collected during the Extension Phase were summarized descriptively.

CHMP's comments:

The statistical methods are considered acceptable in this setting.

Results

Participant flow

Core Phase

A total of 83 subjects were screened in the Core Phase, of whom 75 were enrolled in the study.

Eight subjects were considered screen failures because of failure to meet inclusion/exclusion criteria (7 subjects) and other reasons (1 subject).

A total of 75 subjects were randomly assigned to 3 age cohorts in a 2:2:1 ratio as shown below:

- Cohort 1: ≥12 to <18 years (n=21 avatrombopag; 8 placebo)
- Cohort 2: ≥6 to <12 years (n=20 avatrombopag; 8 placebo)
- Cohort 3: ≥1 to <6 years (n=13 avatrombopag; 5 placebo)

Overall, 54 subjects were randomized to avatrombopag, and 21 subjects were randomized to

placebo in the Core Phase (Table 6 below).

The majority (44 [81.5 %]) of the subjects randomized to avatrombopag completed both the Core Phase and Core Phase study treatment and the percentage of subjects who completed both the Core Phase and Core Phase study treatment was similar across the 3 cohorts. A total of 10 (18.5 %) subjects receiving avatrombopag discontinued the Core Phase and Core Phase study treatment due to lack of efficacy (7 [13.0 %] subjects), AEs (2 [3.7 %] subjects), and investigator discretion (1 [1.9 %] subject). In subjects randomized to placebo, 1 (4.8 %) subject completed both the Core Phase and Core Phase study treatment, and 20 (95.2 %) subjects discontinued the Core Phase study treatment, either due to lack of efficacy (19 [90.5 %] subjects) or an adverse event (1 [4.8 %] subject).

Table 6. Subject disposition in Core Phase - Full Analysis Set

	Cohort 1: ≥12 to <18 years		Cohort 2: ≥6 to <12 years		Cohort 3: ≥1 to <6 years		Overall	
	Avatrombopag (N=21) n (%)	Placebo (N=8) n (%)	Avatrombopag (N=20) n (%)	Placebo (N=8) n (%)	Avatrombopag (N=13) n (%)	Placebo (N=5) n (%)	Avatrombopag (N=54) n (%)	Placebo (N=21) n (%)
Subjects who completed the Core Phase	17 (81.0)	1 (12.5)	16 (80.0)	0	11 (84.6)	0	44 (81.5)	1 (4.8)
Subjects who discontinued from the Core Phase	4 (19.0)	7 (87.5)	4 (20.0)	8 (100.0)	2 (15.4)	5 (100.0)	10 (18.5)	20 (95.2)
Reasons for Core Phase discontinuation[a]								
Adverse event	0	0	1 (5.0)	0	1 (7.7)	1 (20.0)	2 (3.7)	1 (4.8)
Investigator discretion	0	0	1 (5.0)	1 (12.5)	0	0	1 (1.9)	1 (4.8)
Lack of efficacy	4 (19.0)	7 (87.5)	2 (10.0)	7 (87.5)	1 (7.7)	4 (80.0)	7 (13.0)	18 (85.7)
Subjects who completed Core Phase study treatment	17 (81.0)	1 (12.5)	16 (80.0)	0	11 (84.6)	0	44 (81.5)	1 (4.8)
Subjects who prematurely discontinued the Core Phase study treatment	4 (19.0)	7 (87.5)	4 (20.0)	8 (100.0)	2 (15.4)	5 (100.0)	10 (18.5)	20 (95.2)
Reasons for Core Phase study treatment discontinuation[a]								
Adverse event	0	0	1 (5.0)	0	1 (7.7)	1 (20.0)	2 (3.7)	1 (4.8)
Investigator discretion	0	0	1 (5.0)	0	0	0	1 (1.9)	0
Lack of efficacy	4 (19.0)	7 (87.5)	2 (10.0)	8 (100.0)	1 (7.7)	4 (80.0)	7 (13.0)	19 (90.5)

Source: Table 14.1.1.2.
Abbreviations: CRF, Case report form; N, Total number of subjects; n, Number of subjects.
[a] Summary of reasons are based on data collected from CRF.
Note: Percentage is based on the number of subjects in the corresponding column (N) in the Full Analysis Set.

