10 December 2020
EMA/CHMP/7081/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Doptelet

International non-proprietary name: avatrombopag

Procedure No. EMEA/H/C/004722/II/0004/G

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

1G	1st Generation
2G	2nd Generation
AE	Adverse Event
AESI	Adverse Events of Special Interest
ASH	American Society for Hematology
BA	Bioavailability
BCSH	British Committee for Standards in Haematology
CLD	Chronic Liver Disease
C_{max}	Maximum Observed Concentration
c-Mpl	Thrombopoietin Receptor
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Child-Turcotte-Pugh
CYP	Cytochrome P
ELEVATE	Eltrombopag Evaluated for its Ability to Overcome Thrombocytopenia and Enable Procedures
EMA	European Medicines Agency
EOT	End of Treatment
FAS	Full Analysis Set
HCC	Hepatocellular Carcinoma
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITP	Immune Thrombocytopenia
IWG	International Working Group
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
OLE	Open-label Extension
PADER	Periodic Adverse Drug Experience Report
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)

PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred Term
PVT	Portal Vein Thrombosis
QTc	Corrected QT Interval
QTcF	QT Interval Corrected for Heart Rate using Fridericia's Formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SUCRA	Surface Under the Cumulative Ranking Curve
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TPO	Thrombopoietin
USPI	United States Prescribing Information
V/F	Apparent Volume of Distribution
WHO	World Health Organization

1. Background information on the procedure

Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Swedish Orphan Biovitrum AB (publ) submitted to the European Medicines Agency on 11 February 2020 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	I, IIIA and IIIB

Extension of indication to include the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments; consequently, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated. Additionally, the SmPC section 5.3 is updated with data from juvenile toxicity studies. Furthermore, an additional pack size of 30 tablets has been introduced with subsequent updates of sections 6.5 and 8 of the SmPC. The Package Leaflet and Labelling are updated in accordance. Version 2.1 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.1.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0373/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0373/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH did seek Scientific Advice at the CHMP.

The following aspects of the avatrombopag development program were discussed in the CHMP scientific advice procedures, and were implemented in the Phase 3 ITP clinical program as agreed: dosage regimen (including starting dose and dose titration scheme), study patient population, utilisation of a gastric biomarker panel to investigate potential for gastric toxicity (the primary toxicity identified from the nonclinical toxicology program), and analysis sets to be used for efficacy analyses.

Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: Andrea Laslop

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	29 Feb 2020	29 Feb 2020	☐
☐	CHMP Rapporteur Assessment Report	24 Apr 2020	23 Apr 2020	☐
☐	CHMP Co-Rapporteur Assessment Report	24 Apr 2020	24 Apr 2020	☐
☐	PRAC Rapporteur Assessment Report	30 Apr 2020	30 Apr 2020	☐
☐	PRAC members comments	06 May 2020	06 May 2020	☐
☐	Updated PRAC Rapporteur Assessment Report	07 May 2020	07 May 2020	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	14 May 2020	14 May 2020	☐
☐	CHMP members comments	18 May 2020	18 May 2020	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 May 2020	24 May 2020	☐
☐	Request for Supplementary Information	28 May 2020	28 May 2020	☐
☐	Submission deadline	17 Jul 2020	17 Jul 2020	
☐	Re-start of procedure	20 Jul 2020	20 Jul 2020	☐
☐	CHMP Rapporteur Assessment Report	24 Aug 2020	26 Aug 2020	☐
☐	PRAC Rapporteur Assessment Report	21 Aug 2020	21 Aug 2020	☐
☐	PRAC members comments	26 Aug 2020	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	27 Aug 2020	27 Aug 2020	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	04 Sept 2020	04 Sept 2020	☐
☐	CHMP members comments	07 Sept 2020	07 Sept 2020	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	10 Sept 2020	11 Sept 2020	☐

Status of this report and steps taken for the assessment				
☐	Request for Supplementary Information	17 Sept 2020	17 Sept 2020	☐
☐	Submission deadline	13 Oct 2020	13 Oct 2020	
☐	Re-start of procedure	14 Oct 2020	14 Oct 2020	☐
☐	CHMP Rapporteur Assessment Report	28 Oct 2020	28 Oct 2020	☐
☐	PRAC Rapporteur Assessment Report	19 Oct 2020	19 Oct 2020	☐
☐	PRAC members comments	21 Oct 2020	21 Oct 2020	☐
☐	Updated PRAC Rapporteur Assessment Report	22 Oct 2020	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	29 Oct 2020	29 Oct 2020	☐
☐	CHMP members comments	03 Nov 2020	03 Nov 2020	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	05 Nov 2020	05 Nov 2020	☐
☐	Request for Supplementary Information	12 Nov 2020	12 Nov 2020	☐
☐	Submission deadline	17 Nov 2020	17 Nov 2020	
☐	Re-start of procedure	18 Nov 2020	18 Nov 2020	☐
☐	CHMP Rapporteur Assessment Report	25 Nov 2020	27 Nov 2020	☐
☐	PRAC Rapporteur Assessment Report	25 Nov 2020	27 Nov 2020	☐
☐	PRAC members comments	30 Nov 2020	30 Nov 2020	☐
☐	Updated PRAC Rapporteur Assessment Report	03 Dec 2020	03 Dec 2020	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	26 Nov 2020	26 Nov 2020	☐
☐	CHMP members comments	30 Nov 2020	30 Nov 2020	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	03 Dec 2020	03 Dec 2020	☐
☒	Opinion	10 Dec 2020	10 Dec 2020	☐

2. Scientific discussion

2.1 Introduction

This type II variation is for a new indication for Doptelet (avatrombopag); the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments. There remains an important unmet medical need for new treatment options for these patients, given the variable, transient response to the currently approved agents, frequent relapse, and associated toxicities of the available treatments for ITP.

2.1.1 Problem statement

Disease or condition

Immune thrombocytopenia (ITP) is an acquired form of thrombocytopenia that is primarily due to autoantibody-mediated destruction of platelets. The autoantibodies may also affect megakaryocytes and impair platelet production. The condition is defined as a peripheral blood platelet count less than 100 x 10^9/L. ITP can be further classified pathophysiologically in a primary form (monosymptomatic) or secondary (associated with other conditions) and temporally in the acute (0 – 3 months), a persistent (3-12 months' duration) and a chronic (≥ 12 months' duration) form. In adults the condition typically has an insidious onset with no preceding viral or other illness and it normally follows a chronic course, (See Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia, Oncology Working Party).

Epidemiology and risk factors, screening tools/prevention

The reported incidence data for ITP in the European Union (EU) ranges from 1.6 to 4.4 per 100,000 (Moulis et al, Blood 2014; Schoonen et al, Br J Haematol 2009; Neylon et al, Br J Haematol 2003; Frederiksen & Schmidt, Blood 1999). The prevalence is 9.5 per 100,000 adults (Lambert & Gernsheimer, Blood 2017). There is an increasing incidence with older age and equal for the sexes except in the mid-adult years (30-60 years), when the disease is more prevalent in women. Childhood ITP has an incidence of between 1.9 and 6.4 per 100,000 per year with equal distribution between the sexes. There are an estimated 50,000 adult patients with chronic ITP in the EU (Gernsheimer, Eur J Haematol 2008).

Biologic features, Aetiology and pathogenesis

Primary ITP in adults has no known trigger or obvious cause. ITP is characterised by immune-mediated thrombocytopenia resulting from increased clearance of normal platelets and decreased platelet production:

- antibodies bind to circulating platelets and mediate clearance of platelets by tissue macrophages (primarily in spleen, but also liver) via surface fragment crystallizable (Fc) receptors
- antibodies may impair platelet function, resulting in bleeding that is disproportionate to the platelet count

- antibodies may bind to megakaryocytes, resulting in decreased platelet production.

Clinical presentation, diagnosis and stage/prognosis

Signs and symptoms vary widely. Many patients have either no symptoms or minimal bruising, whereas others experience serious bleeding, which may include gastrointestinal haemorrhage, extensive skin and mucosal haemorrhage, or intracranial haemorrhage. The severity of thrombocytopenia correlates to some extent but not completely with the bleeding risk. Additional factors may increase the risk (e.g., advanced age, lifestyle factors, concomitant medications, congenital or acquired bleeding disorders) and should be evaluated before the appropriate management is determined. Although haemorrhagic death is a major concern it has been reported that the estimated rate of fatal haemorrhage is around 0.02 to 0.04 cases per adult patient-year risk.

Diagnosis of ITP is one of exclusion, when the history, physical examination, complete blood count and examination of peripheral blood smear do not suggest other aetiology for the thrombocytopenia. Physical examination should be normal apart from bleeding signs. The peripheral blood count reveals isolated thrombocytopenia and normal red cell and white cell indices. If significant bleeding occurs there may be anaemia proportional to the degree of bleeding with possible iron deficiency. The peripheral blood smear reveals normal to large platelets in size and no abnormalities should be seen in red and white cell morphology. Bone marrow examination is currently not routinely conducted in patients with typical ITP presentations but reserved to selected cases such as those with an atypical presentation (Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia, EMA/CHMP/153191/2013, Oncology Working Party).

Management

The major goal for treatment of ITP is to provide a platelet count that prevents major bleeding rather than correcting the platelet count to normal levels. The management of ITP should be tailored to the individual patient and it is rarely indicated in those with platelet counts above 50 x 10^9/L in the absence of bleeding, trauma, surgery or high risk factors (e.g. patients on anticoagulation therapy). The management of ITP varies widely and current international guidelines recommend several first and second line options, including some medicinal products that have not been approved in the EU for this particular condition. First line treatment options include corticosteroids, intravenous immunoglobulin (IV Ig) and intravenous anti-D immunoglobulin (the latter only for non-splenectomised Rhesus-D positive patients). Patients who fail to respond or who relapse face the options of treatment with second line drug therapy or splenectomy but there is no clear evidence to support the best approach. Splenectomy can provide long term efficacy in around 60% of cases. Second line drug therapies include high dose dexamethasone or methylprednisolone, high dose IV Ig or anti-D Ig, vinca alkaloids and danazol, the immunosuppressants cyclophosphamide, azathioprine and cyclosporine or mycophenolate mofetil, TPO receptor agonists and the anti CD-20 monoclonal antibody rituximab.

ITP is a disease of increased platelet destruction but recent evidence suggests that suboptimal platelet production by suppression of megakaryocyte function also occurs. Thrombopoietin receptor (TPO-R) agonists activate the thrombopoietin receptor (c-Mpl) which is the primary factor that regulates platelet production. Treatment aimed at increasing the platelet production has become a potential treatment option and TPO-R agonists have been approved in the EU for the treatment of chronic ITP splenectomised adult patients who are refractory to other treatments or as second line therapy for non-splenectomised patients where surgery is contraindicated (Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia, EMA/CHMP/153191/2013, Oncology Working Party).

Clinical guidelines recommend the use of TPO receptor agonists for patients with ITP and a risk of severe bleeding who are not candidates for splenectomy, and who have failed at least one other therapy. The unmet medical need for effective and safe therapies for the treatment of patients with chronic ITP remains.

About the product

Avatrombopag maleate (previously known as E5501, AKR-501 monomaleate, YM477 monomaleate, and YM-301477 monomaleate), hereafter avatrombopag, is an orally administered, small molecule TPO receptor (c-Mpl) agonist that mimics the biologic effects of TPO in vitro and in vivo. The agent does not compete with TPO for binding to the TPO receptor and has an additive effect with TPO on platelet production resulting in a measured increase in platelet counts. TPO exerts its effect on megakaryocytopoiesis and thrombocytopoiesis through binding and activation of the TPO receptor, which is expressed on hematopoietic stem cells, cells of the megakaryocytic lineage, and platelets; like the approved TPO receptor agonists, avatrombopag also activates the human TPO receptor. After binding to a different site on the receptor, it stimulates signal transduction and mimics the biologic effects of TPO, which in turn increases platelet counts; this differential binding may limit off-target binding and be the basis for avatrombopag's lack of hepatotoxicity. Given its basic mechanism of action, by directly stimulating the normal production of new platelets by the bone marrow, avatrombopag has the potential to be useful for the treatment of thrombocytopenia of any etiology across a variety of indications and patient populations, including those with ITP.

Doptelet was previously approved for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure.

The development programme/compliance with CHMP guidance/ scientific advice

On 22nd of November 2019 the modification of the agreed paediatric investigation plan for avatrombopag with a deferral and a waiver was accepted by the EMA in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.

On 15th of April 2010 (Procedure No.: EMEA/H/SA/1606/1/2010/III) and on 17th of February 2011 (Procedure No.: EMEA/H/SA/1606/1/FU/1/2011/III) Eisai Limited requested scientific advice for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura, pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

Due to the length of time that has elapsed since the CHMP scientific advice (first scientific advice was issued in 2010 and follow-up scientific advice was issued in 2011), there are several aspects of the completed avatrombopag Phase 3 program that diverged from the original plan as agreed in these scientific advice procedures. Accordingly, a pre-submission meeting with the EU Rapporteur for this variation was conducted to discuss the existing avatrombopag nonclinical and clinical data for avatrombopag, and the suitability of the data to support a type II variation for Doptelet for the treatment of chronic ITP in adult patients who are refractory to other treatments.

2.2 Quality aspects

The addition of the pack size 30 x 20 mg film-coated tablets does not result in any changes to the quality part (module 3, part P.7), because the finished product is packed in blisters (Alu/Alu) and the

change only affects the number of blisters included in the package (10, 15 x 20 mg film-coated tablets is currently approved).

The tablets are supplied in cartons containing one or two aluminium blisters. Each blister contains either 10 or 15 tablets.

The MAH has also, with this variation application, included additional information on impurities in section 3.2.S.3.2. and in section 3.2.P.5.6.

Section 3.2.S.3.2.2.3.2 Control of Mutagenic Impurities:

Results of purge studies with the impurity ER-887068-00 (introduced relatively late in the synthesis) is provided. No carry-over to the drug substance is observed.

Section 3.2.S.3.2.2.3.3 Acceptable Daily Intake for Known or Potential Mutagenic Impurities:
Total daily intake was added for the CLD indication and ITP indication

Section 3.2.P.5.6.3 Elemental Impurities Risk Assessment:

Clarification was provided that the calculation provided for the ratio of potential uptake for each elemental impurity against Permitted Daily Exposure (PDE) described in the guideline for elemental impurities (ICH, Q3D) was based upon a total dose of 60 mg per day per the CLD indication. The total dose of 40 mg per day per the ITP indication would result in less exposure than that calculated for the 60 mg per day dose per the CLD indication.

2.2.1 Conclsion on Quality aspects

The change to the pack size is acceptable.

2.3 Non-clinical aspects

No new nonclinical data have been submitted in this application, which is considered acceptable by the CHMP. A summary of the definitive juvenile study has been included in section 5.3. of SmPC. This study will be summarised and re-assessed below. However, it should be noted that the new indication of ITP is not including children, i.e. the indication wording is as follows: Doptelet is indicated for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments.

2.3.1 Introduction

Avatrombopag is an orally administered, small molecule thrombopoietin receptor (c-Mpl) agonist that mimics the biologic effects of thrombopoietin (TPO), the principal physiologic regulator of platelet production. TPO exerts its effect on megakaryocytopoiesis and thrombocytopoiesis through binding and activation of c-Mpl, which is expressed on hematopoietic stem cells, cells of the megakaryocytic lineage, and platelets. Avatrombopag activates human c-Mpl through a mechanism that is different from TPO binding, but is still capable of stimulating signal transduction and mimicking the biologic effects of TPO.

The pharmacologic effect of avatrombopag is highly species-specific, showing activity only in humans and chimpanzees, and not in any other species tested (rat, hamster, guinea pig, rabbit, dog, common marmoset, squirrel monkey, rhesus monkey, cynomolgus monkey, olive baboon, pig). This species-specific activity of avatrombopag is attributed to histidine amino acid residue at position 499 (His499) in the transmembrane domain of human c- Mpl. His499 is conserved in humans and chimpanzees, but not found in other species.

The target indication for this type II variation is the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments.

The recommended starting dose for avatrombopag in patients with chronic ITP is 20 mg once daily with food in the absence of interacting medications, with the following adjustments to the starting dose based on specific interacting medications:

- Adjustment of the initial dose of avatrombopag to 40 mg once daily in the presence of a moderate or strong dual inducer for CYP2C9 and CYP3A4/5
- Adjustment of the initial dose of avatrombopag to 20 mg three times a week in the presence of a moderate or strong dual inhibitor for CYP2C9 and CYP3A4/5

To maintain platelet counts within the target range of 50×10^9/L to 150×10^9/L, adjustments to the dose level or frequency of dosing are recommended based on patients' platelet counts.

Avatrombopag is available as a 20 mg tablet, round, biconvex, pale-yellow, film-coated, and debossed with "AVA" on one side and "20" on the other side.

The full nonclinical program encompassed pharmacology, safety pharmacology, pharmacokinetics (PK), and toxicology studies designed to support safe clinical use. The performed nonclinical studies conformed to the study types and designs recommended by relevant International Council for Harmonisation (ICH) guidelines and satisfy the requirements of Article 8.3 of EC Directive 2001/83 (as amended). All pivotal toxicology studies and the battery of safety pharmacology studies were conducted in accordance with Good Laboratory Practice (GLP) regulations. In addition, all GLP studies were conducted by laboratories in countries that adhere to the Organisation for Economic Co-operation and Development (OECD) system for mutual acceptance of chemical safety data.

2.3.2 Pharmacology

There are no new primary, secondary or safety pharmacology studies for this Type II variation, nor are there any specific studies of relevance to the ITP indication. The same applies for pharmacodynamic drug interactions.

2.3.3 Pharmacokinetics

There are no new pharmacokinetic studies covering ADME submitted in support of the new indication. In terms of pharmacokinetic drug interactions, the MAH is referring to the Clinical Overview of *in vitro* and *in vivo* (clinical) pharmacokinetic drug interaction studies relevant to the ITP indication.

2.3.4 Toxicology

There are no new toxicology studies submitted in support of the new indication. The toxicity of avatrombopag was evaluated previously in a comprehensive set of toxicology studies encompassing all appropriate toxicologic endpoints based on the relevant regional and ICH guidelines. Avatrombopag was dosed orally, which is the route for clinical use. The toxicology program for avatrombopag is shown in Table 1.

Table 1: Avatrombopag Toxicology Program

Study Type and Duration	Route of Administration	Species	GLP Compliance
Single-dose Toxicity Studies	Oral	F344 Rat Monkey	Yes
Repeated-dose Toxicity Studies			
5 – 8 days	Oral	Mouse F344 Rat Dog Monkey	Yes/No[a]
2 weeks	Oral	Mouse	Yes
4 weeks	Oral	F344 Rat Dog Monkey	Yes
13 weeks	Oral	Mouse SD Rat Monkey	Yes
26 weeks	Oral	SD Rat	Yes
52 weeks	Oral	Monkey	Yes
Genotoxicity Studies			
Ames assay	In vitro	Bacteria[b]	Yes
In vitro chromosome aberration test	In vitro	Human Lymphocytes	Yes
In vivo micronucleus test	Oral	SD Rat	Yes
Carcinogenicity Studies	Oral	Mouse SD Rat	Yes
Reproductive and Developmental Toxicity Studies			
Fertility and early embryonic development	Oral	SD Rat	Yes[c]
Embryo-fetal development	Oral	SD Rat Rabbit	Yes[c]
Prenatal and postnatal development	Oral	SD Rat	Yes
Juvenile toxicity (range-finding)	Oral	SD Rat	No
Juvenile toxicity	Oral	SD Rat	Yes
Local Tolerance Studies			
Skin irritation	Dermal	Rabbit	Yes
Ocular irritation	Eye	Rabbit	Yes
Other Studies			
Toxicity studies on impurities			
Ames assays	In vitro	Bacteria	No
Skin sensitization	Intradermal	Guinea pig	Yes
Phototoxicity	Oral	Long-Evans Rat	Yes
Mechanistic studies	Oral	Mouse SD Rat	No

F344 = Fischer 344, GLP = Good Laboratory Practice, SD = Sprague Dawley.
a: Study conducted in rat was non-GLP
b: *Salmonella typhimurium* TA100, TA1535, TA98, TA1537 and *Escherichia coli* WP2 *uvrA*.
c: Except for range-finding studies.

The pharmacological effects of avatrombopag were shown to be highly species-specific, with signalling occurring only in humans and chimpanzees but not in any other species tested. Thus, there were no relevant species other than chimpanzee and human to investigate on-target effects of avatrombopag, and toxicologic evaluation in chimpanzees was not viable for ethical reasons (EU Directive 2010/63/EU, 22 Sep 2010). Nevertheless, the off-target effects of avatrombopag were thoroughly assessed in species commonly used in toxicology studies (mice, rats, dogs, and monkeys). Rats and monkeys were found to be the most sensitive species, and these 2 species were, therefore, used for the chronic toxicology studies.

The toxicity of avatrombopag was evaluated in single-dose and repeated-dose oral toxicity studies in mice, rats, dogs, and cynomolgus monkeys (for up to 13 weeks in mice, 26 weeks in rats, 4 weeks in dogs, and 52 weeks in cynomolgus monkeys). In addition, mechanistic studies were conducted in mice and rats to elucidate stomach toxicity by avatrombopag.

Repeat dose toxicity

Stomach findings

The primary toxicity of avatrombopag was identified as dose-related changes in the stomach in repeated-dose studies in mice, rats, and *Cynomolgus* monkeys (Study Nos. SNBL.152.03, SNBL.152.04, B-5120, SNBL.152.01, SNBL.152.05, SNBL.152.08, SBL16-95, SNBL.152.02, SNBL.152.07). The histologic change in the fundic glands of the stomach was characterised by primary degeneration of the glandular epithelium with a decrease in matured parietal cells, with accompanying regenerative epithelial hyperplasia particularly in mice, and atrophy of glandular mucosa without inflammatory responses in rats and *Cynomolgus* monkeys. This effect was not associated with an inflammatory response or any evidence of erosion or ulcer formation. These changes were also accompanied by decreases in the gastric acid output with accompanying elevation in intragastric pH and compensatory hypergastrinemia in all of these species. These stomach lesions were dose-, plasma concentration-, and duration-dependent.

Histologic changes in the stomach induced by avatrombopag were identified to be due to systemic rather than local exposures (Study Nos. 929084, T12077). The gastric changes showed a clear trend towards recovery after dosing was stopped. Systemic exposures at no observed adverse effect levels (NOAELs) in all of the pivotal studies were sufficiently above the clinical exposures at the maximum recommended human dose under the intended clinical regimen. In addition, in the Phase 3 studies of avatrombopag in ITP (Study 302 and Study 305) fasting total serum gastrin levels, fasting gastrin-17, pepsinogen (PG)-I, and PG-II were also assessed to evaluate for potential gastric toxicity. There was no significant change in mean fasting gastrin or mean fasting gastrin-17 levels from Baseline to Week 26 (End of Treatment) in the Avatrombopag Treatment Group. No clinically meaningful mean changes in PG-I, PG-II, or the ratio of -I/-II were noted in the Avatrombopag Treatment Group. Overall, the majority of subjects in each treatment group had no shifts from Baseline to the highest or lowest post-Baseline value at any visit.

Mechanistic studies revealed that avatrombopag treatment induced reduction in gastric acid secretion with consequent intragastric pH elevation in rats. This is not via local contact to the gastric mucosa but via action of the absorbed drug on the parietal cell leading to apoptosis and cell loss. The decrease in acid secretion was accompanied by secondary elevation of gastrin. Therefore, the results demonstrate that the primary effect of avatrombopag on the stomach is on the parietal cells, leading to their loss by apoptosis with a resultant decrease in acid output and elevation in gastric pH, followed by gastrin elevation.

The findings in the stomach in the pivotal toxicity studies drove the selection of NOAELs. The systemic exposures (AUC) at NOAELs were 4- (monkey) to 45-fold (mouse) higher than the exposure in humans

at a dose of 20 mg/day (AUC: 3485 ng·h/mL). The 20 mg dose was selected for calculation of safety margins as this dose was the average dose administered in the clinical trials with avatrombopag in patients with ITP. The fact that regenerative capacity is unaffected by avatrombopag even after chronic dosing, and that there is an adequate safety margin supports the conclusion that the gastric findings in nonclinical toxicity studies are of limited clinical significance to humans. This conclusion from nonclinical studies was validated by data collected in the avatrombopag clinical program. In Study 302 and Study 305 there was no trend in the change from Baseline results across all the gastric biomarkers evaluated to suggest a gastric safety signal in patients. These data support that chronic avatrombopag treatment at doses between 5 and 40 mg daily did not result in elevated biomarkers suggestive of gastric toxicity.

Table 2: Comparison between Exposures in Mice, Rats, Dogs, and Cynomolgus Monkeys at NOAEL for Gastric Changes and Effective Human Plasma Concentration

Species	Dosing Period	Doses (mg/kg)	NOAEL (mg/kg)	$AUC_{(0-24)}$ (ng·h/mL) Steady State [a]	Animal-to-Human Ratio [b]
Mouse	13 weeks	80, 160, 320	80 [c]	157000	45
	2 years	20, 60, 160	20	64500	19
Rat	4 weeks	(M) 3, 10, 30, 100 (F) 10, 30, 100, 300	30 [d]	45075	13
	13 weeks	[5, 20, 80] [e] [80, 160, 320] [f]	20	43150	12
	26 weeks	20, 80, 160	20	60400	17
	2 years	20, 50, 160	20	73850	21
Dog	4 weeks	10, 30, 100, 300	30	34826	10
Monkey	4 weeks	3, 10, 100, 1000	10 [g]	22320	6
	13 weeks	1, 5, 15	>15	40100	≥12
	52 weeks	5, 15, 45	5	15247	4

$AUC_{(0-24)}$ = area under the concentration-time curve from zero time to 24 hours, F = female, ITP = immune thrombocytopenia, M = male, NOAEL = no observed adverse effect level, PK = pharmacokinetics.

a: Values are the mean of males and females at the NOAEL.

b: At a dose of 20 mg/day, the mean AUC obtained from the individual derived posthoc PK analysis for the ITP subjects in Phase 2 studies (501-CL-003 and 501-CL-004) and Phase 3 studies (E5501-G000-302 and E5501-G000-305) was 3485 ng·h/mL (see Section 2.7.2.3.2.2). This exposure value was used for calculation of the animal-to-human ratios.

c: Original interpretation was less than 80 mg/kg, which was later reviewed by a third party and interpreted as 80 mg/kg (from Study No. SNBL.152.04).

d: Original interpretation of NOAEL as 10 mg/kg on the basis on the skeletal muscle changes (the ratio to human ×3.2 for the AUC [15642 ng·h/mL]) which were not seen in longerterm- studies (from Study No. B-5120).

e: First 13-Week Study.

f: Second 13-Week Study.

g: Original interpretation of NOAEL was less than 3 mg/kg on the basis on the skeletal muscle changes which were not seen in longer -term studies (13 weeks and longer); the AUC at 3 mg/kg was 7149 ng·h/mL (from Study No. SBL16-95).

Skeletal muscle degeneration findings

In addition to the observed gastric toxicity in animals, reversible skeletal muscle degeneration/necrosis was also a finding but only in 7-day and 4-week studies in F344 rats (but not in SD rats) and *Cynomolgus* monkeys (Study Nos. C-B106, B-5120, SBL16-95). However, these findings were not consistent and limited to the short duration (up to 4 weeks) studies, with no lesions observed in any species that received avatrombopag for 13 weeks and longer, even though skeletal muscles were examined extensively with additional tissue collection from multiple sites with additional parameters in biochemistry in mice, SD rats, dogs, and monkeys.

While musculoskeletal events have been observed in clinical trials with avatrombopag (common events of arthralgia, back pain, pain in extremity, and myalgia), these findings have also been observed in clinical trials with eltrombopag (common events of myalgia, muscle spasm, musculoskeletal pain, bone pain, and back pain, Revolade SmPC) and romiplostim (common events of arthralgia, myalgia, muscle spasms, pain in extremity, back pain, and bone pain, Nplate SmPC). There is no known mechanistic explanation for the occurrence of musculoskeletal events in thrombopoietin receptor agonist treated patients that would be related to the observed effects in nonclinical studies. Similar musculoskeletal adverse events have also been observed in clinical trials with other cell stimulating agents (e.g., G-CSF) which may implicate stimulation of cell production as a potential cause of these adverse events.

Renal toxicity

Reversible renal toxicity was observed at high doses in dogs in 4-week repeated-dose study, including increases in BUN, creatinine, urinary protein, and urinary volume. Decreased glomerular filtration rate and effective plasma flow, accompanied by histologic changes (epithelial cell regeneration of proximal tubules) were also present.

However, the present findings are not relevant since it is known that maleic acid (the salt moiety of avatrombopag) could cause similar lesions in dogs (tubular necrosis in proximal tubules) and this could have played a role in these renal changes (Everett, et al., 1993; Fiume, 2007). Moreover, no renal changes were seen in the repeated-dose toxicity studies in mice, rats, or monkeys, and there have been no significant adverse events in kidneys and renal functions in clinical studies (Study Nos. 6478-390).

Genotoxicity

The genotoxicity of avatrombopag was evaluated in a standard battery of *in vitro* and *in vivo* studies and it was shown to be non-genotoxic. There are no new *in vitro* or *in vivo* genotoxicity studies to report for this type II variation, nor any *in vitro* or *in vivo* genotoxicity data of specific relevance to the ITP indication.

Carcinogenicity

Oral gavage carcinogenicity studies were performed in mice and rats. There are no new carcinogenicity studies to report for this type II variation, nor any carcinogenicity data of specific relevance to the ITP indication.

Reproduction toxicity

Developmental and reproductive toxicity of avatrombopag was evaluated in studies on fertility and early embryonic development in rats, embryo-foetal development in rats and rabbits, and prenatal and postnatal development in rats. In addition, toxicity was evaluated in studies in juvenile/neonatal rats. No new studies of reproduction toxicity were submitted. Avatrombopag did not impact reproduction.

Studies in Juvenile Animals

There are no new juvenile animal studies to report for this type II variation, nor any juvenile animal data of specific relevance to the ITP indication. Juvenile animal studies have been submitted previously.

In brief, the 10-week oral toxicity study in juvenile rats was completed in July 2018, after the submission of the CLD MAA, and therefore it could not be included in the original submission.

Avatrombopag (Lot No. 16080101) was administered by oral gavage to juvenile rats Crl:CD(SD) (10 or 16 animals/sex/group) from postnatal day (PND) 7 once daily for 10 weeks at a dose level of 20, 100, or 300 mg/kg. A control group (16 animals/sex) received an equivalent volume (10 mL/kg) of vehicle, a 0.5 w/v% methylcellulose aqueous solution. The reversibility of any effects was also assessed in the 300 mg/kg group following a 4-week recovery period. For toxicokinetic evaluation, avatrombopag or the vehicle was given to toxicokinetic (TK) satellite rats (4 animals/sex/group) in the same manner.

Assessment was based on the following: mortality, clinical signs, body weights, food consumption, sexual development, haematology, clinical chemistry, toxicokinetics, organ weights, and macroscopic and microscopic examinations.

There was no test article-related mortality or clinical signs, or changes in body weights, food consumption, sexual development, haematology, clinical chemistry, organ weights, or macroscopic examination at doses up to 300 mg/kg.

In the stomach, test article-related histologic changes were the same as reported in adult rat studies in males and females at 100 and 300 mg/kg: dose-dependent degeneration, regenerative hyperplasia, and atrophy of the glandular epithelium. Increased incidences of background focal mineralization were observed in the kidney in females at 300 mg/kg. After a 4-week recovery period, the test article-related changes were reversible, although residual mineralization was observed in the kidneys.

In conclusion, when avatrombopag was administered by oral gavage to juvenile Crl:CD(SD) rats from PND 7 once daily for 10 weeks at a dose level of 20, 100, or 300 mg/kg, gastric changes that were the same as those reported in adult rats were observed at 100 and 300 mg/kg. These changes were reversed after a 4-week recovery period. The no-observed-adverse-effect-level (NOAEL) of avatrombopag was considered to be 20 mg/kg/day in male and female juvenile rats.

Toxicokinetic data

Refer to Table 2 above.

Local tolerance

The potential for skin and eye irritation with avatrombopag was evaluated in rabbits.

There are no new local tolerance studies to report for this type II variation, nor any local tolerance data of specific relevance to the ITP indication.

Other Toxicity studies

Antigenicity

Based on the established safety profile of avatrombopag, no specific studies have been conducted. That is considered acceptable.

Mechanistic Studies

Non-GLP compliant mechanistic studies were conducted in mice and rats to elucidate stomach toxicity by avatrombopag. Dose-dependent changes in the gastric mucosa, as well as increased serum gastrin levels were observed in both mice and rats. It was considered that the decrease in mature parietal cells is the primary cause of decreased gastric acid secretion with increased intragastric pH, leading to the subsequent compensatory hypergastrinemia. From the results of the comparative study of local versus systemic avatrombopag effects, it can be concluded that histologic changes in the stomach induced by avatrombopag treatment were due to systemic rather than local exposures.

Studies on Impurities

The mutagenic potential for 12 possible impurities in avatrombopag maleate, including starting materials, intermediates, and others, were assessed. Seven of these compounds were positive or inconclusive in the *in vitro* mutagenicity assay using Salmonella typhimurium and Escherichia coli tester strains (Study Nos. 14K3688G, K12014, 964106, 15K3898G, K12006) or triggered an alert in the in silico assessment (DEREK and Multi-CASE software). The results of these *in vitro* assays or *in silico* assessment for mutagenic potential are summarised in the Table 3:

Table 3: Summary of Mutagenic Potential for 7 Possible Impurities in Avatrombopag Maleate

Identified Related Substances	Origin	Mutagenic Assessment			Conclusion
		In-silico assessment		Ames Test	
		DEREK	CASE Ultra		
ER-878003-00	Non-isolated intermediate of ER-878005-00 synthesis	No Alert	Alert	Not tested	pMGI
ER-878005-00	Precursor of ER-878006-00	Alert	Alert	Positive	MGI
ER-878415-00	Non-isolated intermediate of ER-878006-00 synthesis	Alert	No alert	Not tested	pMGI
ER-887068-00	Starting material (used in the synthesis	No alert	Alert	Inconclusive	MGI

	of ER-878008-00)				
ER-885097-00	Non-isolated intermediate of ER-878008-00 synthesis	Alert	Alert	Not tested	pMGI
ER-880423-00	Process impurity of ER-878006-00 synthesis	Alert	Alert	Positive	MGI
ER-885056-00	Process impurity of ER-878005-00 synthesis	Alert	No alert	Not tested	pMGI

MGI = mutagenic impurity; pMGI = potential mutagenic impurity

The 7 potential or known mutagenic impurities which have been identified include four Class 3 and three Class 2 impurities. Six out of the seven impurities are below the detection level in any batch, and the remaining impurity, ER-887068-00, is controlled at less than 100 ppm in the intermediate ER-878008-00. A purge study has also been conducted to confirm that ER-887068-00 does not persist through the subsequent synthetic steps which are conducted to convert ER-878008-00 to avatrombopag maleate drug substance. Therefore, all mutagenic or potential mutagenic impurities are not expected to be present in the avatrombopag maleate drug substance as they are controlled at the intermediate steps.

2.3.5 Ecotoxicity/environmental risk assessment

Avatrombopag maleate is an orally administered, small molecule thrombopoietin receptor (c-Mpl) agonist that mimics the biologic effects of thrombopoietin (TPO) *in vitro* and *in vivo.* Avatrombopag activates human c-Mpl through a mechanism that is different from TPO binding but is still capable of stimulating signal transduction and mimicking the biologic effects of TPO. The pharmacological effect of avatrombopag maleate is highly species-specific with signalling occurring only in chimpanzees and humans, but not in any other species tested.

In this environmental risk assessment (ERA), all doses are expressed as the amount of avatrombopag free base, where relevant.

Avatrombopag film-coated tablets (Doptelet) in the 20 mg strength (expressed as free base equivalent) are packaged in an aluminium/aluminium blister.

An ERA has been performed to evaluate the potential environmental risk resulting from the use of avatrombopag film-coated tablets in the treatment of:

- Severe thrombocytopenia in patients with chronic liver disease who are scheduled to undergo an invasive procedure (i.e. the CLD indication), which is the currently authorised indication. The maximum daily dose (DOSEai) is 60 mg avatrombopag (free base); the dosing duration is 5 consecutive days for each treatment period, and there may be up to 3 treatment periods per year.

- Chronic immune thrombocytopenia in adult patients who are refractory to other treatments (i.e. the ITP indication), which is the proposed indication for this type II variation. The maximum daily dose (DOSEai) is 40 mg avatrombopag (free base); this indication requires chronic dosing.

Environmental exposure to avatrombopag has been shown to be low based on the calculation of predicted environmental concentration in surface water ($PEC_{SURFACEWATER}$) which has utilised refined values for market penetration (Fpen) of avatrombopag film-coated tablets, rather than the default value as discussed in the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00, 01 June 2006).

Using a refined F_{pen} value of 0.00015 for the CLD indication, the $PEC_{SURFACEWATER}$ for avatrombopag has been calculated to be 0.0045 µg/L.

Using a refined F_{pen} value of 0.00026 for the ITP indication the $PEC_{SURFACEWATER}$ for avatrombopag has been calculated to be 0.0052 µg/L.

The combined $PEC_{SURFACEWATER}$ value for avatrombopag for both indications is 0.0097 µg/L, which is below the action limit of 0.01 µg/L.

A partition coefficient study was performed using the shake flask method with HPLC analysis. At approximately 25ºC, Log D values of avatrombopag maleate at pH 3.1, 5.4, 7.1 and 9.3 were >4.5, >4.5, >4.5 and 4.1, respectively (ionic strength I = 0.3) (Study Report W-20140941, 2014). This study was followed by a partition coefficient study, which was performed using the slow-stirring method (OECD Test Guideline 123) with HPLC analysis. At 25ºC, the Log D value of avatrombopag maleate at pH 7.1 was >4.5 (ionic strength I = 0.3) (Study Report W-20140961, 2014).

In a GLP-compliant ready biodegradability study (OECD 301F), avatrombopag maleate was found not to be readily biodegradable (Study Report A160181, 2016).

On the basis that Log D has been found to be greater than 4.5 using the shake flask and slow-stirring methods and avatrombopag maleate was not readily biodegradable, avatrombopag maleate will be further screened in a step-wise procedure for persistence, bioaccumulation and toxicity (PBT), in accordance with the CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2, 01 June 2006).

The following was detailed in the Assessment report, Doptelet (International non-proprietary name: avatrombopag), Procedure No. EMEA/H/C/004722/0000 (26 April 2019, EMA/CHMP/322871/2019, CHMP); the company is currently in the process of addressing these items.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommended the following points to be addressed:

A step-wise PBT assessment post-marketing:

- *Persistence (P): Persistence will be assessed in a GLP-compliant OECD 308, study of aerobic transformation in freshwater aquatic sediment systems.*
- *Bioaccumulation (B): Bioaccumulation will be assessed in a GLP-compliant OECD 305 fish bioaccumulation study.*
- *Toxicity (T): As stated in Section 1.2.3 of Guideline EMA/CVMP/ERA/52740/2012: "For animal welfare reasons it is recommended that the evaluation of persistence and bioaccumulation is carried out first. When the criteria for persistence and/or bioaccumulation are not met, there is no requirement to carry out evaluation of the T criterion within the PBT assessment."*

- *Available mammalian toxicity data for avatrombopag show no evidence of any endocrine disruption or mutagenicity, and no evidence of other toxicities indicative of environmental risk, based on secondary pharmacodynamics (lack of significant binding to 86 receptors, transporters or ion channels) and repeat dose toxicity, reproductive toxicity and carcinogenicity data.*

The MAH therefore proposes to provide, as a post-marketing commitment, an updated ERA after the OECD 305 and 308 studies have been performed with an assessment of:

- *Whether avatrombopag does or does not fulfil the P or vP criteria, as detailed in Guideline EMA/CVMP/ERA/52740/2012.*
- *Whether avatrombopag does or does not fulfil the B or vB criteria, as detailed in Guideline EMA/CVMP/ERA/52740/2012.*
- *Whether or not there is considered to be a need to carry out evaluation of the T criterion within the PBT assessment, as detailed in Guideline EMA/CVMP/ERA/52740/2012.*

This assessment will be provided in a follow-on updated ERA to this ERA for avatrombopag.

The excipients in avatrombopag film-coated tablets are, for the core: lactose monohydrate, colloidial silicon dioxide, crospovidone, magnesium stearate and microcrystalline cellulose; and for the film coat: Opadry II 85F42244 Yellow. These excipients present no environmental risks. The packaging (aluminium/aluminium blister) used for avatrombopag film-coated tablets presents no environmental risks.

2.3.6 Discussion on non-clinical aspects

No new nonclinical studies were submitted in support of the new indication of ITP. Unlike the first indication in CLD, the new indication requires chronic dosing. The documentation was assessed with this view in mind. The nonclinical program was already designed to support a small molecule MAA and included a full carcinogenicity program as well as reproduction toxicity and studies in juvenile animals. Hence, no further studies are required.

Primary pharmacology was well described and *in vitro* and *in vivo* proof of concept is considered well-established. Avatrombopag does not stimulate platelet production in mice, rats, monkeys, or dogs because of the unique TPO receptor specificity. Therefore, data from these animal studies do not fully model potential adverse effects related to platelet count increases due to avatrombopag in humans. Nonetheless, there are no new concerns regarding safety pharmacology.

There are no new concerns regarding pharmacokinetics either.

The non-clinical aspects of relevance to this type II variation for the treatment of chronic immune thrombocytopenia are focused on:

1) dose-related gastric changes, which were identified as the primary toxicity of avatrombopag in repeated-dose studies in mice, rats, and cynomolgus monkeys;

2) skeletal muscle changes, which are assessed due to the observance of musculoskeletal adverse events in clinical trials of avatrombopag in patients with ITP;

3) assessment of the acceptable intake of potential mutagenic impurities based on the chronic dosing regimen required for patients with ITP.

The major toxic effects of avatrombopag were in the gastric mucosa, including degeneration, regenerative hyperplasia, and glandular atrophy with gastrin elevation without an inflammatory response or any evidence of erosion or ulcer formation. Mechanistic studies demonstrated that the primary effect

of avatrombopag on the stomach is on the parietal cells, leading to their loss by apoptosis with a resultant decrease in acid output and elevation in gastric pH, followed by gastrin elevation. The systemic exposures (AUC) at NOAELs were 2- (monkey) to 23-fold (mouse) higher than the exposure in humans at a dose of 40 mg/day (AUC: 3485 ng·h/mL).

Even if the safety margin is considered to be sufficiently large relying on the maximum human dose of 60 mg daily for the CLD indication, the significant differences in duration of treatment between the two indications should be taken into account. For the ITP indication, the highest recommended clinical dose is 40 mg (dose level 6 from the SmPC) for an unknown period of time (based on the platelet count response), while for CLD indication, the highest recommended clinical dose is 60 mg for not more than 5 days. The relevant information is reflected in the SmPC sections 5.3 and 4.2.

Skeletal muscle changes were observed only in F344 rats and *Cynomolgus* monkeys, but these findings were reversible and limited to the short duration (up to 4 weeks) studies. Musculoskeletal events have been observed in clinical trials with avatrombopag. However similar musculoskeletal adverse events have also been observed in clinical trials with eltrombopag (Revolade SmPC) and romiplostim (Nplate SmPC), and with other haematological cell stimulating agents (e.g., G-CSF). There is no known mechanistic explanation for the occurrence of musculoskeletal events in thrombopoietin receptor agonist treated patients that would be related to the observed effects in non-clinical studies. As a potential cause of these adverse events the stimulation of cell production in the bone marrow may be implicated. The relevant information is indicated in the SmPC, section *4.8. Undesirable effects: Musculoskeletal and connective tissue disorders: Classified as common: Arthralgia, Back pain, Pain in extremity, Myalgia, Musculoskeletal pain*

The purity of avatrombopag used for the pivotal toxicology studies ranged from 98.8% to 99.3%. This range is comparable with the active substance specification of 98.0% to 102.0%. Based on the hazard risk assessment including Ames testing and in silico predictions, it is found that ER-878005-00, ER-887068-00, and ER-880423-00 are mutagenic impurities (Class 2); ER-878003-00, ER-878415-00, ER-885097-00, and ER-885056-00 are potential mutagenic impurities (Class 3).

All seven mutagenic or potential mutagenic impurities are not expected to be present in the avatrombopag maleate drug substance, as they are controlled at the intermediate steps.

For a 40 mg per day dose of avatrombopag, the maximum daily dose for patients with ITP, for a duration of >10 years to a lifetime, the assessment of the acceptable intake of multiple and individual mutagenic impurities indicate the total known mutagenic impurities are at a level less than the acceptable total daily intake of 5 µg/day for multiple, in accordance with ICH M7.

The SmPC section 5.3 was updated with a summary from the definitive juvenile animal study.

This application aims to broaden the indication for avatrombopag from CLD to ITP. An updated environmental risk assessment was presented using refined F_{PEN} for both indications leading to a combined $PEC_{SURFACE}$ water of 0.0097 µg/L. However, as Log D of avatrombopag is > 4.5, the MAH has committed to perform a stepwise PBT evaluation. A timeline for submission of an updated environmental risk assessment including the PBT evaluation was provided (Q3 2021) and agreed to.

Assessment of paediatric data on non-clinical aspects

In general, the gastric changes observed in juvenile animals were the same as those reported in adult rats. The NOAEL in the initial 4-week dose-range finding appeared to be 10 mg/kg/day, while in the completed 10-week oral toxicity study in juvenile rats, the NOAEL was 20 mg/kg/day.

Notably, the indication in both CLD and ITP is at present restricted to adult patients.

2.3.7 Conclusion on the non-clinical aspects

From a non-clinical point of view, the current extension application for avatrombopag can be recommended for marketing authorisation.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommended the following points to be addressed:

A step-wise PBT assessment post-marketing:

- *Persistence (P): Persistence will be assessed in a GLP-compliant OECD 308 study of aerobic transformation in freshwater aquatic sediment systems.*
- *Bioaccumulation (B): Bioaccumulation will be assessed in a GLP-compliant OECD 305 fish bioaccumulation study.*
- *Toxicity (T): As stated in Section 1.2.3 of Guideline EMA/CVMP/ERA/52740/2012: "For animal welfare reasons it is recommended that the evaluation of persistence and bioaccumulation is carried out first. When the criteria for persistence and/or bioaccumulation are not met, there is no requirement to carry out evaluation of the T criterion within the PBT assessment."*
- *Available mammalian toxicity data for avatrombopag show no evidence of any endocrine disruption or mutagenicity, and no evidence of other toxicities indicative of environmental risk, based on secondary pharmacodynamics (lack of significant binding to 86 receptors, transporters or ion channels) and repeat dose toxicity, reproductive toxicity and carcinogenicity data.*

The MAH therefore proposes to provide, as a post-marketing commitment, an updated ERA after the OECD 305 and 308 studies have been performed with an assessment of:

- *Whether avatrombopag does or does not fulfil the P or vP criteria, as detailed in Guideline EMA/CVMP/ERA/52740/2012.*
- *Whether avatrombopag does or does not fulfil the B or vB criteria, as detailed in Guideline EMA/CVMP/ERA/52740/2012.*
- *Whether or not there is considered to be a need to carry out evaluation of the T criterion within the PBT assessment, as detailed in Guideline EMA/CVMP/ERA/52740/2012.*

This assessment will be provided in a follow-on updated ERA to this ERA for avatrombopag.

2.4 Clinical aspects

2.4.1 Introduction

GCP

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

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Tabular overview of clinical studies.

Table 3: Summary of clinical studies utilised in the development of the ITP population PK and population PK/PD model

Study Type	Study Phase	Study Number	Formulation	Study Description
Safety and Efficacy Studies	2	501-CL-003	1G Tablet	A double-blind, randomized, dose-ranging, placebo-controlled, parallel-group study of avatrombopag administered QD for 28 days in patients with ITP to assess responder rate and the PK and PD of avatrombopag.
	2	501-CL-004	1G Tablet	Parallel-group rollover study from Protocol AKR-501-CL-003 of avatrombopag in patients with ITP to evaluate the effectiveness of avatrombopag and the PK and PK/PD relationship of avatrombopag in patients with ITP.
	3	E5501-G000-302	2G Tablet	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study with an open-label extension phase to evaluate the safety and efficacy of avatrombopag in patients with ITP.
	3	E5501-G000-305	2G Tablet	A multicenter, randomized, double-blind, active-controlled, parallel-group study with an open-label extension phase to evaluate safety and efficacy of avatrombopag versus eltrombopag in patients with ITP.
Single Dose Studies	1	477-CL-001	Suspension	Single ascending dose safety PK and PD study in healthy subjects
Multiple Dose Study	1	477-CL-002	Suspension	Multiple ascending dose safety, PK and PD study in healthy subjects
Effect of Intrinsic Factors on PK and PD	1	E5501-A001-006	2G Tablet	Japanese and Chinese PK, PD and safety bridging study of 10, 40, and 80 mg avatrombopag (fasted) in healthy subjects (completed in US)
	1	E5501-A001-018	2G Tablet	Confirmatory Japanese PK and PD bridging study of 40 and 60 mg avatrombopag (fed) in healthy subjects (completed in US)
BA and Food Effect	1	501-PK-902	Suspension & 1G Tablet	Relative BA study of 1G tablet versus oral suspension formulation and food effect assessment for 1G tablet
	1	E5501-A001-005	1G and 2G Tablets	Relative BA study of 2G tablet versus 1G tablet and food effect assessment for 2G tablet
	1	E5501-A001-007	2G Tablet	Relative BA study for estimation of intra- and inter-subject PK variability for 2 manufacturing lots of 40-mg 2G tablet under fasted state
	1	E5501-G000-010	2G Tablet	Food effect study to evaluate effect of high-fat meal on BA and PK variability of 2G tablet of avatrombopag
	1	E5501-A001-017	2G Tablet	Food effect study to evaluate effect of low-fat meal on BA and PK variability of 2G tablet of avatrombopag

This Type II variation concerns treatment of chronic immune thrombocytopenia (ITP). The original clinical pharmacology assessment of avatrombopag was based on studies conducted in healthy subjects, subjects with chronic ITP, and subjects with thrombocytopenia associated with CLD. Based on that program, avatrombopag was approved for the treatment of severe thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo an invasive procedure. The four avatrombopag studies conducted in patients with ITP were: Study 501-CL-003 (Study CL-003), Study 501-CL-004

(Study CL-004), Study E5501-G000-302 (Study 302) and Study E5501-G000-305 (Study 305).

The clinical pharmacology program for this variation includes: 1) population PK and PK/PD modelling and simulations conducted to determine the proposed avatrombopag dosage and administration instructions for patients with ITP, and 2) results of a simulated non-inferiority study conducted to compare the avatrombopag durable platelet response rate to that of eltrombopag based on the established PK/PD models for avatrombopag and eltrombopag. No new clinical data have been generated.

The Phase 3 ITP studies (studies 302 and 305) were conducted with multiple tablet strengths to allow for titration of the daily avatrombopag dose to maintain platelet counts in the target range (between 50×10^9/L and 150×10^9/L). The dosage regimen proposed for commercial use in ITP patients utilizes only one avatrombopag tablet strength of 20 mg. Dose titration simulations has been used to support modifying either the dose or dosing frequency of avatrombopag to achieve the goal of maximizing the percentage of subjects achieving a platelet count between 50×10^9/L and 150×10^9/L.

Alternative, intermittent dosing regimens are also known to be used clinically, with a recently published long-term study with eltrombopag (EXTEND) reporting that even with the availability of multiple eltrombopag tablet strengths, 36% (n=108/302) of subjects utilized an alternate daily dosing regimen of 25 mg every other day or less frequently to maintain platelets within the target range (Wong, 2017). A PK/PD non-inferiority simulation evaluating the durable platelet response during a 26-week course of treatment in 10,000 simulated adult ITP patients, using the published eltrombopag PK/PD model (Hayes, 2011) and the avatrombopag PK/PD model for ITP, has been conducted to provide additional data comparing the efficacy of avatrombopag versus eltrombopag.

A single-dose, six-sequence cross-over BA-BE study in healthy adults have been completed (Study AVA-PED-101). This study determined the relative oral bioavailability of a pediatric age-appropriate avatrombopag suspension and compared it to the commercial tablet formulation in healthy adult subjects under fed and fasted conditions.

2.4.2 Population PK and PK/PD analyses

The popPK and popPK/PD analyses were performed using NONMEM, Version 7.3 with FOCE-I. All graphical analyses were performed using R, Version 3.5.1. Goodness of fit plots were performed using Xpose4, Version 4.5.3. Bootstrapping and visual predictive checks (VPCs) were conducted using Perl-speaks for NONMEM, Version 4.4.8.

A total of 17067 observation records (for avatrombopag concentrations) from 577 healthy volunteers and ITP patients were included in the popPK analysis. A total of 1724 observation records (for platelet counts) from 97 ITP patients were included in the popPK/PD analysis. A total of 7 and 12 ITP patients were excluded from the popPK and popPK/PD analyses, respectively, due to incomplete data or changes in background ITP therapies. The total number of BLQ observations was 7.61%. These records were included with estimated values. No obvious outliers were present in either the popPK or popPK/PD data sets.

PopPK model for ITP-patients

The structure of the PK model was a one-compartment model with zero-order input into the depot compartment (i.e., the gut) followed by first-order absorption and elimination in the central compartment.

Covariate analysis indicated that moderate or strong dual inducers for CYP2C9 and CYP3A4, moderate or strong CYP2C9 inhibitors, moderate or strong CYP3A4 inhibitors, patient population (healthy or ITP)

and baseline weight all were statistically significant covariates of CL/F1. Weight was also significant for V/F1 while formulation was significant for Ka and oral bioavailability F1.

The previous final model (Model 25_new) was updated (Model 20) upon request. The allometric coefficient of CL was fixed to 0.75; the effect on Ka was set to be similar for the suspension and the 2G tablet but different for the 3G tablet; IOV was added to the relative bioavailability for the 2G tablet; and different residual error depending on TAD before or after 4 hours was allowed.

Parameter estimates from the updated final popPK model (Model 20) of avatrombopag compared to the previous model are shown in Table 4.

Table 4: Population PK parameter estimates from the updated final model (model 20) compared to the previous final model (Model 25_new) (cont'd)

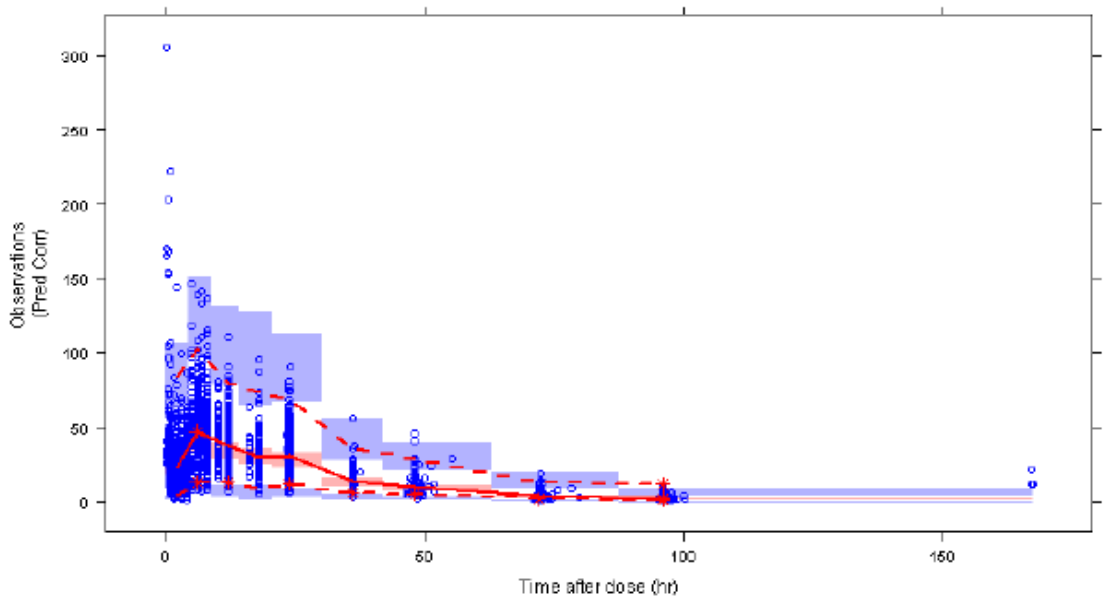
Symbol	Unit	Estimate	RSE (%)	2.5th-97.5th Percentile (Bootstrap)	Shrinkage (%)	CV (%)	Estimate	RSE (%)	2.5th-97.5th Percentile (Bootstrap)	Shrinkage (%)	CV (%)
		Updated Final Model (Model 20)					Previous Final Model (Model 25_new)				
F1	.	1 (Fixed)	--	--	.	.	1 (Fixed)	--	--	.	.
fract. diff. in F1 for FORM=0 vs FORM=3	.	0.317	19.0	(0.197, 0.443)	.	.	0.325	20.4	(0.186, 0.454)	.	.
fract. diff. in F1 for FORM=1 vs FORM=3	.	0 (Fixed)	--	--	.	.	0 (Fixed)	--	--	.	.
fract. diff. in F1 for FORM=2 vs FORM=3	.	-0.720	2.94	(-0.758, -0.678)	.	.	-0.658	6.39	(-0.725, -0.557)	.	.
F1 IIV	.	0.146	10.0	(0.122, 0.176)	20.1	38.2	0.192	8.38	(0.163, 0.225)	4.89	43.8
F1 IOV	.	0.135	8.23	(0.113, 0.158)	27.7, 26.9, 42.5[b]	36.8	.	.	.	.	.
PROP1	.	0.220	3.59	(0.208, 0.235)	.	.	0.393	1.81	(0.382, 0.405)	.	.
ADD1	ng/mL	0.372	18.0	(0.163, 0.477)	.	.	0.496	16.6	(0.169, 0.640)	.	.
PROP2	.	0.500	1.86	(0.484, 0.517)	.	.	.	.	.	.	.
ADD2	ng/mL	0.808	17.3	(0.489, 1.30)	.	.	.	.	.	.	.

ALAG1: lag time in absorption; CV: coefficient of variation; CL: clearance; D1: zero-order input duration; F1: (relative) bioavailability; fract. diff.: fractional difference; IIV: inter-individual variability; IOV: inter-occasion variability; KE: the first-order elimination rate constant; KA: the first-order absorption rate constant; MSIND2C9: moderate or strong dual inducer for CYP2C9 and CYP3A4; MSINH2C9: moderate or strong CYP2C9 inhibitor; MSINH3A4: moderate or strong CYP3A4 inhibitor; POP: patient population (0 for healthy, 1 for ITP); RSE: relative standard error of the parameter estimate; V: volume of distribution; WGT: weight.
FORM (formulation): 0 for suspension, 1 for 1G tablet (excluding lot number 56789-101), 2 for 1G tablet lot number 56789-101, and 3 for 2G tablet.
PROP1 and PROP2: proportional residual error for TAD (time after dose) > 4 hrs and ≤ 4 hrs, respectively, for the updated final model (Model 20).
ADD1 and ADD2: additive residual error for TAD > 4 hrs and ≤ 4 hrs, respectively, for the updated final model (Model 20).
PROP1: proportional residual error for all time points, for the previous final model (Model 25_new).
ADD1: additive residual error for all time points, for the previous final model (Model 25_new).
For the updated final model (Model 20), 15 runs with minimization terminated and 2 runs with estimates near a boundary out of 500 bootstrap replicates were skipped when calculating the bootstrap results.
[a] For the updated final model (Model 20), KA was the same between FORM=0 & 1. [b] Shrinkage values for the 1st, 2nd, and 3rd occasions, respectively.

