

Avatrombopag for the Treatment of Adult Patients with Chronic Immune Thrombocytopenia (cITP): Focus on Patient Selection and Perspectives

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Abstract: Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by a reduced number of circulating platelets due to immune-mediated destruction and decreased platelet production in the bone marrow. Thrombopoietin receptor agonists (TPO-RAs) are highly effective and widely used in the treatment of patients with steroid treatment failure or dependency. Avatrombopag represents a new supplement to the TPO-RAs family. It was originally approved for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo an invasive procedure. However, labeled indications for avatrombopag have been relatively recently expanded to include treatment of chronic ITP in adults with insufficient response to the previous treatments. In this article, we provide an overview of pharmacodynamics and pharmacokinetics of avatrombopag as well as results of the clinical trials related to safety and efficacy of avatrombopag with a perspective on current clinical use. Available data so far suggests that avatrombopag can be effectively used in ITP patients and has a favorable safety profile. Though further studies are needed to affirm the efficacy and safety, avatrombopag has the potential to become a TPO agonist of choice for many patients with ITP.

Keywords: ITP, thrombopoietin receptor agonists, avatrombopag

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by immune-mediated platelet destruction combined with impaired platelet production in the bone marrow resulting in thrombocytopenia and increased risk of bleeding.¹ Primary ITP is characterized by isolated thrombocytopenia (platelet counts of less than $100 \times 10^9/L$) in the absence of other causes. Clinical manifestations of ITP range from being asymptomatic to having mild mucocutaneous bleeding to more severe life-threatening bleeding from various organs, occasionally. Other symptoms include fatigue and various psychological manifestation.^{2,3} The risk of bleeding depends on many factors but most importantly on the number of platelets in the peripheral blood. Generally, the risk of life-threatening and fatal hemorrhage is highest when platelet counts drop below $10-20 \times 10^9/L$.⁴

The pathological mechanisms behind ITP are multifactorial and complex. Antiplatelet antibodies towards the different platelet receptors (such as GPIa/GPIIb/IIIa; GPIb/IX/V) seem to play a central role. In addition, T-cell mediated platelet destruction also plays a role in the pathophysiology of the disease. Antibodies facilitate the destruction of platelets by phagocytes through the Fc-dependent mechanism primary in the spleen. In addition, they lead to impaired megakaryocytic functions resulting in decreased platelet production.⁵

Studies have shown that thrombopoietin (TPO) levels in ITP patients are unexpectedly low for the degree of thrombocytopenia and are usually normal or only slightly elevated.⁶ Pathogenetic mechanisms behind remain not fully understood. TPO levels vary inversely with megakaryocyte- and platelet mass.⁷ It has also been suggested that platelet

desialylation in the presence of platelet antibodies and the direct GPIIb/IIIa antibody-mediated reduction of hepatic TPO regulation may also play a role.⁸

The annual incidence of adult ITP is estimated to be approximately 3–6/100,000 subjects.^{9,10} The prevalence in adults is 9.5/100,000.¹¹ Bleeding remains the major cause of morbidity and mortality in ITP.¹² As such, the main goal of the therapy is to maintain a safe (hemostatic) platelet count to prevent clinically significant bleeding episodes. Treatment, in general, should be considered when platelet counts drop to under $20\text{--}30 \times 10^9/\text{L}$.^{13,14} Occasionally, treatment is indicated in patients with higher platelet count eg, $50 \times 10^9/\text{L}$ in those on anticoagulation.

Corticosteroids and IVIG have remained a cornerstone of first-line treatment in ITP for many years. Unfortunately, despite a relatively high initial response rate, only about 30% of all steroid-treated patients can achieve long-term remissions. Thus, many adult ITP patients will require subsequent therapy.

Current guidelines from the American Society of Hematology recommend thrombopoietin receptor agonists (TPO-RAs) as a preferred second-line therapy for patients who fail to respond to steroids or become steroid-dependent.¹³ That is in line with the recommendations from the Updated international consensus report,¹⁴ which suggests rituximab or TPO-RAs as non-surgical treatment alternatives.

Thrombopoietin Receptor Agonists – Mechanism of Action, Development, and Role in ITP

Thrombopoietin (or Mpl-ligand) is a glycoprotein produced primarily on the liver and in minimal amounts in the kidney and bone marrow. Thrombopoietin acts as a regulator of platelet production through binding to thrombopoietin (TPO) receptor (c-Mpl)¹⁵ located at the megakaryocyte surface. This provides a powerful stimulus for the proliferation and differentiation of megakaryocytes by inducing intracellular mechanisms such as JAK2/STAT5, STAT 3, PI3K/Akt, ERK, MAPK/STAT1, thereby leading to increased platelet production. The process is regulated through the autoregulatory loop by binding circulating TPO to high-affinity receptors on platelets.¹⁶

Understanding of mechanisms of thrombopoiesis led to the development of the first generation thrombopoietic agents, recombinant thrombopoietin (rhTPO). Unfortunately, its further development was soon restrained due to immunogenicity resulting in the emergence of neutralizing TPO-antibodies which cross-reacted with endogenous TPO¹⁷ causing severe thrombocytopenia in healthy volunteers.