Recruitment

Core phase conduct period:

First Subject First Visit: 05 March 2021

Last Subject Last Visit: 08 November 2023

Extension Phase Conduct Period:

First Subject First Visit: 16 April 2021

Last Subject Last Visit: Ongoing

Database Cut-off Date: 18 DEC 2023

Baseline data

Table 7. Demographics and baseline characteristics for Core Phase – Full Analysis Set

	Cohort 1: ≥12 to <18 years		Cohort 2: ≥6 to <12 years		Cohort 3: ≥1 to <6 years		Overall	
	Avatrombopag (N=21)	Placebo (N=8)	Avatrombopag (N=20)	Placebo (N=8)	Avatrombopag (N=13)	Placebo (N=5)	Avatrombopag (N=54)	Placebo (N=21)
Age (years) at randomization								
n	21	8	20	8	13	5	54	21
Mean (SD)	13.6 (1.57)	14.0 (1.60)	7.7 (1.69)	9.5 (1.20)	3.4 (1.39)	4.0 (1.00)	8.9 (4.36)	9.9 (4.13)
Median	13.0	13.5	7.5	9.5	3.0	4.0	8.5	10.0
Min, Max	12, 17	12, 17	6, 11	8, 11	1, 5	3, 5	1, 17	3, 17
Sex, n (%)								
Male	13 (61.9)	3 (37.5)	9 (45.0)	2 (25.0)	8 (61.5)	4 (80.0)	30 (55.6)	9 (42.9)
Female	8 (38.1)	5 (62.5)	11 (55.0)	6 (75.0)	5 (38.5)	1 (20.0)	24 (44.4)	12 (57.1)
Ethnicity, n (%)								
Hispanic or Latino	0	0	1 (5.0)	2 (25.0)	2 (15.4)	0	3 (5.6)	2 (9.5)
Not Hispanic or Latino	20 (95.2)	6 (75.0)	19 (95.0)	6 (75.0)	11 (84.6)	3 (60.0)	50 (92.6)	15 (71.4)
Not Reported	0	1 (12.5)	0	0	0	1 (20.0)	0	2 (9.5)
Unknown	1 (4.8)	1 (12.5)	0	0	0	1 (20.0)	1 (1.9)	2 (9.5)
Race, n (%)								
Asian	1 (4.8)	0	0	0	2 (15.4)	1 (20.0)	3 (5.6)	1 (4.8)
White	18 (85.7)	7 (87.5)	19 (95.0)	6 (75.0)	11 (84.6)	2 (40.0)	48 (88.9)	15 (71.4)
Other	2 (9.5)	0	0	1 (12.5)	0	1 (20.0)	2 (3.7)	2 (9.5)
Not Reported	0	1 (12.5)	1 (5.0)	1 (12.5)	0	1 (20.0)	1 (1.9)	3 (14.3)
Region, n (%)								
United States	1 (4.8)	0	3 (15.0)	3 (37.5)	4 (30.8)	2 (40.0)	8 (14.8)	5 (23.8)
Europe	20 (95.2)	8 (100.0)	17 (85.0)	5 (62.5)	9 (69.2)	3 (60.0)	46 (85.2)	16 (76.2)

	Cohort 1: ≥12 to <18 years		Cohort 2: ≥6 to <12 years		Cohort 3: ≥1 to <6 years		Overall	
	Avatrombopag (N=21)	Placebo (N=8)	Avatrombopag (N=20)	Placebo (N=8)	Avatrombopag (N=13)	Placebo (N=5)	Avatrombopag (N=54)	Placebo (N=21)
Weight (kg)								
n	21	8	20	8	13	5	54	21
Mean (SD)	58.97 (12.043)	53.73 (11.474)	31.99 (11.232)	38.90 (14.487)	17.76 (6.439)	17.41 (3.174)	39.06 (19.916)	39.43 (18.018)
Median	62.60	53.75	31.70	35.05	16.70	19.00	36.40	37.82
Min, Max	36.1, 82.8	37.8, 72.0	16.3, 64.0	24.5, 70.8	9.8, 36.0	13.8, 20.3	9.8, 82.8	13.8, 72.0
Height (cm)								
n	21	8	20	8	13	5	54	21
Mean (SD)	163.5 (9.48)	159.9 (8.08)	131.2 (13.62)	140.8 (11.53)	101.8 (12.96)	104.7 (10.82)	136.7 (27.10)	139.5 (23.70)
Median	165.0	160.0	129.3	140.5	102.8	107.0	136.3	142.0
Min, Max	149, 179	149, 170	103, 159	128, 166	78, 118	89, 119	78, 179	89, 170
BMI (kg/m^2)								
n	21	8	20	8	13	5	54	21
Mean (SD)	22.08 (4.418)	20.90 (3.402)	18.08 (3.237)	19.13 (4.012)	16.83 (3.089)	15.81 (1.747)	19.33 (4.289)	19.01 (3.780)
Median	22.79	20.23	17.58	18.97	16.05	16.60	17.94	18.28
Min, Max	14.3, 29.6	17.1, 25.2	14.0, 26.1	14.1, 25.9	14.2, 26.3	13.4, 17.4	14.0, 29.6	13.4, 25.9

Source: Table 14.1.3.1.
Abbreviations: BMI, Body mass index; Max, Maximum; Min, Minimum; N, Total number of subjects; n, Number of subjects; SD, Standard deviation.
Note: Percentage is based on the number of subjects in the corresponding column (N).