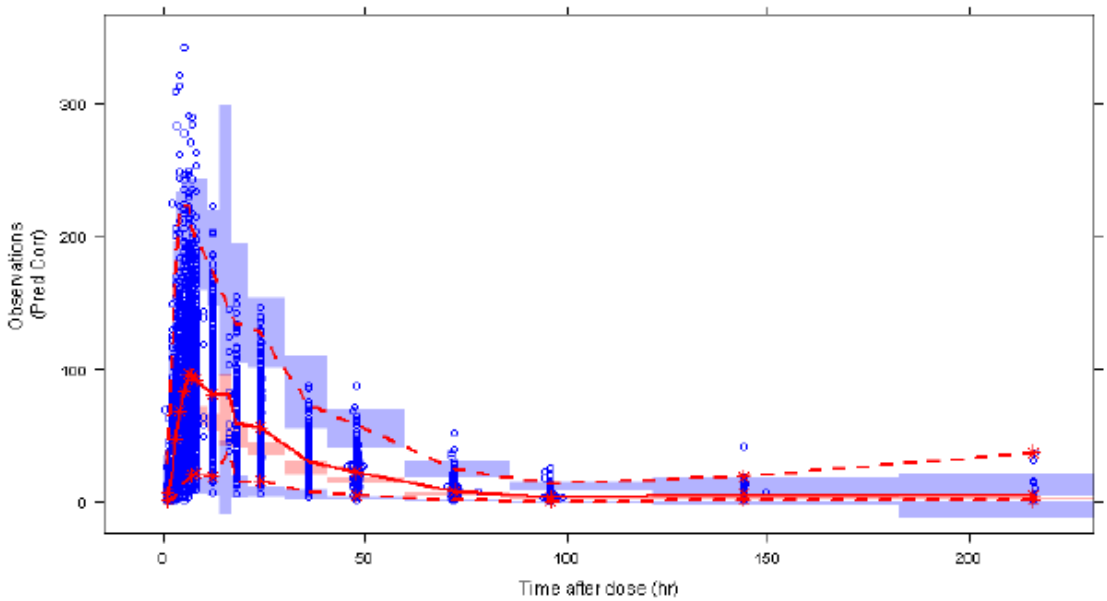
The models were evaluated by bootstrap analysis, goodness of fit plots and visual predictive check (VPC). The pc-VPC plots for healthy subjects and for ITP patients are shown in Figure 7.1.10 at doses 10 mg and 20 mg avatrombopag for the previous final model (Model 25_new). Figure 8-2 shows the pc-VPC for all time points for the updated final Pop PK model (Model 20).

Appendix 7.1.10. Prediction-Corrected Visual Predictive Check (pcVPC) Plots for Final PK Model (Model 25_new) (Cont'd)

Healthy Volunteers, Dose = 10 mg

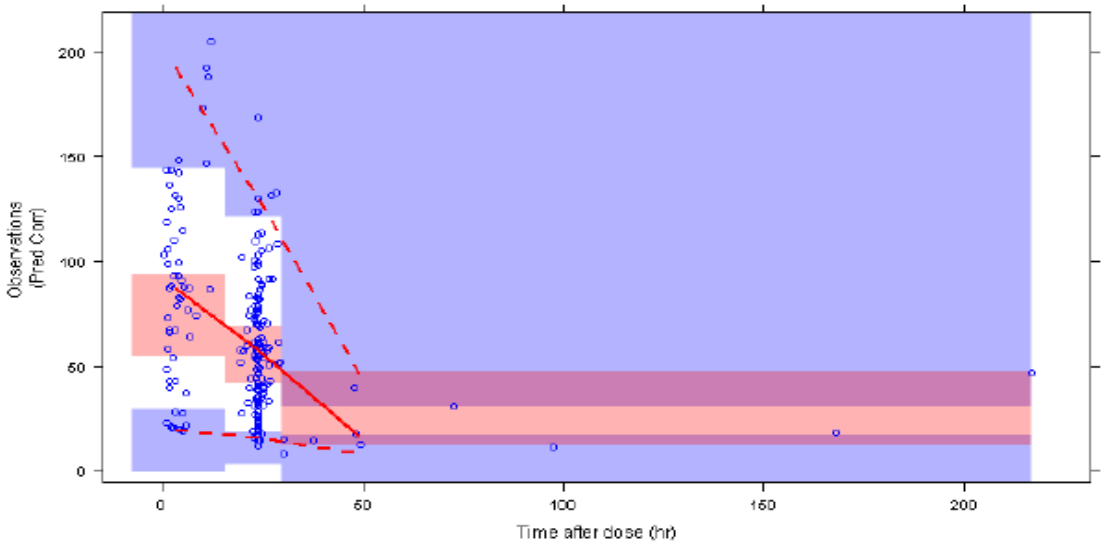


Healthy Volunteers, Dose = 20 mg

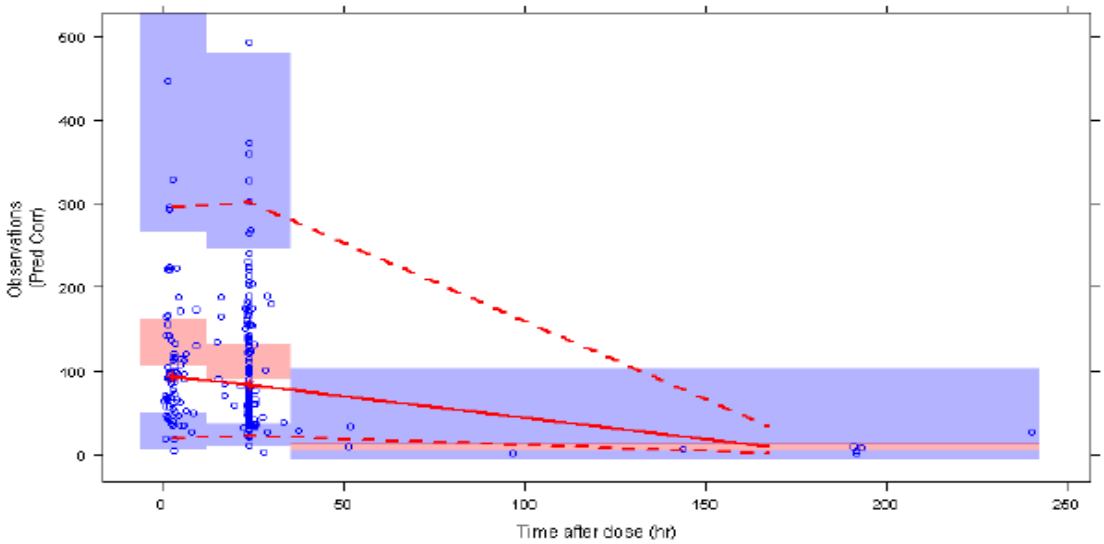


Appendix 7.1.10. Prediction-Corrected Visual Predictive Check (pcVPC) Plots for Final PK Model (Model 25_new) (Cont'd)

ITP Patients, Dose = 10 mg



ITP Patients, Dose = 20 mg



The population estimates of CL/F1 and V/F1 for avatrombopag were 5.74 L/hr and 235 L, respectively, for an average ITP patient of 74.0 kg, that received the 2G tablet formation and no DDI perpetrators. Under these conditions, the model-predicted AUC values were 2255 and 3485 ng×hr/mL, respectively, for a typical healthy volunteer and a typical ITP patient. The model-predicted AUC values correspond to AUC(0-inf) after a single 20 mg dose or AUCss after multiple 20 mg doses at steady state.

Figure 8-2 Prediction-Corrected VPC Plots for the Updated Final Population PK Model (Model 20)

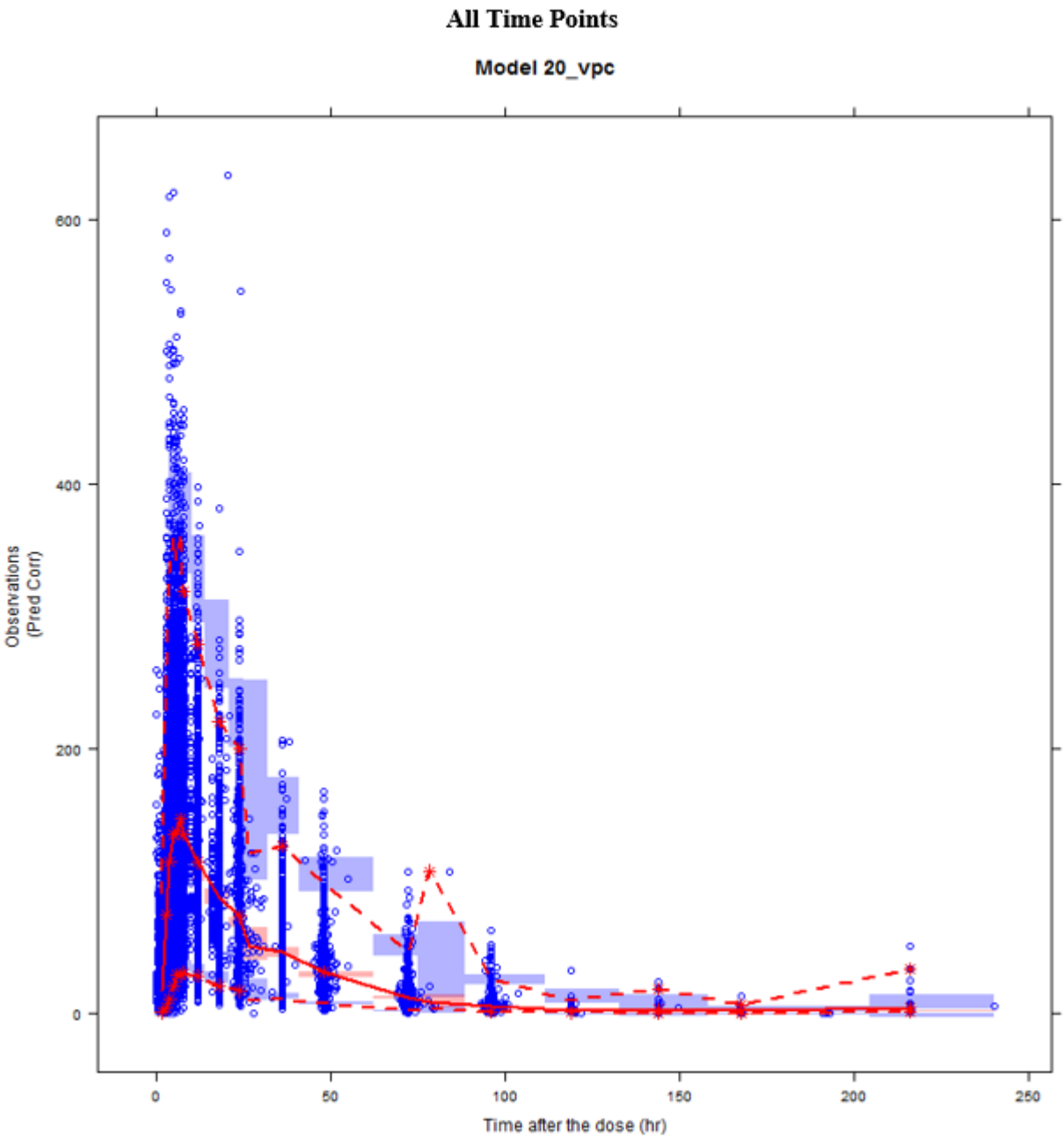
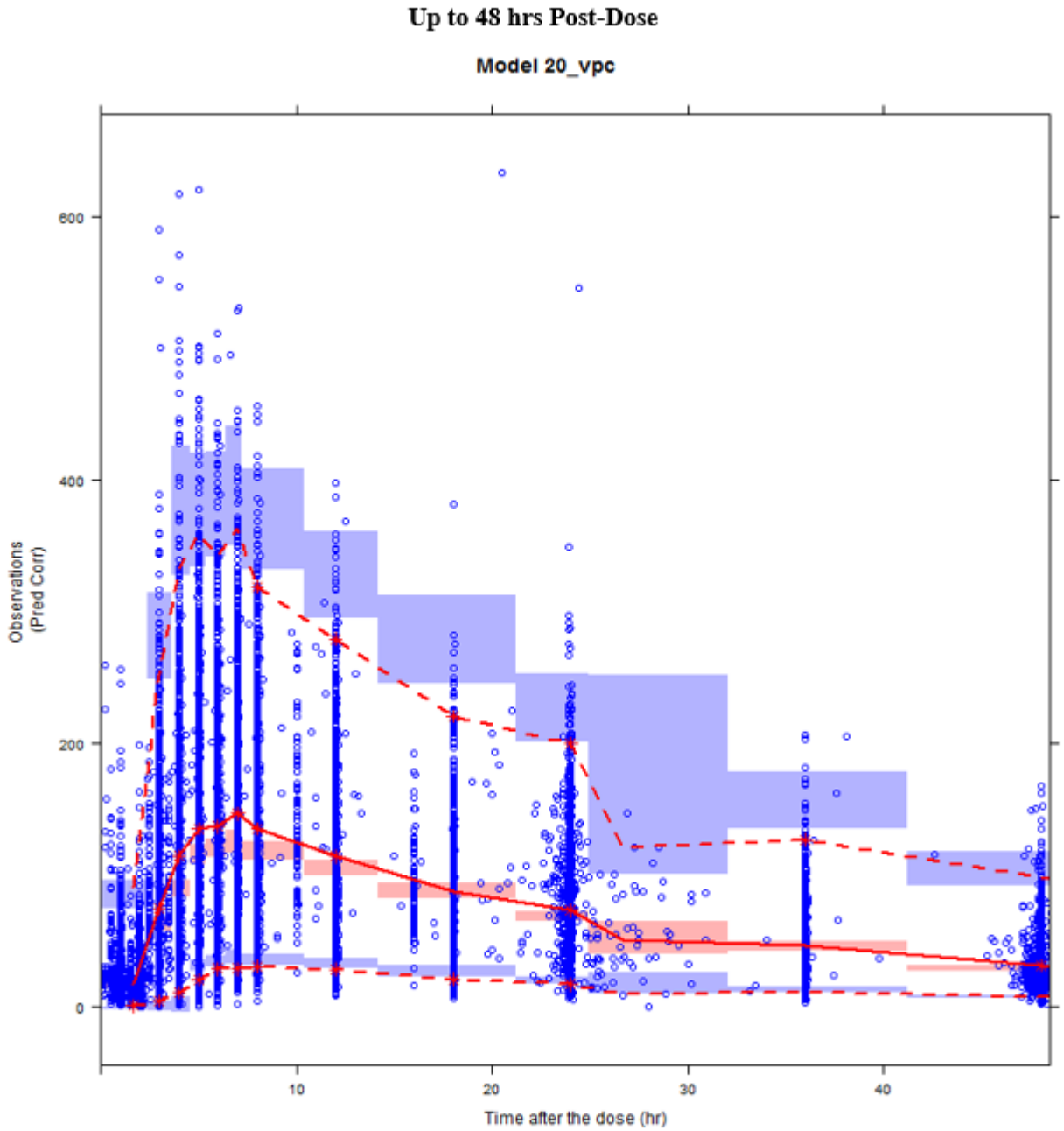


Figure 8-2 Prediction-Corrected VPC Plots for the Updated Final Population PK Model (Model 20) (Cont'd)



Blue circles: observed individual data; dashed and solid red lines: 2.5th, 50th, and 97.5th percentiles of the observed data; blue and red shaded areas: 95% CI based on the simulated data's 2.5th, 50th, and 97.5th percentiles.

Table 8-3. Percentage of Observations Outside of 90% and 95% Prediction Interval for Prediction-Corrected VPC Plots for the Updated Final Population PK Model (Model 20)

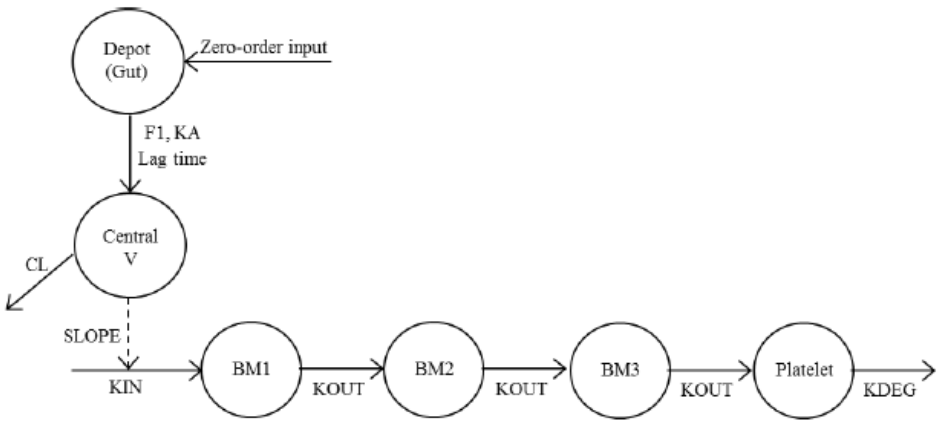
	90% PI	95% PI
Total observations	17067	17067
Total points below the PI	816	413
Total points above the PI	746	317
Total points outside of the PI	**1562**	**730**
% below the PI	4.78	2.42
% above the PI	4.37	1.86
% outside of the PI	**9.15**	**4.28**

PI: prediction interval.

PK/PD model for ITP patients

A six-compartment PK/PD lifespan model (Figure 7) with a linear drug effect on platelet production was employed. This model comprised two PK compartments and four PD compartments to characterise the relationship between avatrombopag concentrations and platelet count in ITP patients from Studies CL-003, CL-004, 302 and 305. Individual post-hoc parameter estimates from the final PK model were used to generate PK exposure input for the PK/PD model.

Figure 7. Structure of the Population PK/PD Model for Avatrombopag

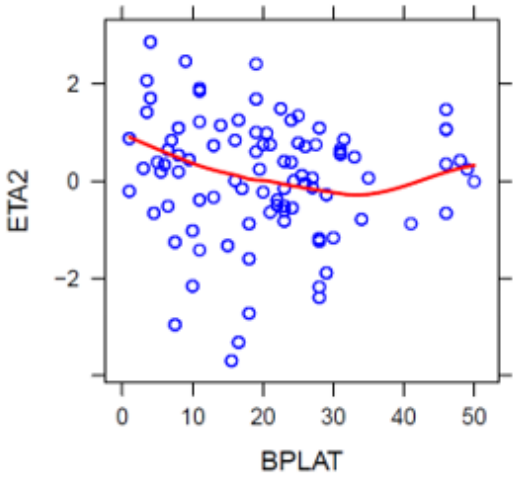


The model was parameterized for the baseline platelet count (BASE) in the blood, SLOPE for the linear drug effect on platelet production, zero-order production rate of platelet precursors (KIN) and the first-order maturation rate constant (KOUT). The first-order platelet degradation rate constant (KDEG) was calculated as KIN divided by BASE. The observed individual baseline platelet count (BPLAT) was used as the typical value for a given subject, hence the IIV term estimated the residual (unexplained) intra-individual variability of the baseline value. A proportional error model was used for the residual error for the platelet count post-baseline.

The ITP population PK/PD model were updated upon request. The model structure remained the same as in the previous final PK/PD model submitted in the type II variation (Figure 7). The individual estimates from the updated PK model were included in the PK/PD model. The baseline platelet count (BASE) was estimated; the relationship between SLOPE and observed baseline platelet count (BPLAT) was removed. An attempt was made to estimate additive residual error (ADD). However, because the estimate of ADD was found to be almost zero with a very large relative standard error (RSE=294%), it was removed from the final updated PK/PD model. Even though a relationship between the SLOPE and

observed Baseline platelet count (BPLAT) was still apparent (Figure 9 2), it was no longer statistically significant, and was removed from the updated model.

Figure 9-2 Plots of ETA vs. Observed Baseline Platelet Count (BPLAT) for the Updated Final Model (Model 24)



ETA2: for SLOPE
BPLAT: the observed individual baseline platelet count.
Red lines: smooth lines.

Table 9 1 shows the population PK/PD parameter estimates and shrinkage values from the updated final model (Model 24), compared to the previous final model (Model 32).

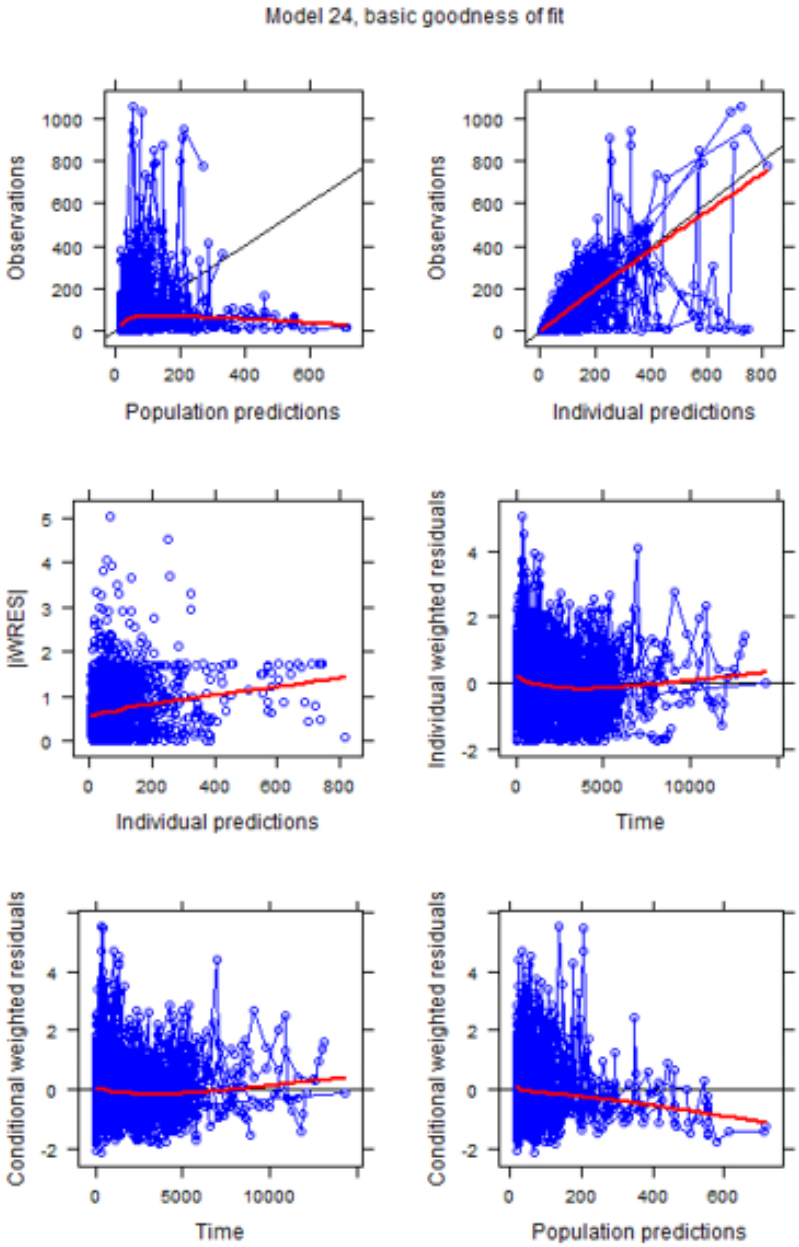
Table 9-1 Population PK/PD Parameter Estimates from the Updated Final Model (Model 24) Compared to the Previous Final Model (Model 32)

Symbol	Unit	Estimate	RSE (%)	2.5th-97.5th Percentile (Bootstrap)	Shrinkage (%)	CV (%)	Estimate	RSE (%)	2.5th-97.5th Percentile (Bootstrap)	Shrinkage (%)	CV (%)
		Updated Final Model (Model 24)					Previous Final Model (Model 32)				
BASE	$\times 10^9$/L	16.2	6.31	(13.3, 21.1)	.	.	--	--	--	.	.
BASE IIV[a]	.	0.390	14.8	(0.231, 0.634)	6.31	62.4	0.369	24.1	(0.231, 0.974)	20.0	60.7
SLOPE	mL/ng	0.0418	19.5	(0.0303, 0.0659)	.	.	0.0257	27.7	(0.00964, 0.0450)	.	.
SLOPEBPLAT1	.	--	--	--	.	.	-0.404	-50.2	(-1.40, -0.0350)	.	.
SLOPEBPLAT2	.	--	--	--	.	.	0.0120	191	(-0.0131, 0.170)	.	.
SLOPE IIV	.	1.91	17.7	(1.04, 2.97)	9.75	138	1.52	21.4	(0.695, 2.82)	14.0	123
KIN	$\times 10^9$/L/hr	0.353	43.6	(0.191, 1.24)	.	.	0.507	48.5	(0.0775, 1.13)	.	.
KIN IIV	.	3.97	26.7	(1.08, 9.56)	37.6	199	5.93	28.5	(0.785, 17.7)	37.7	243
KOUT	/hr	0.0395	20.7	(0.0258, 0.101)	.	.	0.0359	16.5	(0.0209, 0.246)	.	.
KOUT IIV	.	0.672	50.7	(0.265, 4.01)	48.3	82.0	0.529	51.2	(0.0794, 4.12)	49.7	72.7
ADD	$\times 10^9$/L	--	--	--	.	.	0.352 (Fixed)	--	--	.	.
PROP	.	0.573	0.898	(0.498, 0.646)	.	.	0.576	0.910	(0.506, 0.657)	.	.

ADD: additive residual error; BASE: the model-predicted baseline platelet count in the blood; BPLAT: the observed individual baseline platelet count; CV: coefficient of variation; IIV: inter-individual variability; KIN: zero-order production rate of platelet precursors; KOUT: the first-order maturation rate constant; PROP: proportional residual error; RSE: relative standard error of the parameter estimate; SLOPE: slope for the linear drug effect on platelet production.
For the updated final model (Model 24), 2 runs with minimization terminated out of 100 bootstrap replicates were skipped when calculating the bootstrap results.
[a] For the updated final model (Model 24), BASE IIV was an inter-individual variability term around the model-predicted population typical baseline value. For the previous final model (Model 32), BASE IIV was a residual error around the observed individual baseline value.

The updated parameter estimates from the NONMEM output were within the 2.5th-97.5th percentile from the bootstrap. For the updated final model (Model 24), only 2 runs failed out of 100 bootstrap replicates, indicating that the updated final model is stable. Goodness of fit plots for the updated final population PK/PD model (Model 24) are shown in Figure 9-3.

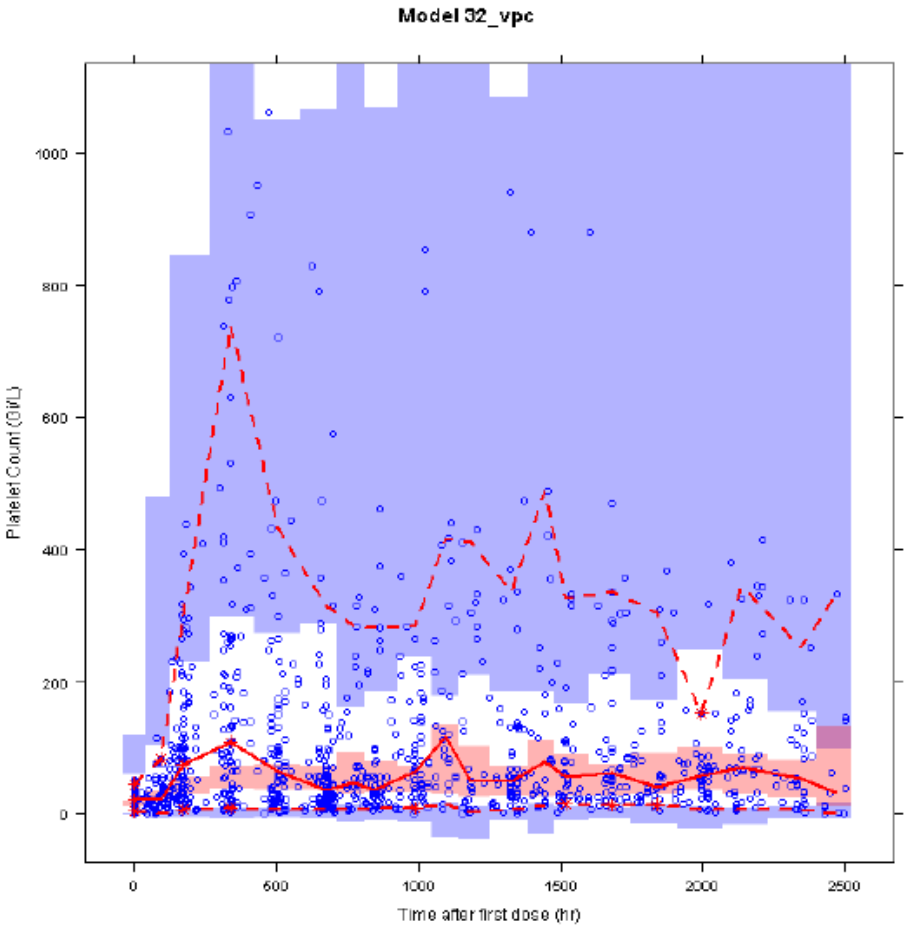
Figure 9-3 Goodness of Fit Plots for the Updated Final Population PK/PD Model (Model 24)



Blue circles: observed or model-predicted data points. Black lines: line of unity or horizontal line with y=0.
Red lines: smooth lines.
|iWRES|: absolute value of individual weighted residuals.
Unit of observations, population predictions and individual predictions: $\times 10^9$/L.
Time: actual time after the 1st dose (hr).

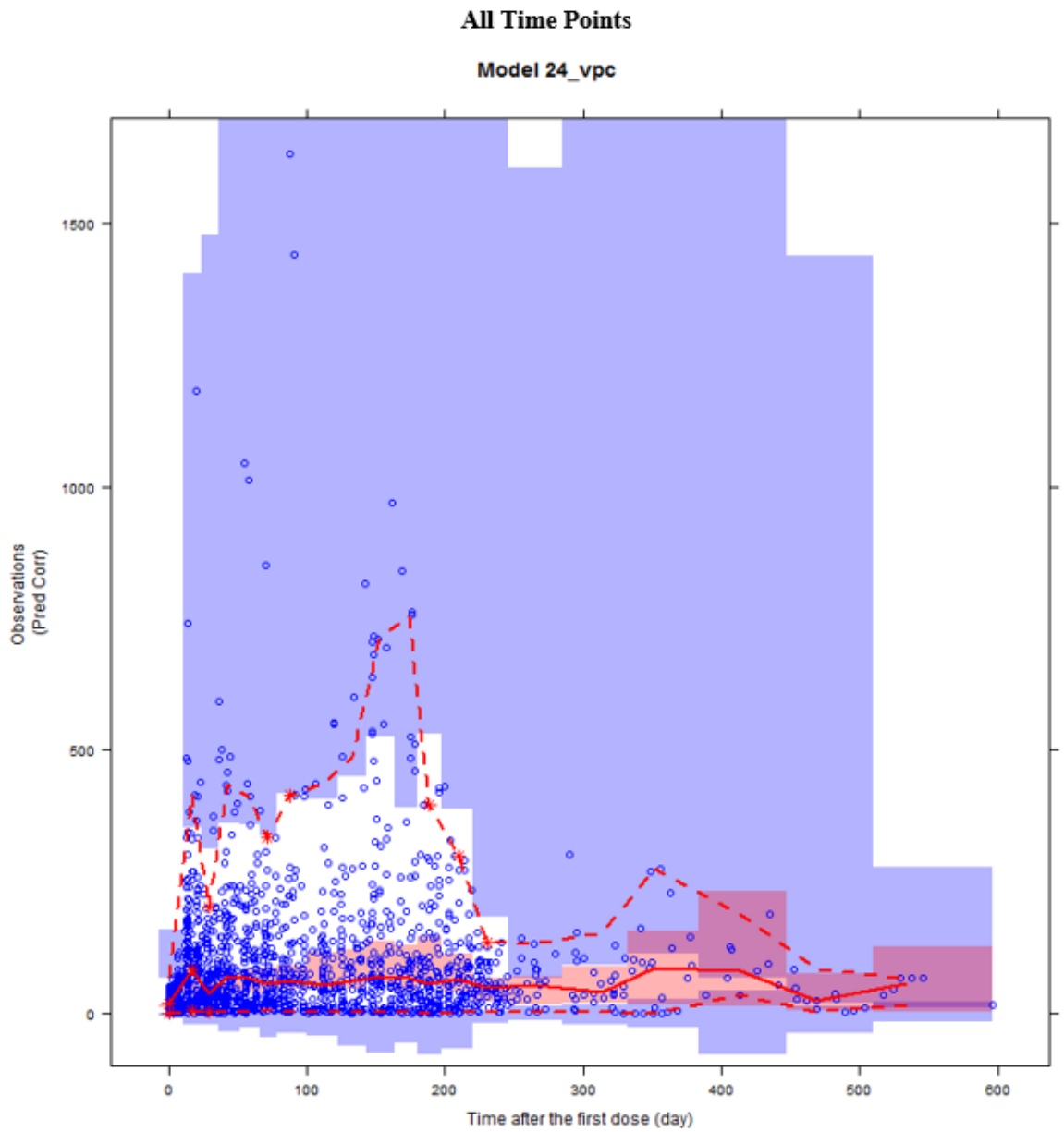
Visual predictive checks for the previous final model (Model 32) and the final updated final model (Model 24) are shown in Figures 11 and 9-4, respectively.

Figure 11. Visual Predictive Check Plot for Final Population PK/PD Model (Model 32)



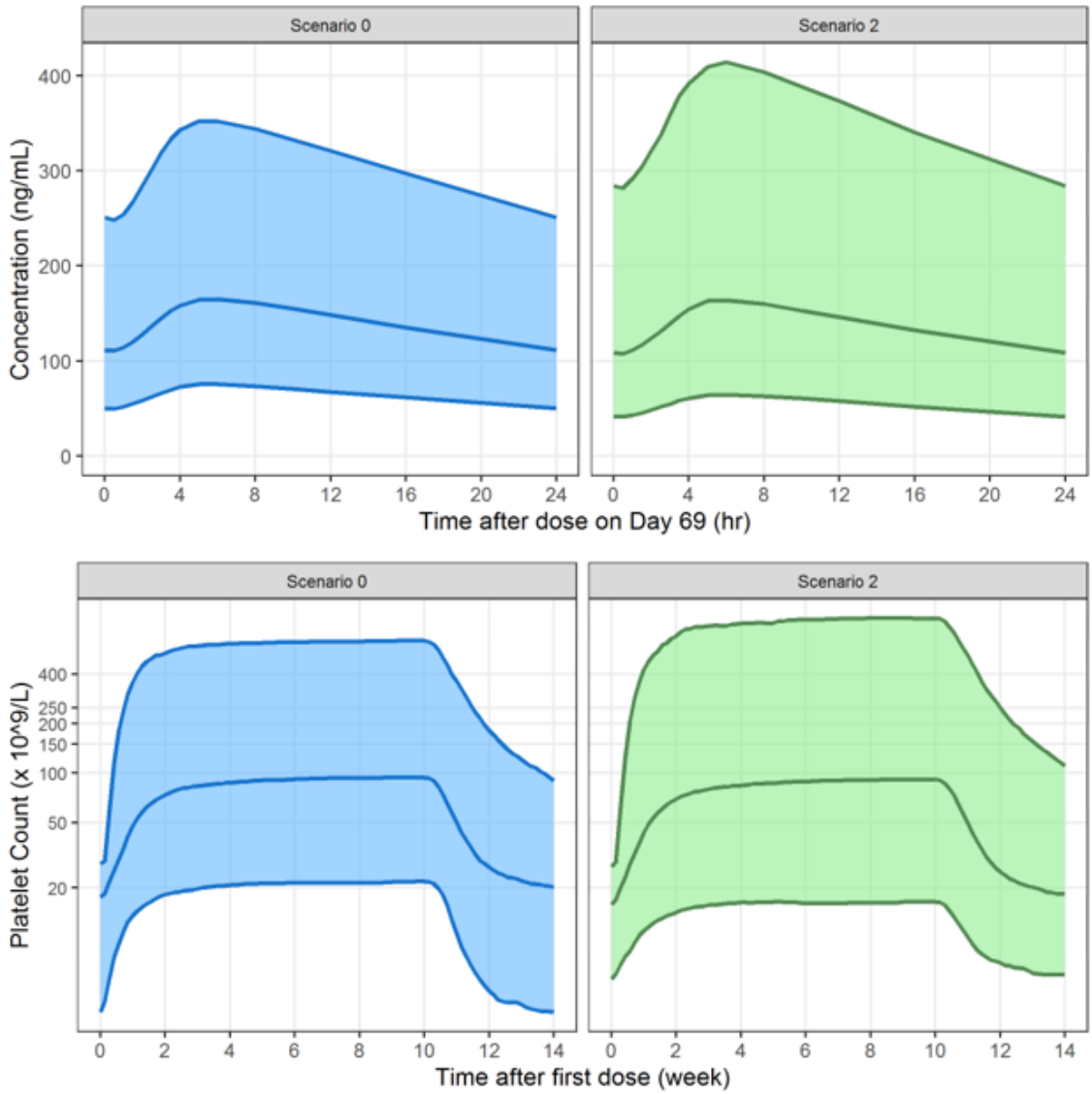
Blue circles: observed individual data; dashed and solid red lines: 5th, 50th, and 95th percentiles of the observed data; blue and red shaded areas: 95% CI based on the simulated data's 5th, 50th, and 95th percentiles.
Only data with DOSE<50 mg are shown. There are very few data points for DOSE ≥ 50 mg.
Gi/L: $\times 10^9$/L.

Figure 9-4 Prediction-Corrected VPC Plots for the Updated Final Population PK/PD Model (Model 24)



Model-predicted avatrombopag concentration and platelet count versus time profiles based on the previous and updated PK/PD models are shown in Figure 9 6. Model-predicted avatrombopag exposure and percentages of ITP patients within different platelet count bins at Week 10 based on the previous and updated PK/PD models are shown in Table 9 3 and Table 9 4, respectively.

Figure 9-6 Model-Predicted Avatrombopag Concentration and Platelet Count versus Time Profiles Based on the Previous and Updated PK/PD Models



Scenarios 0 and 2 were based on the previous and updated PK/PD models, respectively.
Lines: 5th, 50th, and 95th percentiles of the simulated values.
Shaded area: 90% prediction interval.

Table 9-3 Model-Predicted Avatrombopag Exposure Based on the Previous and Updated PK/PD Models

Scenario (group)	QD Dose (mg)	N	$C_{max,ss}$ (ng/mL)			$AUC_{0\text{-}24hrs,ss}$ (ng·hr/mL)		
			GeoMean	GeoCV (%)	GeoMean Ratio	GeoMean	GeoCV (%)	GeoMean Ratio
0	20	4000	**168**	49.6	**1.00**	**3356**	49.8	**1.00**
2	20	4000	**165**	61.3	**0.981**	**3277**	62.2	**0.976**

GeoMean: geometric mean; GeoCV: geometric coefficient of variation; GeoMean Ratio: geometric mean ratio (relative to Scenario 0); QD: once daily; SS: steady state For QD dosing, $AUC_{0\text{-}24hrs,ss}$ = Dose/(CL/F).

Formulation: 2G tablet.

Each simulated patient received 10 weeks of avatrombopag treatment followed by 4 weeks off-treatment.

Scenarios 0 and 2 were based on the previous and updated PK/PD models, respectively.

Table 9-4 Model-Predicted Percentages of ITP Patients Within Different Platelet Count Bins at Week 10 Based on the Previous and Updated PK/PD Models

Scenario (group)	QD Dose (mg)	N	% of Patients within Each Bin[a]			
			Bin 1 (Low)	Bin 2 (Target)	Bin 3 (High)	Bin 4 (Very High)
0	20	4000	26.1	**38.8**	14.4	20.8
2	20	4000	31.0	**33.3**	12.1	23.6

QD: once daily.

[a] Bin=1: Low platelet count ($<50\times10^9$/L); Bin=2: Target platelet count (≥50 to $\leq150\times10^9$/L); Bin=3: High platelet count (>150 to $\leq250\times10^9$/L); Bin=4: Very high platelet count ($>250\times10^9$/L).

Formulation: 2G tablet.

Each simulated patient received 10 weeks of avatrombopag treatment followed by 4 weeks off-treatment.

Scenarios 0 and 2 were based on the previous and updated PK/PD models, respectively.

The simulation results with the updated model show that the central tendency (e.g., median and geometric mean) of avatrombopag concentrations did not change, but the prediction interval and variability were larger compared to the simulations with the original model. The simulation results also show that the distribution of patients within each platelet count bin (low, target, high, very high) changed; however, the 20 mg QD was still predicted to have the largest % of patients achieving the target range using the updated model.

Overall, the results show that the previous model and the updated model are not substantially different from each other.

Simulation of avatrombopag dose titrations

Figure 9-5 Observed and Model-Predicted Baseline Platelet Count

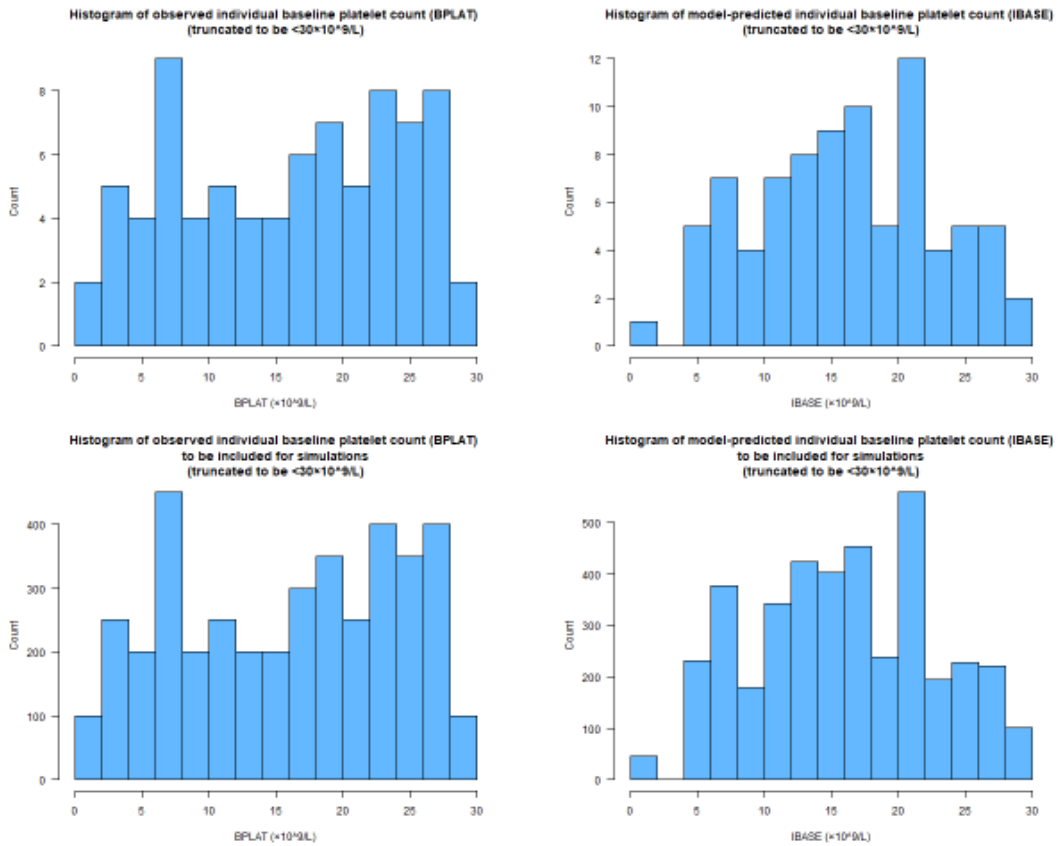


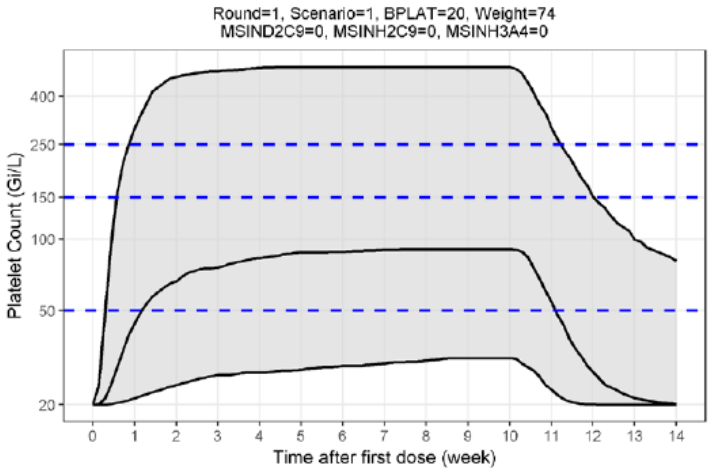
Table 9-2 shows the characteristics of hypothetical ITP patients used for simulations. Each simulated patient received 10 weeks of treatment followed by 4 weeks off treatment.

First simulations with fixed dosing regimen for all subjects (no individualized titration) was conducted to evaluate the impact of significant PK and PK/PD covariates on attainment of target platelet counts (50-150 × 10^9/L) following avatrombopag 20 mg QD. 500 subjects were included in each simulation scenario that were based on ITP patients, the 2G tablet, a weight of 74 kg, a baseline platelet count of 20 × 10^9/L, each receiving 10 weeks treatment followed by 4 weeks off-treatment, with and without DDI perpetrators.

The simulated results suggest that a typical ITP patient (the median line) will have platelet counts well within the target range (50-150 × 10^9/L). See Figure 12. However, there will be some ITP patients who are outside of the target range and need dose titration by either adjustment of the dose or dosing frequency after the initial dose of 20 mg QD.

Further simulations indicated that the effect of body weight on platelet count is modest and no dose adjustments are required. For a typical ITP patient, the platelet count is predicted to be within the target range after 2 weeks of 20 mg QD dosing when the baseline platelet count is within 5-30 × 10^9/L. Therefore, no adjustment of the initial dose is needed with regard to baseline platelet count in ITP patients. DDI perpetrators had large effect on platelet counts. Simulations showed that adjusting the initial dose of avatrombopag to 40 mg QD when a moderate or strong dual inducer for CYP2C9 and CYP3A4 is present a higher percentage of subjects (45.6%) will achieve the target range compared to 20 mg QD (39.4%). It also shows that adjusting the initial dose of avatrombopag to 20 mg three times a week when a moderate or strong dual inhibitor for CYP2C9 and CYP3A4 is present will result in a higher percentage of subjects (45.0%) achieving the target range compared to 20 mg QD (36.2%).

Figure 12. Simulated Platelet Count for the Base Scenario (Baseline Platelet=20 × 10^9/L, Weight=74 kg, No Perpetrator, Dose=20 mg QD)

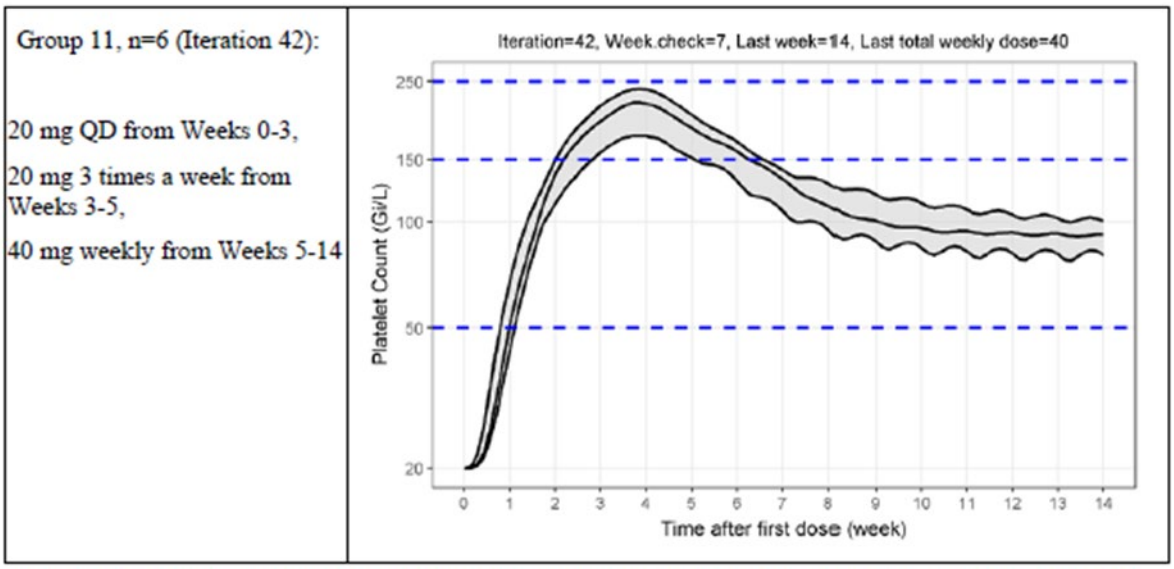


Black solid lines: 5th, 50th, and 95th percentiles for the base scenario; gray shaded area: 90% PI for the base scenario; blue horizontal reference lines: 50, 150 and 250 × 10^9/L. Y-axis is on the log-scale. Gi/L: × 10^9/L.

For the second round of simulations, a total of 1000 subjects in the base scenario (baseline platelet = 20 × 10^9/L, weight = 74 kg, no DDI perpetrators, avatrombopag initial dose = 20 mg QD) went through dose adjustments, by modifying as appropriate either the dose or frequency of dosing.

At each week, the platelet count was binned into 4 bins from low to very high. Based on the bin status each week and the observed platelet-count patterns, the subjects were divided into 15 groups. For each group, multiple titrations (or iterations) were conducted with a goal of maximizing the percentage of subjects achieving a platelet count of 50-150 × 10^9/L. Figure 19 and 22 are two examples of platelet profiles for groups that achieved the target range during titration.

Figure 19. The Range of Simulated Platelet Count for Group 11 (n=6) who Achieved the Target Range from Week 7 Through Week 14



Gray shaded area: the range; Black solid line in the middle: median; Blue horizontal reference lines: 50, 150 and 250 × 10^9/L. Y-axis is on the log-scale. Gi/L: × 10^9/L.

Figure 22. The Simulated Platelet Count for Group 15 (n=9) who Achieved the Target Range on Day 67 and Day 98

Group 15, n=9 (Iteration 100):

20 mg QD from Weeks 0-1,

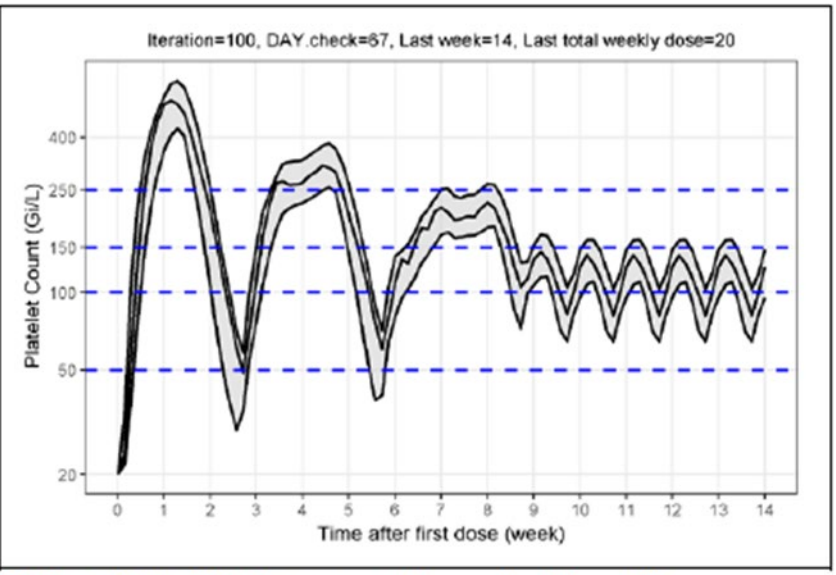
stop dosing from Days 7-18,

20 mg 3 times a week from Days 18-32,

stop dosing from Days 32-39,

20 mg twice a week from Days 39-53,

20 mg weekly from Days 53-98



Blue horizontal reference lines: 50, 150 and 250 × 10^9/L. Y-axis is on the log-scale. Gi/L: × 10^9/L.

The second round of simulations support the following dose titration algorithm with 20 mg QD as the initial dose:

Platelet Count (x10^9/L)	Dose Adjustment or Action
Less than 50 after at least 2 weeks of avatrombopag	• Increase *One Dose Level* per the following table. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
Between 150 and 250	• Decrease *One Dose Level* per the following table. • Wait 2 weeks to assess the effects of this regimen and any subsequent dose adjustments.
Greater than 250	• Stop avatrombopag. • Increase platelet monitoring to twice weekly. • When platelet count is less than or equal to 100 x10^9/L, decrease *One Dose Level* per the following table and reinitiate therapy.
Less than 50 after 4 weeks of avatrombopag 40 mg once daily	• Discontinue avatrombopag.
Greater than 250 after 2 weeks of avatrombopag 20 mg weekly	• Discontinue avatrombopag.

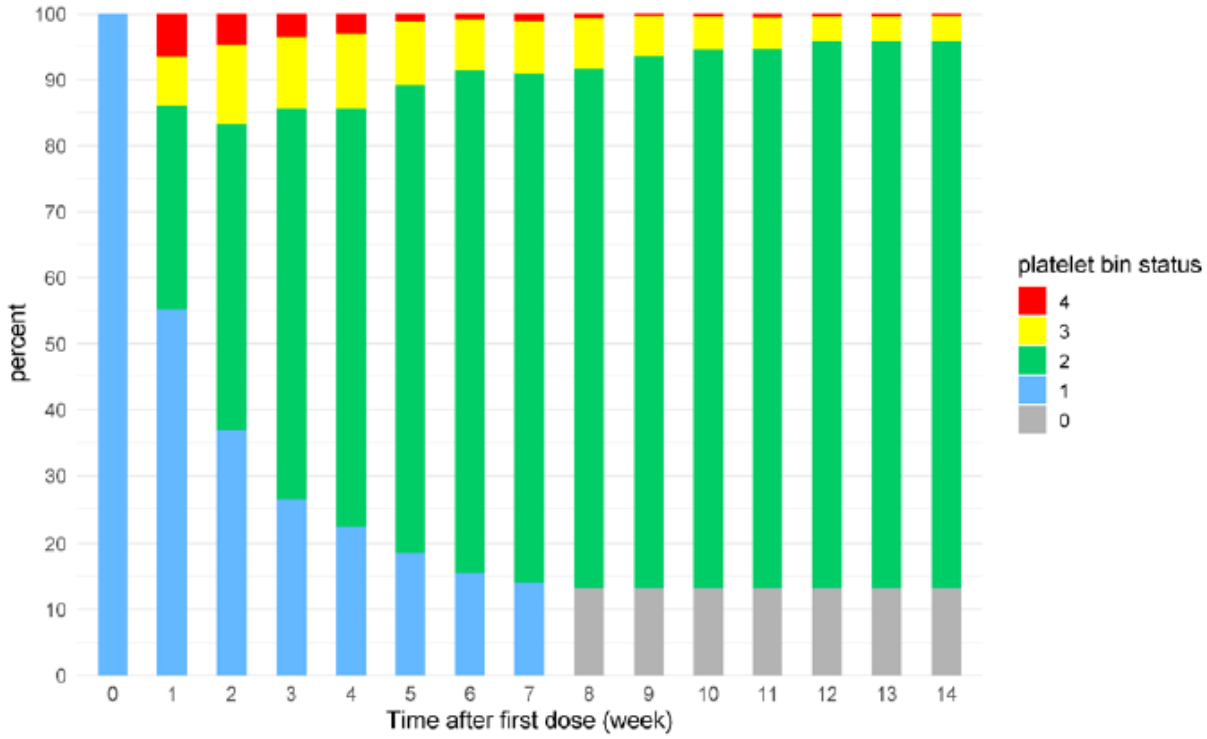
During therapy with avatrombopag, assess platelet counts weekly until a stable platelet count has been achieved and obtain platelet counts monthly thereafter.
Twice weekly monitoring is conducted on Monday and Friday.

Dose	Dose Level
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*	4
20 mg Three Times a Week	3
20 mg Twice a Week *OR* 40 mg Once Weekly	2
20 mg Once Weekly	1

*Initial dose regimen for all patients *except* those taking *Moderate or Strong Dual Inducers* or *Moderate or Strong Dual Inhibitors* of CYP2C9 and CYP3A4.
Three times a week: dose on Monday, Wednesday, and Friday.
Twice a week: dose on Monday and Friday.

The 2nd round simulations demonstrate that when all subjects start with a low baseline platelet count at 20 × 10^9/L, by using the dose titration algorithm above, the percentage of subjects achieving the target range (50-150 × 10^9/L) increases over time and stabilizes around Week 10. By the end of the 14-week treatment period, 82.4% of the subjects have achieved the target range. At Week 14, the breakdown of the 82.4% of subjects who have achieved the target range is as follows: 33.7% from the subjects dosed at 20 mg QD dosing without any dose titration, 27.8% through down titration, and 20.9% through up titration. See Figure 23.

Figure 23. Stack Bar Plot of Percentages of Subjects within Different Platelet Count Bins at Each Week During Dose Titration



Bin=0: discontinued due to low platelet count (< 50 × 10^9/L) after up-titration to 40 mg QD (maximum dose) for 4 weeks;
Bin=1: low platelet count (<50 × 10^9/L);
Bin=2: target platelet count (50-150 × 10^9/L);
Bin=3: high platelet count (≥150 × 10^9/L to ≤250 × 10^9/L);
Bin=4: very high platelet count (>250 × 10^9/L).

Initiation of Doptelet at a dose of 20 mg once daily resulted in an increase in platelet count within the first 8 days of treatment (Figure 1 below). Table 1 describes the percentage of subjects at each visit with thrombocytosis and the corresponding maximum observed platelet count by visit.

Figure 1 **Median Local Platelet Counts Over Time (Study 302)**

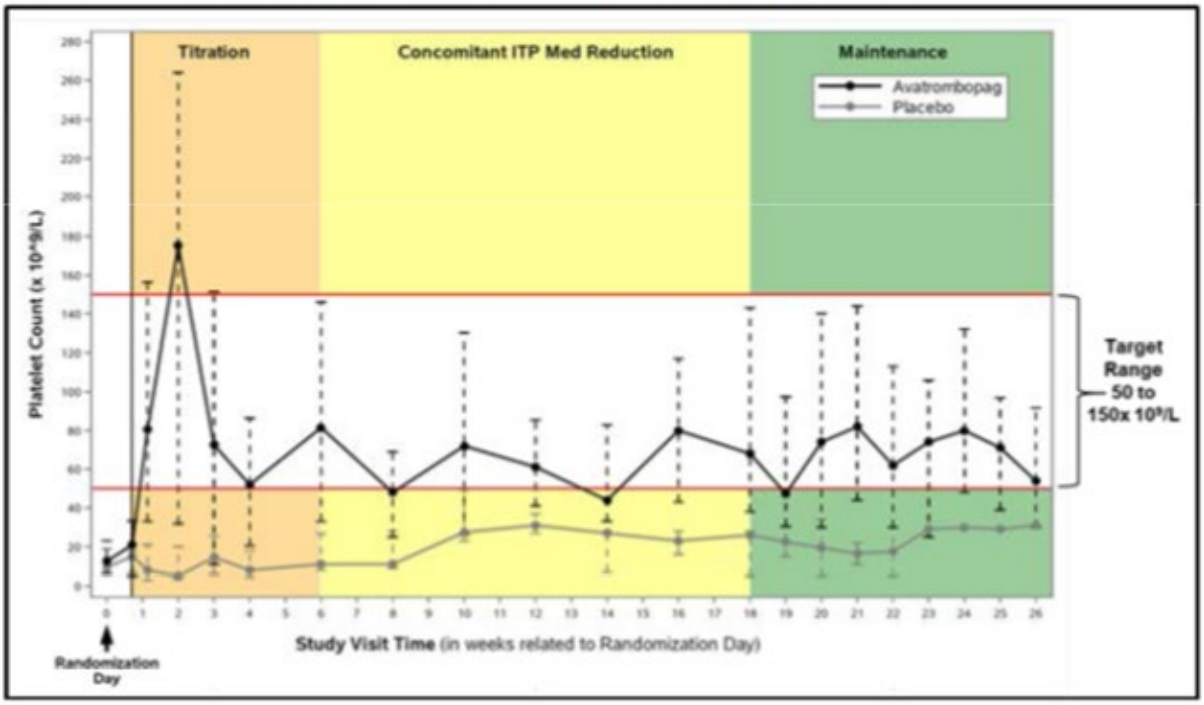
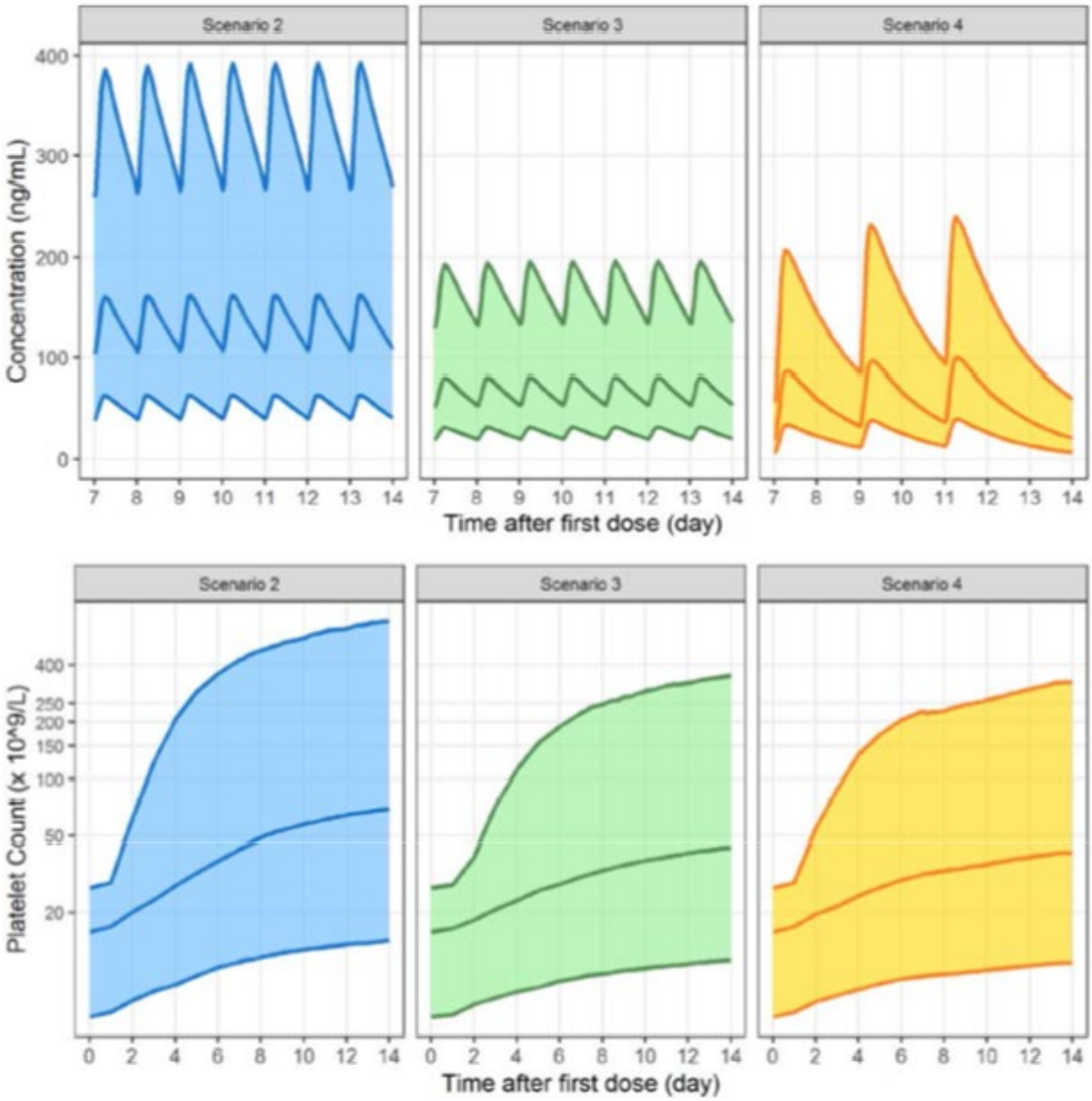


Table 1 **Incidence of Thrombocytosis and Maximum Observed Platelet Count by Visit – Study 302**

	N at Each Visit	Percentage of Patients with Platelet Count >400x10^9/L	Maximum Observed Platelet Count (x10^9/L)
Day 5	30	0	185
Day 8	32	0	297
Week 2	32	15.6%	805
Week 3	32	3.1%	721
Week 4	32	0	242
Week 6	30	3.3%	476
Week 8	30	6.7%	940
Week 10	30	6.7%	520
Week 12	28	3.6%	427
Week 14	25	0	252
Week 16	28	0	385
Week 18	25	0	362
Week 20	24	0	440
Week 22	25	0	240
Week 26	22	0	187

Figure 2 **Model-Predicted Avatrombopag Concentration and Platelet Count versus Time Profiles Using Different Starting Dose Regimens**



Scenarios 2, 3 and 4 were for 20 mg once daily (QD), 10 mg QD, and 20 mg three times a week (TIW), respectively.
Lines: 5th, 50th, and 95th percentiles of the simulated values.
Shaded area: 90% prediction interval.

Table 4 Model-Predicted Avatrombopag Exposure During the 2nd Week of Active Dosing Using Different Starting Dose Regimens

Scenario (group)	Dosing Regimen	N	C_{max} (ng/mL)			$AUC_{0\text{-}24hrs}$ (ng·hr/mL)		
			GeoMean	GeoCV (%)	GeoMean Ratio	GeoMean	GeoCV (%)	GeoMean Ratio
2	20 mg QD	4000	**163**	59.5	**1**	**3227**	60.4	**1**
3	10 mg QD	4000	**81.6**	59.5	**0.500**	**1613**	60.4	**0.500**
4	20 mg TIW	4000	**102**	58.7	**0.626**	**1386**	60.4	**0.430**

GeoMean: geometric mean; GeoCV: geometric coefficient of variation; GeoMean Ratio: geometric mean ratio (relative to Scenario 2); QD: once daily; TIW: three times a week.

For both QD and TIW dosing, C_{max} was the maximum concentration during the 2nd week of active dosing, and $AUC_{0\text{-}24hrs} = AUC_{0\text{-}168hrs}/7$ where $AUC_{0\text{-}168hrs}$ was for AUC during the 2nd week of active dosing and calculated using trapezoidal rule.

Formulation: 2G tablet.

Each simulated patient received 2 weeks of avatrombopag treatment.

Table 5 Model-Predicted Percentages of ITP Patients Within Different Platelet Count Bins on Day 14 Using Different Starting Dose Regimens

Scenario (group)	Dosing Regimen	N	% of Patients Within Each Bin[a]			
			Bin 1 (Low)	Bin 2 (Target)	Bin 3 (High)	Bin 4 (Very High)
2	20 mg QD	4000	39.7	**32.2**	10.5	17.6
3	10 mg QD	4000	55.8	**28.9**	7.33	8.05
4	20 mg TIW	4000	58.2	**27.5**	7.18	7.15

QD: once daily; TIW: three times a week.

[a] Bin=1: Low platelet count ($<50\times10^9$/L); Bin=2: Target platelet count (≥50 to $\leq150\times10^9$/L); Bin=3: High platelet count (>150 to $\leq250\times10^9$/L); Bin=4: Very high platelet count ($>250\times10^9$/L).

Formulation: 2G tablet.

Each simulated patient received 2 weeks of avatrombopag treatment.

Clinical trial simulation

Eltrombopag is another TPO-RA approved for the treatment of ITP. The objective of the clinical trial simulation was to evaluate the efficacy of avatrombopag (test) compared to eltrombopag (control) as measured by the durable response rate.

In the population PK model for eltrombopag (Gibiansky, Zhang et al. 2011), body weight, dose <20 mg, healthy subjects vs ITP patients, East Asians (such as Chinese, Japanese, or Korean) vs non-East Asians, sex, and concomitant corticosteroids were significant covariates. In the population PK/PD model for eltrombopag (Hayes, Ouellet et al. 2011), sex and age were significant covariates. See Table 5 for demographics of ITP patients for eltrombopag and avatrombopag.

Table 5. Demographics of ITP Patients (from Phase 2 and Phase 3 Trials) Evaluated in Eltrombopag and Avatrombopag Population PK/PD Modeling

Demographics/Covariates	Eltrombopag (N=88)			Avatrombopag (N=97)		
	Statistics	Significant Covariate on		Statistics	Significant Covariate on	
		PK	PD		PK	PD
Age, year, median (range)	51 (18-85)	No	Yes	51.0 (18.0-82.0)	No	N.E.
Weight, kg, median (range)	75.5 (43.0-122)	Yes	No	77.2 (53.0-161)[a]	Yes	N.E.
Baseline platelet count, × 10^9/L, median (range)	16.0 (1.00-40.0)	N.E.	No	20.0 (1.00-50.0)	N.E.	Yes
Sex, n (%)		Yes	Yes		No	N.E.
Female	57 (65)			61 (62.9)		
Male	31 (35)			36 (37.1)		
Race, n (%)		Yes	No		No	N.E.
Asian	18 (20)			5 (5.15)		
Caucasian, African American, & Other	70 (80)			92 (94.8)		
Concurrent corticosteroids, n (%)		Yes	No		N.E.	No
No	61 (69)			57 (58.8)		
Yes	27 (31)			40 (41.2)		

Additionally, in the population PK model for eltrombopag (Gibiansky, Zhang et al. 2011) dose <20 mg was a significant covariate. This was not relevant to the current simulations because only doses ≥25 mg were used for titration.

N.E.: Not evaluated as a covariate.

[a] One ITP patient had baseline body weight of 161 kg. The next heaviest patient had baseline body weight of 129.5 kg.

Virtual ITP patients

After applying a baseline platelet count cutoff <30×10^9/L (to align with inclusion criteria of Study E5501-G000-305) and excluding Asian patients, the observed demographic information from a total of 77 ITP patients dosed with avatrombopag were used to create 10,000 virtual ITP patients in the simulation datasets. The demographic information included age, weight, observed baseline platelet count, sex, race, and concurrent corticosteroid use (yes/no). The demographic information for each patient was treated as one unit and randomly resampled with replacement to account for correlations across demographic covariates.

Non-inferiority evaluation

Eltrombopag and avatrombopag treatments were administered to the same virtual 10,000 ITP patients, each for 26 weeks. For avatrombopag, the commercial formulation (i.e., the 2G tablet) was used. IIV on the observed baseline platelet count was large for avatrombopag (60.7%CV). The value for eltrombopag was used in the simulations for both eltrombopag and avatrombopag (i.e., 29.5% CV random variability was added to the sampled observed baseline platelet count). Inter occasion variability for the absorption rate constant was included in the population PK model for eltrombopag. Residual errors on platelet count were large but similar in magnitude between eltrombopag and avatrombopag models. Residual errors on the concentration and platelet count were not included in the simulations.

For the non-inferiority simulations, the doses of both eltrombopag and avatrombopag were titrated to maximize the percentage of subjects achieving a platelet count of 50-150×10^9/L over time. The dose titration algorithms were based on the algorithms used in the Study E5501-G000-305 protocol (Phase 3 study evaluating safety and efficacy of avatrombopag versus eltrombopag in ITP patients) and were

similar for both treatments. The current simulations did not include DDI perpetrators (i.e., moderate or strong dual inducers or moderate or strong dual inhibitors of CYP2C9 and CYP3A4).

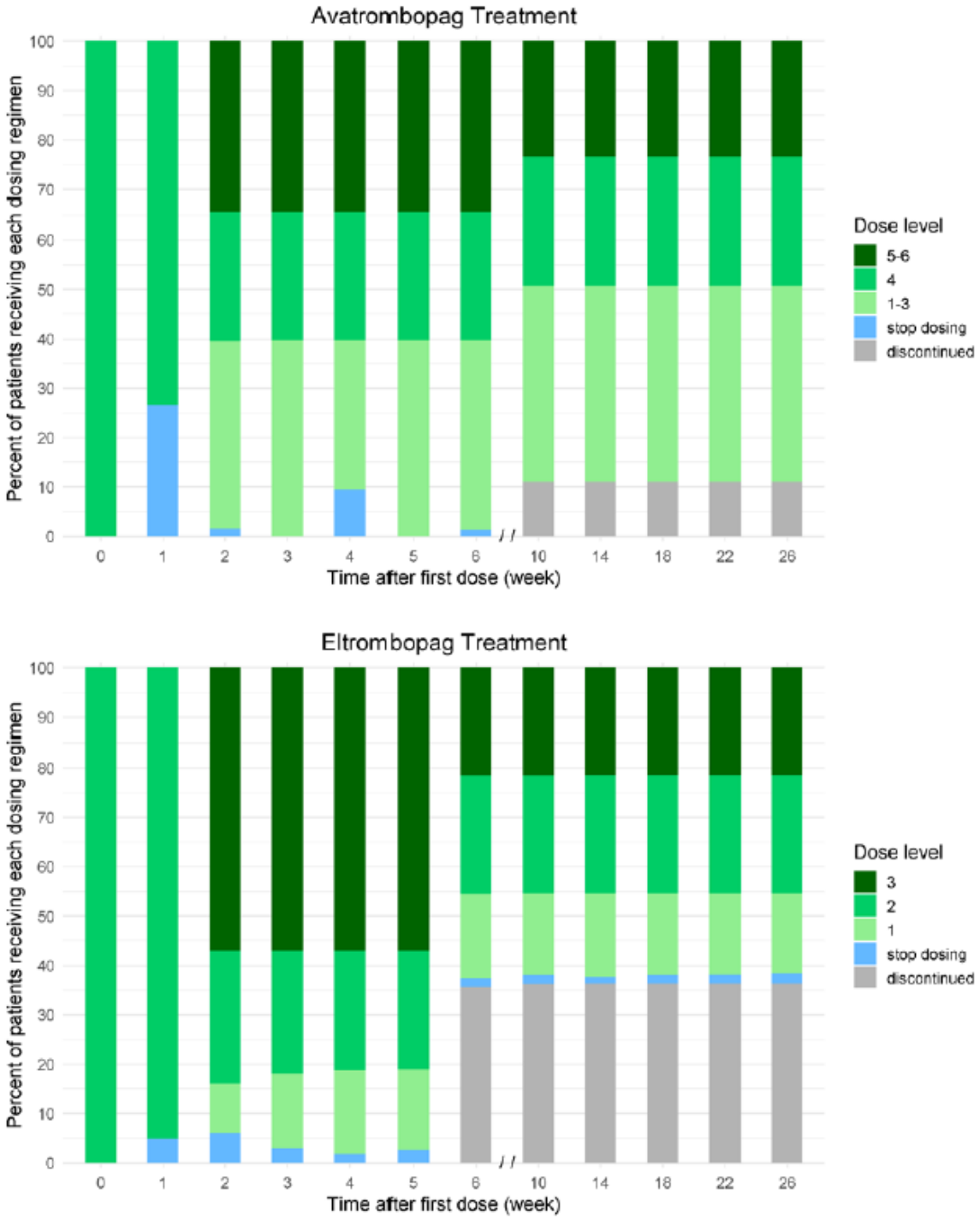
The primary endpoint was the durable platelet response rate, which was defined as the proportion of patients who had at least 75% (e.g., 6 out of 8 weekly monitoring) platelet responses $\geq 50 \times 10^9$/L during the last 8 weeks of the 26-week treatment period in the absence of rescue therapy.

A total of 1000 simulated clinical trial datasets were generated. Each dataset was created by random sampling with replacement N=143 avatrombopag patients and N=143 eltrombopag patients from the 10,000 simulated patients in each treatment group. The sample size of 143 was similar to that of Study E5501-G000-305. Each patient was identified as either having or not having a durable platelet response. The null hypothesis was that avatrombopag was not as effective as eltrombopag. The alternative hypothesis was that avatrombopag was at least as effective as eltrombopag. Non-inferiority would be demonstrated if the upper bound of the 2-sided 95% confidence interval (based on normal approximation) for the difference in the durable platelet response rate between eltrombopag and avatrombopag (control – test) was below 15%. The choice of the non-inferiority margin of 15% was based on a combination of statistical reasoning and clinical judgment. To strengthen the non-inferiority comparison, both the pre-specified primary analysis (all patients), and a sensitivity analysis excluding the 18.9% non-responders of eltrombopag (patients with a zero PD slope factor) were conducted. Individual plots in the population PK/PD analysis for avatrombopag suggested that some subjects may also be non-responders to avatrombopag. The IIV for the PD slope factor for avatrombopag was large (%CV=123%) and would allow individual PD slope factors to be small (=mimicking non-responders behaviour).

For avatrombopag, 79.4% of the patients were predicted to have a durable platelet response rate, defined as the proportion of patients who had at least 75% platelet responses $\geq 50 \times 10^9$/L during the last 8 weeks of treatment over the 26-week treatment period in the absence of rescue therapy. For eltrombopag, 52.5% and 64.7% of the patients were predicted to have a durable platelet response rate for the primary analysis (all patients, including 18.9% of patients who had a zero PD slope factor and thus not responding to eltrombopag treatment) and sensitivity analysis (excluding the patients with a zero PD slope factor), respectively. These durable platelet response rates for eltrombopag are similar to the reported durable platelet response of 60% from a 6-month eltrombopag Phase 3 study (RAISE).

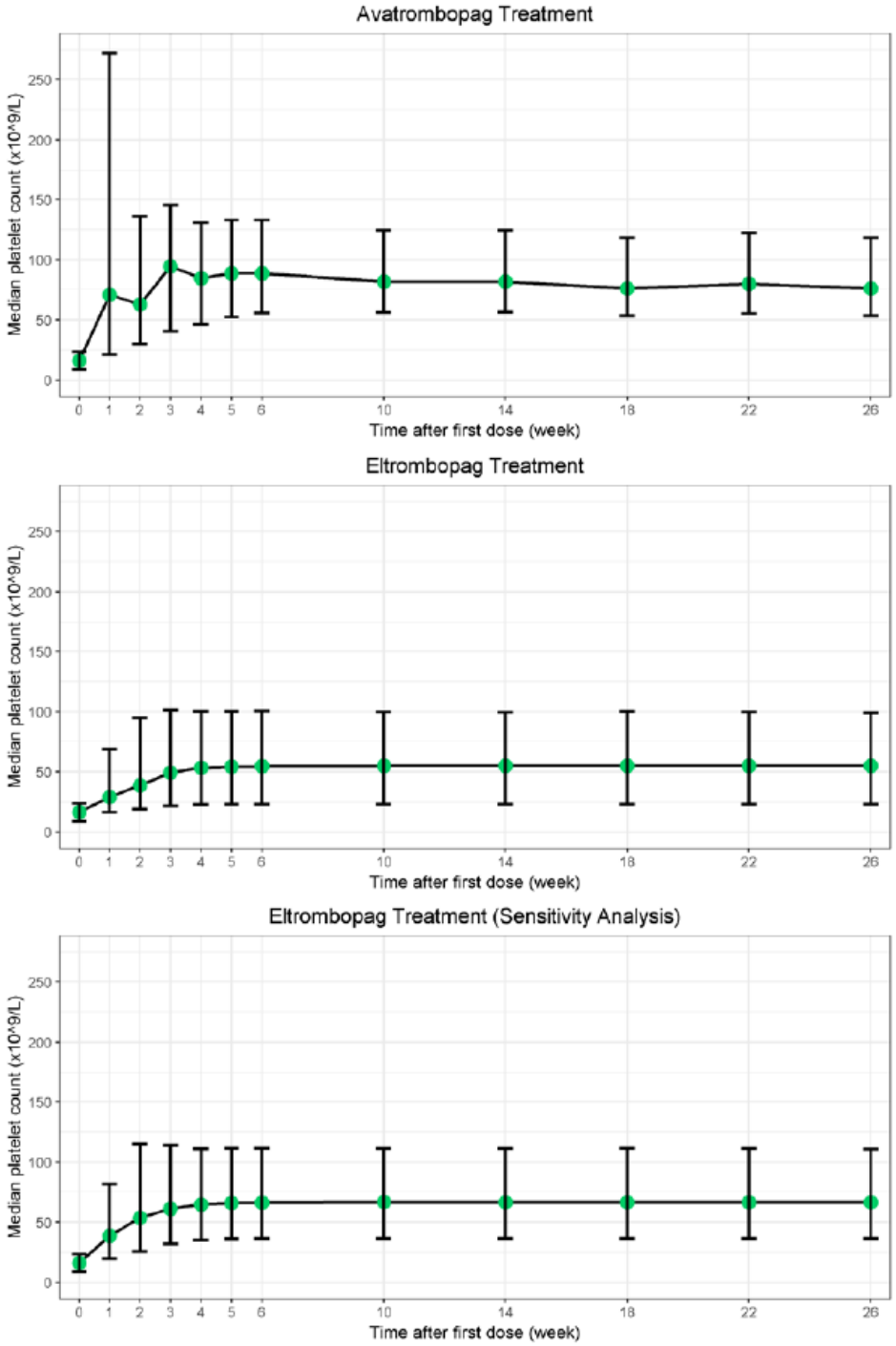
For avatrombopag, the starting dose was 20 mg once daily and the dosing regimen became stable for the entire population by Week 10. For eltrombopag, the starting dose was 50 mg once daily and the dosing regimen became stable for the entire population by Week 6. Eltrombopag reached a stable dosing regimen sooner than avatrombopag because eltrombopag had fewer dose levels available for titration. See Figure 3.

Figure 3. Proportions of Patients Receiving Each Dosing Regimen During Treatment



For avatrombopag, the median platelet count was ≥76×10^9/L as early as Week 3 and sustained through Week 26. For eltrombopag, the median platelet count was 55 and 67×10^9/L for the primary analysis (all patients, including 18.9% of patients who had a zero PD slope factor and thus not responding to eltrombopag treatment) and sensitivity analysis (excluding the patients with a zero PD slope factor), respectively.

Figure 4. Median (25th and 75th Percentiles) Platelet Count for Each Treatment



If a patient discontinued, the last platelet count before discontinuation was carried forward in the plots.
For a non-responder to eltrombopag by the PK/PD model definition (for the primary analysis), platelet count over the 26 weeks of treatment period remained the same as the baseline value.

Overall, the difference in the proportion of avatrombopag responders compared to eltrombopag responders in the 10,000 simulated patients ranged from 8.4% to 44% in the primary analysis and from - 1.4% to 32% in the sensitivity analysis. Thus, the lower bound of the 2-sided 95% confidence interval for the difference in the proportion of patients with a durable platelet response between avatrombopag and eltrombopag was above -15% for all 1000 simulated trials for both the primary and sensitivity non-inferiority analyses demonstrating that avatrombopag is non-inferior to eltrombopag.

Absorption

Below is a summary of ADME properties of avatrombopag.

Oral administration of the avatrombopag 2G commercial tablet resulted in a short lag time (0.5 to 0.75 hours) with peak exposure at 6 to 8 hours post-dose. Co-administration with food, irrespective of the type of food, significantly reduced both the inter- and intra-subject variability in avatrombopag PK parameters by up to 50%.

Distribution

The population estimate of V/F1 for avatrombopag was 235 L in ITP patients.

Elimination

The population estimate of CL/F1 for avatrombopag was 5.74 L/hr in ITP patients

The half-life of avatrombopag was independent of dose and time, approximately 19 hours.

The primary route of excretion of avatrombopag and its metabolites was by the faecal route (88%). The primary metabolite of avatrombopag, the 4-hydroxy derivative, was only detected in faeces (44%). No metabolites of avatrombopag were detectable in plasma.

Avatrombopag metabolism is mediated by CYP3A4 and CYP2C9 enzymes where CYP2C9 plays the major role relative to CYP3A4 in the oxidative metabolism of avatrombopag.

Dose proportionality and time dependencies

Avatrombopag exhibited linear PK up to the highest tested dose of 80 mg using the 2G tablet formulation.

Special populations

There were no clinically important differences in PK or PD parameters between healthy subjects of Asian origin and white subjects administered avatrombopag. Avatrombopag does not require dose modifications in subjects with mild or moderate renal impairment. Population PK/PD simulations suggest that body weight differences in subjects with ITP (ranging from 55 kg – 110 kg) have minimal impact on platelet counts.

Pharmacokinetic interaction studies

No new interaction studies have been conducted. Below is a summary of the effects observed with avatrombopag in clinical DDI studies.

Coadministration of rifampin with avatrombopag resulted in mild to moderate induction of avatrombopag clearance. Avatrombopag is also a substrate of P-gp transport. Strong P-gp inhibitors such as verapamil and CsA had mild, but clinically unimportant effects on systemic exposures of avatrombopag. Co-administration of a single 20 mg dose of avatrombopag with a dual moderate inhibitor of CYP3A and CYP2C9, fluconazole, at study state resulted in a moderate DDI, as demonstrated by an approximately 2.2-fold increase in avatrombopag AUC(0-inf) and a 17% increase in Cmax. In addition, co-administration of a single 20 mg dose of avatrombopag with a strong CYP3A and a moderate CYP2C9 inducer, rifampin, resulted in a mild-moderate interaction as demonstrated by approximately 0.5-fold

decrease in avatrombopag AUC(0-inf) without any effect on the Cmax of avatrombopag. In order to maintain efficacy, dose adjustments may be necessary when avatrombopag is co-administered with moderate or strong dual CYP2C9 and CYP3A4 inducers or inhibitors.

The PopPK model for ITP was able to capture the magnitude of impact from the DDI perpetrators on avatrombopag exposure observed in clinical DDI studies with verapamil (P-gp inhibitor, moderate CYP3A inhibitor), cyclosporine (P-gp inhibitor, weak CYP2C9 and CYP3A inhibitor), fluconazole (moderate inhibitor of CYP2C9 and CYP3A), iltraconazole (strong CYP3A inhibitor, P-gp inhibitor), rifampin (strong CYP3A and moderate CYP2C9 inducer, P-gp inducer). See Table 5.

Table 5. Drug-Drug Interaction Summary from the Final Population PK Model vs Observed

DDI Perpetrator		Model Prediction							Observed (with vs without the Perpetrator)		
									Geometric LS Mean Ratio (90% CI)		Mean Ratio
		CL/F1 with INHPGP	CL/F1 with MSIND2C9[d]	CL/F1 with MSINH2C9	CL/F1 with MSINH3A4	CL/F1[a] Impact	AUC_{inf}[b] Fold Change	$t_{1/2}$[c] Fold Change	C_{max}	AUC_{inf}	$t_{1/2}$
+Verapamil	Role	1	0	0	1						
	Impact	1	1	1	0.679	0.679	1.47	1.47	1.26 (0.96, 1.66)	1.61 (1.21, 2.15)	1.28
+Cyclosporine	Role	1	0	0	0	0					
	Impact	1	1	1	1	1.00	1.00	1.00	0.66 (0.54, 0.82)	0.83 (0.65, 1.04)	1.07
+Fluconazole	Role	0	0	1	1	0					
	Impact	1	1	0.705	0.679	0.479	2.09	2.09	1.17 (0.964, 1.42)	2.16 (1.71, 2.72)	2.02
+Itraconazole	Role	1	0	0	1	0					
	Impact	1	1	1	0.679	0.679	1.47	1.47	1.07 (0.855, 1.35)	1.37 (1.10, 1.72)	1.43
+Rifampin[d]	Role	0	1	0	0	0					
	Impact	1	1.93	1	1	1.93	0.519	0.519	1.04 (0.882, 1.23)	0.568 (0.465, 0.623)	0.481

[a] CL/F1 Impact represents the overall fold change in CL/F1 associated with presence (Role =1) or absence (Role =0) of DDI perpetrators. CL/F1 Impact is calculated as the product of the individual perpetrator impacts: INHPGP Impact × MSIND2C9 Impact× MSINH2C9 Impact × MSINH3A4 Impact.

[b] AUC_{inf} fold change represents the fold change in AUC_{inf} in the presence of DDI perpetrator(s) vs without perpetrator(s) and is calculated as: 1/(CL/F1 Impact).

[c] $t_{1/2}$ fold change represents the fold change in $t_{1/2}$ in the presence of DDI perpetrator(s) vs without perpetrator(s) and is calculated as: 1/(CL/F1 Impact).

Note: since none of the CYP or P-gp inhibitors or inducers were found to be significant covariates on the volume of distribution, changes in $t_{1/2}$ were dependent only on changes in CL/F1.

[d] The effect of rifampin on CL/F1 was likely due to the dual effect of CYP2C9 and CYP3A4 induction.

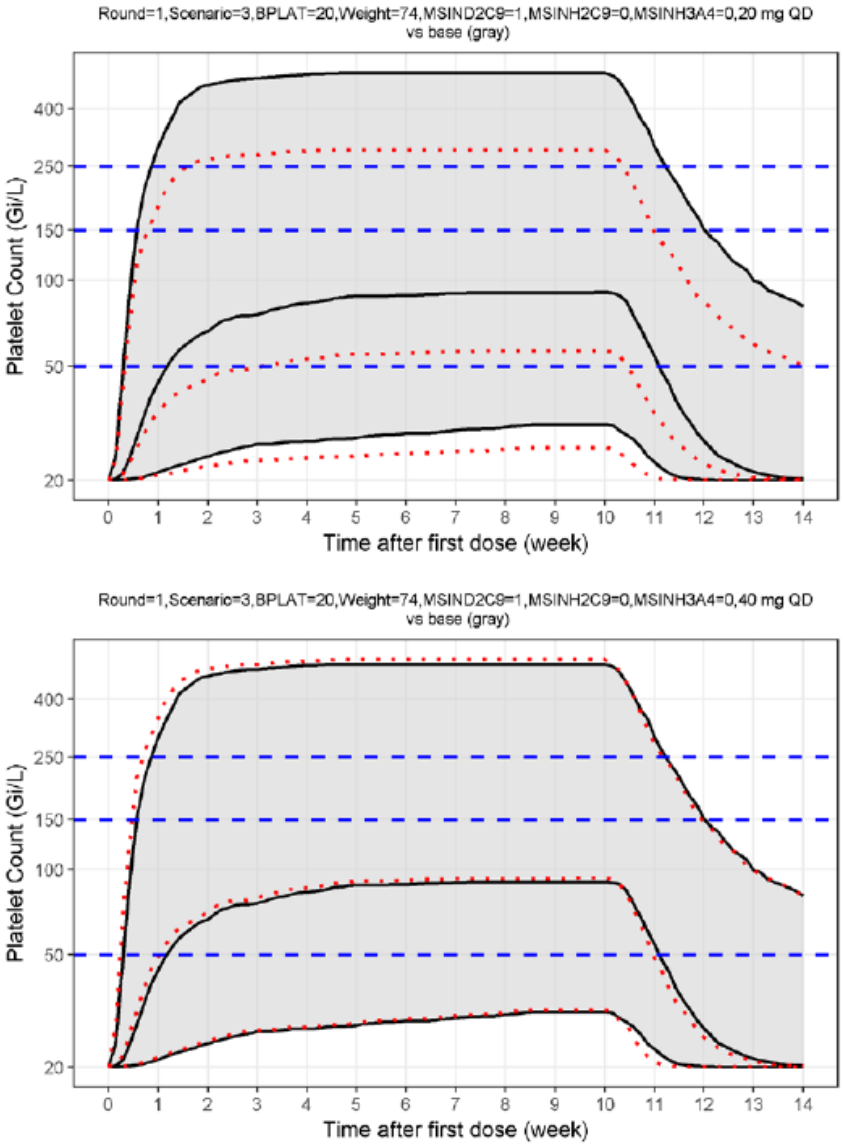
INHPGP = P-gp inhibitor, MSINH2C9 = moderate or strong CYP2C9 inhibitor, MSINH3A 4= moderate or strong CYP3A4 inhibitor, MSIND2C 9= moderate or strong CYP2C9 inducer.

Source of observed results for C_{max}, AUC_{inf} and $t_{1/2}$ (respectively): for verapamil, from Study 008 CSR Tables 9, 9 and 8; for cyclosporine, from Study 008 CSR Tables 9, 9 and 8; for fluconazole, from Study 019 CSR Tables 8, 8 and 7; for itraconazole, from Study 019 CSR Tables 10, 10 and 9; for rifampin, from Study 019 CSR Tables 12, 12 and 11.

Simulations of DDI

Simulations with the final PK/PD model over 14 weeks, indicated that after adjusting the initial dose of avatrombopag to 40 mg QD when a moderate or strong dual inducer for CYP2C9 and CYP3A4 is present, the platelet count is comparable to the base scenario which is no DDI perpetrators and avatrombopag 20 mg QD dosing. See Figure 14.

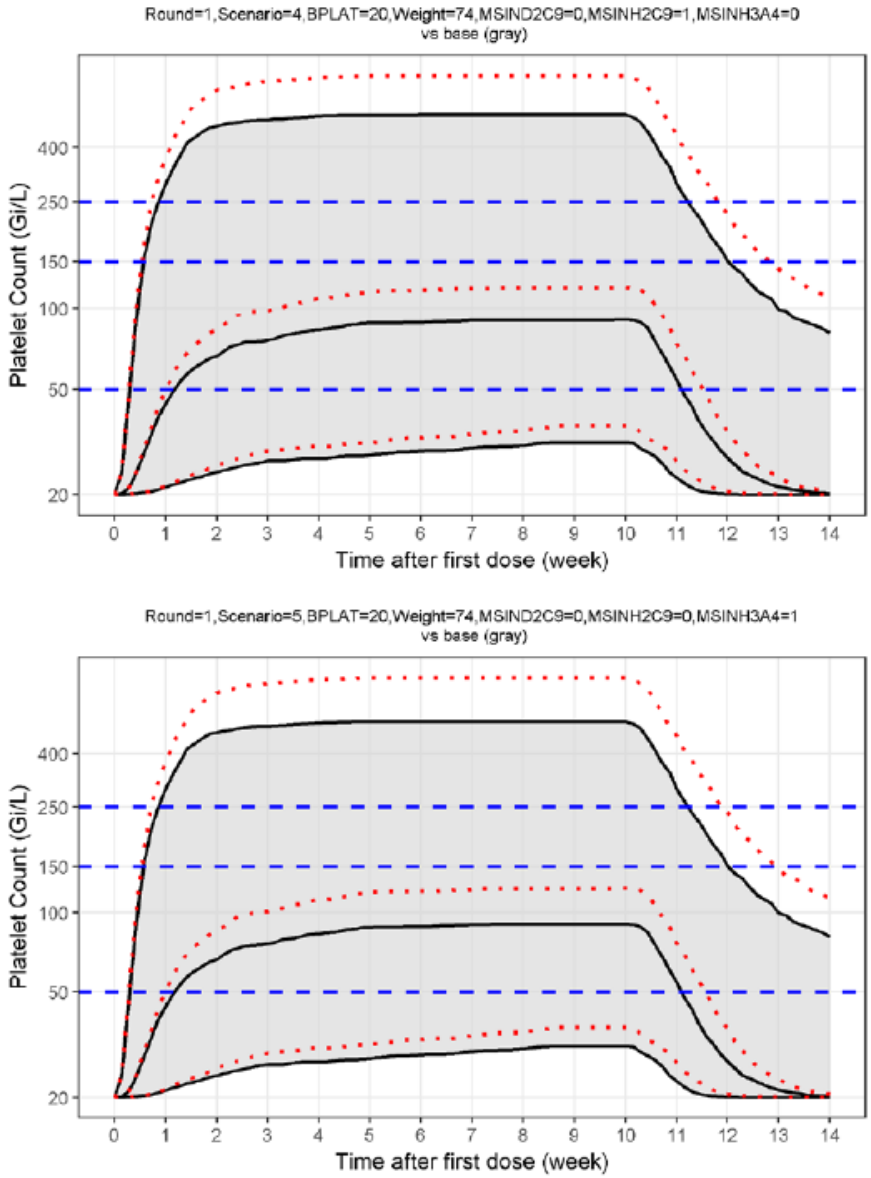
Figure 14. Effect of Concomitant Moderate or Strong Dual Inducers for CYP2C9 and CYP3A4 on Platelet Count (Top Panel: 20 mg QD; Bottom Panel: 40 mg QD; both with Perpetrator) Overlaid with the Base Scenario (No DDI Perpetrators, 20 mg QD)



Black solid lines: 5th, 50th, and 95th percentiles for the base scenario (no DDI perpetrators, 20 mg QD); gray shaded area: 90% PI for the base scenario; red dotted lines: 5th, 50th, and 95th percentiles for the scenario other than the base; blue horizontal reference lines: 50, 150 and 250 × 10^9/L. Y-axis is on the log-scale. Gi/L: × 10^9/L.

Figure 15 shows the simulated effects of a concomitant moderate or strong inhibitor for CYP2C9 only or a moderate or strong inhibitor for CYP3A4 only on platelet count are very similar to each other and modest in extent compared to the base scenario. Therefore, there is no need to adjust the initial dose (20 mg QD) when avatrombopag is co-administered with an inhibitor for CYP2C9 only or with an inhibitor for CYP3A4 only.

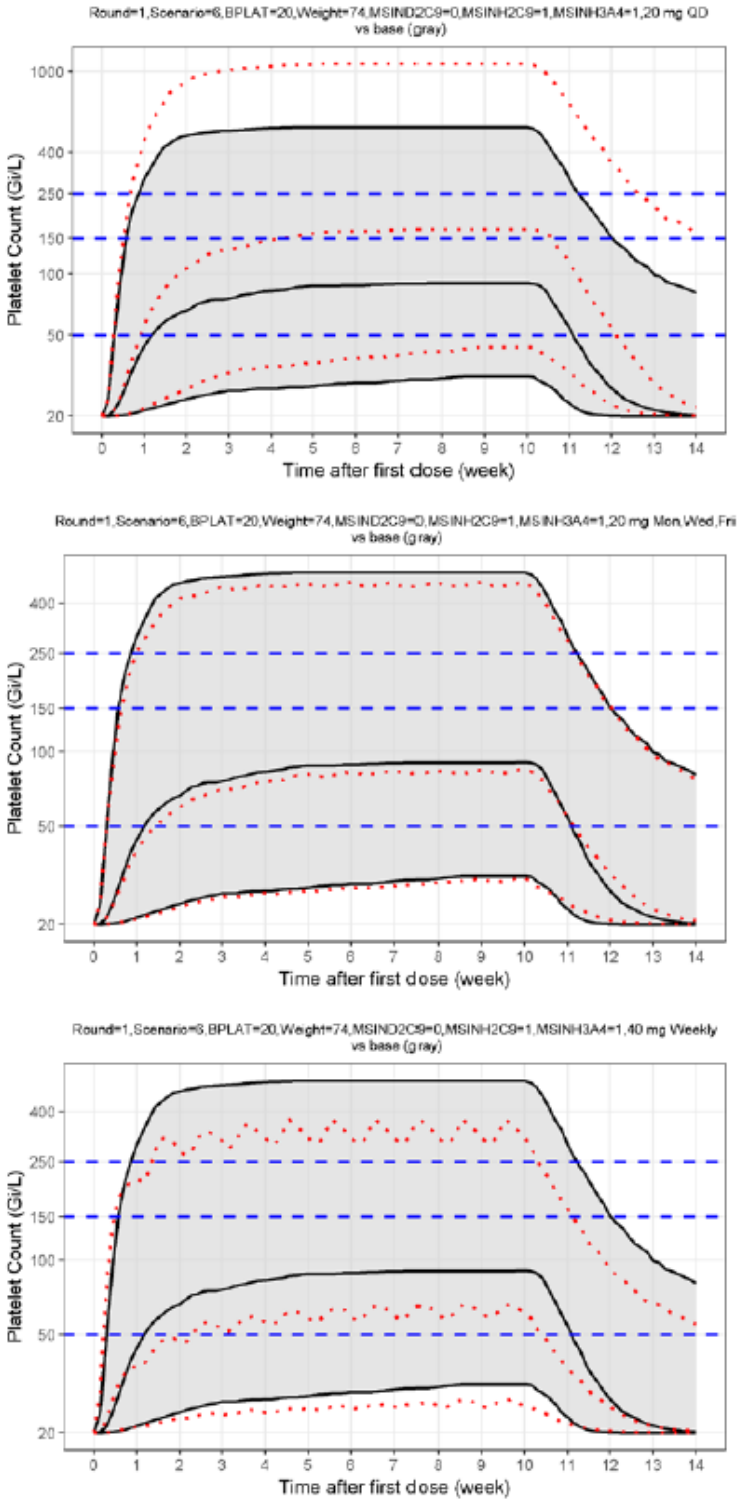
Figure 15. Effect of Concomitant Moderate or Strong CYP2C9 Inhibitor Alone (Top Panel) and Moderate or Strong CYP3A4 Inhibitor Alone (Bottom Panel) on Platelet Count Overlaid with the Base Scenario (No DDI Perpetrators, 20 mg QD)



Black solid lines: 5th, 50th, and 95th percentiles for the base scenario (no DDI perpetrators); gray shaded area: 90% PI for the base scenario; red dotted lines: 5th, 50th, and 95th percentiles for the scenario other than the base; blue horizontal reference lines: 50, 150 and 250 × 10^9/L. Y-axis is on the log-scale. Gi/L: × 10^9/L.

Figure 16 shows the effect of concomitant moderate or strong dual inhibitors for CYP2C9 and CYP3A4 on the platelet count. Among the three dosing regimens evaluated (Top Panel: 20 mg QD; Middle Panel: 20 mg three times a week; Bottom Panel: 40 mg weekly), 20 mg three times a week was able to produce platelet counts comparable to the base scenario.

Figure 16. Effect of Concomitant Moderate or Strong Dual Inhibitors for CYP2C9 and CYP3A4 on Platelet Count (Top Panel: 20 mg QD; Middle Panel: 20 mg Three Times a Week; Bottom Panel: 40 mg Weekly) Overlaid with the Base Scenario (No DDI Perpetrators, 20 mg QD)



Black solid lines: 5th, 50th, and 95th percentiles for the base scenario (no DDI perpetrators); gray shaded area: 90% PI for the base scenario; red dotted lines: 5th, 50th, and 95th percentiles for the scenario other than the base; blue horizontal reference lines: 50, 150 and 250 × 10^9/L. Y-axis is on the log-scale. Gi/L: × 10^9/L.

Although use was limited during the ITP clinical studies, based on the mechanism of action and pharmacology of other potential background ITP medications such as danazol, mycophenolate, azathioprine, CsA, cyclophosphamide, or vinca alkaloids, these medications are not expected to have any clinically meaningful impact on avatrombopag PK or PD.

With dose adjustments proposed for only moderate or strong dual inhibitors or inducers, the potential list of interacting medications is reduced dramatically as described in Table 2.

Table 2 Moderate or Strong Dual Inducers or Inhibitors of CYP2C9 and CYP3A4

	Agents	Indication/Use
Inducer	Carbamazepine	Anti-epileptic
	Nevirapine	Anti-retroviral
	Phenobarbital	Anti-epileptic/Sedation
	Rifampin	Antibiotic
	St. John's Wart	Herbal
	Enzalutamide	Treatment of prostate cancer
Inhibitor	Voriconazole	Anti-fungal
	Fluconazole	Anti-fungal
	Amiodarone	Anti-arrhythmic
	Fluvoxamine	Anti-depressant

Reference: https://drug-interactions.medicine.iu.edu/MainTable.aspx

Pharmacokinetics using human biomaterials

There are no new *in vitro* studies using human biomaterials.

2.4.3 Pharmacodynamics

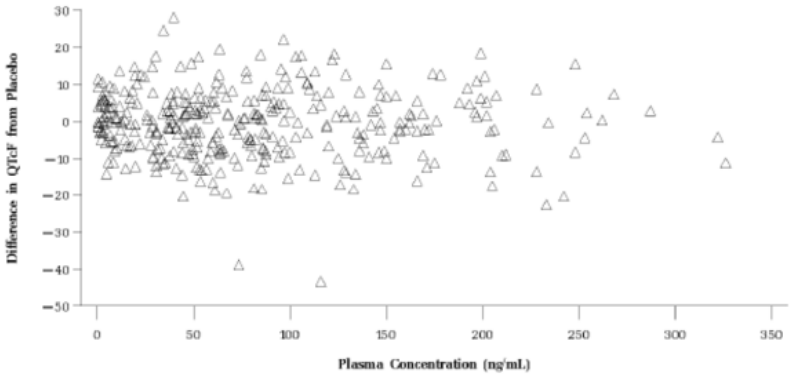
Mechanism of action

Avatrombopag is an orally active, small molecule thrombopoietin (TPO) receptor agonist that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells resulting in increased production of platelets.

Primary and secondary pharmacology

A thorough QT study (Study E5501-A001-001) was completed which evaluated the effects of a single 100 mg dose of avatrombopag using the 1G formulation on the QT interval corrected for heart rate using Fridericia's formula where QTcF = QT/(RR)1/3 (QTcF). In this study, avatrombopag had no effect on the QTcF interval. Although variability in plasma avatrombopag concentrations were observed with some subject's exposures exceeding 300 ng/mL, as shown in Figure 12 1, no relationship was identified between avatrombopag plasma exposure and the difference between avatrombopag and placebo for change from Baseline in QT interval.

Figure 12-1 Difference Between Avatrombopag and Placebo for Change From Baseline in QTcF (ΔΔQTcF) Versus Plasma Avatrombopag Concentration (N = 45) in E5501-A001-001



QTcF = QT interval corrected for heart rate using Fridericia's formula where QTcF = QT/(RR)1/3.
Source: CSR E5501-A001 Figure 4

In order to draw relevant conclusions from different formulations of avatrombopag used during the course of its development, a conversion factor of 0.6 was assigned after comparing relative AUC values between the 1G lot used in the thorough QT study and 2G formulations. Therefore, a 100 mg dose of this avatrombopag 1G formulation can be considered, in terms of exposure, equivalent to a 60 mg dose of the avatrombopag 2G formulation. The maximum recommended daily ITP dose is 40 mg.

2.4.5 Discussion on clinical pharmacology

This Type II variation is for approval of a new doptelet indication for long-term treatment of patients with chronic immune thrombocytopenia (ITP). The dosage regimens are based on one 20 mg tablet strength. The clinical data come from 4 clinical studies conducted in ITP patients earlier Study 501-CL-003 (Study CL-003), Study 501-CL-004 (Study CL-004), Study E5501-G000-302 (Study 302) and Study E5501-G000-305 (Study 305). No new data have been submitted. The AVA-PED-101 study (avatrombopag oral suspension) will not be assessed in this procedure as not directly linked to the indication applied for.

A dose-dependent rise of platelet counts was observed in study 003. A dose of 20mg was selected as startng dose for the phase III trial. There remains uncertainty whether 20mg can be considered an optimal starting dose. In a previous SA a starting dose lower than 20mg was advised and a dosage justification for the starting dose in the phase III trial was requested. No justification was provided to justify the dose recommendation of 20mg in the dossier. As can be seen from the results of the phase III study 302, the median daily dose was 19.4mg (please refer to efficacy discussion). In the responses to the CHMP question on dosing the MAH discusses information from the Phase 2 dose-finding studies CL-003 and the roll over CL-004. The responder rate as well as the average daily doses are further elaborated suggesting the 20mg dose. However, no justification for the starting dose of 20mg was provided. The results from studies CL-003 and CL-004 seems to support the starting dose of 10mg. However, the evidence from Phase 3 studies (study 302 and 305) and post-marketing experience from the US seems to support the 20mg starting dose.

Data from 577 healthy volunteers and 97 ITP patients were included in the PopPK analysis. The Pop PK parameters for ITP were estimated from the original 1-compartment model developed for CLD patients with only absorption lag time and oral bioavailability fixed. Patient population had significant impact on CL. Simulation showed ITP patients had about 50% higher exposure than healthy subjects. Formulation

was a significant covariate of Ka. Less than half of ITP patients received the commercial 2G tablet (42 patients and 325 observations). DDI perpetrators also had major impact on avatrombopag exposure.

For the updated final model (Model 20), the population estimate of V/F1 and CL/F1 for avatrombopag was 232 L and 5.75 L/hr in ITP patients. Precision of estimated parameters were within acceptable range. The random variability was low to moderate for all parameters except for Ka with a CV% of 91.5%. The random effect of V1 could not be estimated. The pc-VPCs for healthy subjects indicated slight underprediction of Cmax at doses <60 mg with a better fit at higher doses. The pc-VPCs stratified for ITP could capture the observed data after 10 and 20 mg dosing with large prediction intervals. The CHMP expressed concern that at doses >20 mg, data in ITP patients was too limited for any meaningful interpretation. The contribution of patient data to the data pool was considered low and possibly not sufficient to reflect the ITP population. The lack of external validation with patient data was also a concern (please refer to the discussion below).

A six-compartment PK/PD lifespan model was used to characterise the relationship between avatrombopag concentrations and platelet count in ITP patients. Updating the model improved stability and removed the hockey-stick relation between ETA and BPLAT. The prediction intervals of the PK/PD model are wide, the precision of parameter estimates range from 6.31%- 50.7%, the random variabilities are large (%CV 62.4% - 199%) and the proportional residual error >50%. The predictive value of the PK/PD model is considered limited. The MAH updated the PK/PD model for the ITP population as requested. The final PK/PD model for ITP patients was used to simulate various dosing scenarios, all with a starting dose of 20 mg continued with 20 mg QD with or without dose adjustments for 14 weeks. The dose could be adjusted to a less frequent dosing down to 20 mg once weekly or increased up to 40 mg QD dosing, giving the option of 6 dose levels. The outcome of the simulations led to the proposed dose titration algorithms with 20 mg QD as the starting dose, which is also recommended in the SmPC Section 4.2. No clinical data are available that support the dosing adjustments as proposed in the SmPC. To address a concern that the patients may drop out of the target range due to fluctuations in relation to once or twice weekly dosing the SmPC Section 4.2 has been updated with the suggestion of closer monitoring at the beginning of treatment and proposals for specific intervals monitoring of the platelet count if avatrombopag is not administered on a daily basis.

The MAH provided a discussion on potential safety concerns related to platelet counts outside of the target range (50 - 150 $x10^9$/L). Two subjects experienced an AESI in the Thromboembolic Events category during the time interval of 1 to less than 4 weeks. However, the individual platelet counts of these patients at the day of diagnosis were below the applied definition of thrombocytosis (platelet count >400×10^9/L) and did not indicate a direct relation to elevated platelet counts per se. Simulations of lower starting doses indicate that more patients would remain below 50 - 150 $x10^9$/L compared to a starting dose of 20mg. On the other hand, more patients would reach levels above 150 $x10^9$/L with the 20mg starting dose. The MAH argues that in selecting the starting dose of doptelet, the benefit of a rapid increase in platelet count to reduce the risk of bleeding must be balanced against the potential risk of causing adverse events related to platelet counts above the target range. Considering that in clinical practice the major goal for treatment in primary ITP is to provide a sufficient platelet count to prevent or stop bleeding rather than correcting the platelet count to normal levels (in asymptomatic patients) the MAH's preference for keeping the 20mg starting dose can be endorsed. The risk for thrombocytosis is reflected in the SmPC, emphasising careful monitoring of signs, symptoms and platelet counts at the beginning of the treatment at least once weekly until a stable platelet count $\geq$ 50 x 10^9/L and $\leq$ 150 x 10^9/L has been achieved. Specific recommandations for intervals monitoring of the thrombocyte count following dose adjustments of avatrombopag are given in Section 4.2. Hence the following recommendation is given in section 4.2 of the SmPC: "The recommended starting dose of Doptelet is 20 mg (1 tablet) once daily with food" and to monitor and make dose adjustment as follows: "After initiating therapy, assess platelet counts at least once weekly until a stable platelet count $\geq$ 50 x 10^9/L and $\leq$ 150

x 10^9/L has been achieved. Twice weekly platelet count monitoring should be conducted during the first weeks of therapy in patients receiving avatrombopag only once or twice weekly. Twice weekly monitoring should also be conducted after dose adjustments during the treatment. Due to the potential risk of platelet counts above 400 x 10^9/L within the first weeks of treatment patients should be carefully monitored for any signs or symptoms of thrombocytosis. After a stable platelet count has been achieved, obtain platelet counts at least monthly. After discontinuation of avatrombopag, platelet counts should be obtained weekly for at least 4 weeks."

CHMP recommends to further evaluate the efficacy of avatrombopag in the post-marketing setting with regards to the dosing recommendations, including the risks associated with the 20mg starting dose and platelet fluctuations in the initial period after treatment initiation as well as after dose adjustment to once or twice weekly.

Data from 77 ITP patients dosed with avatrombopag were used to create 10,000 virtual ITP patients by sampling with replacement. Multiple simulations were conducted for a virtual non-inferiority trial between avatrombopag to eltrombopag. Difference in the proportion of avatrombopag responders compared to eltrombopag responders in the 10,000 simulated patients ranged from 8.4% to 44%. Based on these results, the company concludes that the non-inferiority criteria of 15% is fulfilled and that avatrombopag is "at least as effective" as eltrombopag. The presented non-inferiority evaluation was not accepted by the CHMP. Due to the heterogeneity among ITP patients, data from 77 patients were not considered sufficient to reflect the overall patient population. The predictive value of the updated PK/PD model was considered limited as based on a limited number of patients and assumptions that were not verifiable, for example the distribution of the baseline platelet counts. The lack of external validation precluded the assessment of the quality of the Pop PK model and the uncertainties of the PK/PD model were considererd too much. The results presented by the company did not provide evidence of non-inferiority to eltrombopag in the CHMP's view. The presented simulations could, however, be of value for informing dose for future clinical trials in ITP patients.

No new DDI studies have been conducted. The Pop PK model adequately captured the observed effects of DDI perpetrators verapamil, cyclosporine, fluconazole, itraconazole and rifampin on avatrombopag PK performed in healthy subjects. The MAH proposed adjustments to the starting dose of avatrombopag based on PK/PD simulations when ITP patients were concomitantly dosed with dual modulators of CYP3A4 and CYP2C9. The proposed dose adjustments are reflected in the SmPC Section 4.2. The SmPC section 4.5 mentions that concomitant use of moderate or strong modulators of CYP2C9 may led to changes in starting dose in line with the recommendations given for dual inhibitors or inducers of CYP2C9/CYP3A4. The SmPC Section 4.2 has also been amended to state that avatrombopag exposure may increase in patients with CYP2C9*2 and CYP2C9*3 loss-of-function polymorphisms. Poor metabolisers [PMs, n=2]) had approximately 2-fold higher exposure compared to subjects wild-type for CYP2C9.

The thorough QT study evaluated the QTc effects of a single 100 mg dose of avatrombopag using the 1G formulation. This dose is considered equivalent to 60 mg 2G formulation. ECGs were also monitored in patients receiving 40 mg QD during the development program of avatrombopag. No relations were identified between exposure and the QTc-response. The C-QTc relation is considered sufficiently documented to cover also the highest proposed dosing regimen of 40 mg QD in the ITP population.

2.4.6 Conclusions on clinical pharmacology

The PK profile of avatrompag has been studied in detail. The benefit of a rapid increase in platelet count to reduce the risk of bleeding must be balanced against the potential risk of causing adverse events related to platelet counts above the target range. Hence, the following recommendation is given in section 4.2 of the SmPC: "The recommended starting dose of Doptelet is 20 mg (1 tablet) once daily

with food" and to monitor and make dose adjustment as follows: "After initiating therapy, assess platelet counts at least once weekly until a stable platelet count $\geq 50 \times 10^9$/L and $\leq 150 \times 10^9$/L has been achieved. Twice weekly platelet count monitoring should be conducted during the first weeks of therapy in patients receiving avatrombopag only once or twice weekly. Twice weekly monitoring should also be conducted after dose adjustments during the treatment. Due to the potential risk of platelet counts above 400 x 10^9/L within the first weeks of treatment patients should be carefully monitored for any signs or symptoms of thrombocytosis. After a stable platelet count has been achieved, obtain platelet counts at least monthly. After discontinuation of avatrombopag, platelet counts should be obtained weekly for at least 4 weeks."

CHMP recommends to further evaluate the efficacy of avatrombopag in the post-marketing setting with regards to the dosing recommendations, including the risks associated with the 20mg starting dose and platelet fluctuations in the initial period after treatment initiation as well as after dose adjustment to once or twice weekly.

2.5 Clinical efficacy

2.5.1 Dose response studies

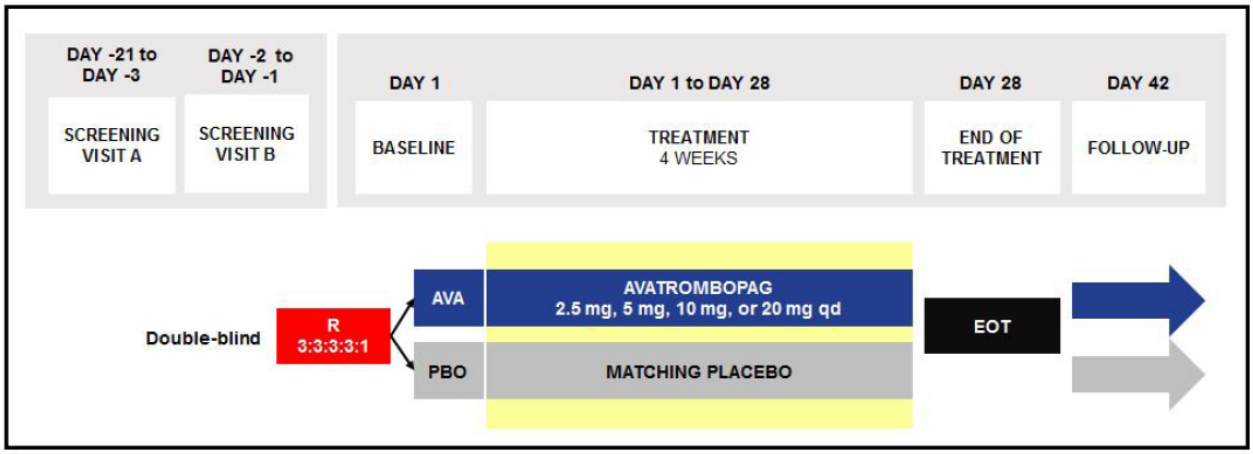
Study CL-003 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2 study of 4 different doses of avatrombopag taken once daily for 28 consecutive days in adult patients with ITP. Subjects were randomly assigned to avatrombopag 2.5 mg, 5 mg, 10 mg or 20 mg, or placebo in a 3:3:3:3:1 ratio, respectively, for a period of 28 days. Fifteen subjects were to be treated at each dose level of avatrombopag, while 5 subjects were to receive placebo.

Objectives

- Primary: To assess responder rate (ie, platelet count) on Day 28 of treatment with E5501 in subjects with ITP.
- Secondary: To assess: 1) the pharmacokinetics (PK) and pharmacodynamics (PD) of E5501; 2) other markers of effectiveness, including peripheral blood platelet count; and 3) the safety/tolerability of E5501.

Study CL-003 enrolled 64 subjects, 24 men and 40 women, with chronic ITP that was either refractory or relapsed after at least one prior ITP therapy; 59 subjects were randomized (3:3:3:3:1) to avatrombopag (2.5 mg, 5 mg, 10 mg, or 20 mg,) and 5 subjects to placebo. At the end of the study, subjects who completed 28 days of treatment were eligible for enrollment in the rollover study (Study CL-004).

Figure 2.7.3-6 Study Design (Study CL-003)



AVA = avatrombopag, EOT = end of treatment, PBO = placebo, qd = once daily, R = randomized.
Source: Study CL-003 CSR, Section 9.