Overall, the mean (SD) age was similar in subjects receiving avatrombopag (8.9 [4.36] years) and placebo (9.9 [4.13] years), with a slightly higher percentage of male than female subjects in the avatrombopag group (55.6 % and 44.4 %) and a lower percentage of male than female subjects in the placebo group (42.9 % and 57.1 %) (Table 7). Most subjects in the study were not Hispanic or Latino (92.6 % in the avatrombopag group and 71.4 % in the placebo group), were White (88.9 % in the avatrombopag group and 71.4 % in the placebo group) and were from Europe (85.2 % in the avatrombopag group and 76.2 % in the placebo group). The mean weight, height, and BMI were

similar between the subjects receiving avatrombopag and placebo. The demographic and baseline characteristics were generally similar among Cohorts 1, 2, and 3 except for age, weight, and height, as expected based on the defined age ranges for each cohort.

CHMP's comments:

Overall, baseline characteristics were comparable between groups when considering the low number of participants in some of the groups.

Number analysed

All randomized subjects (54 subjects receiving avatrombopag and 21 subjects receiving placebo) were included in the FAS in the Core Phase and Safety Analysis Set; 48 subjects receiving avatrombopag and 19 subjects receiving placebo were included in the PPS.

A similar proportion of subjects in the avatrombopag (6 [11.1 %] subjects) and placebo (2 [9.5 %]) groups were excluded from the PPS. The reasons for exclusion from the PPS were accidental unblinding, mis-stratification at randomization, and major protocol deviations which could impact endpoint evaluation.

Efficacy results

Primary endpoint – durable platelet response

Table 8. Primary efficacy analysis: Durable platelet response in the absence of rescue therapy in Core Phase – Full Analysis Set

	Cohort 1: ≥12 to <18 years		Cohort 2: ≥6 to <12 years		Cohort 3: ≥1 to <6 years		Overall	
	Avatrombopag (N=21)	Placebo (N=8)	Avatrombopag (N=20)	Placebo (N=8)	Avatrombopag (N=13)	Placebo (N=5)	Avatrombopag (N=54)	Placebo (N=21)
Durable platelet response, n (%)								
Yes	9 (42.9)	0	4 (20.0)	0	2 (15.4)	0	15 (27.8)	0
No	12 (57.1)	8 (100.0)	16 (80.0)	8 (100.0)	11 (84.6)	5 (100.0)	39 (72.2)	21 (100.0)
Baseline platelet count ≤15×10⁹/L[a]								
n	17	6	16	6	12	5	45	17
Yes	7 (41.2)	0	3 (18.8)	0	2 (16.7)	0	12 (26.7)	0
No	10 (58.8)	6 (100.0)	13 (81.3)	6 (100.0)	10 (83.3)	5 (100.0)	33 (73.3)	17 (100.0)
Baseline platelet count >15×10⁹/L[a]								
n	4	2	4	2	1	0	9	4
Yes	2 (50.0)	0	1 (25.0)	0	0	0	3 (33.3)	0
No	2 (50.0)	2 (100.0)	3 (75.0)	2 (100.0)	1 (100.0)	0	6 (66.7)	4 (100.0)
95 % CI for proportion of response	21.8, 66.0	0.0, 36.9	5.7, 43.7	0.0, 36.9	1.9, 45.4	0.0, 52.2	16.5, 41.6	0.0, 16.1
Difference of proportion (avatrombopag – placebo) (95 % CI)	42.9 (21.7, 64.0)		20.0 (2.5, 37.5)		15.4 (-4.2, 35.0)		27.8 (15.8, 39.7)	
CMH test (avatrombopag vs. placebo) p-value	-		-		-		0.0077[b]	

Source: Table 14.2.1.2.

Abbreviations: CI, Confidence interval; CMH, Cochran–Mantel–Haenszel; IRT, Interactive response technology; N, Total number of subjects; n, Number of subjects; vs, Versus.

a Percentage is based on the number of subjects with corresponding baseline platelet count (n).

b Denotes p-value from Fisher's Exact Test, which was used in place of CMH test due to sparse number of responders in the strata.