A lower percentage of subjects in the Avatrombopag Treatment Group (n=52/59, 88.1%) completed treatment per protocol compared with the Placebo Treatment Group (n=5/5, 100%). The majority of subjects from CL-003 (n=53/64; 82.8%) enrolled in the **rollover Study CL-004.**

Table 2.7.3-20 Demographic and Baseline Characteristics - Full Analysis Population (Study CL-003)

Category	PBO (N=5)	AVA 2.5 mg (N=15)	AVA 5 mg (N=15)	AVA 10 mg (N=14)	AVA 20 mg (N=15)
Age, years					
Mean (SD)	39.6 (20.63)	52.9 (17.84)	55.6 (18.03)	57.5 (17.88)	47.9 (16.54)
Median	29.0	56.0	58.0	60.0	44.0
Min, Max	23, 73	20, 81	18, 79	22, 82	22, 77
Sex, n (%)					
Male	2 (40.0)	6 (40.0)	6 (40.0)	6 (42.9)	4 (26.7)
Female	3 (60.0)	9 (60.0)	9 (60.0)	8 (57.1)	11 (73.3)
Race, n (%)					
Black, African Heritage	0	2 (13.3)	0	1 (7.1)	2 (13.3)
Asian	0	1 (6.7)	2 (13.3)	0	1 (6.7)
Hispanic	1 (20.0)	1 (6.7)	1 (6.7)	1 (7.1)	1 (6.7)
White	4 (80.0)	11 (73.3)	11 (73.3)	12 (85.7)	10 (66.7)
Other	0	0	1 (6.7)	0	1 (6.7)
History of Splenectomy, yes	2 (40.0)	5 (33.3)	4 (26.7)	3 (21.4)	6 (40.0)
Baseline Steroid Usage, yes	3 (60.0)	4 (26.7)	8 (53.3)	6 (42.9)	10 (66.7)
Baseline Platelet Count $\leq 15\times10^9$/L	2 (40.0)	5 (33.3)	2 (13.3)	5 (35.7)	4 (26.7)

In Study CL-003, the Randomized, Full Analysis, and Safety populations were identical.

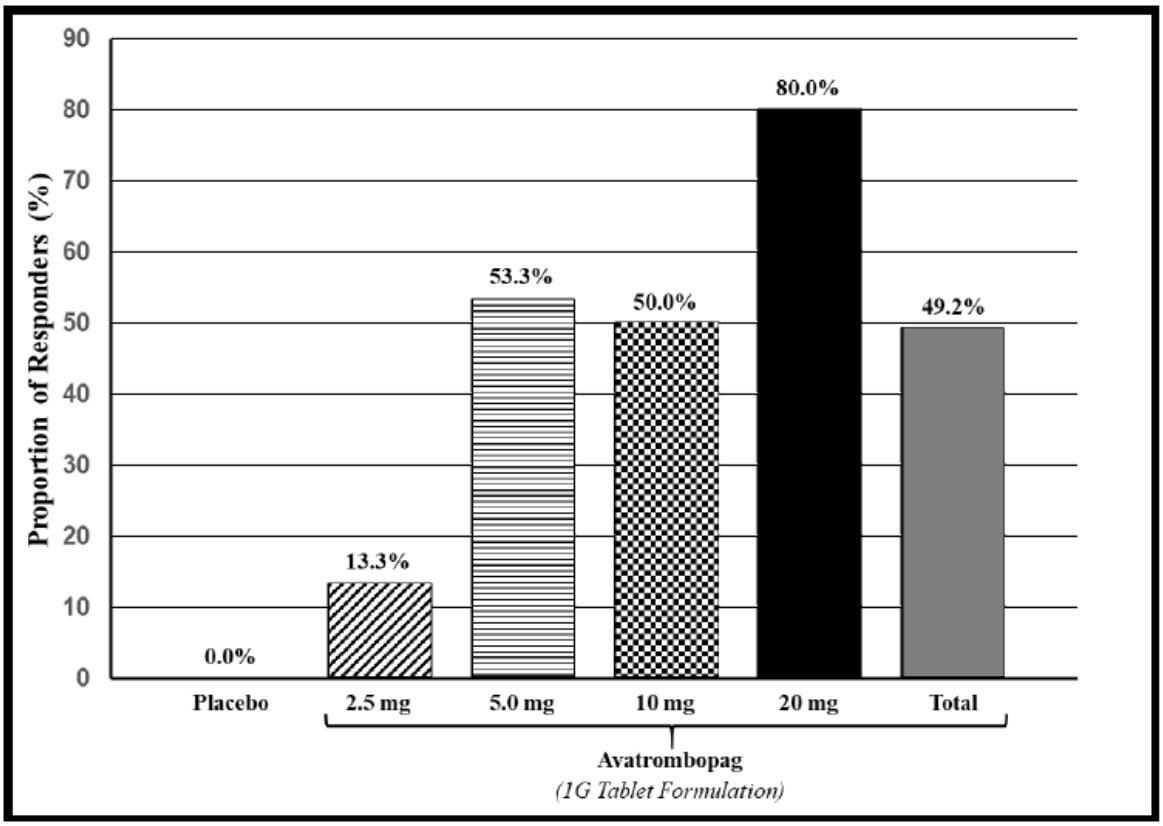
AVA = avatrombopag, Max = maximum, Min = minimum, N = total number of subjects in sample group, n = number of subjects in specified group, PBO = placebo, SD = standard deviation.

Source: Study CL-003 CSR, Table 14.1.2.1.

The primary efficacy endpoint for Study CL-003 was the Responder Rate on Day 28 for avatrombopag versus placebo in subjects with chronic ITP. Responder Rate was defined as the proportion of any subjects with a Screening Visit B (Day 1) platelet count of $<30\times10^9$/L who achieved a platelet count of $\geq50\times10^9$/L on Day 28, together with the proportion of subjects receiving steroids who had a Day 1 platelet count of $\geq30\times10^9$/L, but $<50\times10^9$/L, who achieved a platelet count $\geq20\times10^9$/L higher than their Day 1 platelet count.

Results

Figure 2.7.3-17 Responder Rate on Day 28 (LOCF Method) – Full Analysis Population (Study CL-003)



1G = first generation, LOCF = last observation carried forward.

Source: Study CL-003 CSR, Table 14.2.1.1.1.

Table 2.7.3-22 Responder Rate on Day 28 (LOCF Method) – Full Analysis Population (Study CL-003)

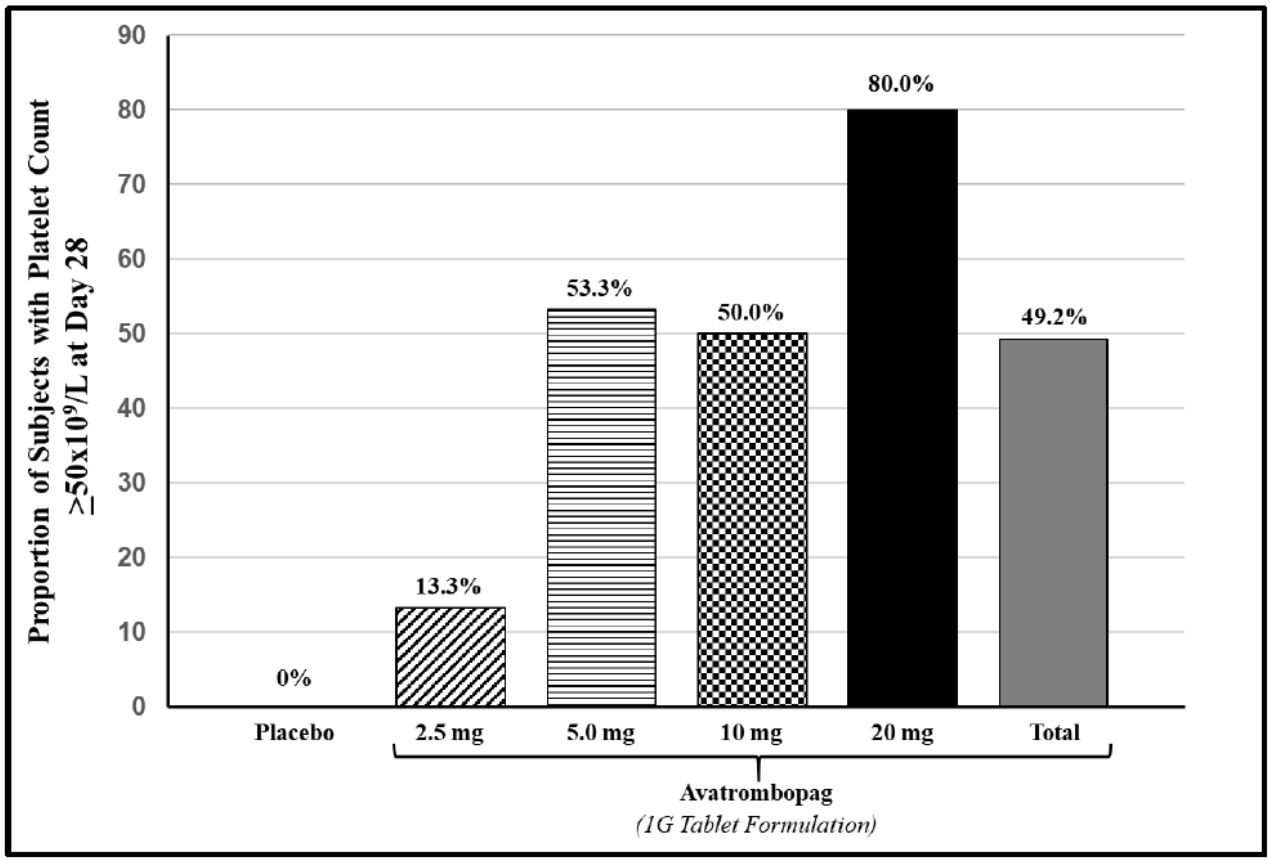
Category	PBO (N=5)	AVA 2.5 mg (N=15)	AVA 5 mg (N=15)	AVA 10 mg (N=14)	AVA 20 mg (N=15)	Total AVA (N=59)
Responder Rate on Day 28, n (%)	0	2 (13.3)	8 (53.3)	7 (50.0)	12 (80.0)	29 (49.2)
P-values						
vs PBO	-	1.0000	0.0547	0.1060	0.0036	-
vs AVA 2.5 mg	-	-	0.0502	0.0502	0.0007	-
vs AVA 5 mg	-	-	-	1.0000	0.2451	-
vs AVA 10 mg	-	-	-	-	0.1281	-

AVA = avatrombopag, LOCF=last observation carried forward, N = total number of subjects in sample group, n = number of subjects in specified group, PBO = placebo.

P-values determined using Fisher's Exact test.

Source: Study CL-003 CSR, Table 14.2.1.1.1.

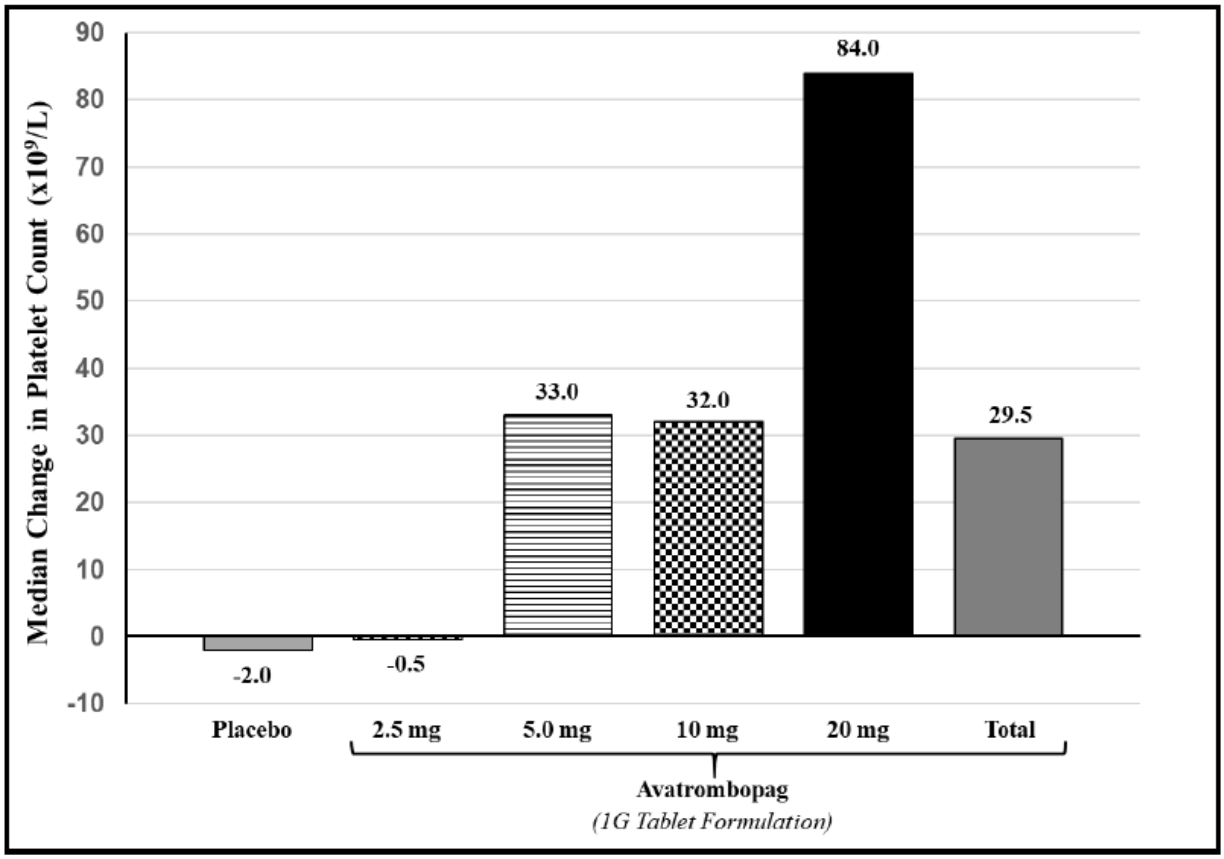
Figure 2.7.3-20 Proportion of Subjects with Platelets ≥50×10^9/L at Day 28 (LOCF Method) – Full Analysis Population (Study CL-003)



1G = first generation, LOCF = last observation carried forward.

Source: Study CL-003 CSR, Table 14.2.4.1.1.1.

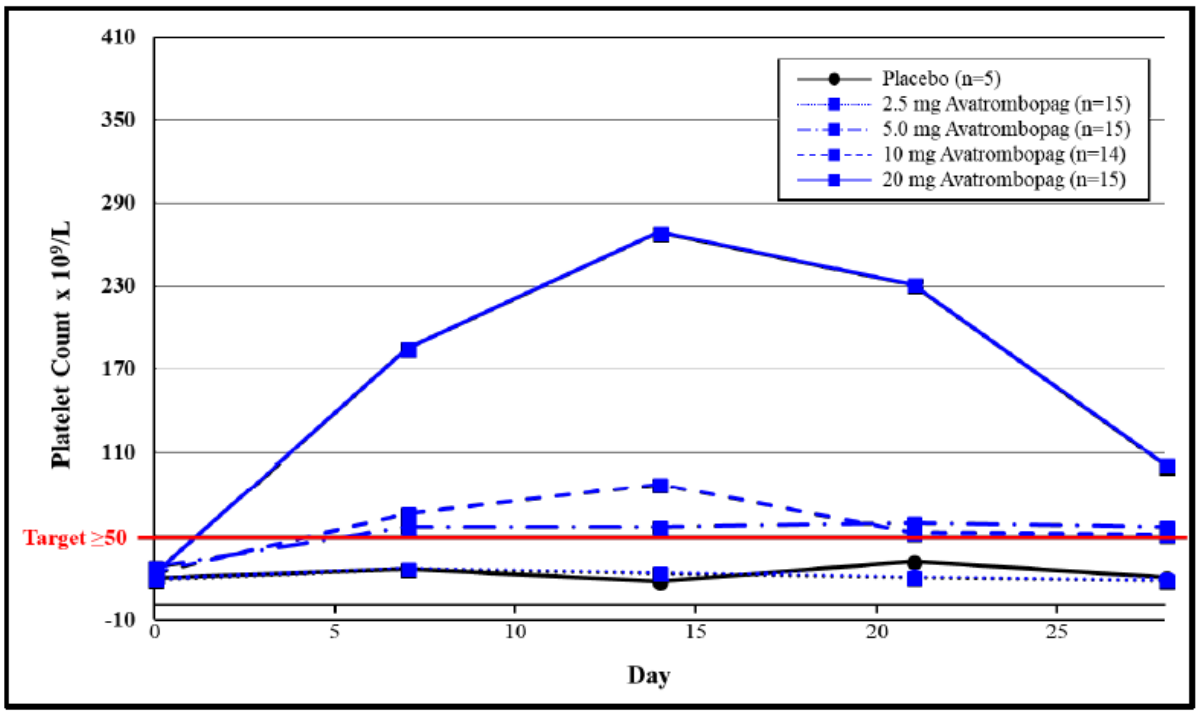
Figure 2.5-8 Median Change in Platelet Count from Baseline to Day 28 (LOCF Method) – Full Analysis Population (Study CL-003)



1G = first generation, LOCF = last observation carried forward.

Source: Study CL-003 CSR, Table 14.2.2.1.1.

Figure 2.7.3-18 Median Platelet Counts by Visit and Treatment Group (LOCF Method) – Full Analysis Population (Study CL-003)



LOCF = last observation carried forward.

Source: Study CL-003 CSR, Table 14.2.2.1.1.

Table 2.7.3-25 Proportion of Subjects with Platelet Count ≥100×10⁹/L by Visit (LOCF Method) – Full Analysis Population (Study CL-003)

Visit	PBO (N=5)	AVA 2.5 mg (N=15)	AVA 5 mg (N=15)	AVA 10 mg (N=14)	AVA 20 mg (N=15)	Total AVA (N=59)
Day 7, n (%) [a]	0	1 (6.7)	3 (20.0)	4 (28.6)	12 (80.0)	20 (33.9)
Day 14, n (%) [a]	0	0	4 (26.7)	6 (42.9)	13 (86.7)	23 (39.0)
Day 21, n (%) [a]	0	0	3 (20.0)	3 (21.4)	11 (73.3)	17 (28.8)
Day 28, n (%) [a]	0	1 (6.7)	5 (33.3)	4 (28.6)	8 (53.3)	18 (30.5)

AVA = avatrombopag, LOCF = last observation carried forward, N = total number of subjects in sample group, n = number of subjects in specified group, PBO = placebo.

a: Percentages were based on the total number of subjects with non-missing data in relevant treatment group.

Source: Study CL-003 CSR, Table 14.2.5.2.1.1.

Study 501-CL-004: A Phase 2, Parallel-Group, Rollover Study of AKR-501 in Patients With Chronic Idiopathic Thrombocytopenia Purpura (ITP) Who Completed 28 Days' of Study Treatment in Protocol AKR-501-CL-003

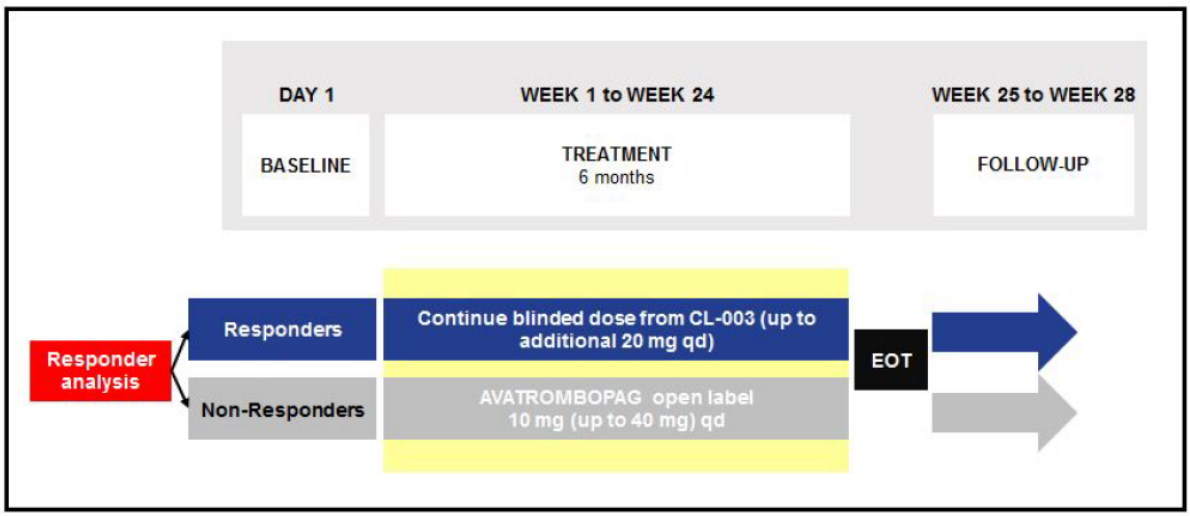
Objectives

- Primary: To assess the safety and tolerability of E5501 administered for an additional 6 months in subjects with chronic ITP who completed 28 days' of treatment in study 501-CL-003.
- Secondary:

- To evaluate markers of effectiveness of E5501, including changes in, and maintenance of, peripheral blood platelet count (PC) and decreasing need for ITP-directed concomitant medications.
- To evaluate the pharmacokinetics (PK) and the pharmacokinetic/pharmacodynamic (PK/PD) relationship of E5501 in subjects with ITP.

In Study CL-004, subjects who had responded to treatment in Study CL-003 were able to continue receiving the same double-blind study treatment and daily dose (placebo or avatrombopag 2.5, 5, 10, or 20 mg) to which they had been randomly assigned in Study CL-003; dose titration (2.5 to 40 mg) was also permitted in Study CL-004. The blind was maintained in Study CL-004 to ensure that the data from the then ongoing Study CL-003 were not unblinded before the latter study was completed. Subjects who did not meet the primary response criteria in Study CL-003 (ie, "Non-Responders") were also eligible to enter this rollover study and receive open-label avatrombopag at a starting dose of 10 mg once daily.

Figure 2.7.3-7 Study Design (Study CL-004)



EOT = end of treatment, qd = once daily.

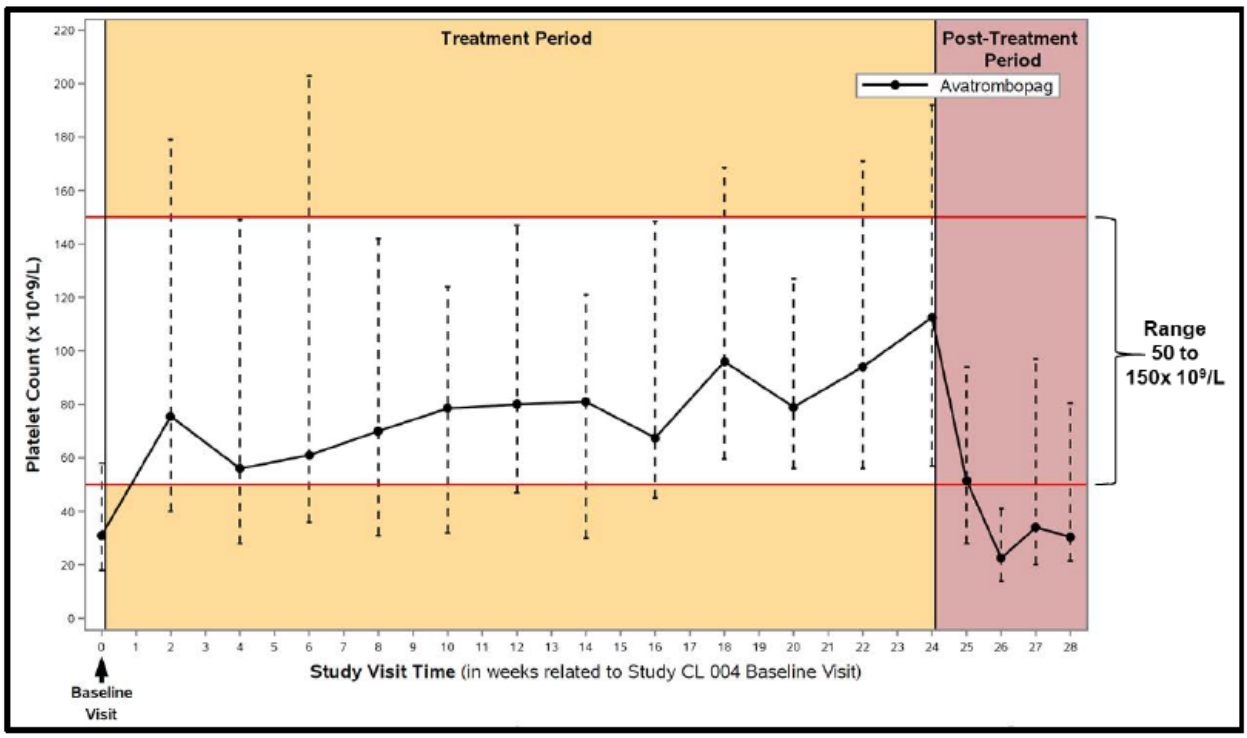
Source: Study CL-004 CSR, Section 9.

Sixty-four subjects enrolled in Study CL-003; among them, 53 subjects continued into the rollover study, Study CL-004, at a total of 17 centers. Of the 11 subjects who did not continue into Study CL-004, 7 were ineligible for enrollment in Study CL-004 after having withdrawn prematurely from Study CL-003. The remaining 4 subjects completed Study CL-003 but chose not to participate in Study CL-004.

The FAS population included the 53 subjects who enrolled in Study CL-004. Of those 53 subjects, approximately two-thirds (66%) completed the 6-month treatment period. A higher percentage of subjects in the Responder group (20/25, 80%) completed treatment per protocol compared with the Non-Responder group (15/28, 53.6%).

Results

Figure 2.7.3-24 Median Platelet Count over Time, Observed Case Method, All Subjects Combined – Full Analysis Set (Study CL-004)



Source: Study CL-004 CSR, Figure 14.2.1.1.

At most time points, median platelet counts were higher in the 10 mg and 20 mg Responder dose groups compared with the 5 mg Responder dose group. Median platelet counts among Non-Responders, who received open-label treatment with avatrombopag 10 mg, increased most noticeably in subjects who had previously received placebo or the lower avatrombopag doses (2.5 mg or 5 mg), suggesting that some subjects need a higher dose of avatrombopag to demonstrate a platelet response.

Table 2.7.3-31 Proportion of Subjects Who Achieved or Maintained a Platelet Count of 100×10^9/L or Higher by Response Status in Study CL-003 and Selected Study Visit, Observed Case Method - Full Analysis Set (Study CL-004)

Platelet Count Assessment Time point in Study CL-004	Number (%) of Subjects		
	Responder Group [a] Total (N=25)	Non-Responder Group [b] Total (N=28)	AVA Total (N=53)
Proportion of Subjects (n [%]) with Platelet Count ≥100×10⁹/L at:			
Treatment Period			
Week 2	13 (59.1)	7 (25.0)	20 (40.0)
Week 4	14 (58.3)	5 (18.5)	19 (37.3)
Week 8	11(52.4)	4 (15.4)	15 (31.9)
Week 12	6 (42.9)	7 (35.0)	13 (38.2)
Week 16	7 (63.6)	3 (17.6)	10 (35.7)
Week 20	4 (40.0)	3 (25.0)	7 (31.8)
Week 24	15 (71.4)	6 (35.3)	21 (55.3)
Post-Treatment Period			
Follow-up Week 1	2 (18.2)	3 (27.3)	5 (22.7)
Follow-up Week 2	0	4 (33.3)	4 (18.2)
Follow-up Week 3	3(25.0)	1 (11.1)	4 (19.0)
Follow-up Week 4	3 (23.1)	2 (13.3)	5 (17.9)
Proportion of Subjects Who Maintained Platelet Count ≥100×10⁹/L [c]			
Total n (%) subjects	8 (32.0)	NA	8 (32.0)

Grouping Method B was based on dose of study drug received in Study CL-003 and platelet response to study drug on Day 28 in Study CL-003.

The dose of study drug could be titrated up if a subject's platelet count did not meet platelet response criteria.

Percentages were based on the total number of subjects with non-missing platelet count values for the relevant visit and treatment group.

AVA = avatrombopag, N = total number of subjects in sample group, n = number of subjects in specified group, NA = not applicable.

a Responders received their initial dose of study drug in Study CL-004 at the same double-blind dose as in the CL-003 study.

b Non-Responders from Study CL-003 received open-label avatrombopag at a dose of 10 mg in Study CL-004.

c Subjects were considered to have maintained their platelet count at 100×10^9/L or above if they were Responders in Study CL-003, had no upward dose titration, and a platelet count ≥100×10^9/L in at least 75% of the observed cases of the 7 analysis windows at Week 12 through Week 24 during the Treatment Period, and had a response-level platelet count in at least 3 of the 7 analysis windows. Subjects who took rescue medication for controlling platelet count were considered to be failures for maintaining a platelet count ≥100×10^9/L.

Source: Study CL-004 CSR, Table 14.2.3.4 and Table 14.2.2.

Proportion of subjects who achieved a Durable Response, defined as subjects who had at least 3 platelet count values measured in the last 14 weeks of the 24-week treatment period in Study CL-004 and whose platelet count was at a response level for at least 75% of the measured values during those 14 weeks. Also, the subject could not have received rescue medication during the 24-week treatment period. The last 14 weeks of the treatment period comprised seven analysis windows, at the Weeks 12, 14, 16, 18, 20, 22, and 24 time points. Windows with missing platelet counts were not included. In addition:

o Subjects with fewer than three windows with non-missing platelet counts were classified as failures for Durable Response;

o Subjects who received any rescue medication to control their platelet count during Study CL-004 were considered failures for Durable Response;

o A "cured" subject was one who had an early response to avatrombopag and no longer required avatrombopag to maintain a high platelet count, but who remained in the study for the entire duration of the planned 24-week treatment period. Classification of these subjects was based on assessment by clinical review.

For the FAS, the observed Durable Response Rate during the 6-month treatment period was 52.8% for all subjects, 72.0% for Responders, and 35.7% for Non-Responders

Table 2.7.3-33 Changes in Concomitant Steroid Use in Subjects Who Were Taking Steroids, Observed Case Method - Full Analysis Set (Study CL-004)

Steroid Use Category	Number (%) of Subjects		
	Responders[a]	Non-Responders[b]	AVA Total
Full Analysis Set, N	25	28	53
Total n (%) with Baseline steroid use[c]	12/25 (48.0)	12/28 (42.9)	24/53 (45.3)
Permanently discontinued[d]	4/12 (33.3)	4/12 (33.3)	8/24 (33.3)
Decreased by ≥50%[e]	7/12 (58.3)	6/12 (50.0)	13/24 (54.2)

Grouping Method B was based on dose of study drug received in Study CL-003 and platelet response to study drug on Day 28 in Study CL-003.

The dose of study drug could be titrated up if platelet count did not meet the platelet response criteria.

AVA = avatrombopag, N = total number of subjects in sample group, n = number of subjects in specified group.

f Responders received their initial dose of study drug in Study CL-004 at the same double-blind dose as in the CL-003 study.

g Non-Responders from Study CL-003 received open-label avatrombopag at a dose of 10 mg in Study CL-004.

h Subjects who used steroids at study entry of CL-004 were those subjects who used steroid during the 2-week period before Day 1 of Study CL-004. The number of subjects who used steroids at study entry of CL-004 served as the denominator for percentage calculation for the rows "permanently discontinued" and "decreased by ≥50%".

i A subject who used steroids at study entry of CL-004 was considered to have permanently discontinued steroid use if he or she had no steroid use during the last 8 weeks of the treatment period of Study CL-004.

j A subject who used steroids at study entry of CL-004 was considered to have decreased concomitant steroid medication by at least 50% if he or she permanently discontinued steroids, or if no dose of steroid was higher than 50% of his/her Baseline steroid dose during the last 8 weeks of the treatment period of Study CL-004.

Source: Study CL-004 CSR, Table 14.1.3.2 and Table 14.2.4.

Dose

Table 14.1.2.2
Extent of Exposure for Method B*
Full Analysis Population

Category	Responder - 2.5 mg (N=2)	Responder - 5 mg (N=6)	Responder - 10 mg (N=7)	Responder - 20 mg (N=10)
Average daily dose (mg/Day)				
n	2	6	7	10
Mean (SD)	8.4 (0.88)	4.7 (0.28)	10.3 (1.62)	18.6 (2.87)
Median	8.4	4.7	9.8	19.4
Min, Max	8, 9	4, 5	9, 14	12, 23

Category	Non-responder-Placebo (N=5)	Non-responder-2.5mg (N=10)	Non-responder-5 mg (N=5)	Non-responder-10mg (N=5)	Non-responder-20mg (N=3)
Average daily dose (mg/Day)					
n	5	10	5	5	3
Mean (SD)	11.9 (3.52)	12.1 (7.01)	8.8 (0.92)	12.3 (3.74)	18.9 (8.43)
Median	10.0	8.9	9.0	11.0	21.4
Min, Max	9, 17	4, 25	8, 10	8, 17	9, 26

Category	Responder Total (N=25)	Non-responder Total (N=28)	Total (N=53)
Average daily dose (mg/Day)			
n	25	28	53
Mean (SD)	12.1 (6.13)	12.2 (5.72)	12.2 (5.86)
Median	9.9	9.9	9.9
Min, Max	4, 23	4, 26	4, 26

*Treatment grouping Method B is based on dose received in 501-CL-003 and platelet response to study drug on Day 28 in 501-CL-003.
Full Analysis population includes all subjects who provided adequate data to derive at least one efficacy assessment
501-CL-004.
Exposure duration = Last dose day of active study drug during combined active treatment period – first dose day of active study drug+1.
Accumulated dose = the sum of daily dose during the combined active treatment period of 501-CL-003 and 501-CL-004.
Average daily dose = the accumulated dose / exposure duration.
Number of skipped doses = the number of missed doses during the combined treatment period.

Data Source: Data Listing 16.2.5.6. Program: t_expo.sas, Date:07APR2010 6:06

Study E5501-G000-202 was one of 4 randomized, double-blind, placebo-controlled clinical studies conducted in subjects with thrombocytopenia and chronic liver disease (N=604 in total), and one of 2 Phase 2 studies, which included N randomized=130 patients, avatrombopag-FAS=93. Subjects received daily dosing with avatrombopag (10, 20, 40, 60, or 80 mg, with loading doses of 80 or 100 mg in Study 202) for 5 days, 10 to 13 days prior to the date of the planned, invasive procedure (the endpoint event). The E5501-G000--202 study is thus supportive, because the pathophysiologic circumstances are very different from ITP. A dose-response was also documented in liver-associated thrombocytopenia, and the study proved the principle to use avatrombopag as a TPO-analogue in acquired thrombocytopenia.

The starting dose of avatrombopag used in the Phase 3 protocols requiring chronic dosing with avatrombopag with subsequent titration was based on:

• Safety and efficacy evaluations from the results from the Phase 2 study (501-CL-003) in subjects with ITP

• PK analysis from all Phase 1 studies and 3 Phase 2 studies (2 studies in chronic ITP [501-CL-003 and 501-CL-004] and 1 study conducted in subjects with thrombocytopenia-induced liver disease [E5501-G000-202])

• Sequential PK/PD modeling using data from Study 501-CL-003 followed by PK/PD simulations.

In Phase 3 trials requiring chronic dosing in subjects with ITP, the primary objectives for the selected avatrombopag starting dose were to raise and to maintain the platelet counts and a secondary objective

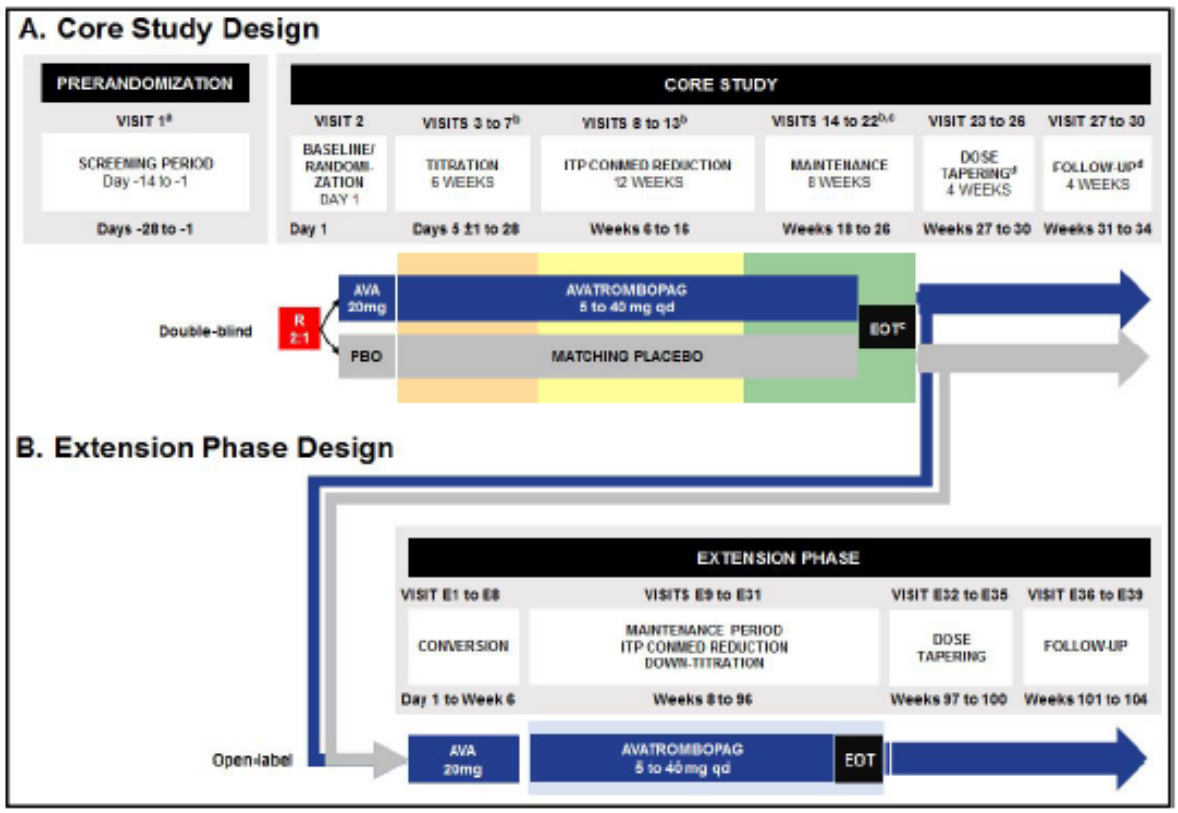
was to decrease the need for concomitant ITP medications (if applicable). The avatrombopag dose regimen (20-mg starting dose followed by flexible-dosing regimen to optimize and maintain platelet response for individual ITP subjects was designed to produce a rapid platelet response that could be maintained for the 6-month treatment period. Titration of study drug was performed in accordance with protocol-specified titration guidelines in order to find the minimum dose required to maintain platelet counts of ≥50 × 10^9/L and ≤150 × 10^9/L.

2.5.2 Main study – Study 302

Title of Study

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Trial with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Oral E5501 (Avatrombopag) Plus Standard of Care for the Treatment of Thrombocytopenia in Adults with Chronic Immune Thrombocytopenia (Idiopathic Thrombocytopenic Purpura)

Figure 2.7.3-4 Study Design (Study 302)



AVA = avatrombopag, CONMED = concomitant medication, E = Extension, EOT = end of treatment, ITP = immune thrombocytopenia, PBO = placebo, qd = once daily, R = randomized.

a The Screening Visit and Day 1 Baseline/Randomization Visit platelet counts were averaged to obtain the Baseline platelet count value. The two samples were obtained ≥48 hours and ≤2 weeks apart and the results were available prior to randomization. Therefore, an additional screening platelet count may have been required due to issues with scheduling

b Patients who discontinued early who met the criteria for a lack of treatment effect may have moved directly into the Open-label Extension Phase

c At EOT Visit (Visit 22), patients could enter the Extension Phase and receive open-label avatrombopag therapy. Patients who did not continue into the Extension Phase entered the Dose-tapering and Follow-up Phase

d Only for patients who did not enter the Extension Phase

Those subjects who met all the eligibility requirements and who were willing and able entered the Extension Phase. Subjects who discontinued the Core Study early because of lack of treatment effect remained eligible to continue into the Extension Phase. Subjects who entered directly into the Extension Phase did not enter the Dose-tapering and Follow up Periods of the Core Study.

Methods

Study participants

Key Inclusion Criteria

Core Study

1. Male or female, ≥18 years of age.

2. Diagnosed with chronic ITP (≥12 months duration) according to the American Society for Hematology/British Committee for Standards in Hematology (ASH/BCSH) guidelines, and an average of 2 platelet counts $<30 \times 10^9$/L (no single count should have been $>35 \times 10^9$/L). In addition, a peripheral blood smear should have supported the diagnosis of ITP with no evidence of other causes of thrombocytopenia (eg, pseudothrombocytopenia, myelofibrosis). The physical examination was not to have suggested any disease that might have caused thrombocytopenia other than ITP.

3. Previously received 1 or more ITP therapies (including, but not limited to corticosteroids, immunoglobulins, azathioprine, danazol, cyclophosphamide and/or rituximab).

4. Must have either initially responded (platelet count $>50 \times 10^9$/L) to a previous ITP therapy or have had a bone marrow examination consistent with ITP within 3 years to rule out myelodysplastic syndrome (MDS) or other causes of thrombocytopenia.

5. Prothrombin time/International Normalized Ratio and activated partial thromboplastin time must have been within 80% to 120% of the normal range with no history of hypercoagulable state.

6. Had a complete blood count (excluding platelet count), within the reference range (with white blood cell (WBC) differential not indicative of any significant hematological disorder), with the following exceptions:

• Hemoglobin: Subjects with hemoglobin levels between 10 g/dL (100 g/L) and the lower limit of normal (LLN) were eligible for inclusion, if anemia was clearly attributable to ITP (excessive blood loss)

• Absolute neutrophil count (ANC) ≥1500/µL (1.5×10^9/L)

• Elevated WBC or ANC (eg, due to corticosteroid treatment) provided this was discussed with the medical monitor

7. Females could not be pregnant at screening or baseline (as documented by a negative serum beta-human chorionic gonadotropin (β-hCG) test with a minimum sensitivity 25 IU/L or equivalent units of β-hCG). A separate baseline assessment was required if a negative screening pregnancy test had been obtained more than 72 hours before the first dose of study drug.

8. All females were considered to be of childbearing potential unless they were postmenopausal (at least 12 months' consecutive amenorrhea, in the appropriate age group and without other known or suspected cause) or had been sterilized surgically (ie, bilateral tubal ligation, hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

9. Females of childbearing potential were to not have had unprotected sexual intercourse within 30 days prior to study entry and had to agree to use a highly effective method of contraception (eg, abstinence, an intrauterine device, a double-barrier method such as condom + spermicide or condom + diaphragm with spermicide, a contraceptive implant/injection, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. If currently abstinent, the subject had to agree to use a double-barrier method as described above if they became sexually active during the study period or for 30 days after study drug discontinuation. Females who were using hormonal contraceptives had to be on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and had to continue to use the same contraceptive during the study and for 30 days after study drug discontinuation.

10. Provide written informed consent.

11. Were willing and able to comply with all aspects of the protocol.

Extension Phase

1. Completed 6 months of study treatment in the Randomization Phase provided the open-label Extension Phase was still ongoing.

2. Discontinued from the Core Study early due to lack of treatment effects provided the open-label Extension Phase was still ongoing.

3. No significant safety or tolerability concerns with the subject's participation of Randomization Phase as determined by the investigator.

Key Exclusion Criteria

Core Study

Subjects who met any of the following criteria were excluded from participation in the Core Study:

1. Subjects who had known secondary immune thrombocytopenia (eg, subjects with known Helicobacter pylori-induced ITP, infected with known human immunodeficiency virus [HIV] or hepatitis C virus [HCV] or subjects with known systemic lupus erythematosus).

2. Subjects were considered unable or unwilling to comply with the study protocol requirements or give informed consent, as determined by the investigator.

3. Subjects with significant medical conditions that may impact the safety of the subject or interpretation of the study results (eg, acute hepatitis, active chronic hepatitis, lymphoproliferative disease myeloproliferative disorders, leukemia).

4. History of MDS.

5. History of gastric atrophy.

6. History of pernicious anemia or subjects with vitamin B12 deficiency (defined as <LLN) who did not have pernicious anemia excluded as a cause.

7. Any prior history of arterial or venous thrombosis (stroke, transient ischemic attack, myocardial infarction, deep vein thrombosis, or pulmonary embolism), and more than 2 of the following risk factors: estrogen-containing hormone replacement or contraceptive therapies, smoking, diabetes, hypercholesterolemia, medication for hypertension, cancer, hereditary thrombophilic disorders (eg,

Factor V Leiden, antithrombin III deficiency, etc.), or any other family history of arterial or venous thrombosis.

8. Subjects with a history of significant cardiovascular disease (eg, congestive heart failure [CHF] New York Heart Association Grade III/IV, arrhythmia known to increase the risk of thromboembolic events [eg, atrial fibrillation], subjects with a QT interval corrected for heart rate (QTc) >450 msec, angina, coronary artery stent placement, angioplasty, and coronary artery bypass grafting).

9. Subjects with a history of cirrhosis, portal hypertension, and chronic active hepatitis.

10. Subjects with concurrent malignant disease.

11. Use of immunoglobulins (IVIg and anti-D) within 1 week of randomization.

12. Splenectomy or use of rituximab within 12 weeks of randomization.

13. Use of romiplostim or eltrombopag within 4 weeks of randomization.

14. Subjects who were being treated with corticosteroids or azathioprine, but had not been receiving a stable dose for at least 4 weeks prior to randomization or had not completed these therapies more than 4 weeks prior to randomization.

15. Subjects who were being treated with mycophenolate mofetil (MMF), CsA, or danazol but had not been receiving a stable dose for at least 12 weeks prior to randomization or who had not completed these therapies more than 4 weeks prior to randomization.

16. Use of cyclophosphamide or vinca alkaloid regimens within 4 weeks of randomization.

17. Subjects who were being treated with proton pump inhibitor (PPIs) or histamine (H2)-receptor antagonist therapy but had not been receiving a stable dose for at least 6 weeks prior to randomization or had not completed these therapies more than 2 weeks prior to randomization.

18. Fasting gastrin-17 blood levels exceeding the ULN at Screening for subjects not on PPIs or H2 antagonists.

19. Fasting gastrin-17 blood levels exceeding 1.5 times the ULN at Screening for subjects on PPIs or H2 antagonists.

20. Blood creatinine exceeding ULN by more than 20% OR total albumin below the LLN by 10%.

21. Alanine aminotransferase (ALT) OR aspartate aminotransferase (AST) levels exceeding 3 times the ULN OR total bilirubin exceeding 2 times the ULN.

22. Subjects with a history of cancer treatment with cytotoxic chemotherapy and/or radiotherapy. Subjects with a history of ITP treatment with cytotoxic chemotherapy were still eligible for enrollment.

23. Females who were pregnant (positive β-hCG test) or breastfeeding.

24. Subjects with a known allergy to avatrombopag and any of its excipients.

25. Evidence of clinically significant disease (eg, cardiac, respiratory, gastrointestinal, renal disease) that in the opinion of the investigator could affect the subject's safety or study conduct.

26. Any history of or concomitant medical condition that, in the opinion of the investigator, would compromise the subject's ability to safely complete the study.

27. Subjects who had participated in another investigational trial within 30 days prior to Day 1 Baseline/Randomization.

Extension Phase

1. Participation in the Extension Phase was considered unsafe, based on the investigator's judgment.

2. Considered unable or unwilling to comply with the study protocol requirements or to give informed consent, as determined by the investigator.

3. Required the following drugs or treatments at the time of enrollment in the Extension Phase:

o Rituximab

o Splenectomy

o Other thrombopoietin (TPO) agonists.

Treatments

Identity of Investigational Products (Chemical Name, Structural Formula, Etc. of Avatrombopag)

• Test drug code: E5501

• Generic name: avatrombopag maleate

• Chemical name: 1-(3-chloro-5-{[4-(4-chloro-2-thienyl)-5-(4-cyclohexylpiperazin-1-yl)-1,3-thiazol-2-yl]carbamoyl}-2-pyridyl) piperidine-4-carboxylic acid monomaleate

• Molecular formula: C29H34Cl2N6O3S2C4H4O4

• Molecular weight: 765.73 (free form 649.66; conversion factor 1.179)

Treatments Administered

Core Study

Avatrombopag treatment group: avatrombopag administered orally as 5, 10, 20, 30, or 40-mg doses, in a flexible dose design.

Avatrombopag was started at a dose of 20 mg, with dose titration down to 5 mg or up to 40 mg as per specified guidelines.

Placebo treatment group: placebo administered orally to match the 5, 10, 20, 30, or 40-mg doses, in a flexible dose design.

Extension Phase

Subjects who entered the Extension Phase received a starting dose of 20 mg once daily of open-label avatrombopag and underwent dose titration in accordance with protocol-specified titration guidelines. Subjects who discontinued the Core Study early because of lack of treatment effect and entered the Extension Phase received open-label avatrombopag treatment at a starting dose of 20 mg once daily.

Study Drug Dose Adjustment Guidelines

Avatrombopag (or matching Placebo) was started at a dose of 20 mg. Subjects were allowed to have their dose titrated up (maximum dose 40 mg for avatrombopag or matching placebo) or down (minimum dose 5 mg or matching placebo) in accordance with their individual response to study drug; a placebo titration was used to maintain the blind. The overall goal of any dose modification was to maintain the

peripheral platelet count ≥50 × 10^9/L and ≤150 × 10^9/L, and to decrease the need for concomitant ITP medications, if possible.

Investigators were to consider dose adjustment in accordance with a subject's platelet counts every 2 weeks (as most subjects take approximately 10 to 14 days to demonstrate the full effect of study drug on platelet count). However, dose adjustment was performed weekly for subjects with platelet counts <50 × 10^9/L or >250 × 10^9/L. If the platelet count remained >250 × 10^9/L after 3 consecutive weeks, the subject's concomitant ITP medication, if possible, was to be down titrated provided:

a) the subject was in the concomitant ITP medication reduction period of the Core Study (ie, Visits 8 to 13) or

b) maintenance period/concomitant ITP medication reduction period of the Extension Phase (ie, Visits E9 to E31).

Otherwise, the subject was to be discontinued. Avatrombopag dose adjustments in the Extension Phase of the study were identical to those of the Core Study but were performed with open-label avatrombopag, as defined by avatrombopag dose adjustment guidance for the Extension Phase (see Table 2).

Table 2 Avatrombopag Dose-Adjustment Guidelines (Core Study and Extension Phase)

Platelet Counts	Avatrombopag Dose Adjustment
<50 × 10^9/L	Up titrate 1 dose level: 5 mg to 10 mg 10 mg to 20 mg 20 mg to 30 mg 30 mg to 40 mg
≥50 × 10^9/L to ≤ 150 × 10^9/L	Keep on the current dose
>150 × 10^9/L to ≤ 250 × 10^9/L	Down titrate 1 dose level: 10 mg to 5 mg 20 mg to 10 mg 30 mg to 20 mg 40 mg to 30 mg
>250 × 10^9/L	Stop dose, return for twice weekly platelet counts, then down titrate study drug 1 dose level when platelet count is ≤ 150 x 10^9/L 10 mg to 5 mg 20 mg to 10 mg 30 mg to 20 mg 40 mg to 30 mg

Note: The study was blind to treatment only, not to dose level.

Lack of treatment effect was defined as:

o Platelet count remained <30 × 10^9/L after more than 3 weeks at the maximum dose (subjects could be discontinued after 7 days of therapy at the maximum dose if they had dangerously low platelet counts in the opinion of the investigator) or

o Subjects who required rescue therapy more than 3 times or continuous rescue therapy for more than 3 weeks (Core Study only).

Permitted Concomitant Therapy

Subjects were instructed to contact site personnel before starting any new treatments. Treatments not specified as prohibited were permitted during the study.

Permitted ITP concomitant background therapies were as follows:

• Corticosteroids and/or azathioprine taken at a stable dose for 4 weeks before randomization

• MMF or danazol taken at a stable dose for at least 12 weeks before randomization

• CsA (due to the fact that it is a P-glycoprotein–mediated transport [P-gp] inhibitor) was to be avoided unless deemed medically necessary; CsA taken at a stable dose for at least 12 weeks before randomization.

At the discretion of the investigator, subjects were allowed to use aspirin, other salicylates, or approved adenosine diphosphate (ADP) receptor antagonists, (eg, clopidogrel, prasugrel) during the study once their platelet count had risen.

Subjects treated with PPIs and H2 antagonist therapy received a stable dose for at least 6 weeks prior to randomization. Treatment with these therapies must have been completed at least 2 weeks prior to randomization.

Avatrombopag is a substrate and an inhibitor of P-gp. Co-administration with strong inhibitors of P-gp was to be avoided unless deemed medically necessary. If a strong P-gp inhibitor was added to avatrombopag therapy or if the dose of a concomitantly-administered strong P-gp inhibitor was altered, platelet counts were monitored weekly for the following 3 weeks, as a dose adjustment of avatrombopag may have been required. If avatrombopag was administered with any concomitant medications which are substrates of P-gp, clinical signs of toxicity or blood levels (if available) of these concomitant medications were assessed.

Rescue Therapies

Subjects were allowed to receive rescue therapy at the discretion of the investigator or subinvestigator based on clinical assessment. Rescue therapy was to be considered if there was an urgent need to increase platelet count, for example:

• Life-threatening thrombocytopenia, such as a platelet count $<10 \times 10^9$/L

• Major bleed

• Clinical signs or symptoms suggesting potential bleed (ie, wet purpura)

Rescue therapy was defined as:

• The addition of any new ITP medication or medication to treat thrombocytopenia (for example): Corticosteroids; IVIg therapy; Anti-D therapy; MMF; Azathioprine; Danazol; Dapsone; CsA (Due to the fact that it is a P-gp inhibitor, CsA was to be avoided unless deemed medically necessary and/or no other suitable alternative treatment options are available); Platelet transfusion; Any increase in a baseline dose of a concomitant ITP medication. TPO agonists were not allowed as rescue therapy.

Prohibited Concomitant Therapy

Platelet transfusion was prohibited within 7 days before the first dose of study drug. Antifibrinolytic agents (aprotinin, tranexamic acid, and aminocaproic acid) and recombinant activated factor VII were prohibited during the treatment phase of the study. Heparin, warfarin, factor Xa inhibitors, direct thrombin inhibitors, fresh frozen plasma and cryoprecipitate, chronic antiplatelet therapy (>4 weeks) with aspirin, clopidogrel, prasugrel, ticlopidine, or glycoprotein Ib/IIIa antagonists (eg, tirofiban) were

prohibited during the treatment phase of the study. However, short-term use of aspirin, other salicylates, or ADP receptor antagonists were permitted only if the platelet count had risen and the investigator judged that the subject was at risk for thromboembolism. The use of nonsteroidal anti-inflammatory drugs other than aspirin for more than 7 days per month was prohibited.

Some ITP therapies/procedures, such as vinca alkaloids, cyclophosphamide, rituximab, splenectomy, and other TPO receptor agonists (eltrombopag, romiplostim) were prohibited during the treatment phase due to the long-term effects of these treatments, their safety profile, and their potential to confound efficacy results. Subjects requiring these therapies were discontinued from the study.

Objectives

Core Study

Primary Objective

• To demonstrate that the efficacy of avatrombopag (in addition to standard of care) is superior to placebo (in addition to standard of care) for the treatment of adult subjects with chronic immune thrombocytopenia (idiopathic thrombocytopenic purpura) (ITP) as measured by cumulative number of weeks of platelet response over 6 months of once daily treatment in adult subjects who received at least 1 prior ITP therapy

Secondary Objectives

• To demonstrate that the efficacy of avatrombopag (in addition to standard of care) is superior to the efficacy of placebo (in addition to standard of care) as measured by platelet response rate at Day 8

• To demonstrate that the efficacy of avatrombopag (in addition to standard of care) is superior to the efficacy of placebo (in addition to standard of care) as measured by the proportion of subjects with reduction in concomitant ITP medication use

• To evaluate the safety of avatrombopag compared with placebo.

Exploratory Objectives

• To evaluate if the efficacy of avatrombopag (in addition to standard of care) is superior to the efficacy of placebo (in addition to standard of care) as measured by a durable platelet response

• To evaluate if the efficacy of avatrombopag (in addition to standard of care) is superior to the efficacy of placebo (in addition to standard of care) with regard to bleeding minimization and use of rescue therapy

• To collect population pharmacokinetic (PK)/pharmacodynamic (PD) data on plasma avatrombopag exposure and effect on platelet counts.

Extension Phase

Primary Objective

• To evaluate the safety and tolerability of long-term therapy with avatrombopag in subjects with chronic ITP.

Secondary Objective

• To evaluate the effectiveness of long-term therapy with avatrombopag as measured by platelet response, bleeding, and the use of rescue medication.

Outcomes/endpoints

Primary Endpoint

• The primary endpoint is the cumulative number of weeks of platelet response, which is defined as the cumulative number of weeks in which the platelet count is ≥50 × 10^9/L during 6 months of treatment (ie, at Visit 3 to 22 inclusive) in the absence of rescue therapy.

Secondary Endpoints

• Platelet response rate at Day 8 (as defined by the proportion of subjects with a platelet count ≥50 x 10^9/L at Day 8)

• Proportion of subjects with a reduction in use of concomitant ITP medications from baseline. The guideline for reduction is given in this table 3:

Table 3 Concomitant ITP Medication Downward Titration Guidelines

Platelet count	ITP Concomitant Dose Adjustment
≤150 × 10^9/L	Keep current dose
>150 × 10^9/L to ≤250 × 10^9/L	Downward titration ≤ 25% of the original dose for 14 days
>250 × 10^9/L	Downward titration ≤ 50% of the original dose for 14 days

ITP = idiopathic thrombocytopenic purpura

Exploratory Endpoints

• Durable platelet response rate, which is defined as the proportion of subjects who have at least 6 out 8 (ie, ≥75%) weekly platelet counts ≥50 × 10^9/L during the last 8 weeks of treatment (ie, at Visit 15 to 22 inclusive) over the 6-month treatment period in the absence of rescue therapy.

• Alternative durable platelet response rate, which is defined as the proportion of subjects who have at least ≥75% of platelet count ≥50 × 10^9/L and ≤400 × 10^9/L from the time of first response over the 6-month treatment period in the absence of rescue therapy (durability by flexible period).

• Proportion of subjects who have at least 6 of 8 (ie, ≥75%) weekly platelet counts ≥50 × 10^9/L during the last 8 weeks of treatment (ie, at Visit 15 to 22 inclusive) over the 6-month treatment period in the absence of rescue therapy and who do not have excessive bleeding (≥ Grade 3 based on the WHO Bleeding Scale, see Appendix III).

• Incidence and severity of bleeding events associated with cITP, including bleeding, bruising, and petechiae, measured using the WHO Bleeding Scale.