Note: CMH test is adjusted for baseline platelet count withing each age cohort. In the overall group, the CMH test is adjusted for age cohort and baseline platelet count.

Note: Baseline platelet count category is based on the data at randomization per IRT presented in Appendix 16.1.7.

Note: Durable platelet response is defined as subjects achieving at least 6 out of 8 weekly platelet counts ≥50× 109/L during the last 8 weeks of the 12-week treatment period in the Core Phase in the absence of rescue medication. In the case of rescue medication being used, platelet count assessments from the start date of rescue medication up until 4 weeks after the end date of rescue medication will be excluded from analysis.

Note: Percentage is based on the number of subjects in the corresponding column (N).

The primary efficacy endpoint was durable platelet response as defined by the proportion of subjects achieving at least 6 out of 8 weekly platelet counts ≥50×109/L during the last 8 weeks of the 12-week Treatment Period in the Core Phase in the absence of rescue medication.

Avatrombopag met the primary endpoint, showing superiority over placebo (p=0.0077; 95 % CI: 16.5, 41.6) in adolescents and children with ITP ≥6 months duration.

Overall, 27.8 % of subjects achieved durable platelet response with avatrombopag. The durable platelet response was highest in Cohort 1 (42.9 %); however, the study was not powered to demonstrate durable platelet response within cohorts. No subject in the placebo group had a durable platelet response.

CHMP's comments:

The primary endpoint, durable platelet response, was met with statistical significance. There were differences in response between the cohorts with the highest response in cohort 1. There were responders in all cohorts. No subject in the placebo group had a durable platelet response.

Alternative primary efficacy endpoint - platelet response

Table 9. Alternate primary efficacy analysis: Platelet response in the absence of rescue therapy in Core Phase – Full Analysis Set

	Cohort 1: ≥12 to <18 years		Cohort 2: ≥6 to <12 years		Cohort 3: ≥1 to <6 years		Overall	
	Avatrombopag (N=21)	Placebo (N=8)	Avatrombopag (N=20)	Placebo (N=8)	Avatrombopag (N=13)	Placebo (N=5)	Avatrombopag (N=54)	Placebo (N=21)
Platelet response, n (%)								
Yes	17 (81.0)	0	17 (85.0)	0	10 (76.9)	0	44 (81.5)	0
No	4 (19.0)	8 (100.0)	3 (15.0)	8 (100.0)	3 (23.1)	5 (100.0)	10 (18.5)	21 (100.0)
Baseline platelet count ≤15×10⁹/L[a]								
n	17	6	16	6	12	5	45	17
Yes	14 (82.4)	0	13 (81.3)	0	9 (75.0)	0	36 (80.0)	0
No	3 (17.6)	6 (100.0)	3 (18.8)	6 (100.0)	3 (25.0)	5 (100.0)	9 (20.0)	17 (100.0)
Baseline platelet count >15×10⁹/L[a]								
n	4	2	4	2	1	0	9	4
Yes	3 (75.0)	0	4 (100.0)	0	1 (100.0)	0	8 (88.9)	0
No	1 (25.0)	2 (100.0)	0	2 (100.0)	0	0	1 (11.1)	4 (100.0)
95 % CI for proportion of response	58.1, 94.6	0.0, 36.9	62.1, 96.8	0.0, 36.9	46.2, 95.0	0.0, 52.2	68.6, 90.7	0.0, 16.1
Difference of proportion (avatrombopag – placebo) (95 % CI)	81.0 (64.2, 97.7)		85.0 (69.4, 100.0)		76.9 (54.0, 99.8)		81.5 (71.1, 91.8)	
CMH test (avatrombopag vs. placebo) p-value	-		-		-		<0.0001[b]	

Source: Table 14.2.2.1.

Abbreviations: CI, Confidence interval; CMH, Cochran–Mantel–Haenszel; IRT, Interactive response technology; N, Total number of subjects; n, Number of subjects; vs, Versus.

a Percentage is based on the number of subjects with corresponding baseline platelet count (n).

b Denotes p-value from Fisher's Exact Test, which was used in place of CMH test due to sparse number of responders in the strata.

Note: CMH test is adjusted for baseline platelet count withing each age cohort. In the overall group, the CMH test is adjusted for age cohort and baseline platelet count.

Note: Baseline platelet count category is based on the data at randomization per IRT presented in Appendix 16.1.7.

Note: Percentage is based on the number of subjects in the corresponding column (N).

Note: Platelet response defined as proportion of subjects for whom at least 2 consecutive platelet assessments are ≥ 50×109/L over the 12 weeks of treatment in the Core Phase in the absence of rescue medication. In the case of rescue medication being used, platelet count assessments from the start date of rescue medication up until 4 weeks after the end date of rescue medication were excluded from analysis.