• Time-to-first bleeding event

• Time-to-first bleeding event with WHO Bleeding Scale score ≥ Grade 3

• Maximum duration (in weeks) of continuous platelet response for each subject

• Proportion of subjects receiving rescue therapy during the 6-month treatment duration of the study

• Proportion of subjects with a discontinuation in use of concomitant ITP medications from baseline

• Complete platelet response by International Working Group (IWG) criteria, defined as a platelet count ≥100 x 10^9/L and in the absence of bleeding

• Platelet response by IWG criteria, defined as a platelet count ≥30 x 10^9/L and at least a 2-fold increase in baseline platelet count and in the absence of bleeding

Health-related Quality of Life (QoL) and Health Outcome Economics

• Medical Outcomes Study 36-Item Short Term Health Survey (SF-36), Treatment Satisfaction Questionnaire for Medication (TQSM), and European Quality of Life – 5 Dimensions (EQ-5D) scale scores

• Health outcome economics

Extension Phase Study Endpoints

The effectiveness of avatrombopag was assessed by measuring platelet counts, reduction in use of concomitant ITP medication, and bleeding events. Specifically,

• Median platelet count of all subjects at selected time points (monthly)

• Proportion of subjects needing rescue therapy

• Incidence and severity of bleeding (in accordance with the WHO Bleeding Scale)

Sample size

Based on data from the completed avatrombopag Phase 2 chronic ITP clinical trial, Study 501-CL-003, the cumulative number of weeks of platelet response during the 4-week treatment period (primary endpoint, last observation carried forward [LOCF]) was confirmed for placebo and avatrombopag 20 mg, respectively as follows:

The cumulative number of weeks of platelet response in Study 501-CL-003 study (FAS, LOCF)					
	0 weeks	1 week	2 weeks	3 weeks	4 weeks
Placebo (n=5)	4 (80%)	1 (20%)	0	0	0
Avatrombopag 20 mg (n=15)	1 (7%)	0	1 (7%)	1 (7%)	12 (80%)

Using a resampling method based on Study 501-CL-003 results, and assuming a 15% dropout rate with all dropout subjects being considered to have 0 weeks of platelet response, a total sample size of 45 subjects, 15 subjects in the placebo group and 30 subjects in avatrombopag group, would have more than 95% power to detect a treatment difference between avatrombopag and placebo in the cumulative number of weeks of platelet response during the 4-week treatment period using Wilcoxon rank sum test at a 2-sided α=0.05 significant level. Conservatively, assuming a treatment difference in the cumulative number of weeks of platelet response would be preserved with longer duration of treatment, the sample size of 45 subjects would have more than 95% power to detect a treatment difference in the cumulative number of weeks of platelet response during 6 months of treatment between avatrombopag and placebo using Wilcoxon rank sum test at a 2-sided α=0.05 significant level.

Assuming the platelet response rate at Day 8 was 20% for placebo and 86% for avatrombopag, a total sample size of 45 subjects would have more than 99% power to detect a treatment difference in platelet response rate at Day 8 using the Fisher's exact method at the 2-sided α=0.05 significance level.

Randomisation

Subjects whose screening assessments and evaluations were completed and reviewed by the principal investigator and who continued to meet all of the inclusion and none of the exclusion criteria were entered into the Randomization Phase.

Subjects were centrally stratified by splenectomy status and baseline platelet count ($\leq 15 \times 10^9$/L or >15 to $<30 \times 10^9$/L), and use of concomitant ITP medication (ie, yes or no for the use of concomitant ITP

medication) at baseline and were randomly assigned to either avatrombopag or placebo treatment group in a 2:1 ratio.

Avatrombopag or placebo was administered orally in a flexible dose design. The Randomization Phase lasted for 26 weeks for subjects who rolled over into the open-label Extension Phase and included 4 periods: Baseline, Titration, Concomitant ITP Medication Reduction, and Maintenance.

Subjects who did not achieve a platelet count of ≥30 × 10^9/L during the Randomization Phase despite upward titration to the maximum dose were classified as having a lack of treatment effect. Subjects who met the criteria for a lack of treatment effect were able to enter the open-label extension directly.

For those subjects who did not roll over, the Randomization Phase was 26 weeks in duration, followed by a dose-taper period of up to 4 weeks and a 4-week Follow-up Period. Subjects who required study drug dose adjustments, who underwent concomitant ITP medication reduction, or who received rescue therapy during the periods of Concomitant Medication Reduction and Maintenance Periods were required to return for weekly visits for 3 consecutive weeks.

Baseline/Randomization Period (Visit 2)
During this period, baseline assessments, including platelet count and randomization, were performed. Blinded study drug administration was started. Subjects were required to have their platelet counts available before randomization in order to be assessed for eligibility.

Blinding (masking)

During the Randomization Phase, the subject and all personnel involved with the conduct and the interpretation of the study, including the investigators, investigational site personnel, and sponsor staff, were blinded to the treatment codes (but not dose levels).

Randomization data were kept strictly confidential, filed securely by an appropriate group at the sponsor or designated CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per SOPs.

A master list of all treatments was maintained in a sealed envelope with the sponsor. Corresponding subject numbers associated with treatment were blinded in the IxRS database. In the event that emergency conditions required knowledge of the study treatment given, the blind was broken via the code breaker facility within the IxRS. The Extension Phase was not blinded.

An independent DSMB was established to monitor accumulating safety data. The DSMB safety interim analysis was performed by an independent statistician and governed by an external DSMB. To maintain the blinding and integrity of the study, procedures were implemented to ensure the DSMB and independent statistician has sole access to unblinded interim safety data.

Statistical methods

Definitions of Analysis Sets

The populations of interest for Core Study will be defined as follows:

Full Analysis Set (FAS): The FAS will include all subjects who are randomized into the study. The FAS will be analyzed as randomized.

Per Protocol Set (PP): The PP set will include all randomized subjects who receive protocol-assigned study drug and who do not meet any of the following criteria:

• Subjects who have any major protocol violations (major inclusion/exclusion violations, [eg, subject did not have cITP])

• Subjects who use a prohibited concomitant medication that affects the assessment of study endpoints

• Subjects who skip more than 20% of their daily dose for a reason other than a high platelet count

• Subjects who have major protocol deviations that impact the platelet count evaluation, such as both study drug and/or concomitant ITP medication dose-adjustment deviations.

A comprehensive list of subjects to be excluded from the PP population will be agreed upon by the study team and documented prior to database lock.

Safety Set: The safety set will include all subjects who receive at least 1 dose of study drug and have a postdose safety assessment. The Safety Set will be analyzed as treated.

The FAS will be used as the primary population for all efficacy analyses for Core Study, while the PP will be used in supportive analyses of the primary efficacy endpoint.

Primary endpoint: Cumulative number of weeks of platelet response

The cumulative number of weeks of platelet response is defined as the cumulative number of weeks in which the platelet count ≥50 x 10^9/L during 6-month treatment (ie, at Visit 3 to 22 inclusive) of Core Study in the absence of rescue therapy. A platelet response is defined as a platelet count of ≥50 x 10^9/L. Nonresponse is defined as a platelet count of <50 x 10^9/L.

The comparison of the cumulative number of weeks of platelet response of avatrombopag (in addition to standard of care) is same as that of placebo (in addition to standard of care) will be tested using Wilcoxon rank sum test at the 2-sided α=0.05 significance level.

Subjects using rescue therapy at any time during 6 months of treatment period will be considered to not have any platelet responses at all subsequent scheduled time points after rescue therapy.

First key secondary efficacy endpoint: platelet response rate at Day 8

Platelet response rate at Day 8, is defined as the proportion of subjects with a platelet count ≥50 x 10^9/L at Day 8.

The platelet response rate at Day 8 of avatrombopag (in addition to standard of care) will be compared to that of placebo (in addition to standard of care) using CMH test adjusting for splenectomy status (yes and no) and baseline platelet count (≤15 x 10^9/L and >15 to <30 x10^9/L) at the 2-sided α=0.05 significance level as long as none of the marginal cells equal to 0. If any of the marginal cells count is equal to 0, the Fisher's exact test will be used.

A 2-sided 95% CI for the difference in platelet response at Day 8 between placebo and avatrombopag will be calculated using normal approximation. In addition, a 2-sided 95% CI for platelet response at Day 8 will be calculated for each treatment group using normal approximation method.

Second key secondary efficacy endpoint: Proportion of subjects with a reduction in use of concomitant ITP medications from baseline

Only subjects with use of concomitant ITP medications at baseline will be included in the analysis. If a subject has use of concomitant ITP medication at baseline, has no use of rescue therapy during the 6-month treatment period, and has at least one concomitant ITP medication dose reduced from baseline level during the whole maintenance period, this subject is considered as having a reduction in use of concomitant ITP medication from baseline.

This endpoint will be analyzed the same way as for the first key secondary endpoint.

Handling of Missing Data, Dropouts, and Outliers for all

Unless stated otherwise, for platelet counts, missing platelet assessments at a specific visit will be considered to be a nonresponse at that visit. Subjects who discontinue the study or who are lost to follow up before the 6-month treatment period will have all subsequent unobserved scheduled platelet assessments at the scheduled visits as having missing platelet values.

Unless stated otherwise, a platelet count that occurs within 8 weeks after rescue therapies are used will be considered as a nonresponse in any analysis of platelet response.

Table 31-1 Percent of Time With Platelet Count ≥50×10^9/L during the Core Phase in the Absence of Rescue Medications – 302 Study

	N	Mean (%)	SD	Median (%)	Min (%)	Max (%)
Avatrombopag	32	49.02	33.06	54.50	0	96.13
Placebo	17	0.65	2.67	0	0	11.03
Wilcoxon Test P-value	<0.0001					
Hodges-Lehmann 95% CI	(21.84, 73.62)					

Multiple Comparisons/Multiplicity

The single primary efficacy endpoint will be tested for superiority. Therefore, no adjustment on type I error for multiple comparison for primary efficacy analysis is necessary.

For 2 key secondary endpoints, the multiplicity is adjusted in a fixed sequential fashion. The comparison platelet response at Day 8 between avatrombopag and placebo will be performed first at the 2-sided α=0.05 significance level. If this testing is significant, then the comparison of proportion of subjects with a reduction in use of concomitant ITP medications from baseline will be performed at the 2-sided α=0.05 significance level.

No interim efficacy analysis is planned for the Core study, thus no alpha spending or multiplicity adjustment was necessary.

Results

Participant flow

E5501-G000-302 was conducted between 06 Feb 2012 and 28 Nov 2013 at 27 study sites worldwide. Study completion was the date the last subject completed the Core Study, at which point, the open-label Extension Phase were terminated. Although the E5501-G000-302 study was completed, 1 subject remained ongoing until 09 April 2015. The disposition of subjects up to the database lock of 10 Mar 2014 is displayed in Table 7.

A total of 100 subjects were screened for entry into the study. Of these 100 subjects, 51 were screen failures and 49 were randomized into the study. Of the 51 screen failures, 42 (42.0%) subjects failed to meet inclusion or exclusion criteria, 6 (6.0%) failed for the reason of 'Other', 2 (2.0%) failed due to an AE, and 1 (1.0%) subject was excluded for withdrawal of consent.

Table 7 Subject Disposition and Primary Reasons for Discontinuation from Study – Core Study, FAS Core Study

	Placebo	Avatrombopag
Randomized, n	17	32
Not Treated, n	0	0
Treated, n (%)	17 (100)	32 (100)
Completed core study, n (%)	1 (5.9)	22 (68.8)
Discontinued from core study, n (%)	16 (94.1)	10 (31.3)
Primary Reason for Discontinuation[a], n (%)		
Adverse Event[b]	0	3 (9.4)
Lost to Follow-up	0	0
Subject Choice	0	0
Inadequate Therapeutic Effect	15 (88.2)	7 (21.9)
Withdrawal of Consent	1 (5.9)	0
Pregnancy	0	0
Study Terminated by Sponsor	0	0
Other	0	0

FAS = full analysis set
Percentages are based on the number of subjects randomized and treated in the relevant treatment group.
a: As reported on the Subject Disposition (Core Study) CRF.
b: Corresponding adverse event (s) leading to withdrawal from the study were reported on the Adverse Event CRF
Source: Table 14.1.1.2.1, Listing 16.2.1.2.

10 subjects who received avatrombopag in the Core phase and discontinued the Core phase, 7 of whom entered the Extension phase. Three of these 7 subjects who entered the Extension phase completed, 3 subjects discontinued, and one subject continued to receive open-label avatrombopag after database lock.

Two placebo subjects, including the one who completed the Core phase, did not enrol in the Extension phase and 15 entered the Extension phase after discontinuing the Core Phase. Of these 15 subjects who entered the Extension, 14 completed the Extension phase and one discontinued due to an AE after 155 days.

Recruitment

This study was a multicenter study with 27 investigator sites participating. Due to the small expected number of subjects in each center, the efficacy analyses were performed with all centers pooled across the study unless stated otherwise and consistency of results for the primary efficacy endpoint were examined by the geographic region. The first informed consent form (ICF) was signed on 06 Feb 2012. All subjects exited the study by 26 Nov 2013, except for 1 subject, who continued in the study under Protocol Amendment 01 until 09 Apr 2015.

Conduct of the study

Protocol Amendments

The original protocol was dated 07 Jun 2011, and planned for 84 subjects in total, 28 placebo and 56 active, and ending with 45 patients in the final protocol 302. Protocol Amendment 01 was dated 15 Jun 2012 and Protocol Amendment 02 was dated 25 March 2013. The following significant changes to the protocol were a result of Amendment 01:

• The ability of subjects to be permanently discontinued at the discretion of the investigator after 7 days of therapy at the maximum dose if they had dangerously low platelet counts.

• P-gP wording was revised to include strong P-gP inhibitor was to be added to avatrombopag therapy or if the dose of a concomitantly administered strong P-gP inhibitor was altered, platelet counts would be monitored weekly for the next 3 weeks in the event a dose adjustment of avatrombopag was required.

• Wording was added to the inclusion criteria that patients with neutrophil counts above the reference range may be enrolled upon review and discussion with the Eisai medical monitor.

• The fasting gastrin-17 exclusion requirement was increased to 1.5 times ULN for those subjects on PPIs or H2 antagonists.

• Time-to-first bleeding event and time-to-first bleeding event with WHO Bleeding Scale score endpoints were included to align the current study with analyses planned in the E5501-G000-305 study.

• Repeat screening laboratory evaluations due to potential laboratory error or a transient and/or reversible condition were to be made available prior to Randomization.

• The ability to remove subjects based on gastric biomarkers was added.

• Lack of treatment effect was defined to allow subjects with very low platelet counts to discontinue earlier due to lack of treatment effect and continue into the Extension Phase.

• A follow-up endoscopy was requested if there was a significant abnormal endoscopy during the study.

Per Amendment 02, dated 25 Mar 2013, the study was complete after the last subject completed the Core Study. The primary reason for the amendment was to change the primary endpoint to cumulative platelet response as the study was completed after the last subject completed the Core Study. As a result, other changes were also made to the protocol:

• A secondary objective was made an exploratory objective.
• The secondary objective for the Extension Phase to assess the reduction in the use of steroids and concomitant ITP medication in subjects receiving avatrombopag was removed.

• The effectiveness assessments for the Extension Phase were revised.

• The key secondary endpoint was redefined as exploratory.

• The target sample size was changed to 45 subjects.

• The criterion that 35% of splenectomized subjects will be enrolled in the study was removed.

• The inclusion criterion for subjects enrolling in the Extension Phase to align with study completion was clarified.

• The population PK/PD analysis was revised.

• Study completion was defined.

Amendment 02 was not approved in the Netherlands by the ethics committee. One subject remained on study through the 2-year Extension Phase per Amendment 01. When all other subjects completed the study per Amendment 02, the database was locked on 10 Mar 2014 and the data were analyzed, including Subject 16001001's data up to that point in time.

Other Changes in the Conduct of the Study

There were no other changes in the conduct of the study.

Changes to the Planned Analyses

The original SAP for the Core Study (Version 1.1) was based on the original protocol, and the original SAP for the Extension Phase (Version 1.0) was based on Protocol Amendment 01. With the significant changes including study objectives, primary endpoint, secondary endpoints, and sample size rationale, etc. made to Protocol Amendment 02, SAP (Version 2.0) was updated to reflect those changes and to integrate the planned analyses of the Core Study and Extension Phase into 1 document. Before the database lock and treatment unblinding, SAP (Version 2.1), was updated for the definition of "bone marrow pathology" to ensure there is no overlap between neoplastic events and bone marrow pathology AEs of special interest reporting, 1 of AEs of special interest. The significant changes to the planned analyses in SAP (Version 2.1) included the analyses not performed and the change of "bone marrow pathology" definition.

The analyses of following efficacy endpoints and QoL outcome specified in study Protocol Amendment 02 were not performed:

Core Study

• Per Protocol Set (PP) and sensitivity analyses based on PP analysis set

• Alternative durable platelet response rate

• Proportion of subjects who have at least 6 out of 8 (ie, ≥75%) weekly platelet responses (≥50 x 10^9/L) during the last 8 weeks of treatment (ie, at Visit 15 to 22 inclusive) over the 6-month treatment period in the absence of rescue therapy and who do not have excessive bleeding (≥Grade 3 WHO Bleeding Scale score)

• Time-to-first bleeding event

• Time-to-first bleeding event with WHO Bleeding scale score ≥ Grade 3

• Outcome of TSQM

Extension Phase

• Proportion of subjects needing rescue therapy

• Incidence and severity of bleeding (in accordance with the WHO Bleeding Scale) The definition of bone marrow pathology was changed to bone marrow pathology (excluding neoplasms) to ensure there was no overlap between neoplastic events and bone marrow pathology AEs of special interest reporting. MedDRA SOC 'Neoplasms benign, malignant and unspecified (including cysts and polyps)' were excluded from the definition of bone marrow pathology, and the PTs listed in Appendix IV were updated to exclude PTs belonging to neoplastic events.

Protocol deviations

Major protocol deviations for the Core Study are presented in Table 14.1.1.3.1 and in Table 14.1.1.3.2 for the Extension Phase. Major protocol deviations were conservatively defined as deviations from the protocol that included inadequate or improper informed consent procedure, missed visits or laboratory tests, study drug dispensed or dosing deviations, inclusion/exclusion issues, and failure to report any SAE according to the protocol. A total of 31 subjects (63.3%) had major protocol deviations.

Table 14.1.3.1 Summary of major protocol deviations. Full analysis set of core study

	Placebo (N=17) n (%)	Avatrombopag (N=32) n (%)	Total (N=49) n (%)
Subjects with any protocol deviations	9 (52.94)	22 (68.75)	31 (63.27)
Subjects with Major Deviations	9 (52.94)	22 (68.75)	31 (63.27)
Noncompliance of drug dosage/intervention	3 (17.65)	10 (20.83)	13 (20.00)
Noncompliance with protocol procedures	6 (35.29)	19 (39.58)	25 (38.46)
Use of prohibited treatments	0	2 (4.17)	2 (3.08)
Violations of inclusion/exclusion criteria	0	7 (14.58)	7 (10.77)

Table 14.1.3.2 Summary of major protocol deviations. Modified full analysis set of ectension phase

	Avatrombopag (N=39) n (%)
Subjects with any protocol deviations	24 (61.54)
Subjects with Major Deviations	24 (61.54)
Noncompliance of drug dosage/intervention	10 (24.39)
Noncompliance with protocol procedures	16 (39.02)
Use of prohibited treatments	0
Violations of inclusion/exclusion criteria	0

Baseline data

Table 9 Demography and Baseline Characteristics – Core Study, FAS Core Study

Category	Placebo (N=17)	Avatrombopag (N=32)	Total (N=49)
Age (year)[a]			
n	17	32	49
Mean (SD)	41.2 (14.70)	46.4 (14.20)	44.6 (14.44)
Median	43.0	45.0	44.0
Min, Max	18, 65	20, 69	18, 69
Age group, n (%)			
<65 Years	16 (94.1)	29 (90.6)	45 (91.8)
≥65 Years	1 (5.9)	3 (9.4)	4 (8.2)
Sex, n (%)			
Male	9 (52.9)	9 (28.1)	18 (36.7)
Female	8 (47.1)	23 (71.9)	31 (63.3)
Ethnicity, n (%)			
Hispanic	0	0	0
Non-Hispanic	17 (100)	32 (100)	49 (100)
Race, n (%)			
White	15 (88.2)	31 (96.9)	46 (93.9)
Black or African American	1 (5.9)	0	1 (2.0)
Japanese	0	0	0
Chinese	1 (5.9)	1 (3.1)	2 (4.1)
Other Asian	0	0	0
American Indian or Alaskan Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0

Other	0	0	0
Weight (kg)			
n	17	32	49
Mean (SD)	84.97 (20.476)	81.90 (22.707)	82.97 (21.793)
Median	80.00	80.25	80.00
Min, Max	57.0, 144.0	54.0, 161.3	54.0, 161.3
Height (cm)			
n	17	32	49
Mean (SD)	170.53 (7.459)	167.89 (8.000)	168.81 (7.841)
Median	168.00	168.00	168.00
Min, Max	161.0, 183.0	152.0, 185.0	152.0, 185.0
BMI (kg/m^2)			
n	17	32	49
Mean (SD)	29.24 (6.644)	28.99 (7.321)	29.08 (7.024)
Median	27.35	28.05	27.53
Min, Max	19.2, 46.0	18.7, 52.1	18.7, 52.1
Baseline platelet count (x 10^9/L)			
n	17	32	49
Mean (SD)	12.71 (7.842)	14.06 (8.637)	13.59 (8.312)
Median	9.50	12.50	9.50
Min, Max	4.0, 27.0	1.0, 31.5	1.0, 31.5
Baseline platelet count category, n(%)			
$\leq$ 15 x 10^9/L	10 (58.8)	18 (56.3)	28 (57.1)
> 15 x 10^9/L to < 30 x 10^9/L	7 (41.2)	13 (40.6)	20 (40.8)
$\geq$ 30 x 10^9/L	0	1 (3.1)	1 (2.0)
Splenectomy status, n (%)			
Yes	5 (29.4)	11 (34.4)	16 (32.7)
No	12 (70.6)	21 (65.6)	33 (67.3)
Use of concomitant ITP medication at baseline, n (%)			
Yes	7 (41.2)	15 (46.9)	22 (44.9)
No	10 (58.8)	17 (53.1)	27 (55.1)

FAS = full analysis set

a: Age is calculated at Date of Informed Consent.

Percentages are based on the total number of subjects with nonmissing values in relevant treatment group.

Source: Table 14.1.2.1.1, Listing 16.2.4.1

Table 14.1.2.2 ITP medical history. Full analysis set of core study 302.

	Placebo (N=17) n (%)	Avatrombopag (N=32) n (%)	Total (N=49) n (%)
Previous platelet transfusion			
Yes	3 (17.6)	6 (18.8)	9 (18.4)
No	14 (82.4)	26 (81.3)	40 (81.6)
Number of previous ITP medications			
1	7 (41.2)	7 (21.9)	14 (28.6)
2	1 (5.9)	6 (18.8)	7 (14.3)
3	3 (17.6)	8 (25.0)	11 (22.4)
4	1 (5.9)	1 (3.1)	2 (4.1)
5 or More	5 (29.4)	10 (31.3)	15 (30.6)
Previous use of Rituximab			
Yes	3 (17.6)	6 (18.8)	9 (18.4)
No	14 (82.4)	26 (81.3)	40 (81.6)
Previous use of TPO receptor agonist therapy			
Yes	6 (35.3)	12 (37.5)	18 (36.7)
No	11 (64.7)	20 (62.5)	31 (63.3)
	0	0	0
Type of TPO receptor agonist therapy			
Romiplostim	1 (5.9)	7 (21.9)	8 (16.3)
Eltrombopag	4 (23.5)	6 (18.8)	10 (20.4)
E5501 AKR501	0	0	0
Other	2 (11.8)	1 (3.1)	3 (6.1)
Response to previous ITP therapy			
Yes	16 (94.1)	32 (100.0)	48 (98.0)
No	1 (5.9)	0	1 (2.0)

Numbers analysed

All subjects randomized into the study were included in the FAS for the efficacy analyses in the Core Study, and all subjects who entered into the Extension Phase were included in the mFAS for the efficacy summaries in the Extension Phase. No other efficacy subsets were used in this study.

Outcomes and estimation

Core study

Primary endpoint

Table 10 Summary of the Cumulative Number of Weeks with Platelet Count ≥50 x 10^9/L – FAS of Core Study

	Placebo (N=17)	Avatrombopag (N=32)
Cumulative number of weeks of platelet response		
n	17	32
Mean (SD)	0.1 (0.49)	12.0 (8.75)
Median	0.0	12.4
Min, Max	0, 2	0, 25
P-value of Wilcoxon rank sum test		<0.0001

FAS = full analysis set

Cumulative number of weeks of platelet response is defined as the total numbers of weeks in which the platelet count is ≥50 x 10^9/L during 6 months of treatment of Core Study in the absence of rescue therapy.

Source: Table 14.2.1.1, Listing 16.2.6.1

Figure 14.2.3.7.2 Median (Q1, Q3) of local platelet count over time. 6 months treatment period of core study. Full analysis set of core study 302

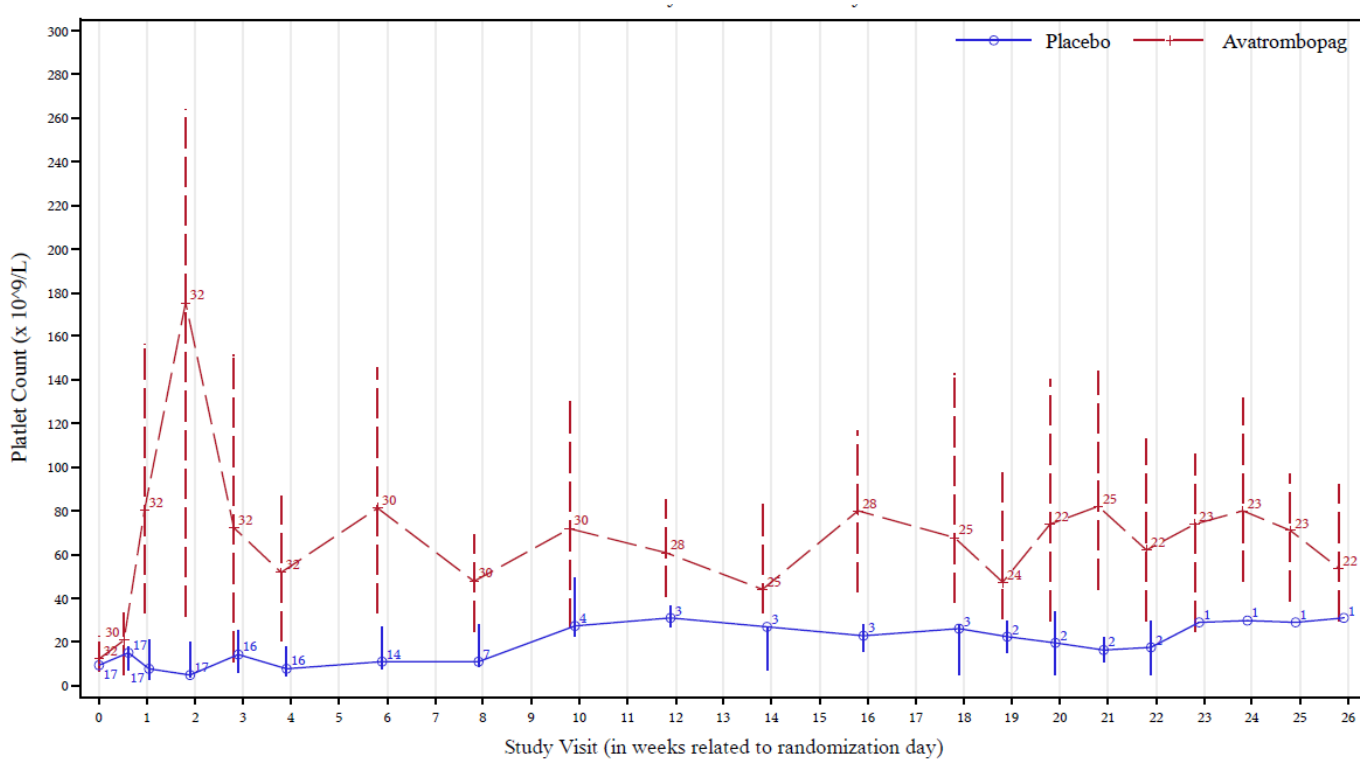


Table 14.2.6.5 Summary of cumulative number of weeks of platelet response by baseline platelet count category. Full analysis set of core study 302.

Subgroup Cumulative number of weeks of platelet response	Placebo (N=17)	Avatrombopag (N=32)
Baseline platelet count (x10⁹/L) category : <=15		
n	10	18
Mean (SD)	0.0 (0.00)	8.7 (7.75)
Median	0.0	5.3
Min, Max	0, 0	0, 22
P-value of Wilcoxon rank sum test		0.0002
Baseline platelet count (x10⁹/L) category : >15		
n	7	14
Mean (SD)	0.3 (0.76)	16.2 (8.34)
Median	0.0	19.2
Min, Max	0, 2	0, 25
P-value of Wilcoxon rank sum test		0.0007

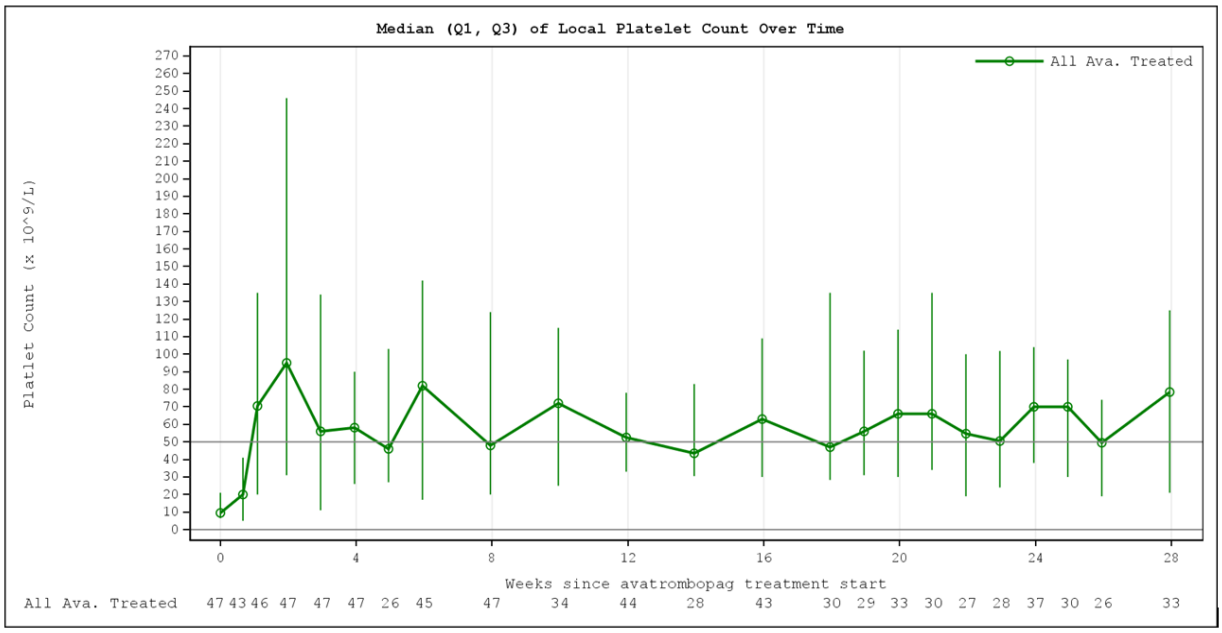
Table 14.2.6.6 Summary of cumulative number of weeks of platelet response by splenectomy status. Full analysis set of core study 302.

Subgroup Cumulative number of weeks of platelet response	Placebo (N=17)	Avatrombopag (N=32)
Splenectomized: Yes		
n	5	11
Mean (SD)	0.0 (0.00)	8.7 (8.54)
Median	0.0	4.9
Min, Max	0, 0	0, 22
P-value of Wilcoxon rank sum test		0.0092
Splenectomized: No		
n	12	21
Mean (SD)	0.2 (0.58)	13.7 (8.57)
Median	0.0	15.9
Min, Max	0, 2	0, 25
P-value of Wilcoxon rank sum test		<.0001

Table 14.2.6.7 Summary of cumulative number of weeks of platelet response by use of concomitant use of ITP medication at baseline. Full analysis set of core study 302.

Subgroup Cumulative number of weeks of platelet response	Placebo (N=17)	Avatrombopag (N=32)
Use of concomitant ITP medications at Baseline: Yes		
n	7	15
Mean (SD)	0.0 (0.00)	9.1 (9.04)
Median	0.0	4.9
Min, Max	0, 0	0, 22
P-value of Wilcoxon rank sum test		0.0021
Use of concomitant ITP medications at Baseline: No		
n	10	17
Mean (SD)	0.2 (0.63)	14.5 (7.91)
Median	0.0	15.9
Min, Max	0, 2	0, 25
P-value of Wilcoxon rank sum test		<.0001

Figure 33-1 Median (Q1, Q3) Platelet Count Over Time – Subjects Treated with Avatrombopag in 302 Study (Core and Extension) - Overall



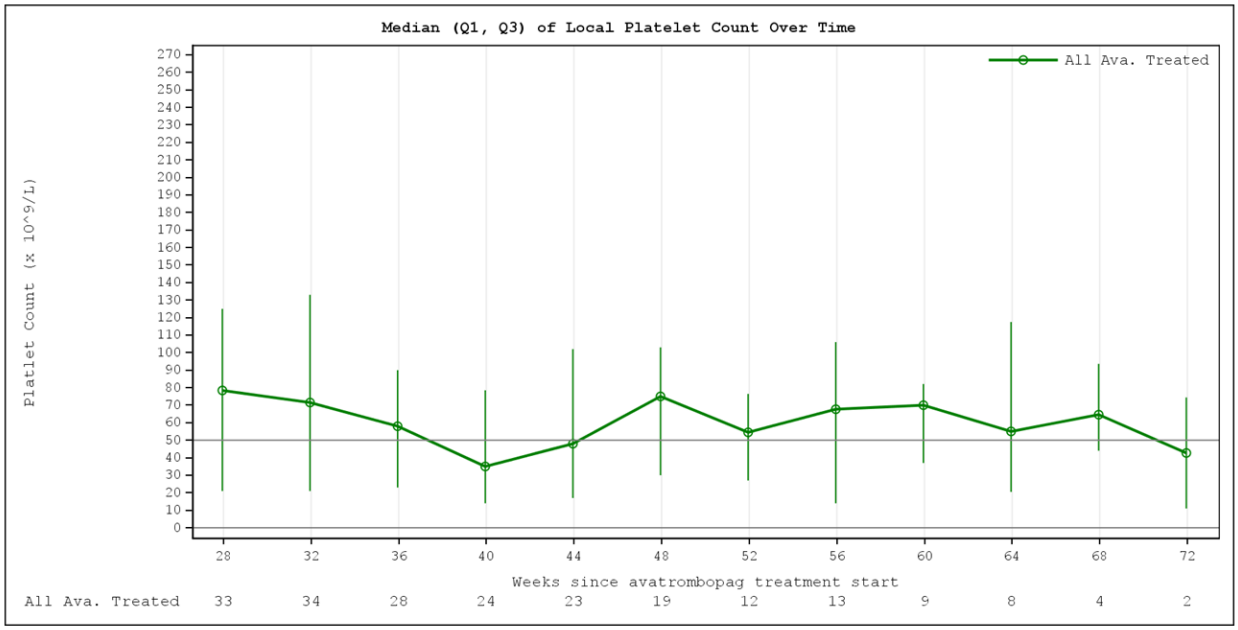
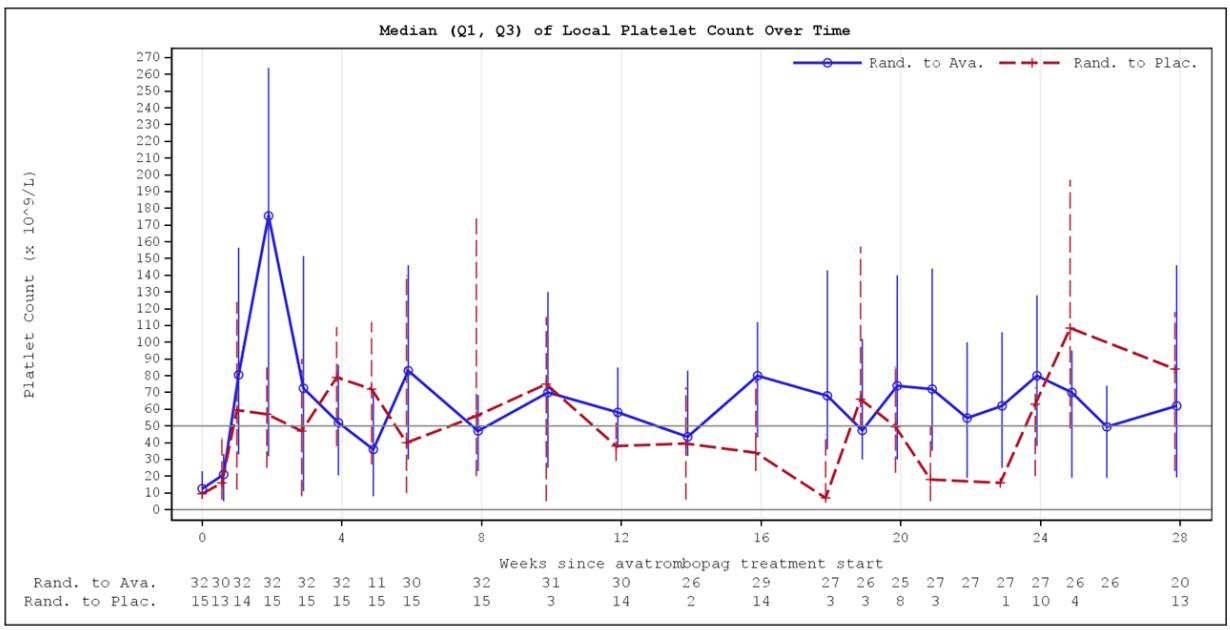
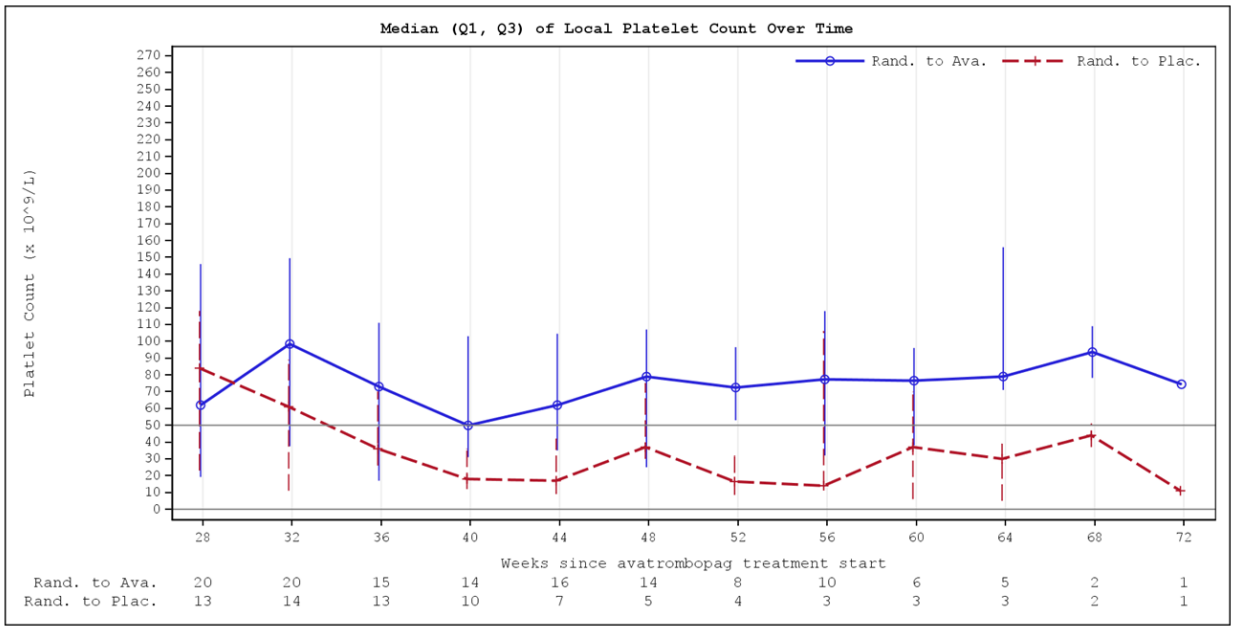


Figure 33-2 Median (Q1, Q3) Platelet Count Over Time – Subjects Treated with Avatrombopag in 302 Study (Core and Extension) - By Treatment Group at Randomization





The primary endpoint "cumulative number of weeks with platelet count ≥ 50 x 10^9/L" is met, as the median number of weeks with platelet counts above threshold in the avatrombopag treatment group is significantly higher compared to the median number of weeks in the placebo group (12.4 and 0 weeks, respectively). This response was stable for at least half a year (core study) and was also be maintained for more than a year (extension study).

Secondary endpoints

Table 11 Summary of Two Key Secondary Efficacy Endpoints – FAS of Core Study

	Placebo	Avatrombopag
	n, percentage (95% CI)	n, percentage (95% CI)
Platelet count ≥50 x 10^9/L at Day 8		
n[a]	17	32
Yes	0, 0.00 (-,-)	21, 65.63 (49.17, 82.08)
No	17, 100.00	11, 34.38
Missing[b]	0	0
Difference of response rate (95% CI)[c]		65.63 (49.17, 82.08)
P-value of Fisher's exact test		<0.0001
Reduction in use of concomitant ITP medications from baseline		
N[d]	7	15
Yes	0 0.00 (-,-)	5 33.33 (9.48, 57.19)
No	7 100.00	10 66.67
Difference of rate of reduction (95% CI)[e]		33.33 (9.48, 57.19)
P value of Fisher's exact test		0.1348

FAS = full analysis set, CI = confidence interval

a: Subjects with platelet response at day 8 are defined as those who had a platelet count ≥50 x 10^9/L at day 8 in the absence of rescue therapy on or before Day 8.

b: Missing values are considered as nonresponse in the P-value calculation.

c: Difference of response rate = platelet response rate at Day 8 of avatrombopag - platelet response rate at Day 8 of placebo, 95% confidence interval (CI) is calculated based on normal approximation.

d: Only subjects with use of concomitant ITP medications at baseline were included in the analysis; this number is used to calculate percentages.

e: Difference of rate of reduction = rate of reduction of in use of concomitant ITP medications from baseline of avatrombopag - rate of reduction of in use of concomitant ITP medications from baseline of placebo, 95% confidence interval (CI) is calculated based on normal approximation.

Table 14.2.3.11 Summary of discontinuation in use of concomitant ITP medication from baseline during 6 months treatment. Full analysis of Coree Study 302

	Placebo (N=17)		Avatrombopag (N=32)	
	n	Percentage (95% CI[b])	n	Percentage (95% CI[b])
Discontinuation in use of concomitant ITP medications from baseline during 6-month treatment				
n[a]	7		15	
Yes	0	0.00 (-,-)	3	20.00 (0.00, 40.24)
No	7	100.00	12	80.00
Difference of rate of discontinuation of concomitant ITP medications (95% CI[c])				20.00 (-0.24, 40.24)
P-value of Fisher's exact test				0.5227

Table 14.1.4.6 Concomitant ITP medications at baseline. Full analysis set of Core Study 302

Anatomical Class/ Therapeutic Subgroup/ Pharmacological Subgroup/ WHO Drug Name (Preferred Term)	Placebo (N=17) n (%)	Avatrombo (N=32) n (%)
Subjects who took at least one medication	1 (5.9)	11 (34.4
ANTIINFECTIVES FOR SYSTEMIC USE	1 (5.9)	2 (6.3
ANTIMYCOBACTERIALS	0	1 (3.1
DRUGS FOR TREATMENT OF LEPRA	0	1 (3.1
DAPSONE	0	1 (3.1
IMMUNE SERA AND IMMUNOGLOBULINS	1 (5.9)	2 (6.3
IMMUNOGLOBULINS	1 (5.9)	2 (6.3
IMMUNOGLOBULIN HUMAN NORMAL	1 (5.9)	2 (6.3
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	0	9 (28.1
CORTICOSTEROIDS FOR SYSTEMIC USE	0	9 (28.1
CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN	0	9 (28.1
METHYLPREDNISOLONE	0	3 (9.4
PREDNISOLONE	0	1 (3.1
PREDNISONE	0	5 (15.6

Subjects with two or more medications within a class level and drug name are counted only once within that class level and drug name. Concomitant ITP medications during Core Study include ITP medications that started or had dose/frequency changed after the day of randomization and up to the last day of 6-month treatment period of Core Study.

Exploratory endpoints

Durable platelet response

Table 12 Summary of Durable Platelet Response – FAS of Core Study		
	Placebo (N=17)	Avatrombopag (N=32)
	n percentage (95% CI)	n percentage (95% CI)
Durable platelet response		
Yes	0 0.00 (-,-)	11 34.38 (17.92, 50.83)
No	2 11.76	14 43.75
Missing	15 88.24	7 21.88
Difference of response rate (95% CI)		34.38 (17.92, 50.83)
P-value of Fisher's exact test		0.0090

FAS = full analysis set

a: Subjects with durable platelet response are defined as those who had at least 6 out of 8 weekly platelet responses (≥50 x 10^9/L) during last 8 weeks of treatment over 6-month treatment period in absence of rescue therapy.
b: 95% confidence interval (CI) is calculated based on normal approximation.
c: Missing values are considered as non-responders in the *P*-value calculation.
d: Difference of response rate = durable platelet response rate of avatrombopag - durable platelet response rate of placebo, 95% CI is calculated based on normal approximation.

Bleeding Events

Table 13 Summary of Bleeding Event during 6-month Treatment – Core Study, FAS of Core Study			
	Placebo (N=17)	Avatrombopag (N=32)	*P*-value[c]
Incidence of bleeding event during 6-month treatment[a], n (%)			
Yes	9 (52.9)	14 (43.8)	0.5394
No	8 (47.1)	18 (56.3)	
P-value of Chi-square test		0.5394	
Incidence of bleeding event during 6-month treatment by WHO bleeding scale, n (%)			
Grade 1	9 (52.9)	11 (34.4)	
Grade 2	0	2 (6.3)	
Grade 3	0	1 (3.1)	
Grade 4	0	0	

Percentages are based on the total number of subjects in relevant treatment group.

a: Subjects with multiple bleeding events are counted only once.
b: Subjects with multiple bleeding events are counted only once in the highest grade category.
c: *P*-value is calculated based on Chi-square test.

Table 43-1 TEAEs of Bleeding Event – Study 302

Event	**Core + Extension Phase Incidence N=45**	**Core Phase Incidence N=32**
Contusion	40.4%	31.3%
Gingival Bleeding	17%	12.5%
Epistaxis	17%	12.5%

Petechiae	14.9%	12.5%
Mouth Haemorrhage	8.5%	9.4%
Ecchymosis	4.3%	0%
Gastritis Haemorrhagic	2.1%	0%
Wound Haemorrhage	2.1%	3.1%
Haematuria	2.1%	3.1%
Uterine Haemorrhage	2.1%	3.1%
Haematoma	2.1%	3.1%

Adverse events of special interest in Study 302 included Grade 3 or 4 bleeding events and are summarised for the Core and Extension phases in Study 302 for treatment-emergent and treatment-related, treatment-emergent events, respectively. Three patients experienced Grade 3 or 4 bleeding events, with preferred terms of gingival bleeding, epistaxis, and gastritis haemorrhagic (Study 302). Only 1 patient experienced a treatment-related Grade 3 or 4 bleeding event, with a preferred term of epistaxis (Study 302 CSR). These incidence rates are similar, despite the much greater exposure to avatrombopag in the Extension phase, to the Core phase of the study in which one patient had a treatment-related Grade 3 or 4 TEAE bleeding event of epistaxis.

Rescue therapy use

Table 14 Summary of Rescue Therapy During 6-Month Treatment – Core Study, FAS of Core Study

	Placebo (N=19)		Avatrombopag (N=30)	
	n	Percentage (95% CI[a])	n	Percentage (95% CI[a])
Rescue therapy during 6-month treatment				
Yes	2	11.76 (0.00, 27.08)	7	21.88 (7.55, 36.20)
No	15	88.24	25	78.13
Difference of rate of rescue therapy (95% CI[b])				10.11 (-10.86, 31.08)
P-value of Fisher's exact test				0.4668

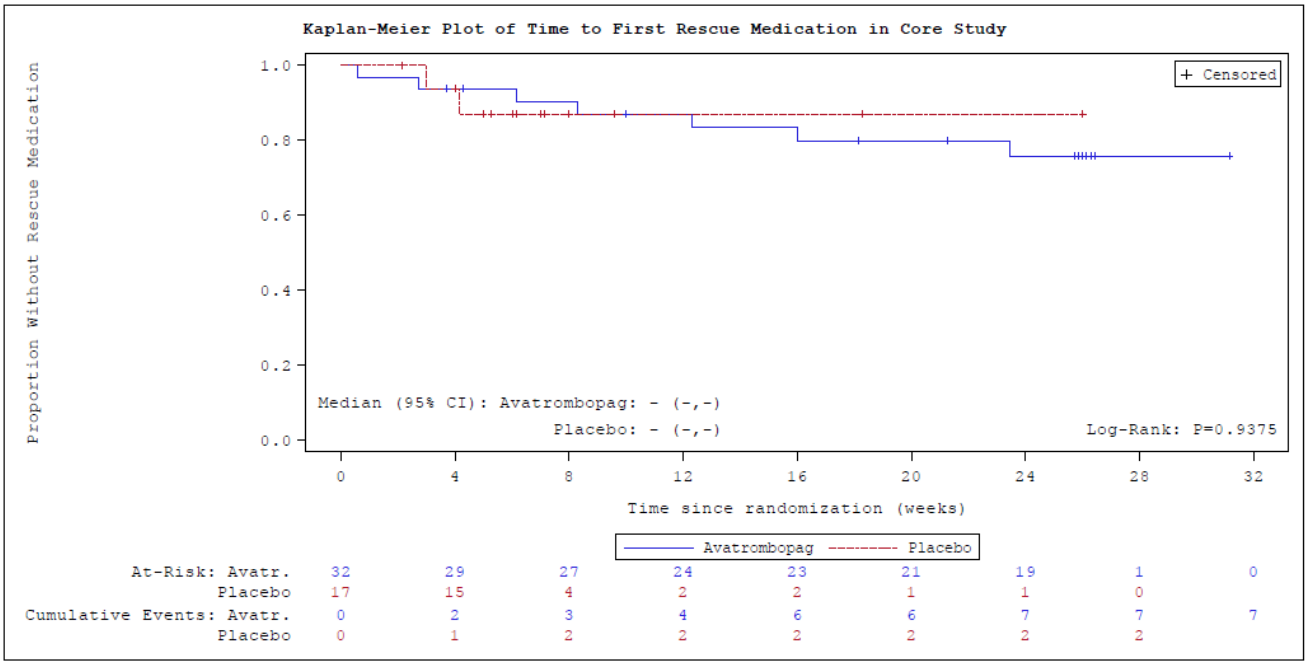
a: 95% confidence interval (CI) is calculated based on normal approximation.
b: Difference of rate of rescue therapy = durable platelet response rate of avatrombopag - durable response rate of placebo, 95% CI is calculated based on normal approximation.
Source: Table 14.2.3.10, Listing 16.2.6.1

Table 14.2.3.12 Summary of rescue therapy Full analysis set of Core study

Rescue Therapy	Placebo (N=17) n (%)	Avatrombopag (N=32) n (%)
Subjects who took at least one rescue therapy	2 (11.8)	7 (21.9)
DAPSONE	0	1 (3.1)
IMMUNOGLOBULIN HUMAN NORMAL	1 (5.9)	2 (6.3)
METHYLPREDNISOLONE	0	2 (6.3)
PREDNISOLONE	0	1 (3.1)
PREDNISONE	0	2 (6.3)
PLATELETS TRANSFUSION	1 (5.9)	1 (3.1)

Subjects with the same preferred term are counted only once for that preferred term.

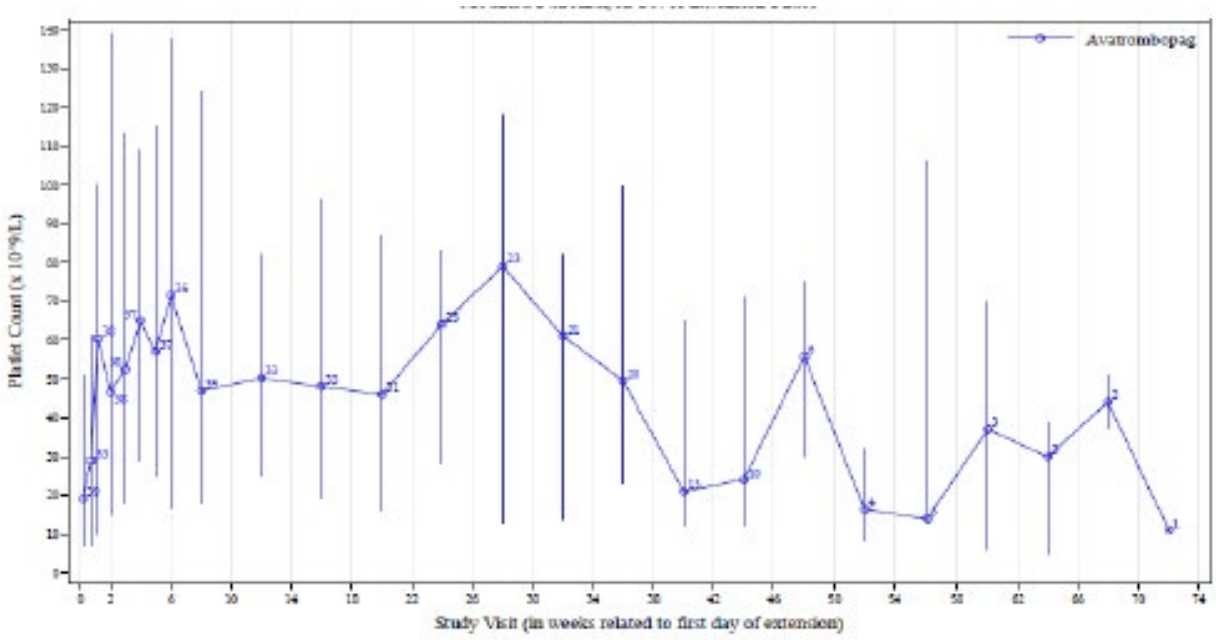
Figure 42-1 Kaplan-Meier Plot of Time to First Rescue Medication in the Core Phase of Study 302



Extension phase

Overall platelet response in the Core study was generally maintained throughout the extension up until around Week 36 (Figure 4). Beyond Week 38, platelet response was noted to be lower and considerably more variable, but these data are difficult to interpret due to the low number of subjects at these time points.

Figure 4 Median (Q1, Q3) Platelet count Over Time for Treatment Period of Extension Phase – mFAS of Extension Phase



mFAS = modified full analysis set

Please, note that the number platelets in this figure is given in intervals of 10.

Table 14.1.4.7 Concomitant ITP medication mFAS of extension phase

Anatomical Class/ Therapeutic Subgroup/ Pharmacological Subgroup/ WHO Drug Name (Preferred Term)	Avatrombopag (N=39) n (%)
Subjects who took at least one medication	14 (35.9)
ALIMENTARY TRACT AND METABOLISM	1 (2.6)
ANABOLIC AGENTS FOR SYSTEMIC USE	1 (2.6)
ANABOLIC STEROIDS	1 (2.6)
DANAZOL	1 (2.6)
ANTIINFECTIVES FOR SYSTEMIC USE	2 (5.1)
IMMUNE SERA AND IMMUNOGLOBULINS	2 (5.1)
IMMUNOGLOBULINS	2 (5.1)
IMMUNOGLOBULIN HUMAN NORMAL	2 (5.1)
BLOOD AND BLOOD FORMING ORGANS	1 (2.6)
ANTIHEMORRHAGICS	1 (2.6)
VITAMIN K AND OTHER HEMOSTATICS	1 (2.6)
ETAMSILATE	1 (2.6)
SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS	12 (30.8)
CORTICOSTEROIDS FOR SYSTEMIC USE	12 (30.8)
CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN	12 (30.8)
DEXAMETHASONE	1 (2.6)

Subjects with two or more medications within a class level and drug name are counted only once within that class level and drug name. Concomitant ITP medications during Extension Phase include ITP medications that started or had dose/frequency changed after the first day of Extension Phase and up to the last day of treatment period of Extension Phase.

Table 43-2 Grade 3 or 4 TEAE Bleeding Events in the Core and Extension Phase of Study 302 – TEAEs

Event	**Core + Extension Phase Incidence N=45**	**Core Phase Incidence N=32**

Gingival Bleeding	2.1%	0%
Epistaxis	2.1%	3.1%
Gastric Haemorrhagic	2.1%	0%

Source: Study 302 CSR Tables 14.3.8.4 and 14.3.8.1

With regards to the use of rescue treatment, Study 302 Table 14.1.4.7 provides a summary of the ITP medications used during the extension phase that were considered rescue therapies. A summary of ITP rescue medication use in the Extension phase compared to the Core phase alone is presented in Table 43-3. Of note, the analysis for Extension phase medications includes concomitant ITP medication use upon entry into the Extension phase and which were not necessarily used as a rescue treatment (e.g., corticosteroids). As a result, the use of corticosteroids as a rescue treatment in the Extension phase is likely overestimated.

Table 43-3 ITP Medications Considered Rescue Therapy in the Core and Extension Phase of Study 302 – TEAEs

Medication	**Extension Phase Incidence* N=39**	**Core Phase Incidence N=32**
Corticosteroids	30.8%	15.6%
IVIg	5.1%	6.3%
Danazol	2.6%	0%
Vitamin K	2.6%	0%
Dapsone	0%	3.1%

*Modified Full Analysis Set of Extension Phase (not Core + Extension)

Ancillary analyses

Mean daily dose in study 302

Eisai Protocol: E5501-G000-302 Page 1 of 1

Table 14.3.1.2
Mean Daily Dose
6-month Treatment Core Study
Safety Analysis Set of Core Study

Extent of Exposure	Placebo (N=17)	Avatrombopag (N=32)
Mean Daily Dose (mg)		
n	17	32
Mean (SD)	34.02 (7.466)	22.52 (11.013)
Median	33.33	19.40
Min, Max	21.3, 55.6	5.9, 37.6
Mean Daily Dose (mg), n (%)		
> 0 mg to <= 5 mg	0	0
> 5 mg to <= 10 mg	0	3 (9.4)
> 10 mg to <= 20 mg	0	14 (43.8)
> 20 mg to <= 30 mg	3 (17.6)	3 (9.4)
> 30 mg	14 (82.4)	12 (37.5)

Eisai Protocol: E5501-G000-302 Page 1 of 1

Table 14.3.1.4
Mean Daily Dose
Core Study
Safety Analysis Set of Core Study

Extent of Exposure	Placebo (N=17)	Avatrombopag (N=32)
Mean Daily Dose (mg)		
n	17	32
Mean (SD)	33.85 (7.410)	22.34 (10.904)
Median	33.33	19.34
Min, Max	21.3, 55.6	5.9, 37.6
Mean Daily Dose (mg), n (%)		
> 0 mg to <= 5 mg	0	0
> 5 mg to <= 10 mg	0	3 (9.4)
> 10 mg to <= 20 mg	0	14 (43.8)
> 20 mg to <= 30 mg	3 (17.6)	4 (12.5)
> 30 mg	14 (82.4)	11 (34.4)

Eisai Protocol: E5501-G000-302 Page 1 of 1

Table 14.3.1.6
Mean Daily Dose
Core Study and Extension Phase
Safety Analysis Set of Extension Phase

Extent of Exposure	Avatrombopag (N=47)
Mean Daily Dose (mg)	
n	44
Mean (SD)	24.46 (10.581)
Median	25.83
Min, Max	5.5, 38.8
Mean Daily Dose (mg), n (%)	
> 0 mg to <= 5 mg	0
> 5 mg to <= 10 mg	3 (6.4)
> 10 mg to <= 20 mg	15 (31.9)
> 20 mg to <= 30 mg	9 (19.1)
> 30 mg	17 (36.2)

The median dose in the core study was 19.4mg. The median dose in the extension phase was 25.83mg.