The alternative primary endpoint, platelet response, was defined as the proportion of subjects for whom at least 2 consecutive platelet assessments are ≥50×109/L over the 12 weeks of treatment in the Core Phase in the absence of rescue medication.

Avatrombopag met the alternative primary endpoint, showing superiority over placebo (p<0.0001; 95% CI: 71.1, 91.8) in adolescents and children with ITP ≥6 months duration. Overall, 81.5 % of subjects in the avatrombopag group had a platelet response and this percentage was consistent across age cohorts.

CHMP's comments:

The alternative primary endpoint, platelet response, was also met with statistical significance. No subject in the placebo group had a platelet response.

Other efficacy results (secondary endpoints)

- Across secondary efficacy endpoints, avatrombopag was superior ($p<0.0001$) to the placebo group for percentage of the total weeks of treatment with the platelet count ≥50×109/L, platelet response at Day 8, and percentage of weeks of platelet count between ≥50×109/L and ≤150×109/L during the 12 weeks of treatment of the Core Phase.
- A significantly lower proportion of subjects in the avatrombopag group than in the placebo group ($p=0.0008$) required rescue therapy.
- The proportion of subjects with any bleeding event (Grade 1 to 4) was similar in the avatrombopag and placebo groups. A higher proportion of subjects in the placebo group experienced moderate (Grade 2) and severe (Grade 3) bleeding events, and a higher proportion of subjects in the avatrombopag group reported no bleeding events (Grade 0).
- The exploratory efficacy endpoint of durable platelet response during Month 3 in the absence of rescue therapy was superior for avatrombopag compared to placebo ($p=0.0008$).
- The palatability and acceptability questionnaire results showed the avatrombopag powder formulation mixed to make an oral suspension to be satisfactory for clinical use.

CHMP's comments:

The secondary endpoints can be considered supportive of the efficacy of avatrombopag in the target population.

Safety results

2.3.2.1. Adverse events

Table 10. Treatment-emergent adverse events by preferred term during Core Phase (≥5 % overall) - Safety Analysis Set

	Cohort 1: ≥12 to <18 years		Cohort 2: ≥6 to <12 years		Cohort 3: ≥1 to <6 years		Overall	
	Avatrombopag (N=21) n (%)	Placebo (N=8) n (%)	Avatrombopag (N=20) n (%)	Placebo (N=8) n (%)	Avatrombopag (N=13) n (%)	Placebo (N=5) n (%)	Avatrombopag (N=54) n (%)	Placebo (N=21) n (%)
Any TEAE	17 (81.0)	6 (75.0)	20 (100.0)	5 (62.5)	13 (100.0)	5 (100.0)	50 (92.6)	16 (76.2)
Petechiae	7 (33.3)	1 (12.5)	4 (20.0)	4 (50.0)	3 (23.1)	1 (20.0)	14 (25.9)	6 (28.6)
Epistaxis	2 (9.5)	1 (12.5)	6 (30.0)	2 (25.0)	4 (30.8)	1 (20.0)	12 (22.2)	4 (19.0)
Ecchymosis	1 (4.8)	0	6 (30.0)	1 (12.5)	3 (23.1)	0	10 (18.5)	1 (4.8)
Headache	2 (9.5)	1 (12.5)	8 (40.0)	3 (37.5)	0	0	10 (18.5)	4 (19.0)
Cough	0	0	3 (15.0)	0	6 (46.2)	0	9 (16.7)	0
Pyrexia	0	0	4 (20.0)	0	5 (38.5)	0	9 (16.7)	0
Oropharyngeal pain	0	0	4 (20.0)	0	3 (23.1)	0	7 (13.0)	0
Upper respiratory tract infection	3 (14.3)	2 (25.0)	3 (15.0)	0	0	0	6 (11.1)	2 (9.5)
Arthralgia	3 (14.3)	0	0	0	1 (7.7)	0	4 (7.4)	0
COVID-19	3 (14.3)	0	1 (5.0)	1 (12.5)	0	0	4 (7.4)	1 (4.8)
Diarrhoea	0	0	2 (10.0)	0	2 (15.4)	0	4 (7.4)	0
Nasopharyngitis	1 (4.8)	0	2 (10.0)	0	1 (7.7)	0	4 (7.4)	0
Vomiting	0	0	2 (10.0)	0	2 (15.4)	0	4 (7.4)	0
Abdominal pain	0	0	1 (5.0)	0	2 (15.4)	0	3 (5.6)	0
Contusion	0	0	1 (5.0)	0	2 (15.4)	1 (20.0)	3 (5.6)	1 (4.8)
Haematoma	3 (14.3)	2 (25.0)	0	1 (12.5)	0	0	3 (5.6)	3 (14.3)
Mouth haemorrhage	0	0	0	0	3 (23.1)	1 (20.0)	3 (5.6)	1 (4.8)
Pain in extremity	0	0	2 (10.0)	0	1 (7.7)	0	3 (5.6)	0
Rhinorrhoea	0	0	2 (10.0)	0	1 (7.7)	0	3 (5.6)	0
Viral upper respiratory tract infection	1 (4.8)	0	1 (5.0)	0	1 (7.7)	0	3 (5.6)	0
Gingival bleeding	1 (4.8)	1 (12.5)	0	1 (12.5)	1 (7.7)	0	2 (3.7)	2 (9.5)
Rectal haemorrhage	0	0	1 (5.0)	0	0	2 (40.0)	1 (1.9)	2 (9.5)