Summary of main study

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

Table 1. Summary of efficacy for trial E5501-G000-302

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Trial with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Oral E5501 Plus Standard Care for the Treatment of Thrombocytopenia in Adults with Chronic Immune Thrombocytopenia (Idiopathic Thrombocytopenic Purpura)	
Study identifier	E5501-G000-302, EudraCT No: 2011-000830-12, IND No: 62,122

Design	A multicenter, multinational, randomized, double-blind, placebo-controlled, parallel group study of avatrombopag in male and female subjects ≥18 years of age with chronic ITP. The study consisted of 3 phases: Pre-randomization, Randomization (Core Study), and Extension. A placebo-controlled design was selected as the design of choice in order to obtain the best possible evidence on the potential efficacy and safety of avatrombopag. The study design allowed for the use of avatrombopag or placebo over and above existing standard of care for chronic ITP and rescue therapy in order to enable the use of placebo in the study design. The primary objective was to demonstrate that the efficacy of avatrombopag (in addition to standard of care) is superior to placebo (in addition to standard of care) for the treatment of chronic ITP as measured by cumulative number of weeks of platelet response over 6 months of once daily treatment in adult subjects who had received at least 1 prior ITP therapy.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		26 weeks not applicable 104 weeks
Hypothesis	Superiority to placebo (in addition to standard of care)		
Treatments groups	Avatrombopag		Avatrombopag. 6 months, n=32, randomized
	Placebo		Placebo 6 months, n=19, randomized
Endpoints and definitions	Primary endpoint	Cumulative Number of Weeks with Platelet Count ≥50 x 10^9/L	The cumulative number of weeks of platelet response was defined as the cumulative number of weeks in which the platelet count is ≥50 x 10^9/L during 6-month treatment (i.e., at Visit 3 to 22 inclusive) of Core Study in the absence of rescue therapy.
	Secondary Endpoint	Platelet response rate at Day 8	The first key secondary efficacy endpoint, platelet response rate at Day 8, was defined as the proportion of subjects with a platelet count ≥50 x 10^9/L at Day 8. Subjects with missing platelet count at Day 8 or use of a rescue therapy on or before Day 8 were considered as platelet non-responders at Day 8.
	Secondary endpoint	Proportion of subjects with a reduction in use of concomitant ITP medications from baseline.	The second key secondary efficacy endpoint was the proportion of subjects with a reduction in use of concomitant ITP medications from baseline. Only subjects with use of concomitant ITP medications at baseline were included in the analysis. Subjects with use of rescue therapy during the 6-month treatment period were counted as a failure.
	Exploratory endpoint	Durable platelet response	Durable platelet response, defined as the proportion of subjects who had at least 6 out of 8 weekly platelet responses during the last 8 weeks of treatment over the 6-month treatment period of the Core Study in the absence of rescue therapy

	Exploratory endpoint	World Health Organization (WHO) Bleeding Scale	Incidence and severity of bleeding events associated with cITP, including bleeding, bruising, and petechiae, measured using the WHO Bleeding Scale.
	Exploratory endpoint	Summary of Rescue Therapy Use	Proportion of subjects receiving rescue therapy during the 6-month treatment duration of the study
Database lock	10 March 2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Cumulative number of weeks with platelet count ≥50 x 10^9/L during the 6-month treatment period		
Descriptive statistics and estimate variability	Treatment group	Placebo	Avatrombopag
	Number of subjects	17	32
	Cumulative number of weeks of platelet response		
	Mean (SD)	0.1 (0.49)	12.0 (8.75)
	Median	0.0	12.4
	Min, Max	0, 2	0, 25
	P-value of Wilcoxon rank sum test		<0.0001
Analysis description	**Secondary Efficacy Endpoint**		
Analysis population and time point description	Summary of two Key Secondary Efficacy Endpoints – Platelet count at Day 8 and Reduction in use of concomitant ITP medications from baseline – FAS of Core Study		
Descriptive statistics		Placebo	Avatrombopag
		n, percentage (95% CI)	n, percentage (95% CI)
	Platelet count ≥50 x 10^9/L at Day 8		
	n[a]	17	32
	Yes	0, 0.00 (-,-)	21, 65.63 (49.17, 82.08)
	No	17, 100.00	11, 34.38

	Missing[b]	0	0
	Difference of response rate (95% CI)[c]		65.63 (49.17, 82.08)
	P-value of Fischer's exact test		<0.0001
	Reduction in use of concomitant ITP medications from baseline		
	N[d]	7	15
	Yes	0, 0.00 (-,-)	5, 33.3 (9.48, 57.19)
	No	7, 100.00	10, 66.67
	Difference of rate of reduction (95%CI)[e]		33.33 (9.48, 57.19)
	P-value of Fischer's exact test		0.1348

FAS = full analysis set, CI = confidence interval
a: Subjects with platelet response at day 8 are defined as those who had a platelet count ≥50 x 10^9/L at day 8 in the absence of rescue therapy on or before Day 8.
b: Missing values are considered as nonresponse in the P-value calculation.
c: Difference of response rate = platelet response rate at Day 8 of avatrombopag - platelet response rate at Day 8 of placebo, 95% confidence interval (CI) is calculated based on normal approximation.
d: Only subjects with use of concomitant ITP medications at baseline were included in the analysis; this number is used to calculate percentages.
e: Difference of rate of reduction = rate of reduction of in use of concomitant ITP medications from baseline of avatrombopag - rate of reduction of in use of concomitant ITP medications from baseline of placebo, 95% confidence interval (CI) is calculated based on normal approximation.

Analysis description	**Exploratory Efficacy Endpoint**		
Analysis population and time point description	Durable platelet response is defined as the proportion of subjects who had at least 6 out of 8 weekly platelet responses during the last 8 weeks of treatment over the 6-month treatment period of the Core Study in the absence of rescue therapy **Summary of Durable Platelet Response – FAS of Core Study**		
Descriptive statistics		Placebo (N = 17)	Avatrombopag (N = 32)
		n percentage (95%CI)	n percentage (95%CI)
	Durable platelet response		
	Yes	0 0.00 (-,-)	11 34.38 (17.92, 50.83)
	No	2 11.76	14 43.75

	Missing	15 88.24	7 21.88
	Difference of response rate (95% CI)		34.38 (17.92, 50.83)
	P-value of Fischer's exact test		0.0090

FAS = full analysis set
a: Subjects with durable platelet response are defined as those who had at least 6 out of 8 weekly platelet responses (≥50 x 10^9/L) during last 8 weeks of treatment over 6-month treatment period in absence of rescue therapy.
b: 95% confidence interval (CI) is calculated based on normal approximation.
c: Missing values are considered as non-responders in the *P*-value calculation.
d: Difference of response rate = durable platelet response rate of avatrombopag - durable platelet response rate of placebo, 95% CI is calculated based on normal approximation.

Analysis description	**Exploratory Efficacy Endpoint**			
Analysis population and time point description	**Summary of Bleeding Event during 6-month Treatment – Core Study, FAS of Core Study**			
		Placebo (N=17)	Avatrombopag (N=32)	*P*- value[c]
	Incidence of bleeding event during 6-month treatment[a], n (%)			
	Yes	9 (52.9)	14 (43.8)	0.5394
	No	8 (47.1)	18 (56.3)	
	P-value of Chi-square test		0.5394	
	Incidence of bleeding event during 6-month treatment by WHO bleeding scale, n (%)			
	Grade 1	9 (52.9)	11 (34.4)	
	Grade 2	0	2 (6.3)	
	Grade 3	0	1 (3.1)	
	Grade 4	0	0	

Percentages are based on the total number of subjects in relevant treatment group.
a: Subjects with multiple bleeding events are counted only once.
b: Subjects with multiple bleeding events are counted only once in the highest grade category.
c: *P*-value is calculated based on Chi-square test.

Analysis description	**Exploratory Efficacy Endpoint**				
Analysis population and time point description	**Summary of Rescue Therapy During 6-Month – Core Study, FAS of Core Study**				
		Placebo (N=19)		Avatrombopag (N=30)	
		N	Percentage (95% CI[a])	n	Percentage (95% CI[a])
	Rescue therapy during 6-month Treatment				
	Yes	2	11.76 (0.00, 27.08)	7	21.88 (7.55, 36.20)
	No	15	88.24	25	78.13
	Difference of rate of rescue therapy (95%CI[b])				10.11 (-10.86, 31.08)
	P-value of Fischer's exact test				0.4668

a: 95% confidence interval (CI) is calculated based on normal approximation.
b: Difference of rate of rescue therapy = durable platelet response rate of avatrombopag - durable response rate of placebo, 95% CI is calculated based on normal approximation.

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

Literature review

A comprehensive search was conducted to identify scientific literature published between January 2000 and October 2019 providing data on the efficacy of TPO receptor agonists in adult patients with ITP. In addition, reference lists of review articles were evaluated to identify other articles for inclusion in this summary. Finally, the Summaries of Product Characteristics (SmPC) for Revolade (eltrombopag, May 2019) and Nplate (romiplostim, July 2019) were reviewed.

A comparison of Study 302 efficacy results to efficacy endpoints (primary or secondary) reported in the current SmPCs for eltrombopag and romiplostim is presented, recognizing the limitations of such historical comparisons. A review of efficacy results from published randomised controlled studies are then presented for eltrombopag and romiplostim. Only publications of studies which allowed for dose titration (n=7) were included in this summary; fixed-dose randomised controlled studies were excluded (n=2). No data pooling or meta-analysis of the data from the included clinical studies is contained in this literature review.

Three predefined endpoints in the avatrombopag Phase 3 Study 302 have corresponding data presented in the labeling for eltrombopag and romiplostim that provide a benchmark for comparison. The Revolade SmPC contains data from a 26-week placebo-controlled study (RAISE) and the Nplate SmPC contains data from two 24-week placebo-controlled studies (Studies 1 and 2), all of which had similar eligibility criteria and durations of treatment to the avatrombopag Study 302.

Table 3 Comparison of Cumulative Number of Weeks with a Platelet Count $\geq 50\times10^9$/L with Avatrombopag (Study 302) to the TPO Receptor Agonist SmPCs

		SmPC*	
	Avatrombopag Study 302	Eltrombopag (RAISE)	Romiplostim (Studies 1&2)
Study Duration, weeks	26	26	24
TPO-RA			
n	32	135	83
Mean Weeks $\geq 50\times10^9$/L, mean (SD)	12.0 (8.75)	11.3 (9.46)	14 (7.8)
Placebo			
n	17	62	42
Mean Weeks $\geq 50\times10^9$/L, mean (SD)	0.1 (0.49)	2.4 (5.95)	1 (2.5)
Treatment Difference			
Mean Weeks $\geq 50\times10^9$/L, mean (SD)	11.9	8.9	13

*Source: Revolade SmPC (May 2019), Nplate SmPC (July 2019).

Table 4 Comparison of the Durable Platelet Response with Avatrombopag (Study 302) to the TPO Receptor Agonist USPI or SmPCs

		USPI/SmPC	
	Avatrombopag Study 302	Eltrombopag (RAISE)	Romiplostim (Studies 1&2)
Study Duration, weeks	26	26	24
TPO-RA			
n	32	95 (of 135) *	83
Durable Platelet Response, n (%)	11 (34)	57 (60)	41 (50)
Placebo			
n	17	39 (of 62) *	42
Durable Platelet Response, n (%)	0 (0)	4 (10)	1 (2)
Treatment Difference			
Durable Platelet Response, %	34	50	48

*Durable Platelet Response percentages for RAISE calculated using 95 eltrombopag-recipients who completed the study, rather than the ITT population of 135 eltrombopag-recipients

Source: PROMACTA® (eltrombopag) USPI (Nov 2018), Nplate SmPC (July 2019).

Table 5 Comparison of Rescue Therapy Use with Avatrombopag (Study 302) to the TPO Receptor Agonist SmPCs

		SmPC*	
	Avatrombopag Study 302	Eltrombopag (RAISE)	Romiplostim (Studies 1&2)
Study Duration, weeks	26	26	24
TPO-RA			
n	32	135	83
Rescue Therapy Use, % (n/N)	21.9% (7/32)	18% (24/135)	23% (19/83)
Placebo			
n	17	62	42
Rescue Therapy Use, % (n/N)	11.8% (2/17)	40% (25/62)	60% (25/42)

*Source: Revolade SmPC (May 2019), Nplate SmPC (July 2019).

Clinical Trial Simulations of Avatrombopag for a Non-Inferiority Comparison

The objective of this simulation study was to evaluate the efficacy of avatrombopag (test) compared to eltrombopag (control) as measured by the durable response rate.

Methods: The published eltrombopag population PK (Gibiansky, Zhang et al. 2011) and population PK/PD models (Hayes, Ouellet et al. 2011) were used to simulate eltrombopag concentration-time and platelet-time profiles, respectively.

The population PK and PK/PD models for avatrombopag (AVA-PKPD-ITP-002) were used to simulate avatrombopag concentration-time and platelet-time profiles.

In the population PK model for eltrombopag (Gibiansky, Zhang et al. 2011), body weight, dose<20 mg, healthy subjects vs ITP patients, East Asians (such as Chinese, Japanese, or Korean) vs non-East Asians, sex, and concomitant corticosteroids were significant covariates. In the population PK/PD model for eltrombopag (Hayes, Ouellet et al. 2011), sex and age were significant covariates.

In the population PK model for avatrombopag (AVA-PKPD-ITP-002), body weight, healthy subjects vs ITP patients, formulation, and concomitant administration of CYP2C9 and CYP3A4 inhibitors or inducers were significant covariates. In the population PK/PD model for avatrombopag, baseline platelet count was the only significant covariate.

Both models were built using data collected from similar populations of patients with ITP.

The primary endpoint was the durable platelet response rate, which was defined as the proportion of patients who had at least 75% (e.g., 6 out of 8 weekly monitoring) platelet responses $\geq 50 \times 10^9$/L during the last 8 weeks of the 26-week treatment period in the absence of rescue therapy.

The primary analysis was pre-specified in the simulation plan.

A total of 1000 simulated clinical trial datasets were generated. Each dataset was created by randomly sampling (with replacement) N=143 avatrombopag patients and N=143 eltrombopag patients from the 10,000 simulated patients in each treatment group. The sample size for each treatment group (N=143) was the same as that planned for Study E5501-G000-305 (Eisai Inc. 2013). Each patient was identified as either having or not having a durable platelet response. The null hypothesis was that avatrombopag was not as effective as eltrombopag. The alternative hypothesis was that avatrombopag was at least as effective as eltrombopag. Non-inferiority would be demonstrated if the upper bound of the 2-sided 95% confidence interval (based on normal approximation) for the difference in the durable platelet response rate between eltrombopag and avatrombopag (control – test) was below 15%, the pre-specified non-inferiority margin in the Statistical Analysis Plan for the E5501-G000-305 Study (Eisai Inc. 2013). Conversely, noninferiority would be demonstrated if the lower bound of the 2-sided 95% confidence interval for the difference in the durable platelet response rate between avatrombopag and eltrombopag (test – control) was above -15%.

The choice of the non-inferiority margin of 15% was based on a combination of statistical reasoning and clinical judgment. For the active comparator, eltrombopag, the Historical Evidence of Sensitivity to Drug Effect (ICH E-10) was established in the RAISE study of 197 subjects (Cheng 2011). The RAISE study was a well-designed, placebo-controlled pivotal study evaluating the efficacy of eltrombopag in patients with chronic ITP during 6-months of treatment compared with placebo. The study found that the durable platelet response (defined as ≥75% of platelet assessments $\geq 50 \times 10^9$/L during the last 8 weeks of treatment over the 6-month treatment period in the absence of rescue therapies) was 42% (57 out of 135 patients) and 7% (4 out of 62 patients) for eltrombopag and placebo, respectively. Further analysis of these study results gave rise to an estimate of the effect size of eltrombopag relative to placebo in terms of durable response rate being 35.8% with a 95% CI of (25.4%, 46.1%). Therefore, a conservative estimate of eltrombopag effect size relative to placebo (M1) was chosen to be 25.4%.

The planned trial non-inferiority margin (M2) should be a fraction of M1 (i.e., <M1) and was chosen by clinical judgment. Avatrombopag has certain potential advantages over eltrombopag including an improved safety profile (e.g., no severe liver toxicity), a quicker onset of platelet response, decreased PK variability when taken with food and therefore allows for convenient administration with food. Avatrombopag has a more predictable PK for liver dysfunction subjects, and no PK race effect. Given

that ITP is an orphan disease, the retention of 41% of the comparator effect size as a choice of non-inferiority margin M2 (delta=15%) was judged to be clinically acceptable.

Results:

- For avatrombopag, 79.4% of the simulated ITP patients were predicted to have a durable platelet response rate, defined as the proportion of patients who had at least 75% platelet responses $\geq 50\times10^9$/L during the last 8 weeks of treatment over the 26-week treatment period in the absence of rescue therapy. For eltrombopag, 52.5% and 64.7% of the simulated ITP patients were predicted to have a durable platelet response rate for the primary analysis (all patients, including 18.9% of patients who had a zero PD slope factor and thus not responding to eltrombopag treatment) and sensitivity analysis (excluding the patients with a zero PD slope factor), respectively.
- For avatrombopag, the median platelet count was $\geq 76\times10^9$/L as early as Week 3 and sustained through Week 26. For eltrombopag, the median platelet count was 55×10^9/L as early as Week 4 and sustained through Week 26 for the primary analysis (all patients, including 18.9% of patients who had a zero PD slope factor and thus not responding to eltrombopag treatment) and 67×10^9/L as early as Week 3 and sustained through Week 26 for the sensitivity analysis (excluding the patients with a zero PD slope factor), respectively.
- The results of the simulated non-inferiority study demonstrate that avatrombopag is non-inferior to eltrombopag.

Network Meta-analysis

An independent network meta-analysis was conducted by Dr. Haitao Chu, MD, PhD (University of Minnesota) to compare the efficacy of avatrombopag to that of eltrombopag in the treatment of chronic immune thrombocytopenia (ITP).

The MAH conducted studies for direct comparison between pre-defined endpoints across studies in comparable patient populations. The aim was to compare the efficacy of avatrombopag to that of eltrombopag. Efficacy data from the 4 avatrombopag ITP studies presented in this type II variation were compared with data from eltrombopag publications and the European Public Assessment Report (EPAR) (EMA/CHMP/279276/2010) for Revolade (eltrombopag, April 2010), using an arm-based network meta-analysis. The methodology for the literature search, study selection criteria, and the meta-analysis are fully described, along with patient population characteristics of each included study, in the Meta-analysis Report.

A total of 6 studies evaluating eltrombopag in adult patients with ITP were included and compared to the 4 avatrombopag studies, assessing 6 outcome measures directly related to platelet count criteria. The Cumulative Weeks of Response (achievement of a platelet count $\geq 50\times10^9$/L) was the primary efficacy endpoint for Study 302, which provides the Pivotal Efficacy Data for this application. The cumulative weeks of response was reported in 5 studies in this meta-analysis. Due to the wide range of observed standard deviations (0.49 – 9.5 weeks) and a wide range of the average duration of exposures (4.1 - 24 weeks) across the 5 studies, the analysis was performed based on 3 statistical models: 1) using the raw data but assuming a truncated normal prior distribution to incorporate the fact that cumulative weeks of response is non-negative; 2) using standardised data, in which cumulative weeks of response is standardised by the average duration of exposure to treatment, with a truncated normal prior distribution; 3) using log transformed data, which assumes that the random variable of cumulative weeks of response is normal on a log-scale.

As examples of these cross-studies between results obtained with avatrombopag and eltrombopag, Figure 2.5-11 presents the overall estimated cumulative weeks of response for eltrombopag,

avatrombopag, and placebo under 3 different models. The treatment differences in the five studies which reported this outcome are presented as a forest plot in Figure 2.5-12.

Figure 2.5-11. Posterior estimates for the cumulative weeks of response

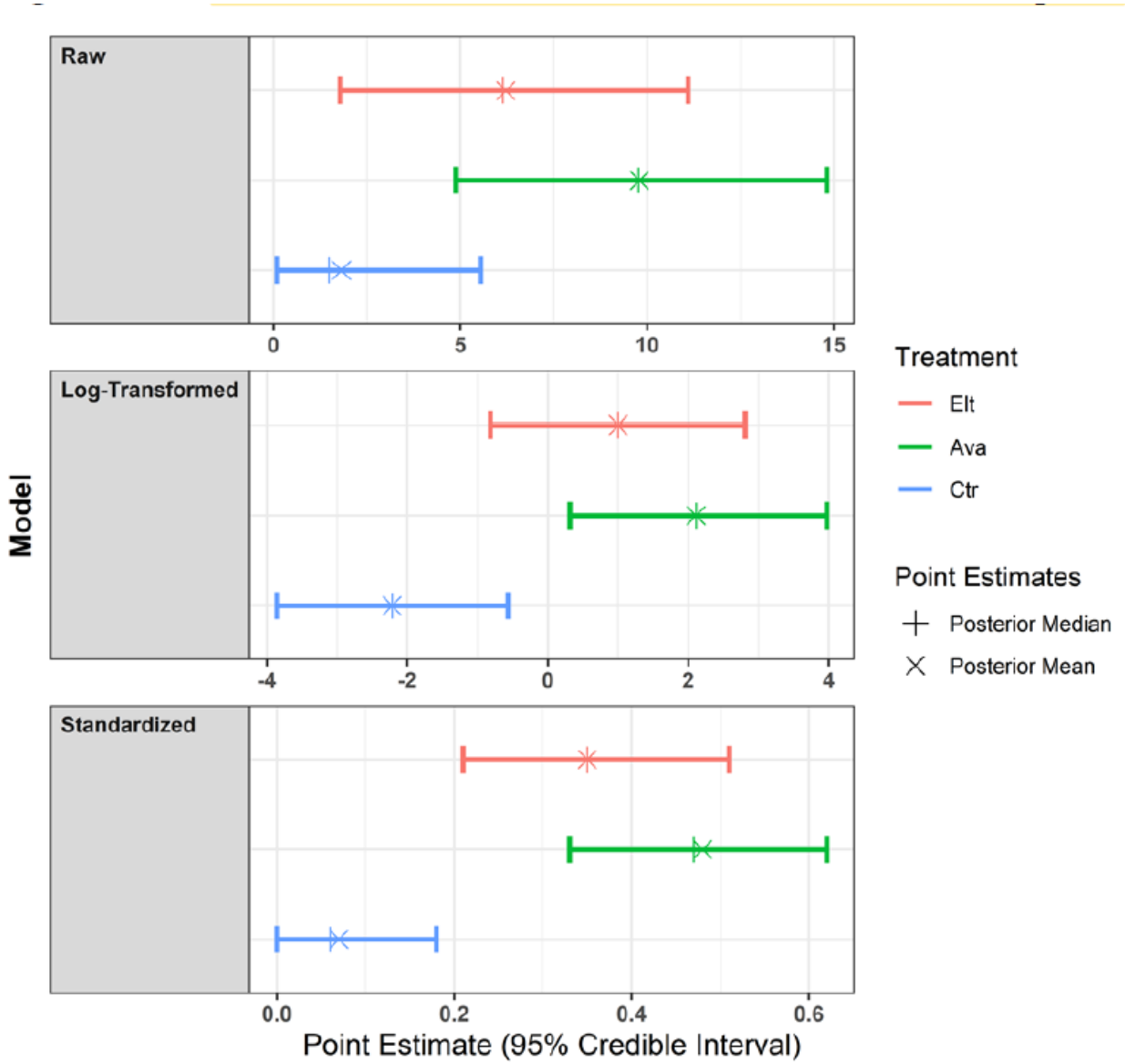


Figure 2.5-12. Forest Plot of cumulative cumulative weeks of response (original scale)

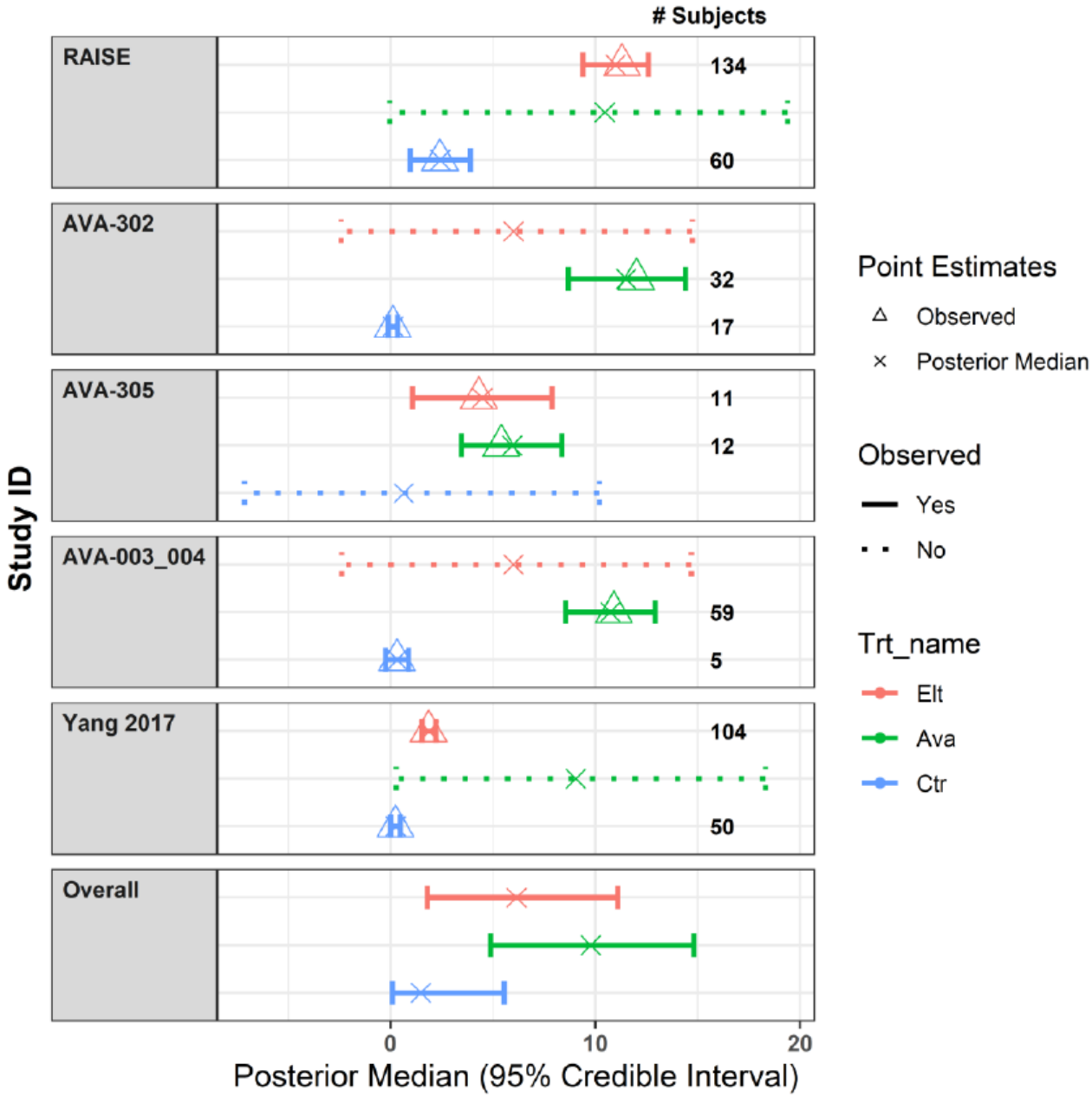
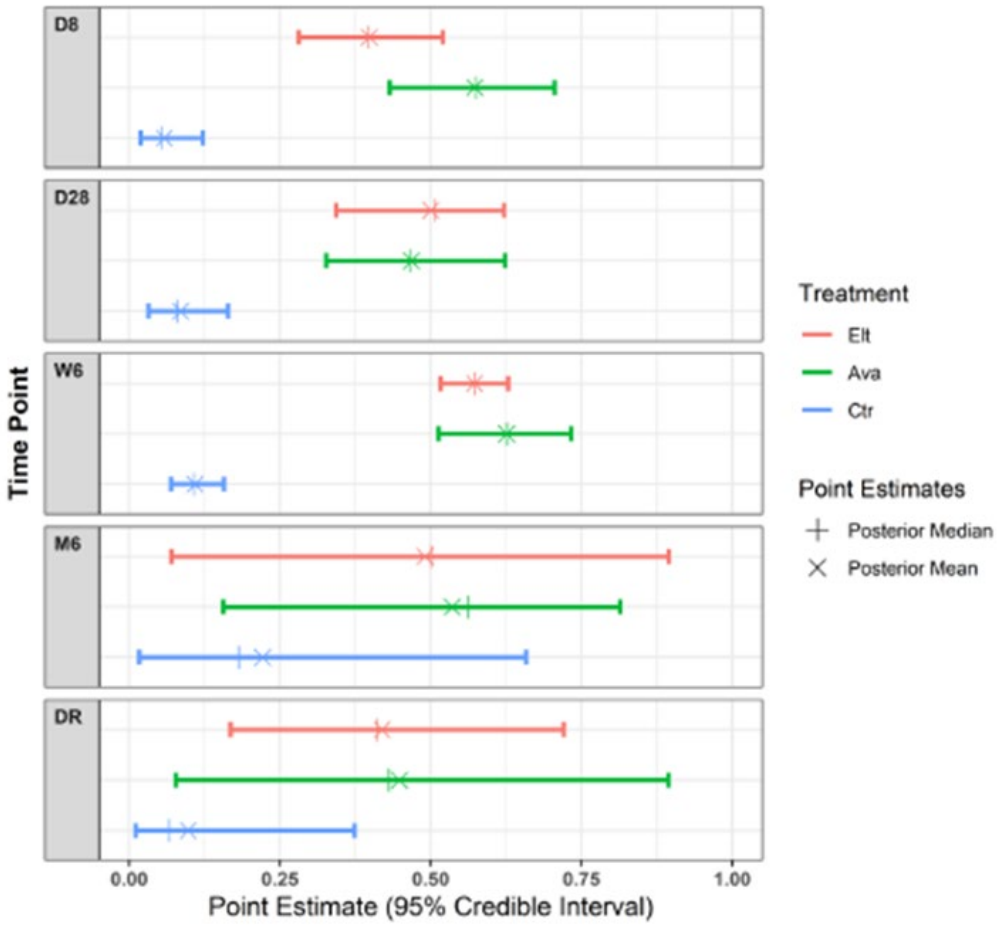


Figure 4. The posterior estimates for response rates at Day 8, Day 28, Week 6, Month 6, and durable response



Ref: RAISE Cheng et al. Lancet 2011; Yang et al. (Both studies on eltrombopag).

Table 6. Summary of estimated response rates at Day 8, Day 28, Week 6, Month 6, and durable response

Time	Treatment	Posterior Median	95% LCI	95% UCI	Posterior Mean	SD
Day 8	Elt	0.397	0.281	0.520	0.398	0.059
Day 8	Ava	0.574	0.431	0.705	0.573	0.069
Day 8	Ctr	0.053	0.019	0.122	0.058	0.028
Day 28	Elt	0.505	0.343	0.621	0.500	0.067
Day 28	Ava	0.466	0.326	0.623	0.468	0.074
Day 28	Ctr	0.080	0.032	0.164	0.085	0.035
Week 6	Elt	0.572	0.516	0.628	0.572	0.029
Week 6	Ava	0.626	0.513	0.733	0.625	0.056
Week 6	Ctr	0.107	0.069	0.157	0.109	0.022
Month 6	Elt	0.501	0.069	0.894	0.490	0.202
Month 6	Ava	0.562	0.156	0.814	0.535	0.166
Month 6	Ctr	0.182	0.017	0.657	0.221	0.160
DR	Elt	0.411	0.167	0.720	0.419	0.138
DR	Ava	0.430	0.077	0.893	0.448	0.215
DR	Ctr	0.066	0.010	0.373	0.097	0.095

Elt = Eltrombopag; Ava = Avatrombopag; Ctr = Placebo; DR = Durable Response; SD = standard deviation; LCI = lower credible interval; UCI = upper credible interval

Clinical studies in special populations

Subgroup analysis according to stratification factors were performed in the pivotal Study 302, but no other specific studies in ITP populations have been presented. Studies specifically in a paediatric population have not been included in the application, but are in preparation (EMA PIP November 2019).

Additional Supportive Efficacy Data are available from clinical studies of avatrombopag for the treatment of thrombocytopenia associated with chronic liver disease (CLD). Given that the mechanism of action of avatrombopag as a TPO receptor agonist results in the increased production of platelets in patients with thrombocytopenia, regardless of the causal disease state or endogenous TPO levels, efficacy results in patients with CLD further support this application for the use of avatrombopag in the treatment of patients with chronic ITP. Support for the approval of avatrombopag for the treatment of thrombocytopenia in patients with CLD came from data from 2 identically designed, global, randomized, double-blind, placebo-controlled pivotal Phase 3 studies (Study 310, N randomized=231, avatrombopag-FAS=149, and Study 311, N randomized=204, avatrombopag-FAS=128).

In these studies, avatrombopag reproducibly met all primary (the proportion of subjects who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following a scheduled procedure) and secondary (the proportion of subjects who achieved platelet counts of at least 50×10^9/L on Procedure Day [Day 10 to Day 13], and the change from Baseline in platelet count on Procedure Day) study endpoints, and resulted in measured increases in platelet counts that were both clinically meaningful and statistically significant.

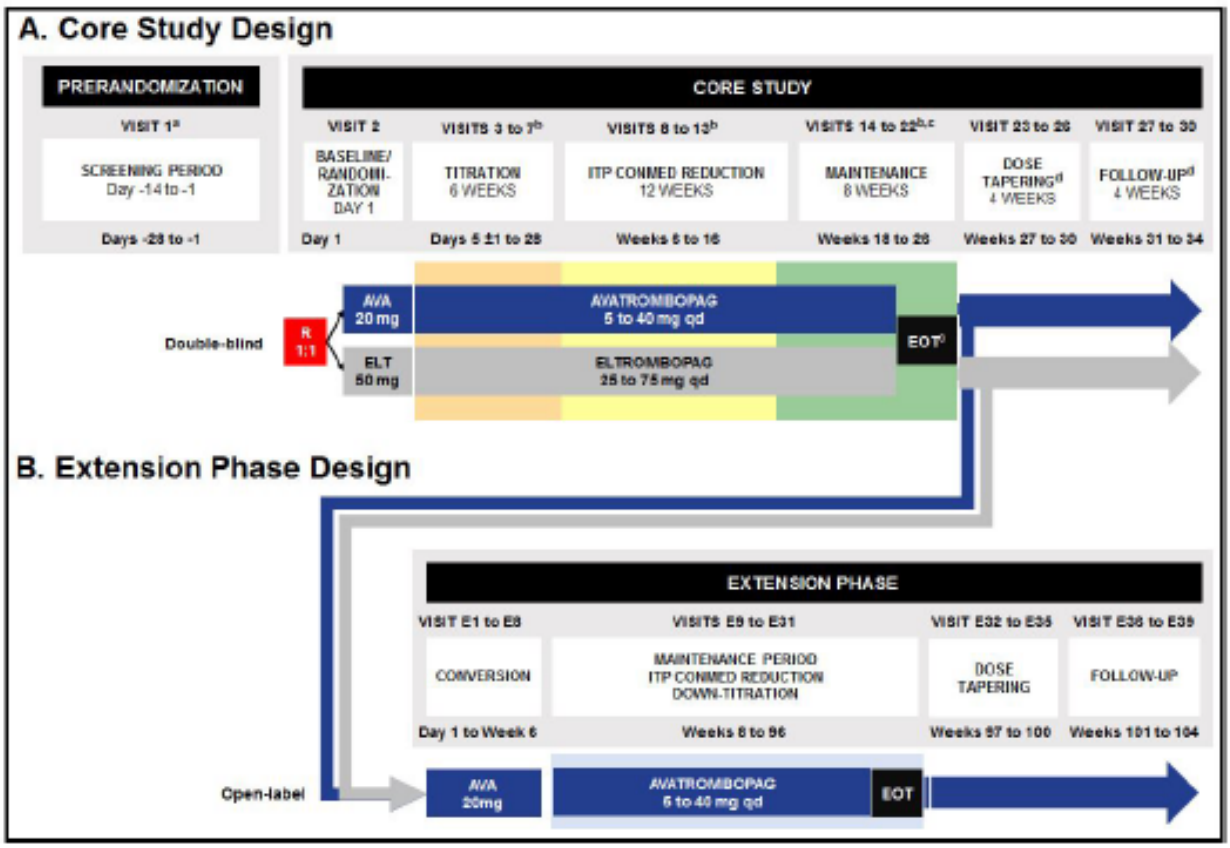
Supportive study(ies)

ITP Study 305

A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel-Group Trial with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Oral E5501 versus Eltrombopag, in Adults with Chronic Immune Thrombocytopenia (Idiopathic Thrombocytopenic Purpura).

The Study was initiated in February 2012 and terminated in April 2015. This study was terminated early by the Sponsor due to significant enrolment challenges.

Figure 2.7.3-5 Study Design (Study 305)



AVA = avatrombopag, CONMED = concomitant medication, E = Extension, ELT = eltrombopag, EOT = end of treatment, ITP = immune thrombocytopenia, qd = once daily, R = randomized.

a The Screening Visit and Day 1 Baseline/Randomization Visit platelet counts were averaged to obtain the Baseline platelet count value. The two samples were obtained ≥48 hours and ≤2 weeks apart and the results were available prior to randomization. Therefore, an additional screening platelet count may have been required due to issues with scheduling.

b Patients who discontinued early who met the criteria for a lack of treatment effect may have moved directly into the Open-label Extension Phase.

c At EOT Visit (Visit 22), patients could enter the Extension Phase and receive open-label avatrombopag therapy. Patients who did not continue into the Extension Phase entered the Dose-tapering and Follow-up Phase.

d Only for patients who did not enter the Extension Phase.

Source: Study 305 CSR

The **target population** for this study was adults with chronic ITP (ie, ≥1 year) who had received at least 1 prior ITP therapy, and who had a platelet count less than 30×10^9/L. The rationale for this target population was based on an unmet medical need in these patients

Treatment: Avatrombopag tablets were administered orally as 5-, 10-, 20-, 30-, or 40-mg doses and eltrombopag tablets were administered orally as 25-, 50-, or 75-mg doses, both in a flexible dose design. This study used the 2G commercial tablet formulation of avatrombopag and a 20 mg daily oral starting dose with dose titration (5 to 40 mg), and with identical stratification as in Study 302.

Objectives

Core Study

Primary Objective

Comparison of the efficacy of avatrombopag (in addition to standard of care) to eltrombopag (in addition to standard of care) for the treatment of adult subjects with chronic immune thrombocytopenia (idiopathic thrombocytopenic purpura [ITP]) as measured by durable platelet response

Secondary Objectives

• To demonstrate that the efficacy of avatrombopag (in addition to standard of care) was superior to the efficacy of eltrombopag (in addition to standard of care) as measured by platelet response rate at Day 8

• To evaluate the safety of avatrombopag compared with eltrombopag

Additional Objectives

• To evaluate the efficacy of avatrombopag (in addition to standard of care) compared with the efficacy of eltrombopag (in addition to standard of care) with regard to alternate durable response, bleeding minimization, use of rescue therapy, and reduction in concomitant ITP medication use

• To evaluate the population pharmacokinetics (PK)/pharmacodynamics (PD) of plasma avatrombopag exposure and effect on platelet counts

Extension Phase

Primary Objective

• To evaluate the safety and tolerability of long-term therapy with avatrombopag in subjects with chronic ITP

Secondary Objectives

• To demonstrate the effectiveness of long-term therapy with avatrombopag as measured by platelet response, bleeding, and the use of rescue therapy

• To assess the reduction in use of steroids and concomitant ITP medication in subjects receiving avatrombopag.

Statistical Methods

This study was terminated on 22 Jan 2013 with 24 subjects randomized and 23 subjects treated. Due to termination of the study, the statistical analysis plan (SAP) was revised to focus on the safety results with limited summaries provided for efficacy.

Efficacy

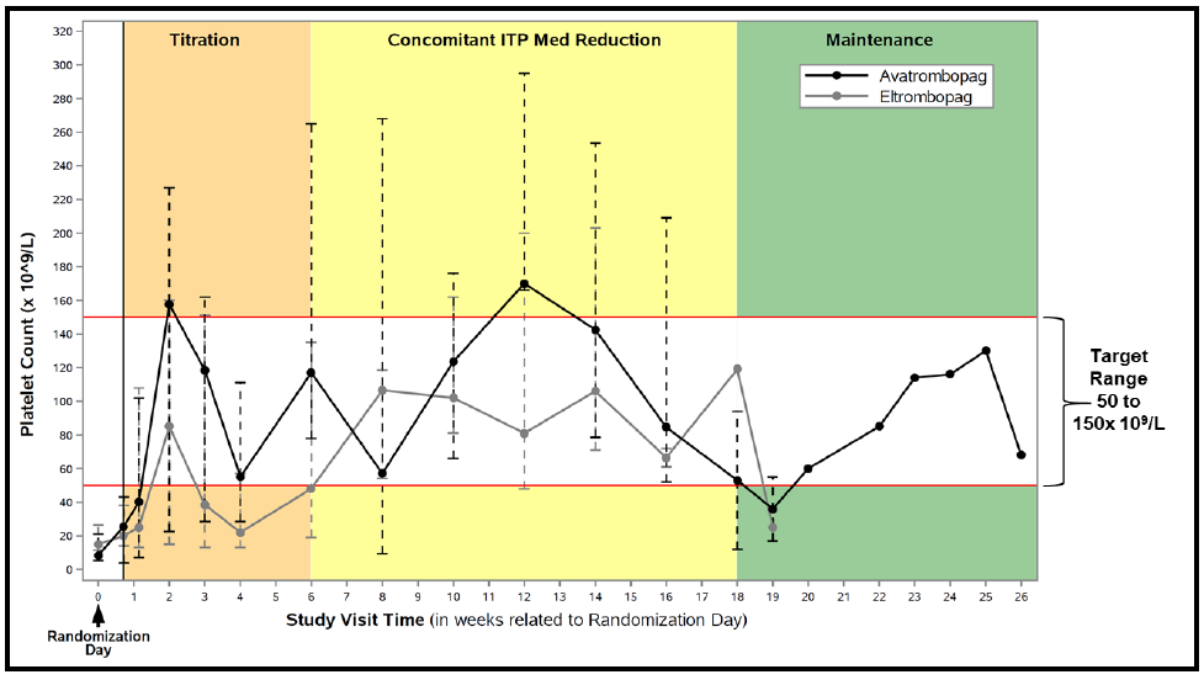
The Full Analysis Set (definition omitted) was used as the population for all efficacy data summaries for Core Study, and mFAS was used as the population for all efficacy data summaries for Extension Phase. For the Core Study, platelet count data was summarized by visit and treatment group for FAS using descriptive statistics (mean, SD, median, minimum, and maximum). For the Extension Phase, platelet count data was summarized for avatrombopag by visit for mFAS using descriptive statistics (mean, SD, median, minimum, and maximum).

In addition, platelet count was categorized and the number and percentage of subjects in each category was summarized by visit and treatment group for FAS for the Core Study and for avatrombopag by visit for mFAS for the Extension Phase.

For the Core Study, the number and percentage of subjects with bleeding events associated with chronic ITP (including bruising and petechiae) after randomization was summarized by treatment group and by highest WHO bleeding grade for FAS. For the Extension Phase, the number and percentage of subjects with bleeding events associated with chronic ITP (including bruising and petechiae) after the enrollment into Extension Phase was summarized for avatrombopag by highest WHO bleeding grade for mFAS.

Results

Figure 2.5-6 Median Local Platelet Counts Over Time, 6-Month Treatment Period of Core Study: Full Analysis Set (Study 305)



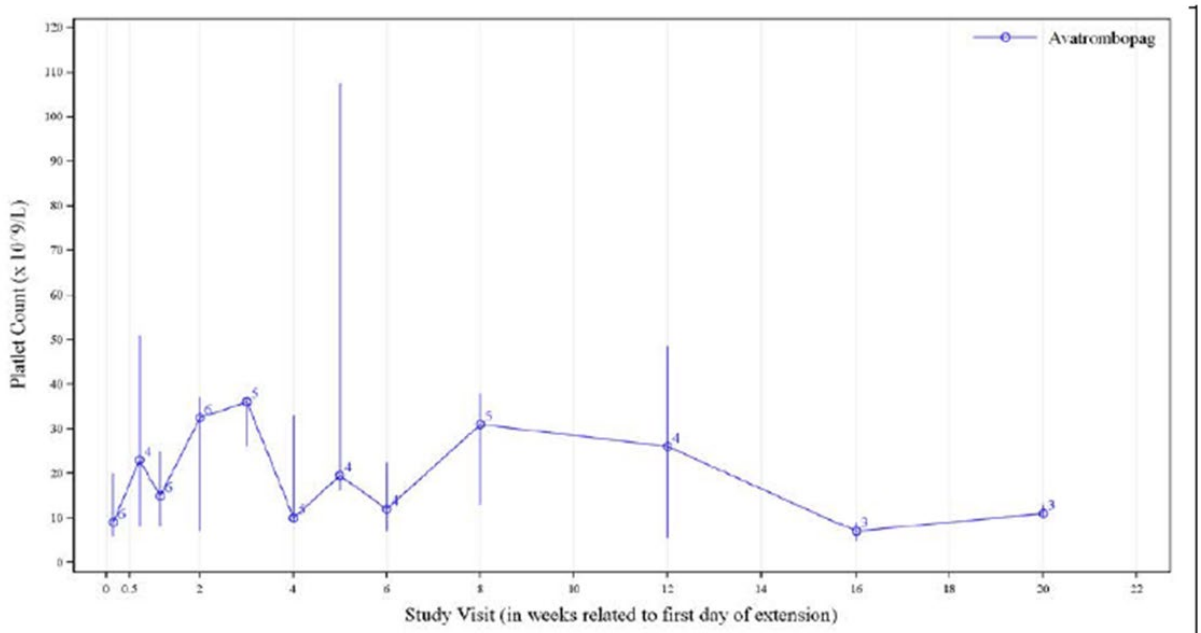


Figure 2 **Median (Q1, Q3) of Local Platelet Count Over Time, Treatment Period of Extension Phase: Modified Full Analysis Set of Extension Phase**
Source: Figure 14.2.2.4.

Comparison of Efficacy Results Across All ITP Studies

No pooling of efficacy data was conducted across the 4 ITP studies. While the limitations regarding post-hoc analyses and comparisons across studies with differing designs are clear, analyses of common quantitative endpoints across the avatrombopag ITP studies were conducted to provide some benchmarking data to assess the consistency of the avatrombopag treatment effect on increasing platelet counts in patients with ITP across the 4 studies. These analyses demonstrate the consistent efficacy of avatrombopag across the ITP studies, and serve to further reinforce the Pivotal Efficacy Data findings from Study 302 using the Supportive Efficacy Data from Study 305, Study CL-003, and Study CL-004. As summarised, demographic and Baseline characteristics were generally similar between treatment groups and across the ITP studies.

Cumulative Number of Weeks of Platelet Response – All ITP Studies

The primary efficacy endpoint for the pivotal Phase 3 ITP Study 302 was the Cumulative Number of Weeks of Platelet Response, defined as the cumulative number of weeks with a platelet count $\geq 50 \times 10^9$/L during 6 months of treatment in the absence of rescue therapy. Since this efficacy endpoint was based on quantitative laboratory assessments of platelet counts, a post-hoc analysis of the same endpoint was conducted on subjects in the other 3 ITP studies to provide some cross-study benchmarking data. This included 24 subjects in Study 305 who participated in the Core Study, and 64 subjects who participated in both Study CL-003 and its rollover Study CL-004.

The mean and median Cumulative Number of Weeks of Platelet Response in the Avatrombopag Treatment Group for the 6-month treatment period in the Study 302 Core Study were 12.0 and 12.4 weeks, respectively, which was superior to placebo with a highly statistically significant treatment difference (P<0.0001). The mean and median Cumulative Number of Weeks of Platelet Response with avatrombopag treatment in the Study 305 Core Study were shorter (5.4 and 5.1 weeks, respectively) than the effect seen in Study 302, but comparable to that seen in the Study 305 Eltrombopag Treatment Group (4.3 and 0.0 weeks, respectively; P=0.3299).

Table 2.5-11 Cumulative Number of Weeks of Platelet Response (Cross Study Comparison)

	Study 302		Study 305		CL-003 and CL-004	
	PBO (N=17)	AVA (N=32)	ELT (N=11)	AVA (N=13)	PBO (N=5)	AVA (N=59)
n	17	32	11	12	5	59
Mean (SD), weeks	0.1 (0.49)	12.0 (8.75)	4.3 (6.27)	5.4 (4.44)	0.3 (0.64)	10.9 (8.91)
Median, weeks	0.0	12.4	0.0	5.1	0.0	11.0
Min, Max, weeks	0, 2	0, 25	0, 15	0, 14	0, 1	0, 26
P-value of Wilcoxon rank sum test	<0.0001		0.3299		0.0079	

Note: Response was defined in the absence of rescue medications.

AVA = avatrombopag, ELT = eltrombopag, Max = maximum, Min = minimum, N = total number of subjects in sample group, n = number of subjects in specified group, PBO = placebo, SD = standard deviation.

Source: ISE Table 4.1.1, ISE Table 4.1.2, ISE Table 4.1.3.

Platelet Response by Study Day- All ITP Studies

Additional cross-study comparisons were conducted on Platelet Response ($\geq 50 \times 10^9$/L) at Study Day 8, Day 28, and Week 24 (6 months). Results for these endpoints all supported that of the primary endpoint and the consistency of the treatment effect across studies. A greater proportion of Responders were seen in the Avatrombopag Treatment Group compared to the placebo group at Day 8, Day 28, and Week 24 in Study 302 and Study CL-003, with numerically greater proportions of Responders at Day 8 and Day 28 for the Avatrombopag Treatment Group compared with the Eltrombopag Treatment Group in Study 305.

For the Avatrombopag Treatment Group in Study CL-003 (28 days of treatment) and Study CL-004 (6 months of treatment), the mean and median Cumulative Number of Weeks of Platelet Response were 10.9 and 11.0 weeks, respectively, which were comparable to that seen in Study 302.

Table 2.5-12 Platelet Response (≥50×10⁹/L) on Day 8, Day 28, and Week 24 (Cross Study Comparison)

	Study 302		Study 305		Study CL-003	
	PBO (N=17)	AVA (N=32)	ELT (N=11)	AVA (N=13)	PBO (N=5)	Total AVA (N=59)
Platelet Response on Day 8 [a]						
n	17	32	11	11	5	58
Yes, n (%)	0	21 (65.6)	4 (36.4)	5 (45.5)	0	32 (55.2)
No, n (%)	17 (100.0)	11 (34.4)	7 (63.6)	6 (54.5)	5 (100.0)	26 (44.8)
P-value[b]	<0.0001		>0.999		0.0242	
Platelet Response on Day 28						
n	16	32	9	12	5	51
Yes, n (%)	0	14 (43.8)	3 (33.3)	5 (41.7)	0	25 (49.0)
No, n (%)	16 (100.0)	18 (56.3)	6 (66.7)	7 (58.3)	5 (100.0)	26 (51.0)
P-value[b]	0.0016		>0.999		0.0584	
Platelet Response on Week 24 [c, d]						
n	1	22	0	1	-	35
Yes, n (%)	0	13 (59.1)	0	0	-	23 (65.7)
No, n (%)	1 (100.0)	9 (40.9)	0	1[e] (100.0)	-	12 (34.3)

Note: Response (≥50×10⁹/L) was defined in the absence of rescue medications.

AVA = avatrombopag, ELT = eltrombopag, N = total number of subjects in sample group, n = number of subjects in specified group, PBO = placebo.

a: For CL-003, platelet count was assessed on Day 7.

b: Fischer's Exact Test based on the subjects with non-missing data.

c: For Study 302 and Study 305, the end-of-treatment platelet count was assessed at Week 26; for Study CL-004, the end-of-treatment platelet count was assessed at Week 24.

d: Data for the total AVA group at Week 24 include data from Study CL-003 and Study CL-004 combined (N=53).

e: In Study 305, the 1 avatrombopag-treated subject who remained on study at Week 24 had a platelet count of 116×10⁹/L at Week 24, but had received rescue medications on Day 4 and Day 200.

Source: ISE Table 4.2.1, ISE Table 4.2.2, ISE Table 4.2.3, ISE Table 4.3.1, ISE Table 4.3.2, ISE Table 4.3.3, ISE Table 4.4.1, ISE Table 4.4.2, and ISE Table 4.4.3.

2.5.3 Discussion on clinical efficacy

Design and conduct of clinical studies

Data are presented to support an authorisation of avatrombopag (Doptelet) by an extension of variation for the applied indication: "Doptelet is indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)."

The wording of indication has been revised and now include the term "primary" in order to specifically reflest the target population. The wording of indication is now aligned with the authorised TPO-Ra, as "Avatrombopag is indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)." All three

indications will characterize the ITP patients as refractory, a term used to associate the indication for treatment with the relapsing disease activity.

The starting dose was 20mg once daily followed by flexible-dosing regimen to optimize and maintain platelet response for individual ITP subjects. Dose adjustment was done by up- or down-titrations of 1 dose level (5-10mg, 10-20mg, 20-30mg and 30-40mg and vice versa). While dose adjustment can be followed, the selected starting dose of 20mg was not considered sufficiently justified by the CHMP (see also the discussion on PK). As discussed in detail in the pharmacology part, the 20mg starting dose was eventually considered acceptable. Considering that in clinical practice the major goal for treatment in primary ITP is to provide a sufficient platelet count to prevent or stop bleeding rather than correcting the platelet count to normal levels (in asymptomatic patients) the choice of the 20mg starting dose was endorsed by the CHMP. Nevertheless, the risk for thrombocytosis remains and therefore the SmPC section 4.2 has been updated to state: Due to the potential risk of platelet counts above 400 x 10^9/L within the first weeks of treatment patients should be carefully monitored for any signs or symptoms of thrombocytosis. After a stable platelet count has been achieved, obtain platelet counts at least monthly. After discontinuation of avatrombopag, platelet counts should be obtained weekly for at least 4 weeks. The revised wording adequately reflects the need for careful monitoring as well as the risk for thrombocytosis at the beginning of the treatment.

The pivotal study E5501-G000-302 was a placebo-controlled phase 3 trial, and initiated enrolment in February 2012 and primary completion date in November 2013. Adult patients had to have a response to at least one prior treatment for ITP, be diagnosed more than 12 months previously and in need of treatment with a platelet count below 30 x10^9/L. Diagnostic criteria were in accordance to international standard of monosymptomatic, autoimmune thrombocytopenia, and exclusion criteria acceptable for this benign condition.

The patient population included 49 patients, randomised 2:1 for avatrombopag or placebo, as add-on to any SOC in the blinded trial. Baseline data reflect a representative, Caucasian population, almost one third had received five or more ITP treatments. Most patients were younger than 65-years at inclusion. A large fraction of patients with (chronic) ITP are older than 60-years, with greater risk for serious bleeding complications and co-morbidities and co-medication, and these patients, with a risk for vascular events and drug-interactions were less well represented due to exclusion criteria, and the issue is reflected in section 5.1 of the SmPC.

The different phases in a 6-month core study may allow to capture relevant information on efficacy at different times, and safety, but reduction in any concomitant ITP medication may be time-consuming and still influence the effect of avatrombopag. Data in the pivotal study, during the core study of 26 weeks, demonstrated the ability to dose reduce and even terminate concomitant ITP medication, when treating with avatrombopag. This is clinically relevant, especially in patients treated with corticosteroids due to the risk of long term-toxicity (e.g. osteoporosis), or immunosuppressants (e.g. infections). Preferably, long-term data in the extension phase would have been collected in more patients.

The sample size calculations are considered adequate, however, the sample size of 49 patients in the main study is limited, and the number of patients causes a concern in the long-term follow-up in the extension phase, due to a low number of patients after one year. The sample size is acceptable following clarification on Amendments, and the MAH has provided more statistical analysis with the correct methods to calculate CI, which are broad due to the limited number of patients.

The primary endpoint was the cumulative number of weeks of platelet response, defined as the cumulative number of weeks with a platelet count ≥50 × 10^9/L during 6 months of treatment, in the absence of rescue therapy. The proposed primary endpoint differs from what was agreed on by the CHMP in the scientific advice from 2011 (EMEA/H/SA/1606/1/FU/1/2011/III; "Durable platelet response,

defined as achieving at least 6 weekly platelet responses (platelet count ≥ 50 x 10^9/L) during the last 8 weeks of treatment, with no rescue medications administered at any time during the treatment period", now included as other efficacy endpoint). This primary endpoint as agreed during the SA was comparable to the primary endpoint for both of the pivotal studies (20030105 and 20030212) that were evaluated for the MAA of Nplate (romiplostim). The primary endpoint of the study is acceptable. The secondary endpoints were a) Proportion of patients Day8 with a response in platelet count ≥50 x 10^9/L, and b) Proportion of subjects with a reduction in use of concomitant ITP medications from baseline, which is clinically meaningfull.

Stratification factors at randomization of the 49 patients were: splenectomy status, baseline platelet count, and use of concomitant ITP medication. This is in accordance to the EMA guideline on ITP, and identical factors were used in the pivotal RAISE study with eltrombopag in chronic, primary ITP, also placebo-controlled.

The justification for a placebo-controlled study is in accordance with the 2014 EMA ITP guideline and is accepted considering the circumstances 10 years ago. Data from an active comparator study has been also requested. The company followed this advice by conducting the RCT Study 305. Study 305, randomized, blinded phase 3 study with eltrombopag as active comparator was terminated early after inclusion of 24 patients due to lack of recruitment. The problem was the interest in results by gastroscopy and bone marrow examination, driven by further (safety) information, and which may not be considered relevant to-day in a population, strictly defined by chronic, primary ITP to be treated with TPO-Ra. Unfortunately, a robust active comparator study was never conducted. The MAH has made statistical analysis cross-studies with avatrombopag, placebo and eltrombopag to support the efficacy of avatrombopag in chronic ITP. Overall the statistical considerations for the design of Study 305 as well as the corresponding planned analysis are considered acceptable. Due to the early termination of the study all presented analyses of results need to be considered as descriptive, and statistical inference that would permit externally valid conclusions is no longer warranted. The results in Study 302 (main) and Study 305 (supportive) cannot be compared due to different trial populations and endpoint at fixed time-point. Nevertheless, the fact that results are by and large in line with results obtained from earlier studies, can be considered supportive of the overall conclusions on efficacy and safety.

There were no critical protocol deviations (ie, protocol deviations which substantially impacted the primary endpoint or safety assessments).

In order to outweigh the missing direct comparison against an approved TPO-R agonist, the following data were submitted: i) literature review review in order to contextualize the results of study 302 by available data from eltrombopag and romiplostim, ii) independent network meta-analysis and iii) a simulated non-inferiority comparison against eltrombopag. Statistical methods are well documented and justified.

The simulated non-inferiority analysis of avatrombopag against eltrombopag was based on data from PK/PD modelling. The primary endpoint was the durable platelet response rate. The result of this endpoint derived by PK/PD modelling and simulation is completely different to that derived by results from study 302, which signicantly questions the reliability of this simulated non-inferiority analysis of avatrombopag against eltrombopag and results are therefore not considered useful to deliver any substantial evidence for B/R assessment.

Based on prospectively defined search and selection criteria the MAH provided a literature review in order to contextualize the results of study 302 by available data from eltrombopag and romiplostim. This literature review is considered helpful for addressing the lack of a direct comparison against an approved TPO-R agonist.

An independent network meta-analysis was conducted to compare the efficacy of avatrombopag to that of eltrombopag in the treatment of chronic ITP. From a methodological perspective the presented network meta-analysis seems to have been carried out properly. Search strategy, in-/exclusion criteria for studies – albeit different from the literature review - appear plausible. Statistical methods are well documented and justified. Nevertheless, major issues concerning the comparability of results between studies are noticed. Specifically, differences in endpoint definitions and exposure times between studies hamper the comparability of results concerning the cumulative number of weeks with response and the proportion of subjects with durable response. In contrast, the comparison of response rates at fixed timepoints may be more reliably compared between studies.