Source: Table 14.3.1.3.1.

Abbreviations: AE, Adverse event; COVID-19, Coronavirus disease 2019; MedDRA, Medical Dictionary for Regulatory Activities; N, Total number of

subjects; n, Number of subjects; TEAE, Treatment-emergent adverse events.

Note: TEAE is defined as any AE that occurs after administration of the first dose of study drug.

Note: Adverse events are coded using MedDRA (Version 26.1).

Note: Subjects with more than 1 AE within a preferred term are only counted once in that category.

Note: TEAEs with starting date prior to the first dose date in the Extension Phase were classified as TEAEs in the Core Phase.

Note: Percentage is based on the number of subjects in the corresponding column (N).

CHMP's comments:

The overall incidence of TEAEs during the 12-week treatment duration was higher in subjects

receiving avatrombopag (92.6 %) vs. placebo (76.2 %). Across the cohorts, all subjects in

Cohorts 2 and 3 (100 % each) and 17 (81.0 %) subjects in Cohort 1 experienced TEAEs.

Curiously, epistaxis, ecchymosis and haematoma were more common in the avatrombopag arm compared with the placebo arm. However, petechiae, gingival bleeding and rectal haemorrhage were more common in the placebo arm.

Table 11. Treatment-emergent adverse events by preferred term during Extension Phase (≥5 % overall) - Extension Phase Safety Analysis Set

	Avatrombopag			
	Cohort 1: ≥12 to <18 years (N=29) n (%)	Cohort 2: ≥6 to <12 years (N=27) n (%)	Cohort 3: ≥1 to <6 years (N=17) n (%)	Overall (N=73) n (%)
Any TEAE	27 (93.1)	26 (96.3)	10 (58.8)	63 (86.3)
Upper respiratory tract infection	8 (27.6)	11 (40.7)	3 (17.6)	22 (30.1)
Epistaxis	1 (3.4)	8 (29.6)	5 (29.4)	14 (19.2)
Cough	2 (6.9)	9 (33.3)	2 (11.8)	13 (17.8)
Pyrexia	2 (6.9)	8 (29.6)	3 (17.6)	13 (17.8)
Nasopharyngitis	4 (13.8)	6 (22.2)	1 (5.9)	11 (15.1)
Headache	3 (10.3)	5 (18.5)	2 (11.8)	10 (13.7)
Oropharyngeal pain	5 (17.2)	3 (11.1)	2 (11.8)	10 (13.7)
Petechiae	6 (20.7)	2 (7.4)	1 (5.9)	9 (12.3)
Diarrhoea	4 (13.8)	3 (11.1)	1 (5.9)	8 (11.0)
Nasal congestion	1 (3.4)	3 (11.1)	3 (17.6)	7 (9.6)
Nausea	3 (10.3)	2 (7.4)	1 (5.9)	6 (8.2)
Rhinitis	3 (10.3)	2 (7.4)	1 (5.9)	6 (8.2)
Rhinorrhoea	2 (6.9)	4 (14.8)	0	6 (8.2)
Ecchymosis	1 (3.4)	2 (7.4)	2 (11.8)	5 (6.8)
Gastroenteritis	3 (10.3)	1 (3.7)	1 (5.9)	5 (6.8)
Influenza	3 (10.3)	1 (3.7)	1 (5.9)	5 (6.8)
Viral upper respiratory tract infection	1 (3.4)	3 (11.1)	1 (5.9)	5 (6.8)
Abdominal pain	2 (6.9)	1 (3.7)	1 (5.9)	4 (5.5)
Contusion	1 (3.4)	2 (7.4)	1 (5.9)	4 (5.5)
Haematoma	1 (3.4)	2 (7.4)	1 (5.9)	4 (5.5)
Head injury	2 (6.9)	2 (7.4)	0	4 (5.5)
Iron deficiency	1 (3.4)	2 (7.4)	1 (5.9)	4 (5.5)
Pharyngitis	2 (6.9)	2 (7.4)	0	4 (5.5)
Thrombocytopenia	3 (10.3)	1 (3.7)	0	4 (5.5)
Toothache	1 (3.4)	2 (7.4)	1 (5.9)	4 (5.5)
Vomiting	2 (6.9)	1 (3.7)	1 (5.9)	4 (5.5)

Source: Table 14.3.1.3.2.