Efficacy data and additional analyses

The primary endpoint was met in the pivotal Study 302, showing patients treated with avatrombopag (as add-on) had 12 weeks with platelet counts ≥50 x 10^9/L in the core study of six months, compared to none in the placebo group. Differences were noted in numbers of cumulative weeks with "safe" platelet-count, which could indicate variable impact of treatment on disease mechanism, between the sub-groups in all three stratification factors, although all superior to placebo. The key secondary endpoint, response Day8 was also statistically significant different and achieved in 66% in the avatrombopag group, compared to none in the placebo group. A rapid response may be critical in ITP, in patients with bleeding, and such response is comparable to glucocorticoid or IVIg. It is acceptable that 41% in placebo group and 47% in the avatrombopag group received concomitant ITP medication at baseline, which reflects variable disease activity in the samle population and because these patients were not manageable without treatment waiting for the inclusion in the trial. Although more patients (30%) in the avatrombopag group had a reduction in the use of concomitant ITP medication, compared to none in the placebo group, this difference was not statistically different from placebo. It is important to emphasize that the trial recommendations for dose-reduction of concomitant ITP-medication were conservative for safety reasons in the time-period of the core-study for 6 months, and that 30% of patients had dose-reduction or termination of co-medicaiton. The dose-reduction documented in glucocorticoid in the avatrombopag-group is clinically meaningful, and will contribute to avoid long-term toxicity (osteoporosis, and increased risk in bacterial and re-activiation of viral infections, like herpes, metabolic) (Rice tal, Clin Ther 2017), as it is the aim in all combination treatments in chroniv ITP – provided no long-term risks are demonstrated, e.g. in the TPO-Ra. The results in the placebo group are as expected in all three endpoints, with minimal if any impact.

Over time, patient data became more limited, and during the extension phase a gradual declining median platelet count may indicate exhaustion of effect – or difficulties stabilizing the dose, which was confirmed to be the reason in four patients, receiving maximal dose of avatrombopag throught the study. As a treatment phenomenon, an exhaustion by avatrombopag could not be revealed previously in the studies in chronic liver disease due to different dosing and pathophysiology. A declining effect effect on thrombopoiesishas not been observed in other TPO-Ra.

The interpretation of results in the group, treated with avatrombopag may be disentangled and clarified by further data in patients in avatrombopag monotherapy or combination therapy. Patients in avatrombopag monotherapy had more weeks with a safe platelet count >50 x10^9/L, (17 weeks/20 visits in the core study) than patients in combination treatment, and on average - although a simple analysis - 61% in the monotherapy group had a platelet count >50 compared to 46% in combination therapy, during the 20 visits. The response rate Day8 was lower in the group treated with avatrombopag as add-on to SOC (53% combination versus 76% monotherapy), who had more rescue therapy, in particular within 60 days. Thus, rescue was provided earlier in subjects receiving avatrombopag as add-on to SOC, 9 episodes / 13 before Day60, compared to 4 episodes (in all) after Day110 in the monotherapy group

– fluctuations are not unusual in treating this disease. These data reflect aspects of avatrombopag effect, which all support the efficacy and the role in the treatment of primary chronic ITP. It may be unexpected that the combination treatment by these three endpoints seems to be inferior to monotherapy, because a combination exploits the different mechanism of drugs in the combination. However, the explanation is (compatible with) a more aggressive disease acitivity in patients in the combination treatment, since this group of patients entered the trial, treated with a SOC. Further, during the core phase of 26 weeks, the co-medication had been tapered, which was a secondary endpoint. There is no indication that the immunosuppressive impact of glucocorticoid may inhibit the thrombopoietic stimulating effect of avatrombopag, functionally or pharmacologically. And there is no test to confirm the disase activity in chronic ITP, only the clinical outcome of a treatment.

Literature review: Main findings are based on results from study 302 and corresponding endpoints from eltrombopag and romiplostim studies as presented in their SmPCs. Both the comparison of cumulative number of weeks with a platelet count above $50x10^9$/L and use of rescue medication suggests comparable results for all TPO-R agonists.

In contrast, there seems to be a difference between avatrombopag and eltrombopag in durable response. However, the number presented for eltrombopag (60%) needs to be questioned as the relative response rate is based on the number of subjects with complete follow-up and not on the total number of subjects randomized to treatment, which would be the relevant analysis population according to the ITT principle. The percentage of patients with durable response based on the total number of subjects (n=135) is 42 and more in line with the result for avatrombopag (34%).

Overall, results from this literature review provide reassuring evidence to some degree that the effect of avatrombopag seems to be comparable to that of other approved TPO-R agonists.

Network Meta-Analysis: By and large response rates on day 8, day 28, week 6 and months 6 appear to be comparable between avatrombopag and eltrombopag. The results of this network meta-analysis do not give rise to concern that avatrombopag treatment response is substantially worse than that of eltrombopag. Treatment response seems to be rather comparable.

The randomized trial with active comparator (eltrombopag), Study 305 had a very similar design as Study 302, is very small with only 24 patients. The results are difficult to compare cross-study with the placebo-controlled avatrombopag studies or the pivotal eltrombopag study, because of differences in patient populations and endpoints. However, the data captured in Study-305 and the "virtual" data by literature review for contextualization, independent network meta-analysis and a simulated non-inferiority comparison against eltrombopag, support the results of Study 302 that avatrombopag is effective and safe, and as effective and safe as eltrombopag in primary, chronic ITP in adults.

The benefit of a rapid increase in platelet count to reduce the risk of bleeding must be balanced against the potential risk of causing adverse events related to platelet counts above the target range. Hence, the following recommendation is given in section 4.2 of the SmPC: "The recommended starting dose of Doptelet is 20 mg (1 tablet) once daily with food" and to monitor and make dose adjustment as follows: "After initiating therapy, assess platelet counts at least once weekly until a stable platelet count $\geq$ 50 x 10^9/L and $\leq$ 150 x 10^9/L has been achieved. Twice weekly platelet count monitoring should be conducted during the first weeks of therapy in patients receiving avatrombopag only once or twice weekly. Twice weekly monitoring should also be conducted after dose adjustments during the treatment. Due to the potential risk of platelet counts above 400 x 10^9/L within the first weeks of treatment patients should be carefully monitored for any signs or symptoms of thrombocytosis. After a stable platelet count has been achieved, obtain platelet counts at least monthly. After discontinuation of avatrombopag, platelet counts should be obtained weekly for at least 4 weeks."

CHMP recommends to further evaluate the efficacy of avatrombopag in the post-marketing setting with regards to the dosing recommendations, including the risks associated with the 20mg starting dose and platelet fluctuations in the initial period after treatment initiation as well as after dose adjustment to once or twice weekly.

2.5.4 Conclusions on the clinical efficacy

Efficacy has been shown treating chronic primary ITP in adults with avatrombopag, as monotherapy or as add-on to concomitant ITP medication. The primary and key-secondary endpoint were met, reflected by a safe platelet count $\geq$ 50 x10^9/L rapidly after initiation of treatment in two out of three patients and maintained for half the time in the core study, without rescue. It is accepted that a direct comparison against an authorised TPO-R agonist was terminated prematurely. Supportive data addressing a comparison against other authorised TPO-R agonists derive from the submitted literature review and the independent network-meta analysis and indicate comparable efficacy of avatrombopag and eltrombopag. Recommendations have been included in section 4.2 of the SmPC to monitor and make dose adjustments considering that no clinical data are available to support the dosing adjustments. CHMP recommends to further evaluate the efficacy of avatrombopag in the post-marketing setting with regards to the dosing recommendations and long-term efficacy of avatrombopag.

2.6 Clinical safety

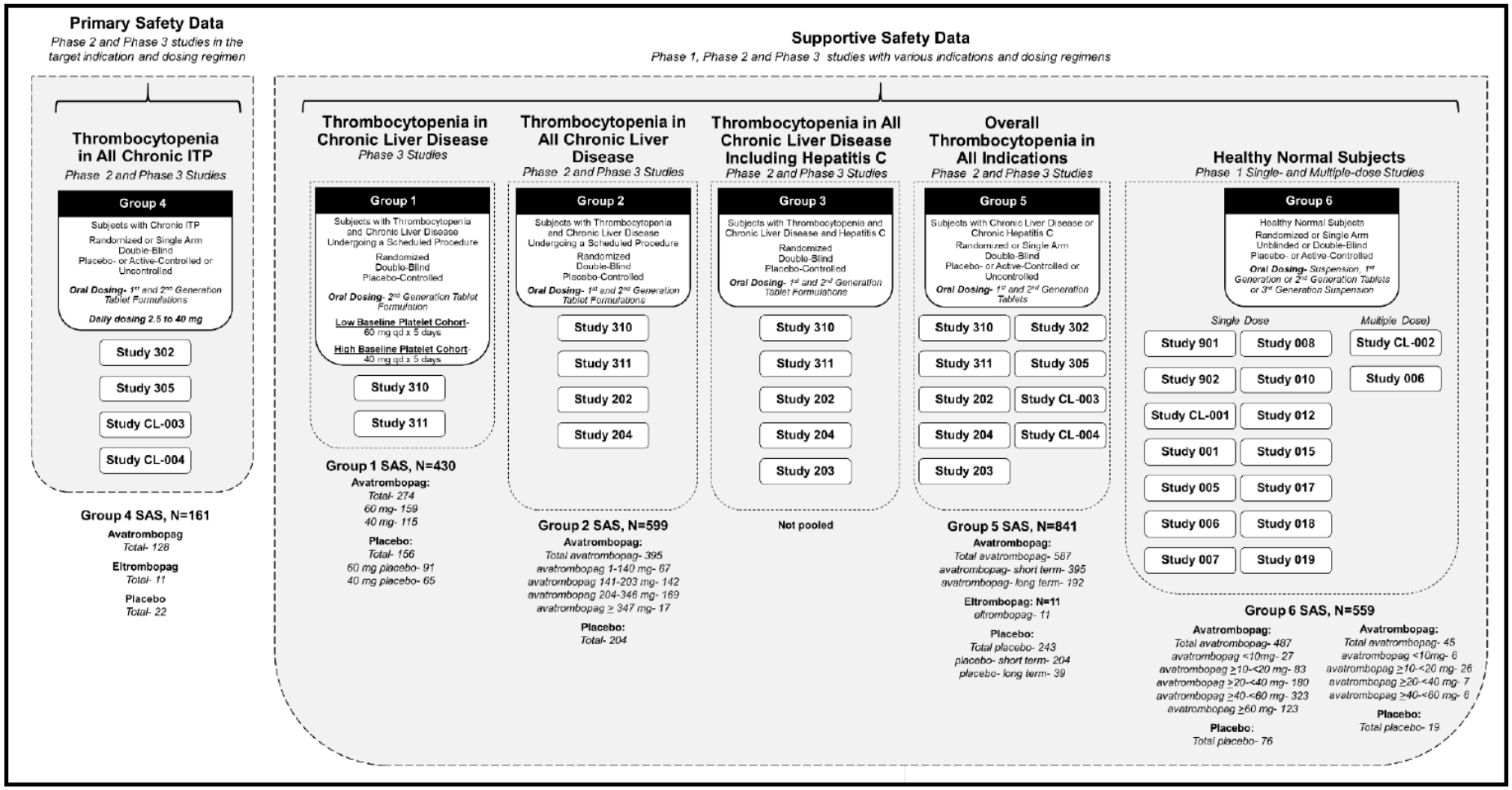
Introduction

Avatrombopag was authorised in June 2019 by the European Commission for the treatment of severe thrombocytopenia in patients with CLD (chronic liver disease) who are scheduled to undergo an invasive procedure. The safety data supporting the CLD indication were summarised in safety analysis Group 1 (Fig. 2.7.4-1 below) and included data from 2 Phase 3 studies that reproducibly demonstrated a safety profile for avatrombopag that was comparable to placebo with no new or unexpected safety signals. The pooled safety data in Group 1 included a total of 430 randomized subjects who received at least 1 dose of study drug and had at least 1 post-dose safety assessment, with 274 subjects treated with avatrombopag and 156 with placebo. The frequency, severity, and types of TEAEs reported were consistent with those reported in patients with CLD. In addition, a Phase 2 study conducted in subjects with thrombocytopenia and hepatitis C receiving antiviral therapy also demonstrated the safety of chronic dosing of avatrombopag in another patient population with thrombocytopenia.

Safety data from the avatrombopag clinical development program consists of 24 sponsor-initiated studies in patients and healthy volunteers, including Phase 1, Phase 2, and Phase 3 studies, with a total of over 1100 subjects exposed to at least 1 dose of avatrombopag. This includes avatrombopag exposures in 520 healthy volunteers, and 587 patients that included acute and chronic dosing for the treatment of thrombocytopenia in several different patient populations and indications, including CLD, hepatitis C, and chronic ITP.

Safety data from the 24 studies in this comprehensive clinical development program were organized into 6 pooled Safety Analysis Sets (SAS), based on the population studied, dose, schedule, formulation, and study phase, which were submitted with the original Marketing Authorisation Application (MAA) for the CLD indication (i.e. CLD MAA). For convenience, these groups were serially numbered Group 1 to Group 6 for the CLD MAA, and to avoid confusion, the same safety group numbering was retained for this type II variation (Figure 2.7.4-1):

Figure 2.7.4-1 Summary of Pooled Safety Analysis Groups



The number of subjects in each group represents the SAS defined as all randomized subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment. Some studies have been included in more than 1 of the pooled safety analysis groups.

ITP = immune thrombocytopenia; SAS = Safety Analysis Set(s).

The Primary Safety Data for this type II variation include the pooled safety data in Group 4 (*Thrombocytopenia in All Chronic ITP Studies*, N=161, see Table 2.7.4-6) to support the registration of avatrombopag for the proposed new indication, ie, the treatment of chronic ITP in adult patients who are refractory to other treatments. Group 4 includes safety data over a range of avatrombopag exposures (5 to 40 mg) to maintain platelet counts between the target range of 50×10^9/L and $<150\times10^9$/L.

The Primary Safety Data include:

- Study 302: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Trial with an Open-label Extension Phase to Evaluate the Efficacy and Safety of Oral avatrombopag Plus Standard Care for the Treatment of Thrombocytopenia in Adults with Chronic Immune Thrombocytopenia
- Study 305: A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled, Parallel-Group Trial with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Oral avatrombopag versus Eltrombopag, in Adults with Chronic Immune Thrombocytopenia
    - The sponsor terminated this study early due to enrollment challenges.
- Study CL-003: A Phase 2, Double-Blind, Randomized, Dose-Ranging, Placebo-Controlled, Parallel-Group Study of avatrombopag Tablets Taken Orally Once Daily for 28 Days in Patients with Chronic ITP
- Study CL-004: A Phase 2, Parallel-Group, Rollover Study of avatrombopag in Patients with Chronic ITP Who Completed 28 Days' of Study Treatment in Protocol AKR-501-CL-003

Table 2.7.4-6 Primary Safety Data: Group 4 – Description of Clinical Safety Studies in Subjects With Thrombocytopenia from All Chronic Immune Thrombocytopenia Studies

Study ID	Design; Control Type	Number of Study Centers (Locations)	Number of Subjects by Arm; Entered/ Completed	Indication Studied	Sex M/F Median Age (Range) Race	Duration	Study and Control Drugs Dose, Route, Regimen	Frequency of Dosing
Study 302	Phase 3	Multicenter (27 sites) in Australia, Belgium, Bulgaria, Czech Republic, Netherlands, New Zealand, Poland, Singapore, Slovakia, South Africa, Ukraine	Avatrombopag group: 32 entered, 22 completed the **Core Study** Placebo group: 17 entered, 1 completed the **Core Study**.	ITP	Avatrombopag group 9 M, 23 F 45.0 (20-69) 31 White, 1 Chinese Placebo treatment group: 9 M, 8 F 43.0 (18-65) 15 White, 1 Black, 1 Chinese	06 Feb 2012 to 09 Apr 2015	Avatrombopag group: Avatrombopag administered orally as 5, 10, 20, 30, or 40-mg doses, in a flexible dose design Placebo group: Placebo administered orally to match the 5, 10, 20, 30, or 40-mg doses, in a flexible dose design.	QD
Study 305	Phase 3 [a]	Multicenter (72 sites) in Australia, Austria, Belgium France, Germany Korea, Netherlands, Spain, United States, United Kingdom	Avatrombopag group: 12 entered, 1 completed the **Core Study** Eltrombopag group: 11 entered, 0 completed the **Core Study**.	ITP	Avatrombopag group: 5 M, 7 F 55.0 (19-88) 11 White, 1 Other Asian Eltrombopag group: 4 M, 7 F 50.0 (20-71) 8 White, 2 Black, 1 Other	26 Mar 2012 to 13 Sep 2013	Avatrombopag group: Avatrombopag administered orally 20 mg and then titrated either up to maximum 40 mg or down to minimum 5 mg. Eltrombopag group: Eltrombopag administered orally at 50 mg then titrated up to maximum 75 mg or down to minimum 25 mg)	QD

Study ID	Design; Control Type	Number of Study Centers (Locations)	Number of Subjects by Arm; Entered/ Completed	Indication Studied	Sex M/F Median Age (Range) Race	Duration	Study and Control Drugs Dose, Route, Regimen	Frequency of Dosing
Study CL-003	Phase 2	Multicenter (25 sites) in the United States	Avatrombopag group: 59 entered, 52 completed Placebo group: 5 entered, 5 completed	ITP	Avatrombopag group: 22 M, 37 F 57.0 (18-82) 44 White, 5 Black, 4 Asian, 4 Hispanic, 2 Other Placebo group: 2 M, 3 F 29.0 (23-73) 4 White, 1 Hispanic	21 Mar 2007 to 20 Jan 2009	Avatrombopag group: Avatrombopag administered orally as 2.5-, 5-, 10-, 20-mg doses, in a flexible dose design Placebo group: Placebo administered orally to match the 2.5-, 5-, 10-, 20-mg doses, in a flexible dose design.	QD
Study CL-004	Phase 2	Multicenter (17 sites) in the United States	53 entered, 35 completed	ITP	24 M, 40 F 55.5 (18-82) 48 White, 5 Black, 5 Hispanic, 4 Asian, 2 Other	14 May 2007 to 25 Jun 2009	Eligible subjects continued the blinded dose they were receiving in the previous study. Eligible subjects would receive open-label avatrombopag dose increase from 10 to 40 mg	QD (minimum of every other day for open-label subjects)

F = female, H = Hispanic, ITP = immune thrombocytopenia, M = male, QD = once daily.

a: Study 305 was terminated early due to significant enrollment challenges as a result of the entry criteria.

Table 1: Listing of Avatrombopag Clinical Studies Referenced in Support of the Chronic Immune Thrombocytopenia (ITP) Indication

Type of Study	Study Identifier Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
Oral Bioavailability and Food Effect	AVA-PED-101 m5.3.1.2	Comparison of the relative bioavailability of the avatrombopag tablet for oral suspension to the commercial film-coated oral tablet	Single-dose, six-sequence cross-over study	Avatrombopag Commercial Film-Coated Oral Tablet 20 mg Avatrombopag Tablet for Oral Suspension	24 planned / 24 analyzed	Healthy adult subjects under fed and fasted conditions	Each subject received a single dose of study drug in each treatment period.	Complete Full CSR
Phase 3 Efficacy and Safety Study	E5501-G000-310 (Study 310) CLD MAA m5.3.5.1	Efficacy and Safety (short term)	Randomized, double-blind, placebo-controlled	Avatrombopag tablets; 40 or 60 mg, once daily dose, depending on patient's Baseline platelet count; oral	231 randomized (149 avatrombopag / 82 placebo)	Patients with thrombocytopenia associated with chronic liver disease	5 days	Complete Full CSR

Type of Study	Study Identifier Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
Phase 3 Efficacy and Safety Study	E5501-G000-311 (Study 311) CLD MAA m5.3.5.1	Efficacy and Safety (short term)	Randomized, double-blind, placebo-controlled	Avatrombopag tablets; 40 or 60 mg, once daily dose, depending on patient's Baseline platelet count; oral	204 randomized (128 avatrombopag / 76 placebo)	Patients with thrombocytopenia associated with chronic liver disease	5 days	Complete Full CSR
Phase 3b Efficacy and Safety Study	AVA-PST-320 m5.3.5.2	Efficacy and Safety	Open-label, uncontrolled	Avatrombopag tablets, 60 mg (3×20 mg tablets) orally once daily	Up to 90 planned / 11 screened; 4 enrolled.	Subjects with thrombocytopenia scheduled for a surgical procedure	5 days	Terminated Abbreviated CSR
Phase 4 Efficacy and Safety Study	AVA-CLD-401 m5.3.5.2	Observe the real-world treatment patterns and effects	Observational Cohort Study	Avatrombopag Commercial Film-Coated Oral Tablet 20 mg	~500 planned / 65 screened; 50 enrolled; 48 included in the analyses.	Patients with thrombocytopenia associated with CLD undergoing a procedure	5 days	Terminated Full CSR
Phase 2 Dose Ranging Efficacy and Safety Study	501-CL-003 (Study CL-003) CLD MAA m5.3.5.4 [a]	Efficacy; Safety and Tolerability; PK and PK/PD Assessment	Randomized, double-blind placebo-controlled	Avatrombopag (or matching placebo) tablets; 2.5, 5, 10, or 20 mg, once daily; oral	64 randomized (59 avatrombopag / 5 placebo)	Patients with chronic ITP	28 days	Complete Full CSR

Type of Study	Study Identifier Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
Phase 2 Rollover Efficacy and Safety Study	501-CL-004 (Study CL-004) CLD MAA m5.3.5.4 [a]	Efficacy; Safety and Tolerability; PK and PK/PD Assessment	Parallel-group, double-blind (CL-003 responders) and open-label (CL-003 nonresponders)	Avatrombopag (or matching placebo) tablets; 2.5, 5, 10, or 20 mg, once daily; oral CL-003 Responders Same starting dose as was received in CL-003 CL-003 Nonresponders Avatrombopag at starting dose of 10 mg	53 enrolled (53 avatrombopag / 0 placebo) (25 Responders / 28 Nonresponders, per primary response criteria in CL-003)	Patients with chronic ITP	6 months	Complete Full CSR
Phase 3 Efficacy and Safety Study	E5501-G000-302 (Study 302) CLD MAA m5.3.5.4 [a]	Core Study Efficacy and Safety; Population PK/PD Extension Phase Long term Efficacy and Safety	Core Study Randomized, double-blind placebo-controlled Extension Phase Open-label uncontrolled	Core Study Avatrombopag (or matching placebo) tablets; 5, 10, 20, 30, or 40 mg, once daily in a flexible dose design; oral Extension Phase Avatrombopag tablets; starting dose of 20 mg once daily with dose titration in accordance with protocol-specified titration guidelines; oral	49 randomized (32 avatrombopag / 17 placebo)	Patients with chronic ITP	Core Study 26 weeks Extension Phase 76 weeks	Complete Full CSR

Type of Study	Study Identifier Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status Type of Report
Phase 3 Efficacy and Safety Study	E5501-G000-305 (Study 305) CLD MAA m5.3.5.4 [a]	Core Study Efficacy and Safety; Population PK/PD Extension Phase Long term Efficacy and Safety	Core Study: Randomized, double-blind active-controlled Extension Phase: Open-label uncontrolled	Core Study Avatrombopag tablets; 5, 10, 20, 30, or 40 mg once daily, in a flexible dose design; oral Eltrombopag tablets; 25, 50, or 75 mg once daily, in a flexible dose design; oral Extension Phase Responders: Starting dose same as the last dose level of the Core Study. Nonresponders: avatrombopag 20 mg once daily	24 randomized, 23 treated (12 avatrombopag / 11 eltrombopag) [1 screen-failed subject was randomized to avatrombopag in error]	Patients with chronic ITP	Core Study 26 weeks Extension Phase 104 weeks	Terminated Synoptic CSR

CLD = chronic liver disease, ITP = immune thrombocytopenia, PD = pharmacodynamic, PK = pharmacokinetic

[a] Clinical study reports for the clinical studies conducted in ITP patients (Study CL-003, Study CL-004, Study 302 and Study 305) were submitted in Module 5.3.5.4 of the CLD MAA, since the studies were not directly related to the CLD indication.

Patient exposure

Safety and efficacy data were collected from both single- and multiple-dose Phase 1, dose escalation studies, and several Phase 2 and Phase 3 studies with various avatrombopag formulations, doses, and dosing regimens. Exposure to avatrombopag across the clinical development program includes doses from 1 to 100 mg administered as single or repeat daily dosing for up to 834 days (2.3 years), with 19.6% (115/587) of all subjects (Table 2.7.4-4) and 63.3% (81/128) of the subjects with ITP (Table 2.7.4-14) receiving treatment for at least 180 days. The mean Duration of Exposure for subjects in each category is summarized in Table 2.7.4-3.

Table 2.7.4-3 Avatrombopag Exposure Durations as of 01 March 2018 – Safety Population

Subject Category	Duration of Exposure [a] (days)	
	Mean (SD)	Min, Max
Healthy Volunteers		
Single Dose Studies [b]	2.7 (1.42)	1, 6
Multiple Dose Studies	9.3 (3.16)	3, 14
Subjects with Chronic ITP	206.4 (135.57)	2, 834
Subjects with thrombocytopenia and CLD who were scheduled to undergo a scheduled procedure	5.4 (0.89)	2, 7
Subjects with chronic HCV-related thrombocytopenia to enable initiation and maintenance of antiviral treatment	194.9 (141.80)	19, 413

CLD = chronic liver disease, HCV = hepatitis C virus, ITP = immune thrombocytopenia.

a Duration of Exposure = date of last dose of study drug – dose of first dose of study drug + 1.

b Duration of Exposure for single dose studies = number of doses. Some subjects in the single dose studies also participated in the multiple dose studies.

Source: CLD MAA ISS Table 20.2.1.2, Table 20.2.1.3, Table 22.2.1.1, Table 22.2.2.1, and Study 203 CSR Table 14.3.1.5.

Table 2.7.4-4 Duration of Avatrombopag Exposure from All Clinical Studies in Patient Populations (Studies CL-003, CL-004, 202, 203, 204, 302, 305, 310, and 311) – Safety Population

Exposure	Subjects with Avatrombopag Exposures
Any Exposure, n (%)	**587**
≥7 days	283 (48.2)
≥30 days	172 (29.3)
≥90 days	140 (23.9)
≥180 days	115 (19.6)
Duration of Exposure (Days)	
n	587
Mean (SD)	70.2 (121.47)
Median	5.0
Min, Max	2, 834
Total Number of Subject-Days [a]	41183

a: Total number of subject-days = summation over all subjects' exposure durations.

Source: CLD MAA ISS Table 20.2.1.4

Table 2.7.4-14 Group 4 Extent of Exposure by Duration (Studies CL-003, CL-004, 302, and 305)

Extent of Exposure	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]
Any Exposure [b], n (%)	22	11	128
≥7 days	22 (100)	11 (100)	127 (99.2)
≥30 days	15 (68.2)	8 (72.7)	115 (89.8)
≥90 days	3 (13.6)	3 (27.3)	100 (78.1)
≥180 days	1 (4.5)	1 (9.1)	81 (63.3)
Duration of Exposure [c] (days)			
N	22 (100)	11 (100)	128 (100)
Mean (SD)	54.9 (47.19)	73.5 (70.47)	206.4 (135.57)
Median	41.0	48.0	204.0
Min, Max	15, 209	11, 238	2, 834
Number of Subject-Days [d]	1208	809	26417

AVA = avatrombopag, ELT = eltrombopag, Max = maximum, Min = minimum, N = total number of subjects in the sample group, n = number of subjects in individual group, PBO = placebo.

a: N denotes all subjects in the Core Study and open-label Extension Phase who received avatrombopag.
b: Subjects were counted in each applicable exposure category.
c: Duration of Exposure = date of last dose of study drug – date of first dose of study drug + 1.
d: Number of Subject-days = summation over all subjects' exposure durations.

Source: CLD MAA ISS Table 20.2.1.3.

Table 2.7.4-15 Group 4 Cumulative Dose – Safety Analysis Set (Studies CL-003, CL-004, 302, and 305)

Extent of Exposure	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]
Cumulative Dose (mg)			
N	22	11	121
Mean (SD)	1686.1 (1918.55)	3868.2 (3200.31)	4252.0 (4961.99)
Median	1275.0	2475.0	2445.0
Min, Max	0, 7275	550, 9800	5, 29380
Cumulative Dose [b] (mg), n (%)			
> 0 mg to ≤ 420 mg	Not Applicable	Not Applicable	16 (12.5)
> 420 mg to ≤ 3640 mg			60 (46.9)
> 3640 mg to ≤ 7280 mg			25 (19.5)
> 7280 mg			20 (15.6)

AVA = avatrombopag, ELT= eltrombopag, Max = maximum, Min = minimum, N = total number of subjects in the sample group, n = number of subjects in individual group, PBO = placebo.

a: N denotes all subjects in the Core Study and open-label Extension Phase who received avatrombopag.

b: Categories used: ≤420 mg (ie, ≤20 mg per day for 3 weeks), >420 mg to 3640 mg (ie, 20 mg per day from 3 weeks to 26 weeks), >3640 to 7280 mg (ie, 20 mg per day for 26 to 52 weeks), and >7280 mg (ie, >20 mg per day for 52 weeks).

Source: CLD MAA ISS Table 20.2.2.3.

Pivotal efficacy RCT 302; Avatrombopag versus placebo:

Extent of exposure was noticeably longer for avatrombopag subjects than for placebo subjects during the Core Study (Table 15).

Table 15 Cumulative Extent of Exposure - Core Study, Safety Analysis Set of Core Study

Category	Placebo (N=17)	Avatrombopag (N=32)
Any exposure[a], n (%)	17 (100)	32 (100)
≥ 6 weeks	10 (58.8)	30 (93.8)
≥ 18 weeks	3 (17.6)	26 (81.3)
≥ 26 weeks	1 (5.9)	17 (53.1)
≥ 30 weeks	0	2 (6.3)
Duration of exposure[b] (weeks)		
n	17	32
Mean (SD)	8.93 (7.356)	22.78 (7.435)
Median	6.00	26.00
Min, Max	2.1, 29.9	3.7, 31.1
Number of subject-day (week)[c]	152	729

a: Subjects were counted in each applicable exposure category.
b: Duration of exposure = date of last dose of study drug - date of first dose of study drug + 1
c: Number of subject-day = summation over all subjects' exposure durations

Source: Table 14.3.1.3, Listing 16.2.5.2

Mean duration of exposure to avatrombopag during the combined Core Study and Extension Phase was 43.9 weeks with the longest treatment exposure being 75.7 weeks (Table 16).

Table 16 Cumulative Extent of Exposure – Core Study and Extension Phase, Safety Analysis Set of Extension Phase

	Avatrombopag (N=47)
Any exposure[a], n (%)	47 (100)
≥ 6 weeks	47 (100)
≥ 18 weeks	43 (91.5)
≥ 26 weeks	41 (87.2)
≥ 32 weeks	34 (72.3)
≥ 52 weeks	14 (29.8)
≥ 122 weeks	0
≥ 126 weeks	0
Duration of exposure[b] (weeks)	
n	47
Mean (SD)	43.90 (17.541)
Median	44.00
Min, Max	7.9, 75.7
Number of subject-day (week)[c]	2063

Source: Table 14.3.1.5, Listing 16.2.5.3

a: Subjects were counted in each applicable exposure category.
b: Duration of exposure = date of last dose of avatrombopag – date of first dose of study drug + 1
c: Number of subject-day = summation over all subjects' exposure durations

Demographic and baseline characteristics of study population (group 4)

The distribution of age, sex, ethnicity, weight, and BMI was generally balanced across the various treatment groups. The mean (SD) overall age was 48.9 (17.65) years and most subjects were <65 years (78.7% [107/136] subjects). There were more females (62.5% [85/136] subjects) than males (37.5% [51/136] subjects) and most subjects were White (83.1% [113/136] subjects). Most subjects were from North America (United States; 58.8% [80/136] subjects). While the majority of subjects in the Avatrombopag Treatment Group (59.4% [76/128] subjects) and Eltrombopag Treatment Group (81.8% [9/11] subjects) were from North America, the majority of subjects in the Placebo Treatment Group were from Europe (68.2% [15/22] subjects).

The mean Baseline platelet counts were 18.5×10^9/L and they were similar between the Avatrombopag Treatment Group (18.3×10^9/L) and the Eltrombopag Treatment Group (18.2×10^9/L), and slightly lower in the Placebo Treatment Group (15.0×10^9/L). Splenectomy status was balanced across groups with most subjects reporting a status of "no" (67.6%, 92/136 subjects). Overall, more than half of subjects used concomitant medications for ITP (65.4%, 89/136 subjects), but most of the subjects in the Eltrombopag Treatment Group (90.9%, 10/11 subjects) did not use concomitant medications for ITP.

Concomitant medications

The percentage of subjects in the Avatrombopag Treatment Group in Group 4 (96.1% [123/128] subjects) who took concomitant medications during the study was higher compared with the Placebo Treatment Group (77.3% [17/22] subjects), and similar to the Eltrombopag Treatment Group (90.9% [10/11] subjects), although the differences in Duration of Exposure (ie, longer duration of exposure for avatrombopag-treated subjects compared with those treated with placebo or eltrombopag [see also Table 2.7.4-14 above]) needs to be considered when interpreting these data. The majority of concomitant medications were under the anatomical classes of drugs for Alimentary Tract and Metabolism and Nervous System.

The percentage of avatrombopag-, placebo-, and eltrombopag-treated subjects taking drugs for Alimentary Tract and Metabolism were 32.8%, 27.3%, and 72.7%, respectively.

The percentage of avatrombopag-, placebo- and eltrombopag-treated subjects taking drugs for Nervous System were 27.3%, 18.2%, and 63.6%, respectively.

Adverse events

Since the Duration of Exposure for avatrombopag-treated subjects was significantly longer than that of both placebo- and eltrombopag-treated subjects in the chronic ITP studies (*see Table 2.7.4-14 in the Patient exposure section*), the analyses of comparative safety profiles are subject to observation-time bias. Therefore, exposure-adjusted incidence rates (number of subjects with an adverse event [AE] divided by the person-time at risk) were also assessed to more accurately reflect the AE frequencies among treatment groups.

Table 2.7.4-17 Group 4 Overview of Treatment-Emergent Adverse Events – Safety Analysis Set (Studies CL-003, CL-004, 302, and 305)

AE Category	Overall Incidence Rate n(%)			Exposure-Adjusted Incidence Rate*		
	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]
Subjects with Any TEAE	**14 (63.6)**	**11 (100)**	**125 (97.7)**	**4.233**	**4.966**	**1.728**
Treatment-Related TEAEs [b]	4 (18.2)	8 (72.7)	85 (66.4)	1.209	3.612	1.175
TEAEs with CTCAE Grade 3 or More	0	3 (27.3)	45 (35.2)	0.000	1.354	0.622
Serious TEAEs	1 (4.5)	0	32 (25.0)	0.302	0.000	0.442
Deaths [c]	0	0	0	0.000	0.000	0.000
Other SAEs [d]	1 (4.5)	0	32 (25.0)	0.302	0.000	0.442
Life Threatening	1 (4.5)	0	4 (3.1)	0.302	0.000	0.055
Requires Inpatient Hospitalization or Prolongation of Existing Hospitalization	1 (4.5)	0	16 (12.5)	0.302	0.000	0.221
Persistent or Significant Disability or Incapacity	0	0	2 (1.6)	0.000	0.000	0.028
Important Medical Events	0	0	8 (6.3)	0.000	0.000	0.111
TEAEs Leading to Study Drug Dose Adjustment	0	3 (27.3)	30 (23.4)	0.000	1.354	0.415
TEAES Leading to Study Drug Withdrawal	0	1 (9.1)	17 (13.3)	0.000	0.451	0.235
TEAEs Leading to Study Drug Dose Increase	0	3 (27.3)	3 (2.3)	0.000	1.354	0.041
TEAEs Leading to Study Drug Dose Reduction	0	0	4 (3.1)	0.000	0.000	0.055
TEAEs Leading to Study Drug Dose Interruption	0	0	11 (8.6)	0.000	0.000	0.152

*Exposure-adjusted incidence rate per subject-year.

A TEAE was defined as an AE that started on or after the date of first dose of study drug, up to 30 days after the last dose of study drug. For each row category, a subject with 2 or more AEs in that category was counted only once.

AE = adverse event, AVA = avatrombopag, CTCAE = common terminology criteria for adverse events, ELT = eltrombopag, ITP = immune thrombocytopenia, N = total number of subjects in the sample group, n = number of subjects in individual group, PBO = placebo, SAE = serious adverse event, TEAE = treatment-emergent adverse event.

a: N denotes all subjects in the Core Study and open-label Extension Phase who received avatrombopag.
b: Includes TEAEs considered by the investigator to be related to study drug or TEAEs with missing causality.
c: Includes all subjects with SAE resulting in death.
d: Includes subjects with nonfatal SAEs only. If a subject had both fatal and nonfatal SAEs, the subject was counted in the previous row and was not counted in this row.

Source: ISS Table 20.3.1.3a.

Table 2.7.4-18 Group 4 Treatment-Emergent Adverse Events by Decreasing Frequency – Occurrence >5% in the Avatrombopag Treatment Group - Safety Analysis Set (Studies CL-003, CL-004, 302, and 305)

MedDRA Preferred Terms	Overall Incidence Rate n(%)			Exposure-Adjusted Incidence Rate*		
	PBO (N=22)	ELT (N=11)	AVA (N=128)[a]	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]
Subjects with Any TEAE	14 (63.6)	11 (100)	125 (97.7)	4.233	4.966	1.728
Headache	3 (13.6)	3 (27.3)	39 (30.5)	0.907	1.354	0.539
Fatigue	2 (9.1)	5 (45.5)	36 (28.1)	0.605	2.257	0.498
Contusion	4 (18.2)	2 (18.2)	33 (25.8)	1.209	0.903	0.456
Epistaxis	4 (18.2)	2 (18.2)	24 (18.8)	1.209	0.903	0.332
Upper Respiratory Tract Infection	1 (4.5)	0	19 (14.8)	0.302	0.000	0.263
Thrombocytopenia	0	0	18 (14.1)	0.000	0.000	0.249
Arthralgia	0	2 (18.2)	16 (12.5)	0.000	0.903	0.221
Gingival Bleeding	0	0	16 (12.5)	0.000	0.000	0.221
Petechiae	2 (9.1)	0	14 (10.9)	0.605	0.000	0.194
Nasopharyngitis	0	3 (27.3)	13 (10.2)	0.000	1.354	0.180
Diarrhea	0	3 (27.3)	12 (9.4)	0.000	1.354	0.166
Insomnia	1 (4.5)	1 (9.1)	12 (9.4)	0.302	0.451	0.166
Nausea	0	2 (18.2)	12 (9.4)	0.000	0.903	0.166
Pain In Extremity	1 (4.5)	0	12 (9.4)	0.302	0.000	0.166
Back Pain	0	0	11 (8.6)	0.000	0.000	0.152
Dizziness	1 (4.5)	2 (18.2)	11 (8.6)	0.302	0.903	0.152
Mouth Hemorrhage	0	0	10 (7.8)	0.000	0.000	0.138

MedDRA Preferred Terms	Overall Incidence Rate n(%)			Exposure-Adjusted Incidence Rate*		
	PBO (N=22)	ELT (N=11)	AVA (N=128)[a]	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]
Vomiting	0	1 (9.1)	10 (7.8)	0.000	0.451	0.138
Cough	0	2 (18.2)	9 (7.0)	0.000	0.903	0.124
Ecchymosis	0	0	8 (6.3)	0.000	0.000	0.111
Platelet Count Increased	0	0	8 (6.3)	0.000	0.000	0.111
Dyspnoea	0	0	7 (5.5)	0.000	0.000	0.097
Hypertension	1 (4.5)	0	7 (5.5)	0.302	0.000	0.097
Oedema Peripheral	0	0	7 (5.5)	0.000	0.000	0.097

*Exposure-adjusted incidence rate per subject-year.

A TEAE was defined as an AE that started on or after the date of first dose of study drug, up to 30 days after the last dose of study drug.

Subjects with 2 or more AEs with the same PT were counted only once for that PT.

MedDRA Version 19.1.

AE = adverse event; AVA = avatrombopag, ELT = eltrombopag, MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects in the sample group, n = number of subjects in individual group, PBO = placebo, PT = preferred term, TEAE = treatment-emergent adverse event.

a: N denotes all subjects in the Core Study and open-label Extension Phases who received avatrombopag.

Source: ISS Table 20.3.3.3a.

TEAEs Grade 3 or 4

Table 2.7.4-19 Group 4 Treatment-Emergent Adverse Events (Grade 3 or 4) of any Causality in at Least 2 Subjects in the Avatrombopag Treatment Group by Preferred Term – Safety Analysis Set (Studies CL-003, CL-004, 302, and 305)

MedDRA Preferred Term	Overall Incidence Rate n (%)			Exposure-Adjusted Incidence Rate*		
	PBO (N=22)	ELT (N=11)	AVA (N=128)[a]	PBO (N=22)	ELT (N=11)	AVA (N=128)[a]
Subjects with Any TEAE	0	3 (27.3)	45 (35.2)	0.000	1.354	0.622
Thrombocytopenia	0	0	13 (10.2)	0.000	0.000	0.180
Platelet Count Increased	0	0	7 (5.5)	0.000	0.000	0.097
Platelet Count Decreased	0	0	5 (3.9)	0.000	0.000	0.069
Vomiting	0	0	3 (2.3)	0.000	0.000	0.041
Gastritis Hemorrhagic	0	0	2 (1.6)	0.000	0.000	0.028
Nausea	0	0	2 (1.6)	0.000	0.000	0.028
Fatigue	0	0	2 (1.6)	0.000	0.000	0.028
Alanine Aminotransferase Increased	0	0	2 (1.6)	0.000	0.000	0.028
Aspartate Aminotransferase Increased	0	0	2 (1.6)	0.000	0.000	0.028
Cerebrovascular Accident	0	0	2 (1.6)	0.000	0.000	0.028
Headache	0	0	2 (1.6)	0.000	0.000	0.028
Epistaxis	0	0	2 (1.6)	0.000	0.000	0.028

*Exposure-adjusted incidence rate per subject-year.

A TEAE was defined as an AE that started on or after the date of first dose of study drug, up to 30 days after the last dose of study drug.

Subjects with 2 or more AEs with the same PT were counted only once for that PT.

Adverse events were graded using CTCAE version 4.03 per SAP.

MedDRA Version 19.1.

AE = adverse event; AVA = avatrombopag, CTCAE = common terminology criteria for adverse events, ELT = eltrombopag, MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects in the sample group, n = number of subjects in individual group, PBO = placebo, PT = preferred term; SAP = Statistical Analysis Plan, TEAE = treatment-emergent adverse event.

a: N denotes all subjects in the Core Study and open-label Extension Phases who received avatrombopag.

Source: ISS Table 20.3.8.3a.

Treatment-related adverse events

Treatment-related TEAEs by PT in Group 4 in decreasing order that were reported in at least 2% of subjects in any treatment group are presented in Table 2.7.4-20. Overall, the percentage of treatment-related TEAEs was similar between the Avatrombopag Treatment Group (66.4% [85/128] subjects) and the Eltrombopag Treatment Group (72.7% [8/11] subjects), and lower in the Placebo Treatment Group (18.2% [4/22] subjects).

Table 2.7.4-20 Group 4 Treatment-Related, Treatment-Emergent Adverse Events by Decreasing Frequency – Occurrence ≥2% in Any Treatment Group by Preferred Term – Safety Analysis Set (Studies CL-003, CL-004, 302, and 305)

MedDRA Preferred Term	Overall Incidence Rate n (%)			Exposure-Adjusted Incidence Rate*		
	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]
Subjects with Any TEAE	**4 (18.2)**	**8 (72.7)**	**85 (66.4)**	**1.209**	**3.612**	**1.175**
Headache	2 (9.1)	1 (9.1)	26 (20.3)	0.605	0.451	0.359
Fatigue	2 (9.1)	2 (18.2)	16 (12.5)	0.605	0.903	0.221
Nausea	0	1 (9.1)	11 (8.6)	0.000	0.451	0.152
Dizziness	1 (4.5)	2 (18.2)	9 (7.0)	0.302	0.903	0.124
Platelet Count Increased	0	0	8 (6.3)	0.000	0.000	0.111
Diarrhoea	0	2 (18.2)	7 (5.5)	0.000	0.903	0.097
Epistaxis	0	0	7 (5.5)	0.000	0.000	0.097
Thrombocytopenia	0	0	6 (4.7)	0.000	0.000	0.083
Vomiting	0	0	6 (4.7)	0.000	0.000	0.083
Arthralgia	0	0	5 (3.9)	0.000	0.000	0.069
Back pain	0	0	5 (3.9)	0.000	0.000	0.069
Pain in Extremity	0	0	5 (3.9)	0.000	0.000	0.069
Insomnia	1 (4.5)	1 (9.1)	4 (3.1)	0.302	0.451	0.055
Abdominal Pain Upper	0	1 (9.1)	3 (2.3)	0.000	0.451	0.041
Blood Lactate Dehydrogenase Increased	0	0	3 (2.3)	0.000	0.000	0.041
Dyspepsia	1 (4.5)	0	3 (2.3)	0.302	0.000	0.041
Flatulence	0	1 (9.1)	3 (2.3)	0.000	0.451	0.041
Hyperlipidemia	0	0	3 (2.3)	0.000	0.000	0.041

MedDRA Preferred Term	Overall Incidence Rate n (%)			Exposure-Adjusted Incidence Rate*		
	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]
Myalgia	0	0	3 (2.3)	0.000	0.000	0.041
Platelet Count Decreased	0	0	3 (2.3)	0.000	0.000	0.041
Rash	0	0	3 (2.3)	0.000	0.000	0.041
Acne	0	1 (9.1)	2 (1.6)	0.000	0.451	0.028
Alanine Aminotransferase Increased	0	1 (9.1)	2 (1.6)	0.000	0.451	0.028
Somnolence	1 (4.5)	0	2 (1.6)	0.302	0.000	0.028
Abdominal Discomfort	0	1 (9.1)	1 (0.8)	0.000	0.451	0.014
Gastrooesophageal Reflux Disease	0	1 (9.1)	1 (0.8)	0.000	0.451	0.014
Glossodynia	0	1 (9.1)	1 (0.8)	0.000	0.451	0.014
Discomfort	0	1 (9.1)	0	0.000	0.451	0.000
Ear swelling	1 (4.5)	0	0	0.302	0.000	0.000
Lymphocyte Count Increased	0	1 (9.1)	0	0.000	0.451	0.000
Pleurisy	0	1 (9.1)	0	0.000	0.451	0.000

*Exposure-adjusted incidence rate per subject-year.

A TEAE was defined as an AE that started on or after the date of first dose of study drug, up to 30 days after the last dose of study drug.

Subjects with 2 or more AEs with the same PT were counted only once for that PT.

MedDRA Version 19.1.

AE = adverse event, AVA = avatrombopag, ELT = eltrombopag, MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects in the sample group, n = number of subjects in individual group, PBO = placebo, PT = preferred term, TEAE = treatment-emergent adverse event.

a: N denotes all subjects in the Core Study and open-label Extension Phases who received avatrombopag.

Source: ISS Table 20.3.4.3a.

Serious adverse event/deaths/other significant events

SAEs

Table 2.7.4-21 Group 4 Treatment-Emergent Serious Adverse Events in ≥2 Subjects in Any Treatment Group by Decreasing Frequency - Safety Analysis Set (Studies CL-003, CL-004, 302, and 305)

MedDRA Preferred Term	Overall Incidence Rate n(%)			Exposure-Adjusted Incidence Rate*		
	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]
Subjects with Any TEAE	1 (4.5)	0	32 (25.0)	0.302	0.000	0.442
Thrombocytopenia	0	0	8 (6.3)	0.000	0.000	0.111
Vomiting	0	0	4 (3.1)	0.000	0.000	0.055
Platelet Count Decreased	0	0	3 (2.3)	0.000	0.000	0.041
Cerebrovascular Accident	0	0	2 (1.6)	0.000	0.000	0.028
Gastritis Hemorrhagic	0	0	2 (1.6)	0.000	0.000	0.028
Headache	0	0	2 (1.6)	0.000	0.000	0.028
Immune Thrombocytopenic Purpura	1 (4.5)	0	2 (1.6)	0.302	0.000	0.028
Nausea	0	0	2 (1.6)	0.000	0.000	0.028

*Exposure-adjusted incidence rate per subject-year.

A TEAE was defined as an AE that started on or after the date of first dose of study drug, up to 30 days after the last dose of study drug.

Subjects with 2 or more AEs with the same PT is counted only once for that PT.

MedDRA Version 19.1.

AE = adverse events, AVA = avatrombopag, ELT = eltrombopag, MedDRA = Medical Dictionary for Regulatory Activities, N = total number of subjects in the sample group, n = number of subjects in individual group, PBO = placebo, PT = preferred term, TEAE = treatment-emergent adverse event.

a: N denotes all subjects in the Core Study and open-label Extension Phases who received avatrombopag.

Source: ISS Table 20.4.1.3a.

Deaths

There were no subject deaths reported in the Primary Safety Dataset (Group 4).

Adverse events of special interest (AESIs)

As predefined in the 2 Phase 3 studies in patients with ITP (Study 302 and Study 305), AESI included Recurrence of Thrombocytopenia, Thromboembolic Events, Bleeding Events, Gastric Atrophy, Neoplastic Events, Bone Marrow Pathology (Excluding Neoplasms), and Clinically Significant Liver Tests. These AESI were specifically identified because they had all been reported as TEAEs with the other 2 TPO receptor agonists, except for Gastric Atrophy, which was a reversible finding in the multiple-dose nonclinical avatrombopag toxicology studies.

Although AESI were not defined in the original Phase 2 Study CL-003 and Study CL-004 protocols or flagged in the study level databases, they were, for completeness, retrospectively identified using the same definitions for this safety analysis. Group 4 treatment-emergent AESI are presented in Table 2.7.4-22.

Table 2.7.4-22 Group 4 Treatment-Emergent Adverse Events of Special Interest – Safety Analysis Set (Studies CL-003, CL-004, 302, and 305)

Adverse Events of Special Interest Preferred Term	Overall Incidence Rate n(%)			Exposure-Adjusted Incidence Rate*		
	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]
Recurrence of Thrombocytopenia	**0**	**0**	**11 (8.6)**	**0.000**	**0.000**	**0.152**
Thrombocytopenia	0	0	11 (8.6)	0.000	0.000	0.152
Thromboembolic Event	**0**	**0**	**9 (7.0)**	**0.000**	**0.000**	**0.124**
Cerebrovascular accident	0	0	2 (1.6)	0.000	0.000	0.028
Deep Vein Thrombosis	0	0	1 (0.8)	0.000	0.000	0.014
Jugular Vein Thrombosis	0	0	1 (0.8)	0.000	0.000	0.014
Myocardial Infarction	0	0	1 (0.8)	0.000	0.000	0.014
Pelvic Venous Thrombosis	0	0	1 (0.8)	0.000	0.000	0.014
Portal Vein Thrombosis	0	0	1 (0.8)	0.000	0.000	0.014
Pulmonary Embolism	0	0	1 (0.8)	0.000	0.000	0.014
Retinal Artery Occlusion	0	0	1 (0.8)	0.000	0.000	0.014
Thrombophlebitis Superficial	0	0	1 (0.8)	0.000	0.000	0.014
Transient Ischemic Attack	0	0	1 (0.8)	0.000	0.000	0.014
Bleeding Event	**1 (4.5)**	**0**	**18 (14.1)**	**0.302**	**0.000**	**0.249**
Contusion	0	0	5 (3.9)	0.000	0.000	0.069
Epistaxis	0	0	4 (3.1)	0.000	0.000	0.055
Gingival Bleeding	0	0	3 (2.3)	0.000	0.000	0.041
Menorrhagia	0	0	3 (2.3)	0.000	0.000	0.041
Petechiae	1 (4.5)	0	3 (2.3)	0.302	0.000	0.041
Gastritis Hemorrhagic	0	0	2 (1.6)	0.000	0.000	0.028
Mouth Hemorrhage	0	0	2 (1.6)	0.000	0.000	0.028
Hematoma	0	0	1 (0.8)	0.000	0.000	0.014
Hemorrhage Intracranial	0	0	1 (0.8)	0.000	0.000	0.014
Hemorrhagic Diathesis	0	0	1 (0.8)	0.000	0.000	0.014
Immune Thrombocytopenic Purpura	0	0	1 (0.8)	0.000	0.000	0.014
Increased Tendency to Bruise	0	0	1 (0.8)	0.000	0.000	0.014
Purpura	0	0	1 (0.8)	0.000	0.000	0.014
Vaginal Hemorrhage	0	0	1 (0.8)	0.000	0.000	0.014

Adverse Events of Special Interest Preferred Term	Overall Incidence Rate n(%)			Exposure-Adjusted Incidence Rate*		
	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]	PBO (N=22)	ELT (N=11)	AVA (N=128) [a]
Gastric Atrophy Event	**0**	**0**	**0**	**0.000**	**0.000**	**0.000**
Neoplastic Event	**0**	**0**	**6 (4.7)**	**0.000**	**0.000**	**0.083**
Chronic Lymphocytic Leukemia	0	0	1 (0.8)	0.000	0.000	0.014
Chronic Myelomonocytic Leukemia	0	0	1 (0.8)	0.000	0.000	0.014
Lipoma	0	0	1 (0.8)	0.000	0.000	0.014
Myelofibrosis	0	0	1 (0.8)	0.000	0.000	0.014
Myeloproliferative Neoplasm	0	0	1 (0.8)	0.000	0.000	0.014
Skin Papilloma	0	0	1 (0.8)	0.000	0.000	0.014
Bone Marrow Pathology	0	0	0	0.000	0.000	0.000
Clinically Significant Liver Test	0	0	5 (3.9)	0.000	0.000	0.069
Alanine Aminotransferase Increased	0	0	4 (3.1)	0.000	0.000	0.055
Aspartate Aminotransferase Increased	0	0	3 (2.3)	0.000	0.000	0.041
Gamma-glutamyltransferase Increased	0	0	1 (0.8)	0.000	0.000	0.014
Hepatic Enzyme Increased	0	0	1 (0.8)	0.000	0.000	0.014

*Exposure-adjusted incidence rate per subject-year.

A TEAE was defined as an AE that started on or after the date of the first dose of study drug, up to 30 days after the last dose of study drug.

Subjects with 2 or more AEs in the same category of AE of special interest (or with the same PT) were counted only once for that category of AE of special interest (or PT).

AE = adverse event, N = total number of subjects in the sample group, n = number of subjects in individual group, PT = preferred term, TEAE = treatment-emergent adverse event.

a: N denotes all subjects in the Core Study and open-label Extension Phases who received avatrombopag.

Source: ISS Table 20.4.12.3a.

Recurrence of (or rebound) **thrombocytopenia** was defined as a platelet count $<10\times10^9$/L and 10×10^9/L below Baseline which occurred after the stopping of study drug and up to 30 days after the last dose of study drug. AESI in the Recurrence of Thrombocytopenia category were reported in 8.6% (11/128) of subjects in the Avatrombopag Treatment Group (Table 2.7.4-22).

In the Avatrombopag Treatment Group, 7.0% (9/128) of subjects reported treatment-emergent AESI in the **Thromboembolic Events** category (Table 2.7.4-22); the exposure-adjusted incidence rate was 0.124. All Thromboembolic Event AESI were reported in only single avatrombopag-treated subjects (0.8%), except for cerebrovascular accident, which was reported by 2 (1.6%) subjects; there was no clustering a specific thromboembolic event type and no safety signal was identified. The time of onset of AESI in the Thromboembolic Events category was greater than 26 weeks for 2 subjects, 12 to less than 26 weeks for 4 subjects, 4 to less than 12 weeks for 1 subject, and 1 to less than 4 weeks for 2 subjects.

Study 302 and Study 305 assessed a panel of gastric biomarkers to evaluate for potential **gastric toxicity**, based on the reversible, nonclinical histologic changes identified in the stomach (gastric atrophy) in repeat-dose toxicology studies; these biomarkers were associated with decreased gastric acid production and a compensatory increase in serum gastrin levels. In addition to serum gastrin levels, fasting gastrin-17, PG-I and PG-II, were also evaluated to further assess gastric safety.

In the Avatrombopag Treatment Group, 4.7% (6/128) of subjects reported a treatment-emergent AESI in the **Neoplastic Event** category; the exposure-adjusted incidence rate was 0.083. All events occurred in single (0.8%) subjects only, and included chronic lymphocytic leukemia, chronic myelomonocytic leukemia, lipoma, myelofibrosis, myeloproliferative neoplasms, and skin papilloma; no safety signal was identified. The time of onset of AESI in the Neoplastic Events category was greater than 26 weeks for 2 subjects, 12 to less than 26 weeks for 1 subject, and 4 to less than 12 weeks for 3 subjects.

Table 2.7.4-23 Group 4 Subjects with Neoplasms/Malignancies by Ascending Day on Study

Case No.	[redacted]	Study	Day of Onset	Neoplasm/ Malignancy Adverse Event	Avatrombopag -related?
1		CL-004	Day 44	Myeloproliferative neoplasm	No
2		305	Day 62	Chronic Lymphocytic Leukemia	No
3		CL-004	Day 70	Lipoma	No
4		CL-004	Day 195	Skin Papilloma (Verrucae Vulgaris)	No
5		302	Day 209	Myelofibrosis	Possibly
6		302	Day 267	Chronic Myelomonocytic Leukemia	No

No treatment-emergent **bone marrow pathology** AESI were reported. One subject in Study 305 experienced a non-treatment emergent TEAE of bone marrow reticulin fibrosis (Study 305 CSR), which was reported as SAE bone marrow reticulin fibrosis (Common Terminology Criteria [CTC] Grade3). However, the subject had no associated clinical signs or symptoms.

The event was reported as ongoing at the time of the last available report.

The investigator classified the event of bone marrow reticulin fibrosis to be probably related to avatrombopag."

The time of onset of AESI in the **Clinically Significant Liver Tests** category was greater than 26 weeks for 1 subject, 12 to less than 26 weeks for 2 subjects, 4 to less than 12 weeks for 1 subject, and 1 to less than 4 weeks for 1 subject.

All 5 subjects who had liver enzyme elevations were asymptomatic and recovered, with 4 of the 5 subjects continuing their current dose of avatrombopag over the period of the elevations (1 subject had avatrombopag briefly interrupted and then restarted at the same dose), suggesting that avatrombopag administration was not the causative factor in these liver enzymes elevations; these elevations were not accompanied by increases in bilirubin or alkaline phosphatase. No significant signal of avatrombopag-induced hepatotoxicity was identified across the 4 studies in patients with ITP.

.

Table 73-1 Summary of Gastric Biomarker Baseline Mean Values and Mean Changes from Baseline at End of Treatment and Follow-up Visits (Studies 302 and 305)

Laboratory Test (unit) [ref. range] Visit Statistic	Placebo	Eltrombopag	Avatrombopag
Gastrin (pmol/L) [<6.25 to 55.32 pmol/L]			
Baseline (n)	17	11	63
Mean (SD)	26.2 (39.54)	16.9 (11.50)	21.9 (23.46)
End of Treatment (n)	7	5	56
Mean Change from Baseline (SD)	-13.7 (34.36)	-2.9 (8.55)	4.9 (37.61)
Follow-up (n)	1	3	40
Mean Change from Baseline (SD)	0.0 (-)	-0.3 (1.99)	3.7 (34.82)
Gastrin-17 (pmol/L) [1 to 10 pmol/L]			
Baseline (n)	17	11	64
Mean (SD)	6.1 (15.01)	3.5 (4.96)	4.3 (8.72)
End of Treatment (n)	7	5	58
Mean Change from Baseline (SD)	-6.7 (17.34)	0.1 (1.95)	1.4 (8.25)
Follow-up (n)	1	3	42
Mean Change from Baseline (SD)	0.0 (-)	-0.4 (1.20)	2.7 (13.20)
Pepsinogen-I (µg/L) [30 to 165 µg/L]			
Baseline (n)	17	11	63
Mean (SD)	96.9 (71.90)	112.0 (84.28)	104.7 (68.64)
End of Treatment (n)	7	5	57
Mean Change from Baseline (SD)	-30.9 (93.40)	1.8 (29.44)	1.6 (62.84)
Follow-up (n)	1	3	42
Mean Change from Baseline (SD)	-6.0 (-)	7.3 (16.77)	23.3 (91.47)
Pepsinogen-II (µg/L) [3 to 15 µg/L]			
Baseline (n)	17	11	62
Mean (SD)	8.5 (3.76)	10.8 (11.89)	10.8 (7.54)
End of Treatment (n)	7	5	56
Mean Change from Baseline (SD)	-0.9 (4.60)	1.0 (2.74)	-0.2 (4.91)
Follow-up (n)	1	3	41
Mean Change from Baseline (SD)	1.0 (-)	-0.3 (1.15)	1.7 (7.43)

Laboratory findings

Haematology (Group 4 – ITP studies)

Mean values over time for all hematology parameters were similar among the Avatrombopag, Eltrombopag, and Placebo Treatment Groups.

There were subjects in all treatment groups in Group 4 with markedly abnormal hematology parameters (excluding platelet count). Markedly abnormal low hemoglobin was observed in a higher percentage of subjects in the Avatrombopag Treatment Group (9.5% [12/126] subjects) when compared to the Placebo Treatment Group (4.5% [1/22] subject) and Eltrombopag Treatment Group (0%). Markedly abnormal low neutrophils and leukocytes were observed in a lower percentage of avatrombopag- (2.4% [3/126] subjects each) and placebo-treated subjects (4.5% [1/22] subject each) when compared to those treated with eltrombopag (9.1% [1/11] subject.

Clinical Chemistry – Group 4

Avatrombopag: Integrated Summary of Safety — Page 3 of 5

Table 20.5.1.3.3
Treatment-Emergent Markedly Abnormal Laboratory Results
ITP (Studies CL-003, CL-004, 302 and 305)
Safety Analysis Set

Laboratory Test	Placebo (N=22) n (%)	Eltrombopag (N=11) n (%)	Avatrombopag (N=128) n (%)
Gamma Glutamyl Transferase (U/L)			
n[a]	5	0	63
Markedly Abnormal High	0	0	3 (4.8)
Glucose (mmol/L)			
n[a]	22	11	127
Markedly Abnormal Low	0	0	7 (5.5)
Markedly Abnormal High	0	1 (9.1)	10 (7.9)
Hemoglobin (g/L)			
n[a]	22	11	126
Markedly Abnormal Low	1 (4.5)	0	12 (9.5)
Lactate Dehydrogenase (U/L)			
n[a]	21	11	125
Markedly Abnormal High	0	0	0
Leukocytes (10^9/L)			
n[a]	22	11	126
Markedly Abnormal Low	1 (4.5)	1 (9.1)	3 (2.4)

Vital Signs, Physical Findings, and Other Observations Related to Safety

Mean values over time for vital sign parameters were generally similar between the Avatrombopag, Eltrombopag, and Placebo Treatment Groups.

Mean and mean change from Baseline ECG results were generally similar between the Avatrombopag, Eltrombopag, and Placebo Treatment Groups. The percentage of subjects in the Avatrombopag, Eltrombopag, and Placebo Treatment Groups who had abnormal ECG results at Baseline (17.5%, 20.0%, and 19.0%, respectively) were generally comparable. At the EOT, a lower percentage of subjects in the Avatrombopag Treatment Group compared to the Placebo Treatment Group had abnormal ECG results (27.1% [13/48] subjects and 38.1% [8/21] subjects, respectively). No subjects in the Eltrombopag Treatment Group had abnormal ECG results at EOT. No subjects in any treatment group had abnormal ECG results at follow-up.

There were subjects in each treatment group with either abnormal post-Baseline QT interval corrected for heart rate using Bazett's (QTcB) and Fridericia's (QTcF) formula results; 1.0% (1/105) of subjects had highly abnormal QTcB results. No subjects in the Eltrombopag or Placebo Treatment Groups had QTcB results that were highly abnormal, and no subjects in any treatment group had highly abnormal QTcF results at Baseline.

Safety in special populations

Safety in special groups and situations was not evaluated in Group 4 because of the population size.

Safety related to drug-drug interactions and other interactions

Avatrombopag has been shown to have potentially clinically important interactions with dual moderate or strong CYP3A4/5 and CYP2C9 inhibitors and inducers, with less significant interactions with strong CYP3A4/5 inhibitors and moderate CYP2C9 inhibitors.

Moderate or Strong CYP3A4/5 Inhibitors

Concomitant use of avatrombopag with strong CYP3A4/5 inhibitors increased avatrombopag exposure. In an open-label cross-over study in healthy adult volunteers, coadministration of itraconazole, a strong CYP3A4/5 inhibitor 200 mg QD at steady state with a single 20 mg dose of avatrombopag resulted in a 7.4% and 37.4% increase in Cmax and AUC(0-inf) of avatrombopag, respectively. Population-based PK/PD simulations at steady state conditions of avatrombopag indicated that co-administration of avatrombopag with a CYP3A4/5 had only minimal impact on platelet counts, and thus modification of the starting dose of avatrombopag (20 mg QD) is not recommended (Study AVA-PKPD-ITP-002). As described in the proposed dosage and administration recommendations, platelet counts should be assessed weekly until a stable platelet count has been achieved and then monthly thereafter.

Dual Moderate or Strong CYP3A4/5 and CYP2C9 Inhibitors

Concomitant use of avatrombopag with dual moderate or strong CYP3A4/5 and CYP2C9 inhibitors increased avatrombopag exposure. In an open-label cross-over study in healthy adult volunteers, coadministration of fluconazole, a moderate dual inhibitor of CYP2C9 and CYP3A4/5, 400 mg QD at steady state with a single 20-mg dose avatrombopag resulted in a 1.17- and 2.16-fold increase in Cmax and AUC(0-inf) of avatrombopag, respectively. Population-based PK/PD simulations at steady state conditions of avatrombopag indicated that a reduction in the frequency of the starting dose of avatrombopag to 20 mg three times a week would result in a higher percentage of patients achieving the target platelet count range (50 to $<150\times10^9$/L) compared with 20 mg QD (Study AVA-PKPD-ITP-002). As described in the proposed dosage and administration recommendations, platelet counts should be assessed weekly until a stable platelet count has been achieved and then monthly thereafter to ensure optimized dosing and maintenance of platelet counts in the target range.

Moderate or Strong CYP2C9 Inhibitors

Concomitant use of avatrombopag with moderate to strong CYP2C9 inhibitors increased avatrombopag exposure. Population-based PK/PD simulations at steady state conditions of avatrombopag indicated that co-administration of avatrombopag with a CYP2C9 inhibitor would have only minimal impact on platelet counts, and thus modification of the starting dose of avatrombopag (20 mg QD) is not recommended (Study AVA-PKPD-ITP-002). As described in the proposed dosage and administration instructions, platelet counts should be assessed weekly until a stable platelet count has been achieved and then monthly thereafter to ensure optimized dosing and maintenance of platelet counts in the target range.

Moderate or Strong Dual CYP2C9 and CYP3A4/5 Inducers

Concomitant use of avatrombopag with moderate or strong CYP3A4/5 or CYP2C9 inducers reduced avatrombopag exposure. This may result in a decrease of efficacy. In an open label cross-over study in healthy adult volunteers, co-administration of rifampin, a strong CYP3A4/5 and a moderate CYP2C9 inducer, 600 mg QD at steady state with a single 20 mg dose of avatrombopag resulted in no change in Cmax, but an approximately 42.1% decrease in AUC(0-inf) of avatrombopag. Population-based PK/PD simulations at steady state conditions of avatrombopag indicated that when avatrombopag is coadministered with moderate or strong dual CYP3A4/5 and CYP2C9 inducers, a significant reduction in overall platelet count elevations is expected. Thus, concomitant use of avatrombopag with either a moderate or strong dual CYP3A4/5 and CYP2C9 inducer, requires a higher starting dose of avatrombopag (40 mg QD), which will result in a higher percent of patients achieving the target platelet count range of (50 to $<150\times10^9$/L) compared with a 20 mg QD starting dose (Study AVA-PKPD-ITP-002). As described in the proposed dosage and administration instructions, platelet counts should be assessed weekly until a stable platelet count has been achieved and then monthly thereafter to ensure optimized dosing.

Proposed recommendations for adjustments of avatrombopag starting dose for concomitant administration with CYP3A4 and CYP2C9 perpetrators, based on PK/PD simulations using population-based methods:

Table 2.7.2-8 Proposed Recommendations for Adjustments of Avatrombopag Starting Dose for Concomitant Administration with CYP3A4 and CYP2C9 Perpetrators

Treatment	Avatrombopag Starting Dose Recommendations
CYP2C9 inhibitor (moderate or strong)	No dose adjustments necessary (20 mg QD)
CYP3A4 inhibitor (moderate or strong)	No dose adjustments necessary (20 mg QD)
Dual CYP2C9 and CYP3A4 inducer (moderate or strong)	40 mg QD
Dual CYP2C9 and CYP3A4 inhibitor (moderate or strong)	20 mg 3 times a week

CYP = cytochrome P450, QD = once daily.

Discontinuation due to adverse events

Table 20.4.7.3a
Treatment-Emergent Adverse Events Leading to Discontinuation from Study Drug by System Organ Class and Preferred Term
ITP (Studies CL-003, CL-004, 302 and 305)
Safety Analysis Set

MedDRA System Organ Class Preferred Term	Placebo (N=22)			Eltrombopag (N=11)			Avatrombopag (N=128)		
	n	(%)	Rate*	n	(%)	Rate*	n	(%)	Rate*
Subjects with any TEAE	0			1	(9.1)	0.451	17	(13.3)	0.235
Blood and lymphatic system disorders	0			0			2	(1.6)	0.028
Haemorrhagic diathesis	0			0			1	(0.8)	0.014
Leukocytosis	0			0			1	(0.8)	0.014
Cardiac disorders	0			0			1	(0.8)	0.014
Myocardial infarction	0			0			1	(0.8)	0.014
Gastrointestinal disorders	0			0			2	(1.6)	0.028
Erosive duodenitis	0			0			1	(0.8)	0.014
Gastritis haemorrhagic	0			0			1	(0.8)	0.014
Nausea	0			0			1	(0.8)	0.014
Vomiting	0			0			1	(0.8)	0.014
General disorders and administration site conditions	0			1	(9.1)	0.451	1	(0.8)	0.014
Discomfort	0			1	(9.1)	0.451	0		
Polyserositis	0			0			1	(0.8)	0.014
Infections and infestations	0			0			1	(0.8)	0.014
Pneumonia	0			0			1	(0.8)	0.014
Injury, poisoning and procedural complications	0			0			1	(0.8)	0.014
Contusion	0			0			1	(0.8)	0.014
Investigations	0			0			5	(3.9)	0.069
Platelet count increased	0			0			5	(3.9)	0.069
Musculoskeletal and connective tissue disorders	0			0			1	(0.8)	0.014
Musculoskeletal chest pain	0			0			1	(0.8)	0.014
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0			0			1	(0.8)	0.014
Chronic myelomonocytic leukaemia	0			0			1	(0.8)	0.014
Nervous system disorders	0			0			5	(3.9)	0.069
Cerebrovascular accident	0			0			1	(0.8)	0.014
Dizziness	0			0			1	(0.8)	0.014
Head discomfort	0			0			1	(0.8)	0.014
Headache	0			0			2	(1.6)	0.028
Transient ischaemic attack	0			0			1	(0.8)	0.014
Psychiatric disorders	0			0			1	(0.8)	0.014
Insomnia	0			0			1	(0.8)	0.014
Skin and subcutaneous tissue disorders	0			0			1	(0.8)	0.014
Petechiae	0			0			1	(0.8)	0.014
Vascular disorders	0			0			1	(0.8)	0.014
Pelvic venous thrombosis	0			0			1	(0.8)	0.014

Source: ADAE
*Exposure Adjusted Incidence Rate per Subject-Year
A TEAE is defined as an adverse event that started on or after the date of first dose of study drug, up to 30 days after the last dose of study drug.
Subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).
MedDRA Version 19.1
Program: S:\Dova\sNDA-ITP\STAT\5_Analysis\PGM\ISS\TLG\t04_07_03a.sas 27MAR2018 11:26

Post marketing experience

The 167 ICSRs received involved a total of 351 individual adverse event (AE) terms.

Of the total AEs reported, the five most commonly involved MedDRA SOCs were:

- **General Disorders and Administrative Conditions** (25.1% [88/351])
- **Gastrointestinal Disorders** (17.1% [60/351])
- **Nervous System Disorders** (13.7% [48/351])
- **Injury, Poisoning & Procedural Complications** (13.7% [48/351])
- **Investigations** (7.1% [25/351])

The most frequently reported (≥ 10) MedDRA PTs were:

- **Headache** (7.4% [26/351])
- **Fatigue** (6.6% [23/351])
- **Nausea** (5.1% [18/351])
- **Off-label use** (3.7% [13/351])
- **Drug ineffective** (3.4% [12/351])
- **Platelet count decreased** (3.4% [12/351])
- **Inappropriate schedule of product administration** (2.8% [10/351])

Fatigue, Headache, and Nausea are "expected" adverse reactions in the approved US prescribing information, while Fatigue is listed as an "expected" adverse reaction in the approved EU Summary of Product Characteristics (SmPC).

Literature review of safety in TPO-RAs

Comparison of the Safety Profile of Avatrombopag in the Treatment of ITP Versus Published Data on Other TPO Receptor Agonists

A comprehensive review of the published literature for the two approved TPO receptor agonists for the treatment of ITP, eltrombopag (Revolade; Novartis) and romiplostim (Nplate; Amgen), was conducted to provide a historical benchmark of the safety of these products for comparison with the safety profile of avatrombopag in the same patient population, acknowledging the limitations of cross-study comparisons.

This summary reviewed the overall incidences of AEs, deaths, and SAEs from 20 selected publications on TPO receptor agonist therapy in adult patients with ITP (*see Table 2*).

Table 2 Characteristics of Included Clinical Studies of TPO Receptor Agonists in Adult ITP Patients

Author, Year	Study Design Number of Patients	Dose and Frequency of Administration
Randomised Controlled Trials		
Eltrombopag		
Placebo Comparator		
Bussel, et al, 2007	Multicentre, double-blind, RCT Baseline platelet count <30×10^9/L 88 eltrombopag, 29 placebo	30, 50, or 75 mg/d for 6 weeks.
Bussel, et al, 2009	Multicentre, double-blind, RCT Baseline platelet count <30×10^9/L 76 eltrombopag, 38 placebo	50 mg daily for 6 weeks; dose was adjusted to achieve target platelet counts of 50 to 200×10^9/L.
Cheng, et al, 2011	Multicentre, double-blind, RCT Baseline platelet count <30×10^9/L 135 eltrombopag, 61 placebo	50 mg daily for 6 months; dose was adjusted to achieve target platelet counts of 50 to 200×10^9/L.
Tomiyama, et al, 2012	Multicentre, double-blind RCT – Japanese patients Baseline platelet count <30×10^9/L 15 eltrombopag, 8 placebo	12.5 mg daily for 6 weeks; dose could be adjusted to 25 mg based on platelet counts at Week 3.
Yang, et al, 2016	Multicentre, double-blind RCT – Chinese patients Baseline platelet count <30×10^9/L 104 eltrombopag, 51 placebo	25 mg daily for 6 weeks; dose was adjusted (maximum 75 mg) to achieve target platelet counts of 50 to 250×10^9/L.
Author, Year	**Study Design Number of Patients**	**Dose and Frequency of Administration**
Romiplostim		
Placebo Comparator		
Bussel, et al, 2006	Multicentre, double-blind RCT (Part B) Baseline platelet count <30×10^9/L if not on corticosteroids, <50×10^9/L if on corticosteroids 17 romiplostim, 4 placebo	1 or 3 µg/kg SC weekly for 6 weeks, no dose adjustments.
Kuter, et al, 2008	Two multicentre, double-blind RCTs – one enrolled non-splenectomized patients, the other patients >4 weeks post-splenectomy Baseline platelet count <30×10^9/L 84 romiplostim, 41 placebo	Starting dose of 1 µg/kg SC weekly for 24 weeks; dose was adjusted to achieve target platelet counts of 50 to 200×10^9/L.
Shirasugi, et al, 2011	Multicentre, double-blind RCT Japanese patients with a baseline platelet count ≤30×10^9/L 22 romiplostim, 12 placebo	Starting dose of 3 µg/kg SC weekly for 12 weeks; dose was adjusted to achieve target platelet counts of 50 to 200×10^9/L.
Standard of Care Comparator		
Kuter, et al, 2010	Multicentre, open-label RCT Baseline platelet count <50×10^9/L, no previous splenectomy 154 romiplostim, 75 standard of care	Starting dose of 3 µg/kg SC weekly for 52 weeks; dose was adjusted to achieve target platelet counts of 50 to 200×10^9/L.
Non-Randomised, Uncontrolled, Open-Label		
Eltrombopag		
Bussel, et al, 2013	Multicentre, open-label, single-arm Baseline platelet count 20-50×10^9/L 66 eltrombopag	50 mg daily (could increase to 75 mg) for up to 6 weeks, then off-therapy for 4 weeks, on-therapy for up to 6 weeks, etc
Tomiyama, et al, 2012	Multicentre, open-label extension – Japanese patients Baseline platelet count <30×10^9/L 23 eltrombopag	12.5 mg daily or previous RCT dose for 6 months; dose could be adjusted based on platelet counts.

Author, Year	Study Design Number of Patients	Dose and Frequency of Administration
Katsutani, et al, 2013	Multicentre, open-label extension study Prior participation in Japanese 6 month RCT 19 eltrombopag	12.5, 25, or 50 mg daily; dose was adjusted to achieve target platelet counts of 50 to 200×10^9/L. QOD dosing was allowed.
Wong, et al, 2017	Multicentre, open-label extension study Prior participation in RCT 302 eltrombopag	25 to 75 mg/d. QOD or less frequent dosing was allowed. Median duration 2.37 years (range 2 days to 8.76 years)
Brynes, et al, 2017	Multicentre, open-label, prospective Effects on bone marrow 162 eltrombopag	5 to 75 mg/d; median 49.7 mg. Median duration 104 weeks
Romiplostim		
Bussel, et al, 2006	Multicentre, open-label, dose-finding study (Part A) Baseline platelet count <30×10^9/L if not on corticosteroids, <50×10^9/L if on corticosteroids 24 romiplostim (6 cohorts of 4 subjects)	0.2, 0.5, 1, 3, 6, and 10 µg/kg SC two doses separated by 2 weeks (Day 1 and Day 15)
Newland, et al, 2006	Multicentre, open-label Baseline platelet count <30×10^9/L if not on corticosteroids, <50×10^9/L if on corticosteroids 16 romiplostim	30, 100, 300, and 500 µg SC two doses separated by 2 weeks (Day 1 and Day 15)
Shirasugi, et al, 2009	Multicentre, open-label, dose-escalation Japanese subjects with a baseline platelet count <30×10^9/L if not on corticosteroids, <50×10^9/L if on corticosteroids 12 romiplostim (3 cohorts of 4 subjects)	1, 3, and 6 µg/kg SC two doses separated by 1 week (Day 1 and Day 8)
Shirasugi, et al, 2012	Multicentre, open-label extension study Prior participation in Japanese RCT and platelet count <50×10^9/L 44 romiplostim	3 µg/kg SC or last dose in RCT; dose was adjusted (maximum 10 µg/kg) to achieve target platelet counts of 50 to 200×10^9/L.
Kuter, et al, 2013	Multicentre, open-label extension study Prior participation in RCT and platelet count ≤50×10^9/L 291 romiplostim	1 to 10 µg/kg SC weekly
Newland, et al, 2016	Multicentre, open-label Baseline platelet count ≤30×10^9/L 75 romiplostim	Starting dose of 1 µg/kg SC weekly for 12 months; dose was adjusted to achieve target platelet counts of 50 to 200×10^9/L.
Steurer, et al, 2016	Multicentre, open-label prospective observational Consecutive patients, local standard of care 340 romiplostim	Median dose 2.8 µg/kg SC weekly, 2-year observation period
Janssens, et al, 2016	Multicentre, open-label, prospective Bone marrow evaluation 169 romiplostim	1 µg/kg SC weekly for up to 3 years; dose was adjusted (maximum 10 µg/kg) to achieve target platelet counts of 50 to 200×10^9/L.

QOD=every other day; RCT=randomised controlled trial; SC=subcutaneous.

Overall, the published literature briefly summarised below in table 4 supports the conclusion that the chronic administration of TPO receptor agonists is generally well tolerated for the treatment of ITP, and the literature review provides a useful historical benchmark supporting the Primary Safety Data with avatrombopag in Group 4. There was a higher risk of clinically significant liver tests and hepatobiliary AEs reported with eltrombopag compared to romiplostim in the published studies, but other AEs were relatively comparable between the 2 approved TPO receptor agonists. The reported overall rates and severity of AEs, TEAEs, SAEs, and AESI with these products were generally comparable to the avatrombopag clinical safety data, except for the lack of significant hepatotoxicity or an increased incidence of thromboembolic or bleeding events in avatrombopag-treated subjects. In addition, review of the AESI identified no significant difference in safety profiles, and there were no new or unique AEs reported with avatrombopag that had not been previously reported with eltrombopag or romiplostim.

Table 4 Treatment-Emergent Adverse Events- Avatrombopag Group 4 Safety Data and Data from Published Studies with the Approved TPO Receptor Agonists

Treatment-emergent Adverse Events	Avatrombopag		Eltrombopag			Romiplostim		
	Group 4		Cheng, et al, 2011 (RAISE) [a]		Wong, et al, 2017 (EXTEND)	Kuter, et al, 2008 2 Pooled RCTs [b]		Kuter, et al, 2013
	AVA n=128	PBO n=22	ELTR n=135	PBO n=61	ELTR n=302	ROMI n=84	PBO n=41	ROMI n=291
Treatment Duration, weeks	Median 29.1 weeks	Median 5.9 weeks	26	26	Median 123 weeks	24	24	Mean 110 weeks
TEAEs, n (%)	125 (97.7)	14 (63.6)	118 (87)	56 (92)	277 (92)	84 (100)	39 (95)	284 (98)
Treatment-related TEAEs, n (%)	39 (30.5)	3 (13.6)	48 (36)	18 (30)	NP	34 (41)	11 (27)	103 (35)
TEAE Grade ≥ 3, n (%)	36 (28.1)	2 (9.1)	20 (15)	7 (12)	97 (32)	28 (33)	16 (39)	NP
Serious TEAEs	33 (25.8)	4 (18.2)	15 (11)	11 (18)	96 (32)	14 (17)	8 (20)	117 (40)
TEAEs Leading to Discontinuation	24 (18.8)	4 (18.2)	13 (10)	4 (7)	41 (14)	3 (4)	1 (2)	26 (9)

AVA = avatrombopag; ELTR = eltrombopag; NP = not provided; PBO = placebo; ROMI = romiplostim; TEAE = treatment-emergent adverse event

a: Data for treatment-related TEAEs and serious TEAEs are not reported in Cheng, et al, 2011 but were extracted from the European public assessment report (EPAR) for Revolade.

b: Data in these columns are not reported in Kuter, 2008, but were extracted from Nplate FDA Medical Review (BLA 125268; 2008)

The most common AEs reported across the studies were headache, nasopharyngitis, diarrhea, and nausea with eltrombopag, and headache, nasopharyngitis, fatigue, and peripheral edema with romiplostim. For reference, Literature Summary of Safety Table 5 summarises the incidence of the common AEs by PT for avatrombopag (those reported at an incidence of 10% or higher) from the 4 ITP studies in Group 4, alongside data from the key published studies with eltrombopag and romiplostim; the types of AEs reported were similar across the various TPO receptor agonists with some variability in incidence, but no new safety signals were identified.

Table 5 Common (>10%) Treatment-Emergent Adverse Events- Avatrombopag Group 4 Safety Data and Data from Published Studies with the Approved TPO Receptor Agonists

Treatment-emergent Adverse Events	Avatrombopag		Eltrombopag			Romiplostim		
	Group 4		Cheng et al, 2011 (RAISE)		Wong, et al, 2017 (EXTEND)	Kuter et al, 2008 2 Pooled RCTs		Kuter et al, 2013
	AVA n=128	PBO n=22	ELTR n=135	PBO n=61	ELTR n=302	ROMI n=84	PBO n=41	ROMI n=291
Treatment Duration, weeks	Median 29.1 weeks	Median 5.9 weeks	26	26	Median 123 weeks	24	24	Mean 110 weeks
Subjects with any TEAE	125 (97.7)	14 (63.6)	118 (87)	56 (92)	277 (92)	84 (100)	39 (95)	284 (98)
Headache	39 (30.5)	3 (13.6)	41 (30)	20 (33)	86 (28)	29 (35)	13 (32)	38%
Fatigue	36 (28.1)	2 (9.1)	13 (10)	8 (13)	50 (17)	28 (33)	12 (29)	32%
Contusion	33 (25.8)	4 (18.2)	2 (1)	3 (5)	NP	21 (25)	10 (24)	31%
Epistaxis	24 (18.8)	4 (18.2)	7 (5)	6 (10)	NP	27 (32)	10 (24)	25%
Upper respiratory tract infection	19 (14.8)	1 (4.5)	14 (10)	7 (11)	69 (23)	14 (17)	5 (12)	26%
Thrombocytopenia	18 (14.1)	0	NP	NP	NP	NP	NP	NP
Arthralgia	16 (12.5)	0	9 (7)	3 (5)	45 (15)	22 (26)	8 (20)	NP
Gingival bleeding	16 (12.5)	0	NP	NP	NP	9 (11)	5 (12)	NP
Petechiae	14 (10.9)	2 (9.1)	NP	NP	NP	14 (17)	9 (22)	NP
Nasopharyngitis	13 (10.2)	0	14 (10)	8 (13)	74 (25)	7 (8)	7 (17)	34%
Diarrhea	12 (9.4)	0	17 (13)	6 (10)	47 (16)	14 (17)	6 (15)	25%
Nausea	12 (9.4)	0	16 (12)	4 (7)	34 (11)	11 (13)	4 (10)	NP
Back pain	11 (8.6)	0	7 (5)	3 (5)	40 (13)	11 (13)	4 (10)	NP
Urinary tract infection	3 (2.3)	0	9 (7)	4 (7)	34 (11)	NP	NP	NP
Cough	9 (7.0)	0	6 (4)	4 (7)	32 (11)	10 (12)	7 (17)	NP
Influenza	6 (4.7)	0	7 (5)	3 (5)	30 (10)	NP	NP	NP
Anemia	4 (3.1)	2 (9.1)	NP	NP	29 (10)	NP	NP	NP

AVA = avatrombopag; ELT = eltrombopag; NP = not provided; PBO = placebo; RCT = randomised controlled trial; ROMI = romiplostim

2.6.1 Discussion on clinical safety

Many of the most commonly observed AEs are well-known from one or both of the two approved TPO-RAs (Very common or Common according to the SmPCs): Headache, Fatigue, Upper respiratory tract infection/ Nasopharyngitis, Nausea, Diarrhoea and Vomiting, Arthralgia and Back pain, Oedema peripheral, Insomnia and Dizziness, and Cough.

The assessment for this type II variation will focus on the safety data provided for the chronic ITP population (Group 4), while keeping in mind the currently known safety profile for patients with chronic liver disease (CLD).

The current safety profile is related to short-term treatment (40-60 mg for up to 5 days) in patients with chronic liver disease ahead of a surgical procedure. The treatment of ITP is continuous as long as there is effect (20 mg initially then modified depending on platelet count). Thus, the safety profile from these two different settings is not comparable. The MAH has presented an integrated safety summary based on four trials in ITP patients: two phase 2 trials; CL-003 (28 days treatment; 59 avatrombopag and 5 placebo) and CL-004 (an extension of the previous trial up to 6 months, avatrombopag only) and two randomised trials; study 302, in which placebo was the comparator (N=17 vs N=32 in the avatrombopag arm in the core study and 47 in the extension part) and study 305, which was terminated early due to "significant enrolment challenges" after including 12 patients in the avatrombopag arm and 11 patients in the eltrombopag arm. Altogether 128 patients received avatrombopag of which 81 (63%) received it for more than 6 months compared to one patient in the placebo arm and one in the eltrombopag arm (3 in each of the comparator arms received treatment for ≥90 days).

The exposure-adjusted incidence rates for adverse events were calculated to account for differences in the duration of exposure across the various treatment groups in the chronic ITP studies. The exposure-adjusted incidence rates enable a comparison between the different study groups and are endorsed in general. However, this can only be viewed as an approximation, due to the very limited long-term exposure data for subjects in the placebo or eltrombopag groups, which weakens the strength of the safety data. As mentioned earlier the RCT 305, where the comparator was eltrombopag, had to be discontinued due to "significant enrolment challenges". Therefore, the MAH will conduct a PASS to further confirm the long-term safety profile (please see pharmacovigilance plan in the RMP section), particularly for adverse events which are rare, and clinical benefit of avatrombopag in patients with chronic ITP as a post-approval comitment and submit the results of the feasibility study for the PASS within 3 months after approval of the extension of indication.

There were nine thromboembolic events; the potential contribution of avatrombopag is difficult to assess without a comparator given to a significant number of patients for a substantial amount of time. The relatedness of 3 cases of various myeloproliferative disease (MPD) is also not assessable and longer exposure in more patients is needed. "Thrombotic/thromboembolic events" has been added as an important identified risk in the RMP. In addition, the following receommendation was already made in section 4.4 of the SmPC and is still considered adequate: "Consider the potential increased thrombotic risk when administering Doptelet to patients with known risk factors for thromboembolism, including but not limited to genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency) advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Doptelet should not be administered to patients with chronic liver disease or chronic immune thrombocytopenia in an attempt to normalise platelet counts". In addition, further safety data will be provided as part of the planned PASS (please see pharmacovigilance plan in the RMP).

Treatment with TPO agonists has been linked to formation of reticulin fibre in the bone marrow. Across the phase III studies, evaluation of fibrosis and reticulin fibre formation by bone marrow biopsies was done in subjects willing to give an additional informed consent. However, only very limited data are available that do not allow for a reliable conclusion on the risk of avatrombopag inducing or promoting fibrosis in the bone marrow. However, to better inform clinicians on the potential risk of increased bone marrow reticulin, a precautionary statement has been included in section 4.4 of the SmPC. As mentioned before, the MAH will conduct a PASS study feasibility, which will investigate the potential to collect bone marrow biopsy data from ITP patients on avatrombopag in order to evaluate the long-term risk of bone marrow fibrosis. Further, 'Bone marrow fibrosis related to long-term and repeat use' and 'Haematological Malignancies' has been included in the RMP as important identified risk.

With regards to QTc prolongation with concomitant medications, the following recommendation has been added in section 4.4 of the SmpC: "At exposures similar to that achieved at the 40 mg and 60 mg dose, Doptelet did not prolong the QT interval to any clinically relevant extent. Mean QTc prolongation effects > 20 ms are not anticipated with the highest recommended therapeutic dosing regimen based on analysis of data from the pooled clinical trials in patients with chronic liver disease. However, caution must be exercised when Doptelet is co-administered with moderate or strong dual CYP3A4/5 and CYP2C9 inhibitors, or with moderate or strong CYP2C9 inhibitors, as these medications can increase avatrombopag exposures. Caution must also be exercised in patients with loss-of-function polymorphisms of CYP2C9, as these can increase avatrombopag exposure."

With regards to progression of existing myelodysplastic syndrome (MDS); the effectiveness and safety of Doptelet have not been established for the treatment of thrombocytopenia due to MDS. Doptelet should not be used outside of clinical studies for the treatment of thrombocytopenia due to MDS (section 4.4 of the SmPC).

As stated in section 4.6 of the SmPC: "Doptelet is not recommended in pregnancy and in women who are able to have children and are not using contraception."

The occurrence of common AEs was similar between core and extension phase. However, for the safety assessment of long-term treatment of chronic ITP with Doptelet, the occurrence of less frequent but potentially more severe events such as progression of MDS, bone marrow fibrosis or thromboembolic events is of particular importance, especially because these less frequent events are harder to capture with a limited safety database (in terms of treatment duration and number of enrolled subjects). Therefore, a PASS has been requested (please refer to the pharmacovigilance plan in the RMP).

All ADRs from the safety data set are reflected in the updated SmPC.

2.6.2 Conclusions on clinical safety

The nature and frequency of the reported adverse events are considered to be consistent with those expected after treatment of chronic ITP patients with TPO receptor agonists. There were no new safety findings. However, the safety database is considered limited, and therefore a PASS is warranted in order to gain more data on the long-term safety profile of avatrombopag, especially to assess the risk of thromboembolic events, bone marrow fibrosis, and MPD (please refer to the pharmacovigilance plan in the RMP).

2.6.3 PSUR cycle

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

2.7 Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 2.7 is acceptable. <In addition, minor revisions were recommended to be taken into account with the next RMP update, as follows:

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.7 with the following content:

Safety concerns

Table Summary of Safety Concerns

Important identified risks	• Thrombotic/thromboembolic events • Bone marrow fibrosis related to long-term and repeat use
Important potential risks	• Hepatic worsening function in patients with Child-Pugh class C • Haematological malignancies
Missing information	• Use in splenectomy patients with chronic liver disease • Use in patients receiving interferon products • Safety in patients undergoing highly invasive procedures • Use in patients with MELD scores > 24

Pharmacovigilance plan

1Table of Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or marketing authorisation under exceptional circumstances				
None				
Category 3 – Required additional pharmacovigilance activities				
Hepatic safety of avatrombopag in patients with Child Pugh class C liver disease or MELD scores > 24 Planned	Primary objective is to assess hepatic worsening function in Child Pugh class C liver disease patients or use in patients with MELD scores > 24 who receive treatment with Doptelet, with a secondary objective of assessing 'other safety data' based on findings from the avatrombopag clinical development programme.	Potential risk of hepatic worsening function in patients with Child Pugh class C liver disease. Missing information in patients with MELD scores > 24.	MAH submitted revised feasibility protocol to EMA and is awaiting a response. Submission to EMA of initial PASS protocol. Interim reports on patient accrual	29 Sep 2020 4Q2021 Provided in each PSUR To be entered as soon

			Submission of final PASS report	as the feasibility study report is agreed by EMA
Further characterisation of the long-term safety profile of avatrombopag in patients with primary chronic immune thrombocytopenia Planned	Further characterise the long-term safety profile of avatrombopag in patients with primary chronic immune thrombocytopenia, especially with regards to the safety concerns of thrombotic/thromboembolic events, the risk of bone marrow fibrosis related to long-term and repeat use, and the risk of haematological malignancies.	Confirm the long-term safety profile of avatrombopag, particularly for rare adverse events. Gather additional information on the: • Identified risk of thrombotic/thromboembolic events • Identified risk of bone marrow fibrosis related to long-term and repeat use • Potential risk of haematological malignancies	Submission of the feasibility results to EMA Submission of final PASS report	Within 3 months of approval of the Type II Variation for the ITP indication To be entered as soon as the feasibility study report is agreed by EMA

*Category 1 studies are imposed activities considered key to the benefit risk of the product.
Category 2 studies are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.
Category 3 studies are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Risk minimisation measures

Safety Concern	**Risk Minimisation Measures**
Thrombotic/Thromboembolic Events	Routine risk minimisation measures: • SmPC sections 4.4 and 4.8 • Package Leaflet (PL) section 2 and 4 Additional risk minimisation measures: None
Bone Marrow Fibrosis Related to Long-Term and Repeat Use	No routine risk minimisation measures specific to bone marrow fibrosis. Routine risk communication for long-term and repeat use: • SmPC sections 4.2, 4.4, and 4.8 • Package Leaflet (PL) section 2 and 4 Additional risk minimisation measures: None

Safety Concern	Risk Minimisation Measures
Hepatic worsening function in patients with Child-Pugh class C	Routine risk communication: • SmPC sections 4.2 and 4.4 • Package Leaflet (PL) section 2 Additional risk minimisation measures: None
Haematologic malignancies	Routine risk communication: • SmPC section 4.4 • Package Leaflet (PL) section 2 Additional risk minimisation measures: None
Use in splenectomy patients with chronic liver disease	No risk minimisation measures
Use in patients receiving interferon	Routine risk communication: • SmPC section 4.4 • Package Leaflet (PL) section 2 Additional risk minimisation measures: None
Safety in patients undergoing highly invasive procedures	Routine risk communication: • SmPC section 4.4 Additional risk minimisation measures: None
Use in patients with MELD scores > 24	Routine risk communication: • SmPC sections 4.2, 4.4, 5.1 and 5.2 • Package Leaflet (PL) section 2 Additional risk minimisation measures: None

2.8 Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2 of the SmPC are updated. Additionally, the SmPC section 5.3 is updated with data from juvenile toxicity studies. Furthermore, an additional pack size of 30 tablets has been introduced with subsequent updates of sections 6.5 and 8 of the SmPC. The Package Leaflet and Labelling are updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.1.

2.8.1 User consultation

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

changes to the package leaflet are minimal, do not affect the readability and do not require user consultation with target patient groups.

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

2.8.2 Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Doptelet (avatrombopag) is already included in the additional monitoring list as

- it contains a new active substance which on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1 Therapeutic Context

3.1.1 Disease or condition

The aim of this application is to support the following indication: "Avatrombopag is indicated for the treatment of primary chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins)."

3.1.2 Available therapies and unmet medical need

Realising the autoimmune nature of chronic ITP divides the therapeutic principles in two. To increase platelet production or to reduce the destruction by phagocytosis of platelets – or both, in a combination therapy. The gold standard is glucocorticoids, which was introduced first as an immune suppressive agent targeting the disease mechanism, in most patients with a rapid effect. Other immune-suppressants have been introduced, like azathioprine, mycophenylat and cyclosporine A and antiCD20 antibody (rituximab), whereas drugs which prevent phagocytosis and the increased degradation of thrombocytes include IVIg, anti-RhD immunoglobulin and dapsone. Danazol was the first drug introduced to stimulate thrombopoiesis and have later been – successfully – followed by TPO-Ra since 2008. Not all medicines are authorised for ITP.

Oral medication is optimal, and most treatments are provided in tablets. Parenteral administration is accepted (e.g. IVIg and antiCD20) because the agents cannot be absorbed otherwise, but still are particularly important in the treatment armamentarium. TPO-Ra is one example where both administration forms are provided. Splenectomy is an ultimate procedure, now by laparoscopy, and despite the long-term risks of bacterial infections, it is still used, because of a high 60-70% and durable remission rate, provided strict precautions are taken for prophylaxis. However, apart from glucocorticoids and IVIg as third line treatment in acute ITP or for rescue, there is no treatment algorithm agreed internationally in chronic ITP, because no agent has an optimal profile. Chemotherapy has no role in primary ITP and platelet transfusion, from HLA-matched donors or pooled concentrate is only used in

critical siuations (Chaturvedi et al. Blood 2018; Cooper & Ghanima N Engl J Med 2019; Puavilai et al. Brit J Haematol 2020).

Instead, the plethora of agents make room for an individualised therapeutic approach related to gender, age, pregnancy and co-morbidities. Today, it may be considered that there is still an unmet medical need in chronic ITP, reflected in the development of novel compounds targeting mechanisms involved in chronic ITP as first-in-class – recently an inhibitor of the enzyme spleen tyrosine kinase (SYK) (Bussel et al. Am J Hematol 2018), The medical need in chronic ITP may also be to extend the spectrum of available options, because no independent prognostic factor has been identified in ITP for treatment response to medical therapy. In addition, adverse events even in the same class of drugs may be perceived differently and overall the aim is to tailor the treatment to the individual subject and contribute to an active weekday, with minimum bleeding and adverse events and to avoid morbidity and mortality due to medication or severe haemorrhage.

3.1.3 Main clinical studies

Main efficacy data derive from study 302, a randomized, double-blind, placebo-controlled phase III study in primary chronic ITP patients (n=49, avatrombopag: n=32, placebo: n=17), including a core study (6 months) and an open-label extension phase (terminated at the date when the last subject completed the core study). Those subjects who met all the eligibility requirements and who were willing and able entered the extension phase. Subjects who discontinued the core study early because of lack of treatment effect remained eligible to continue into the extension phase. Avatrombopag or placebo was administered as daily 5, 10, 20, 30, or 40mg doses in a flexible design. The starting dose was 20mg.

Supportive evidence derives from study CL-003, a phase II, double-blind, randomized, dose-ranging, placebo-controlled study with a duration of 28 days (n=64, randomized 3:3:3:3:1 to a fixed dose of 2.5mg, 5mg, 10mg or 20mg QD of avatrombopag or placebo, respectively); study CL-004, a rollover study from CL-003 (dose titration was permitted, treatment duration of 6 months, n=53, 25/28 for responders/non-responders per primary response criteria in CL-003) and study 305, a phase III, randomized, active-controlled (eltrombopag) study that was terminated prematurely due to recruitment challenges (n=24, avatrombopag, n=12, eltrombopag, n=11).

In addition, a literature review from published data for the 2 TPO-R agonists authorized for treatment of ITP, an independent network meta-analysis comparing the efficacy of avatrombopag to eltrombopag in ITP patients and a simulated NI analysis of avatrombopag versus eltrombopag were submitted.

To support dosing recommendations and dose titration algorithm as proposed in the SmPC data from population PK model and PK/PD modelling and simulation were submitted.

3.2 Favourable effects

As a chronic condition (in most patients) an oral medication is preferred, and with an option to titrate individually the dosing to translate into a stable platelet count of 50-100 (150) $x10^9$/L. Treatment is administered at home and blood sample for monitoring may be with weeks to months interval outside a clinical trial.

The primary efficacy endpoint for Study 302 was the cumulative number of weeks of platelet response, i.e. the target platelet count ≥50 $x10^9$/L during 6 months of treatment, in the absence of rescue therapy. Avatrombopag (n=32) was superior to placebo (n=17) with a significantly longer duration of weeks with a platelet count ≥50×10^9/L in the absence of rescue therapy (median 12.4 (SD 8.75 weeks) vs 0 weeks, respectively, $p<0.0001$). The majority of platelet counts in the avatrombopag treatment group remained

within the target window of ≥50×10^9/L to ≤150×10^9/L over the course of the study. The supportive Study CL-003 demonstrated a median of 11 weeks in avatrombopag, and 0 in the placebo group.

The first key secondary efficacy endpoint for Study 302 was the proportion of subjects with a platelet count ≥50 x10^9/L) at Day8. Avatrombopag was superior to placebo at Day 8 (65.6% vs 0.0%, respectively), (95% CI: 49.17, 82.08), which was statistically significant (P<0.0001). The supportive Study CL-003 showed a response rate at Day8 of 55.2% *versus* 0 in the placebo group.

Analysis based on stratification factors showed in each subgroup a statistically significant response compared with placebo for the primary endpoint. However, the cumulative platelet response was notably lower in splenectomised subjects compared to non-splenectomised subjects (4.9 versus 15.9 weeks), subjects with baseline platelet count ≤15 x10^9/L compared with a baseline count >15 to <30 x10^9/L (5.3 versus 19.2 weeks), and in patients who used concomitant ITP medication at baseline compared to those who did not, i.e. avatrombopag monotherapy (4.9 versus 15.9 weeks). It is likely that differences in effect of avatrombopag in patients who have been splenectomised and are in need of treatment or have an (arbitrary) platelet count below 15, or are dependent upon a SOC entering the trial have a more active ITP disease. There is no test to measure e.g. antibody affinity and concentrations.

The second key secondary efficacy endpoint was the proportion of subjects with a reduction in use of concomitant ITP medications from baseline. An equal minority of subjects in both treatment groups (n=15/32 in avatrombopag; n=7/17 in placebo) were treated concomitantly with other SOC ITP medications at baseline. The results showed that 33.3% (95% CI 9.48, 57.19) of subjects in the avatrombopag treatment group reduced the concomitant use of ITP medication from baseline, compared with 0% for placebo-treated subjects. This treatment difference was not statistically significant (P=0.1348).

In study CL-003 a dose-dependent rise of platelet counts was observed.

Results from study 305 indicate comparable treatment effect on median platelet counts over time as seen in study 302.

The durable platelet response was an exploratory endpoint, defined as the proportion of subjects who had at least 6 out of 8 weekly platelet responses during the last 8 weeks of treatment over the 6-month treatment period of the core study in the absence of rescue therapy. Avatrombopag was shown to be superior to placebo 11/32 (34.4%, 95% CI 17.92, 50.83) versus 0/17, respectively (P=0.009).

Main findings of the literature review are based on results from study 302 and corresponding endpoints from eltrombopag and romiplostim studies as presented in their SmPCs. Both the comparison of cumulative number of weeks with a platelet count above 50x10^9/L and use of rescue medication suggests comparable results for all TPO-R agonists. Also results for durable response are broadly comparable between avatrombopag and eltrombopag. A network-meta-analysis gave response rates on day 8, day 28, week 6 and months 6 comparable between avatrombopag and eltrombopag.

3.3 Uncertainties and limitations about favourable effects

The number of the pivotal study participants is limited. Data from the extension study become more variable from week 38 of the extension study due to the low number of patients. A trend only for positive effect reducing the concomitant ITP medication was observed in the pivotal trial. CHMP recommends to further evaluate the efficacy of avatrombopag in the post-marketing setting to document the use of 20mg tablets in the management of primary chonic ITP long-term, changes in the platelet count and the risk of bleeding events, and reduction in the use of concomitant ITP medications.

3.4 Unfavourable effects

The most commonly observed AEs are well-known from one or both of the two approved TPO-RAs. Very common or Common AEs according to the SmPCs include headache, fatigue, gastro-intestinal symptoms, arthralgia, back pain and more, which were mostly mild and potentially manageable by symptomatic treatment.

Subjects with any TEAE included 63.6% (14/22) in the placebo group, compared to 97.7% (125/128) in the avatrombopag treated group, translating to an exposure-adjusted incidence of 4.233 in the placebo group and 1.728 in the avatrombopag group. TEAEs with CTCAE grade 3 or more were reported in 45/128 (35%) patients treated by avatrombopag, compared to none in the placebo group, corresponding to an exposure-adjusted incidence rate of 0.622 in patients treated by avatrombopag and 0 in the placebo-group. TEAEs leading to study drug withdrawal was captured in 17 patients (13%) on avatrombopag, none in the placebo group.

Recurrence of (or rebound) thrombocytopenia was defined as a platelet count $<10 \times 10^9$/L and 10×10^9/L below baseline, occurring after termination and up to 30 days after the last dose of study drug. Rebound thrombocytopenia were reported in 8.6% (11/128) of subjects, only after treatment with avatrombopag.

Adverse events of special interest included recurrence of thrombocytopenia (8.6%), thromboembolic events (7%, with no clustering of a specific arterial or venous event), bleeding events (14.1%), gastric atrophy events (0%), neoplastic events (4.7%), and clinically significant liver test (3.9%). With exception of bleeding events reported in the placebo group, AESIs occurred only in the avatrombopag treatment group. With regard to clinically significant liver enzyme tests including increased ALT and AST, 4/5 subjects continued their dose of avatrombopag without any deterioration of liver enzyme elevations. Treatment-emergent AESI in the Neoplastic Event category were reported in 6/128 (4.7%) patients treated with avatrombopag. The exposure-adjusted incidence rate was 0.083. All events occurred in single (0.8%) subjects only, and included chronic lymphocytic leukemia, chronic myelomonocytic leukemia, lipoma, myelofibrosis, an unspecified myeloproliferative neoplasm, and skin papilloma. No safety signal was identified. The time of onset in the Neoplastic Events category was greater than 26 weeks for 2 subjects, 12 to less than 26 weeks for 1 subject, and 4 to less than 12 weeks for 3 subjects. No reports in the placebo group. No treatment-emergent bone marrow pathology AESI were reported.

The unfavourable effect of the product are already included in sections 4.4, 4.8 and 5.1 of the approved SmPC.

3.5 Uncertainties and limitations about unfavourable effects

The total number of patients exposed to avatrombopag for ≥52 weeks is limited (14 subjects, 10.9%). The treatment of ITP is continuous as long as there is effect (20 mg initially then titrated depending on platelet count). Therefore, a PASS is warranted in order to gain more data on the long-term safety profile of avatrombopag, especially to assess the risk of thromboembolic events, bone marrow fibrosis, and MPD (please see pharmacovigilance plan in the RMP).

Only very limited bone marrow biopsy data are available. Treatment with TPO agonists has been linked to formation of reticulin fiber. Lack of knowledge in this regard poses a safety concern. This concern has been addressed by including a precautionary statement in section 4.4 of the SmPC. Additionally, the RMP does now include 'Bone marrow fibrosis related to long-term and repeat use' as an important identified risk.

Nine thromboembolic events were observed and six cases of neoplastic event. The potential contribution of avatrombopag is difficult to assess without a comparator given to a significant number of patients for

a substantial amount of time. "Thrombotic/thromboembolic events" has been added as an important identified risk in the RMP. In addition, the following receommendation was already made in section 4.4 of the SmPC and is still considered adequate: "Consider the potential increased thrombotic risk when administering Doptelet to patients with known risk factors for thromboembolism, including but not limited to genetic prothrombotic conditions (Factor V Leiden, Prothrombin 20210A, Antithrombin deficiency or Protein C or S deficiency) advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Doptelet should not be administered to patients with chronic liver disease or chronic immune thrombocytopenia in an attempt to normalise platelet counts". In addition, further safety data will be provided as part of the planned PASS (please see pharmacovigilance plan in the RMP).

Bleeding episodes may most likely be due to insufficient responses, not TEAEs to avatrombopag. Still, three patients were registered with bleeding grade II-III in Study 302, and three times more frequent bleeding episodes were reported in the safety database population, associated with avatrombopag treatment. The current warning stated in section 4.4 of the SmPC is still considered adequate: "There is an increased risk of bleeding if avatrombopag treatment is discontinued in the presence of anticoagulants or anti platelet agents. Patients should be closely monitored for a decrease in platelet count and medically managed to avoid bleeding upon discontinuation of treatment with avatrombopag. It is recommended that, if treatment with avatrombopag is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or antiplatelet therapy, reversal of anticoagulation, or platelet support."

Concurrent anaemia and leukocytosis have been reported in patients exposed to other TPO receptor agonists (within a 4-week window). Leukocytosis can be a sign for progression of MDS into acute leukemia. Considering that this AE occurred in the clinical trial and that a possible involvement of avatrombopag in the progression of MDS cannot be excluded, this remains a safety concern. The precautionary statements have been included in section 4.4 of the SmPC to inform about this possible risk and to indicate that bone marrow aspirates or biopsies should be considered, particularly in patients over 60 years of age or for those with systemic symptoms or abnormal signs such as increased peripheral blast cells.

3.6 Effects Table

Table. Effects Table for Avatrombopag in adult chronic ITP. Date database lock 10 March 2014.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	Refe-rences
Favourable Effects						
Pivotal trial 302			**Avatrombopag N = 32**	**Placebo N = 17**	Double-blind, rando-mized, multicentre trial of 49 patients randomized 2:1	Efficacy section
Responder	Cumulative platelet count ⩾50, No rescue	week	Mean 12.0 ±8.75 Median 12.4	Mean 0.1 Median 0	P<0.0001	
Responder	Platelets ⩾ 50 Day8, No rescue	No. (%)	21/32 (65.6) 95% CI 49.17, 82.08	0	P <0.0001	
Proportion of patients	Reduction in ITP medication	No. (%)	5/15 (33.33) 95% CI 9.48, 57.19	0	P = 0.1348	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	Refe-rences
Proportion of patients	Durable platelet respons*	No. (%)	11/32 (34.38) 95% CI 17.92, 50.83	0	P < 0.0090	
Rescue	Summary**	No. (%)	7/32 (21.9) 95% CI 7.55, 36.20	2/17 (11.8) 95% CI 0, 27.08	P = 0.4668	
Study 305			**Avatrombopag**	**Eltrom-bopag**	Prematurely terminated phase 3 trial	Efficacy
Responder	Cumulative platelet count ⩾50, No rescue	week	Mean 5.4 ±4.4 Median 5.1	4.3 ±6.3 0	P = 0.3299	
Proportion	Response Day8	No. (%)	5/11 (45.5)	4/11 (36.4)	P >0.999	
Unfavourable Effects						
Pivotal trial 302						
Proportion of patients	Bleeding§ Grade I	No. (%)	11 (34.4)	9 (52.9)		Efficacy
	Grade II+III		3 (9.4)	0		
Safety database			**Avatrombopag N = 128**	**Placebo N = 22**		
Proportion of patients	Bleeding episodes	No. (%)	18/128 (14.1)	1/22 (4.5)	N/A	Safety
Proportion of patients	Thrombosis §§	No. (%)	9/128 (7.0)	0/22 (0)	N/A	Safety
Proportion of patients	Neoplastic events^	No. (%)	6/128 (4.7)	0/22 (0)	N/A	Safety

Abbreviations: platelet count stated in $x10^9$/L. Normal range 150-400 $x10^9$/L. N/A statistics not available.

Notes: platelet counts in $x10^9$/L. * defined as at least 6 out of 8 weekly platelet responses during the last 8 weeks of treatment over the 6-months of the core study in the absence of rescue therapy. ** Summary of rescue therapy over six months core study, No. / (%) subjects who took rescue at least once. § Bleeding by WHO-scale. §§Thromboembolic event. ^Four malignant haematological diagnosis.

3.7 Benefit-risk assessment and discussion

3.7.1 Importance of favourable and unfavourable effects

The data show that avatrombopag by an oral, daily treatment increases the platelet count within a week in severely thrombocytopenic adult patients with primary chronic ITP to a safe level, terminating or mitigating the risk of bleeding. This effect may be achieved by avatrombopag monotherapy or as add-on to any ongoing SOC ITP treatment, be maintained for months and without rescue therapy, in patients who respond.

Although the primary endpoint of study 302 differs from what was agreed on during a previous scientific advice, it is considered adequate to address the primary objective of the study, and is clinically relevant

as the cumulative number of weeks in which the platelet count is ≥50 x 10^9/L during 6 months of treatment in the absence of rescue therapy. The pivotal study met this primary endpoint.

Consistent results are presented in supportive, phase II placebo-controlled studies and the pivotal phase III trial on the primary endpoint and response to initial treatment. Although the platelet count is a widely accepted surrogate endpoint, the major goal for treatment in ITP is to provide a sufficient count to prevent or stop bleeding rather than correct the platelet count to normal levels. No negative effect of avatrombopag was observed, but also, no reduced need for rescue medication can be concluded for the avatrombopag treatment compared to the treatment with placebo. Incidents of bleeding events were adjusted for the total duration of treatment, but due to the high difference in duration of exposure (2.6-fold) also the exposure adjusted incidence rate remains inconclusive. The conclusions on bleeding events and rescue treatment are compromised by the low number of subjects in the placebo arm beyond the first two months after treatment start. Most of the subjects that started with placebo treatment soon entered the open-label extension phase due to lack of efficacy within the core study. The lack of a robust conclusion on clinically relevant endpoints (i.e. bleeding events and rescue medication) raises uncertainty about the possible clinical benefit from the treatment with avatrombopag. The requested analyses were provided and the observed results do not suggest a notably negative effect on bleeding events or need for rescue medication.

While the Phase 3 ITP studies were conducted with multiple tablet strengths to allow for titration of the daily avatrombopag dose to maintain platelet counts in the target range, the dosage regimen proposed for commercial use utilises 1 avatrombopag tablet strength (20 mg). PK/PD simulations were conducted to support the proposed, alternative, intermittent dose titration algorithm for avatrombopag that is based on patients' platelet counts and takes into consideration the single 20 mg tablet strength. While this approach is acceptable, CHMP recommends to further evaluate the efficacy of avatrombopag in the post-marketing setting with regards to the dosing recommendations, including the risks associated with the 20mg starting dose and platelet fluctuations in the initial period after treatment initiation as well as after dose adjustment to once or twice weekly. An attempt to conduct an active-comparator study with another TPO-Ra was rational but had to be closed prematurely. The results from this incomplete study are based on limited data, although they did show that avatrombopag was probably non-inferior compared to another TPO-Ra (eltrombopag). The efficacy reflected in the ability to cause a rapid increase in thrombocyte count and to maintain this level over time was not consistent with results, provided in other trials – with avatrombopag, or the comparator, which may be explained by different trial populations.

Thrombocyte-count-control over time by avatrombopag treatment in the extension phase was based on successively fewer patients, which support the need for a long-term safety follow-up study (please see pharmacovigilance plan in the RMP).

The placebo-controlled pivotal trial was planned for a small number of patients. A real-world, robust study with an active comparator and sufficient number of patients included has not been done. It cannot be excluded that some results presented in endpoint analysis in the core studies and extension phase are influenced by the low number of patients, perhaps in combination with the study design. Any impact of a limited data-material may influence efficacy as well as safety issues.

The long-term safety data is very limited. Rebound thrombocytopenia was noticed after cessation of six-months avatrombopag treatment, over four weeks. This observation is in contrast to the experience in chronic liver disease and five-day treatment but is consistent with a risk for insufficient production after interfering with a feed-back control system.

Bleeding episodes and thromboembolic events were observed more often during treatment with avatrombopag and may be associated with an inexpedient effect. These circumstances may reflect

difficulties to manage dose-titrations of avatrombopag, both in monotherapy or in combination with concomitant ITP medication. Both may potentially be life-threatening, and thus most likely associated with an inadequate disease control or serious adverse event, and individually associated with co-morbidity and co-medication. These adverse events may be mild or fatal, and sometimes spontaneously reversible clinically or manifest by permanent sequalae, e.g. cerebral.

The raised concerns were addressed by changing the wording in the SmPC (information about risk factors for thromboembolic events) and by adding a statement that raises the awareness for platelet count monitoring when other medications are taken concomitantly.

The occurrence of neoplasia may be a haphazard event. Cases of chronic myeloproliferative neoplasms were registered among avatrombopag treated patients, but not among placebo patients. Being a megakaryocyte growth and development factor (thrombopoietin) all TPO-R agonists in long-term treatment may potentially increase the risk treating a benign disorder (ITP) to develop malignant, myeloid haematopoietic disease (MDS, MPN). The risk to develop a myeloid condition is increased in patients older than 60-years, never reversible spontaneously, causes withdrawal of the TPO-Ra currently given, and will most likely increase the mortality risk considerably compared to ITP. This risk has not been demonstrated with authorised TPO-Ra, but it further supports the request to perform a PASS, as a long-term follow-up study of avatrombopag as an original drug.

3.7.2 Balance of benefits and risks

The studies in adult patients with primary chronic ITP have shown that avatrombopag treatment is effective and safe during the planned follow-up, albeit in a limited number of patients. The magnitude of the effect increasing the platelet count rapidly, to maintain the effect without rescue treatment, and the ability individually to reduce any concomitant ITP medication is clinically meaningful. Remaining uncertainties on the long-term profile of efficacy and safety can be addressed in the post-authorisation phase.

3.7.3 Additional considerations on the benefit-risk balance

None.

3.8 Conclusions

The overall B/R of avatrombopag in primary chronic ITP in adults is positive.

4. Recommendations

Outcome

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

Variations accepted		**Type**	**Annexes affected**
B.II.e.5.a.2	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules,	Type IB	I, IIIA and IIIB

	etc.) in a pack - Change outside the range of the currently approved pack sizes		
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of indication to include the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments; consequently, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2 of the SmPC are updated. Additionally, the SmPC section 5.3 is updated with data from juvenile toxicity studies. Furthermore, an additional pack size of 30 tablets has been introduced with subsequent updates of sections 6.5 and 8 of the SmPC. The Package Leaflet and Labelling are updated in accordance. Version 2.7 of the RMP has also been updated. Furthermore, the PI is brought in line with the latest QRD template version 10.1.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

This recommendation is subject to the following new conditions:

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

Risk management plan (RMP)

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

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Doptelet-H-C-4722-II-0004-G’