Abbreviations: AE, Adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, Total number of

subjects; n, Number of subjects; TEAE, Treatment-emergent adverse events.

Note: TEAE is defined as any AE that occurs after administration of the first dose of study drug.

Note: Adverse events are coded using MedDRA (Version 26.1).

Note: Subjects with more than 1 AE within a preferred term are only counted once in that category.

Note: TEAEs with starting date on or after the first dose date in the Extension Phase will be classified as TEAEs in the Extension Phase.

Note: Percentage is based on the number of subjects in the corresponding column (N).

As of the cutoff date, the median avatrombopag treatment duration was 78.71 weeks in Cohort 1,

53.57 weeks in Cohort 2, and 25.86 weeks in Cohort 3.

TEAEs were reported in a total of 63 (86.3 %) subjects, which included 27 (93.1 %) subjects in Cohort 1, 26 (96.3 %) subjects in Cohort 2, and 10 (58.8 %) subjects in Cohort 3.

CHMP's comments:

Overall, the most frequently reported (≥5 % overall) TEAEs were upper respiratory tract infection, epistaxis, cough, pyrexia, nasopharyngitis, headache, oropharyngeal pain, petechiae, diarrhoea, nasal congestion, nausea, rhinitis, rhinorrhoea, ecchymosis, gastroenteritis, influenza, viral upper respiratory tract infection, abdominal pain, contusion, hematoma, head injury, iron deficiency, pharyngitis, thrombocytopenia, toothache, and vomiting.

2.3.2.2. Serious adverse events

Core Phase

The overall incidence of SAEs was higher in subjects receiving avatrombopag (9.3 %) than placebo (4.8 %). Across the cohorts receiving avatrombopag, the incidence of SAEs was higher in Cohort 3 (15.4 %) than in Cohorts 1 (4.8 %) and 2 (10.0 %). The most commonly reported SAEs by SOC (≥2 subjects) included blood and lymphatic system disorders and gastrointestinal disorders. All SAEs by PT were reported in 1 subject each.

CHMP's comments:

SAEs were rare and it is difficult to assess whether they can be attributed to the underlying pathology or to treatment.

Extension Phase

Overall, SAEs were reported in 21.9 % of subjects, with higher incidences in Cohort 1 (24.1 %)

than in Cohorts 2 (22.2 %) and 3 (17.6 %).

The most commonly reported SAEs by SOC (≥2 subjects) included blood and lymphatic system disorders; gastrointestinal disorders; general disorders and administration site conditions; infections and infestations; injury, poisoning and procedural complications; respiratory, thoracic and mediastinal disorders; and skin and subcutaneous tissue disorders.

The most commonly reported SAEs by PT included thrombocytopenia and epistaxis (4 [5.5 %] subjects each). Other SAEs were reported in 1 (1.4 %) subject each.

2.3.2.3. Deaths

No deaths were reported in the study as of the data cut-off date.

2.3.2.4. Key safety findings

Key safety findings during the Core Phase of the study include the following:

- Overall, subjects in the avatrombopag group experienced a higher incidence of treatment-emergent adverse events (TEAEs) (92.6 % vs. 76.2 %), related TEAEs (13.0 % vs. 4.8 %), and serious adverse events (SAEs) (9.3 % vs. 4.8 %) than the placebo group. However, the median duration of treatment of avatrombopag subjects (12 weeks) was twice that of placebo subjects (6 weeks).
- The majority of the TEAEs were mild (Grade 1; 48.1 % in avatrombopag and 33.3 % in placebo groups) or moderate (Grade 2; 40.7 % in avatrombopag and 42.9 % in placebo groups). Severe (Grade 3) TEAEs were reported in 2 (3.7 %) subjects receiving avatrombopag.
- No subject in the avatrombopag or placebo groups died or reported an AESI.
- Two (3.7 %) subjects in the avatrombopag group and 1 (4.8 %) subject in the placebo group discontinued study drug due to a TEAE.
- Analyses of changes from baseline over time in chemistry and hematology laboratory analytes did not reveal any clinically meaningful trends, except for platelet count.

Key safety findings during the Extension Phase as of the cutoff date (18 Dec 2023) are as follows:

- Overall, TEAEs were reported in 86.3 % of subjects; SAEs were reported in 21.9 % of subjects, with the most commonly reported preferred terms (PTs) being thrombocytopenia and epistaxis (5.5 % of subjects each). Grade 3 TEAEs were reported in 15.1 % of subjects and 1 subject experienced a Grade 4 TEAE.
- Overall, 6.8 % of subjects experienced TEAEs leading to study discontinuation, including aplastic anemia, bone marrow reticulin fibrosis, deep vein thrombosis, paresthesia and dysarthria, bone marrow disorder, blood lactate dehydrogenase increased, and aspartate aminotransferase increased.
- One subject experienced a thromboembolic event (deep vein thrombosis) and 4 subjects reported Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 bleeding events.

CHMP's comments:

The summary of the key safety findings is agreed upon.

2.3.3. Discussion on clinical aspects

The Core Phase of this Phase 3b, multi-center, randomized, double-blind, placebo-controlled, parallel-group study included a total of 75 adolescents and children with ITP of ≥6 months duration enrolled to 1 of 3 age cohorts, with 54 subjects in total randomized to avatrombopag and 21 subjects in total randomized to placebo.

Avatrombopag met the primary endpoint of durable platelet response, showing superiority over placebo (p=0.0077). Durable platelet response, defined as the proportion of subjects achieving at least 6 out of 8 weekly platelet counts ≥50×109/L during the last 8 weeks of the 12-week Treatment Period

in the Core Phase in the absence of rescue medication, was observed in 27.8 % of subjects in the avatrombopag group and no subjects in the placebo group. The durable platelet response to avatrombopag was the highest in Cohort 1 (42.9 %). An initial peak of median platelet count was observed after 2 weeks in all cohorts and the median platelet count generally remained above 50×109/L during the last 8 of the 12 weeks of treatment.

Avatrombopag met the alternative primary endpoint of platelet response, showing superiority over placebo (p=0.0001). Platelet response, defined as the proportion of subjects for whom at least 2 consecutive platelet assessments are ≥50×109/L over the 12-week Treatment Period in the Core Phase in the absence of rescue medication, was achieved by 81.5 % of subjects in the avatrombopag group, and this percentage was consistent across all cohorts. No subject in the placebo group had a platelet response.

All secondary endpoints related to platelet count responses showed a significant benefit of avatrombopag over placebo. Rescue medication use (corticosteroids or IVIg) was significantly higher in the placebo group. Bleeding events were similar between the avatrombopag and placebo groups with no statistically significant differences observed. A higher proportion of subjects in the placebo group experienced moderate and severe bleeding (WHO Grades 2 and 3) compared to the avatrombopag group and a higher proportion of avatrombopag subjects experienced no bleeding symptoms at all (WHO Grade 0) post-baseline during the Core Phase.

An exploratory efficacy endpoint, the durable platelet response at Month 3 (3 of 4 weekly platelet counts ≥50×109/L in weeks 9-12 in the absence of rescue medication) also showed that avatrombopag was superior to placebo. Results of a palatability and acceptability questionnaire showed the avatrombopag powder formulation mixed to make an oral suspension to be satisfactory for clinical use.

Avatrombopag was safe and well tolerated in this population of paediatric subjects ≥1 to <18 years of age with ITP, and no new or unexpected safety findings were observed. In the Core Phase, there were no deaths or AESIs reported and few discontinuations due to AEs. As of the cut-off date for the Extension Phase, there have been no deaths and few discontinuations due to AEs; 1 thromboembolic event has been reported.

In this placebo-controlled study of heavily pre-treated children and adolescents with persistent and chronic ITP, avatrombopag showed significant efficacy for all platelet count endpoints and a significant reduction in the use of rescue medications.

CHMP's comments:

Overall, the discussion of the efficacy and safety findings are acknowledged.

3. Rapporteur's CHMP overall conclusion and recommendation

The MAH has submitted a CSR for the pediatric study AVA-PED-301, in accordance with Article 46 of Regulation (EC) No1901/2006.

Furthermore, the MAH has expressed that the MAH plans to submit a Type II variation to extend the ITP indication to the paediatric population, and a line extension for the powder for oral suspension formulation.

☒ **Fulfilled:**

No further action required, however further data are expected in the context of a grouped line extension and type II variation prior any conclusion on product information amendments is made. The MAH has committed to submit this grouped line extension and type II variation application.