The second generation of thrombopoietic agents that were structurally different from the native TPO and thus should not trigger antibody production was subsequently developed and licensed for ITP around a decade ago. To date, there are four different thrombopoietin receptor agonists (romiplostim, eltrombopag, avatrombopag, and lusutrombopag), the first three are approved for the treatment in ITP. In addition, a fifth agent, a recombinant TPO that is only licensed in China. While primarily developed for the treatment of ITP, according to the label romiplostim and eltrombopag are licensed for several other conditions such as hematopoietic syndrome of acute radiation syndrome (romiplostim), HCV infection associated thrombocytopenia and aplastic anemia (eltrombopag).

TPO-RAs have a completely different mechanism of action compared to the other known treatment modalities in ITP. They are the only alternative that acts by directly increasing platelet production and not by inducing immunosuppression. Their introduction has dramatically changed our approach to the management of ITP.

Table 1 provides an overview of different TPO-RAs. TPO-RAs are highly effective in elevating platelet counts and prevention bleeding events in ITP. Romiplostim and eltrombopag have shown excellent short and long-term efficacy with a response rate of up to 88%, and in general, very well tolerated.¹⁸

Generally, TPO-RAs are considered as maintenance therapy ie patients need to take the medication continuously to maintain response. However, several recent reports indicate that up to 30% of the patients can discontinue TPO_RA without losing response. Thus, a proportion of ITP patients can discontinue TPO- RAs without losing response.^{19–21}

Table I Overview of Available Thrombopoietin Receptor Agonists and Their Key Characteristics

	Romiplostim	Eltrombopag	Avatrombopag	Lusutrombopag
Structure	Fc-peptide fusion protein (peptibody)	Nonpeptide small molecule	Nonpeptide small molecule	Nonpeptide small molecule
The binding site on the TPO receptor	Thrombopoietin receptor extracellular domain	Thrombopoietin receptor transmembrane domain	Thrombopoietin receptor transmembrane domain	Thrombopoietin receptor transmembrane domain
Route of administration	Subcutaneous	Oral	Oral	Oral
Food interactions	No	Yes	No	No
Dosing	1–10 µg/kg weekly	Once daily ITP: 25–75 mg	Once daily ITP: 20–40 mg	Chronic liver- associated thrombocytopenia: 3 mg for seven consecutive days
Indications	Immune thrombocytopenia (children/ adults). Hematopoietic syndrome of acute radiation syndrome (children and adults)	Immune thrombocytopenia, persistent and chronic (children/adults); Severe aplastic anemia (children/adults) Chronic hepatitis C infection –associated thrombocytopenia	Chronic immune thrombocytopenia (adults) Chronic liver disease-associated thrombocytopenia (adults)	Chronic liver disease-associated thrombocytopenia (adults)

Abbreviation: ITP, immune thrombocytopenia.

Chemical Structure, Pharmacokinetics, and Dynamics of Avatrombopag Chemistry and Administration

Avatrombopag is a highly lipophilic small molecule (Figure 1) and, therefore, is usually prepared as the salt, avatrombopag maleate.²² It is provided as an immediate-release tablet. Avatrombopag is produced as a 20 mg tablet.

Pharmacokinetics/Metabolism

The basis for dosage and treatment schedule in the Phase II studies of avatrombopag was provided from Phase I studies in healthy individuals, such as two double-blind, dose-rising, placebo-controlled Phase 1 studies.²³ It has been shown that the increase in platelet counts is dose-dependent with a maximum increase at days 13–16 related to peak plasma concentrations. Significant platelet counts increase from baseline required avatrombopag doses \geq 10 mg. The median time to achieve a maximum concentration and a half-life was 5–8 hours and 16–19 hours, which were dose-proportional after administration of single doses, with no difference between various ethnic groups.²³

Drug absorption did not vary with food intake. Indeed, unlike eltrombopag, the administration of avatrombopag with food reduced pharmacokinetic variability. Even maximum concentration achieved with avatrombopag differed between ethnics (Figure 2) but, again, unlike eltrombopag, not the area below the concentration-time curve.²⁴

$T_{1/2}$ for avatrombopag is independent of the dose and ranges between 18–24 hours.²³

Avatrombopag is highly bound to plasma proteins (> 95%) and is metabolized mainly via hepatic enzymes CYP2C9 and CYP3A4. The studies suggest²⁵ that CYP2C is a predominant enzyme in the metabolism of avatrombopag, and based on this knowledge, dose adjustment is advised with concomitant use of fluconazole. The drug is primarily excreted through the GI tract with 34% unmetabolized drug. Only 6% is excreted via the kidney.

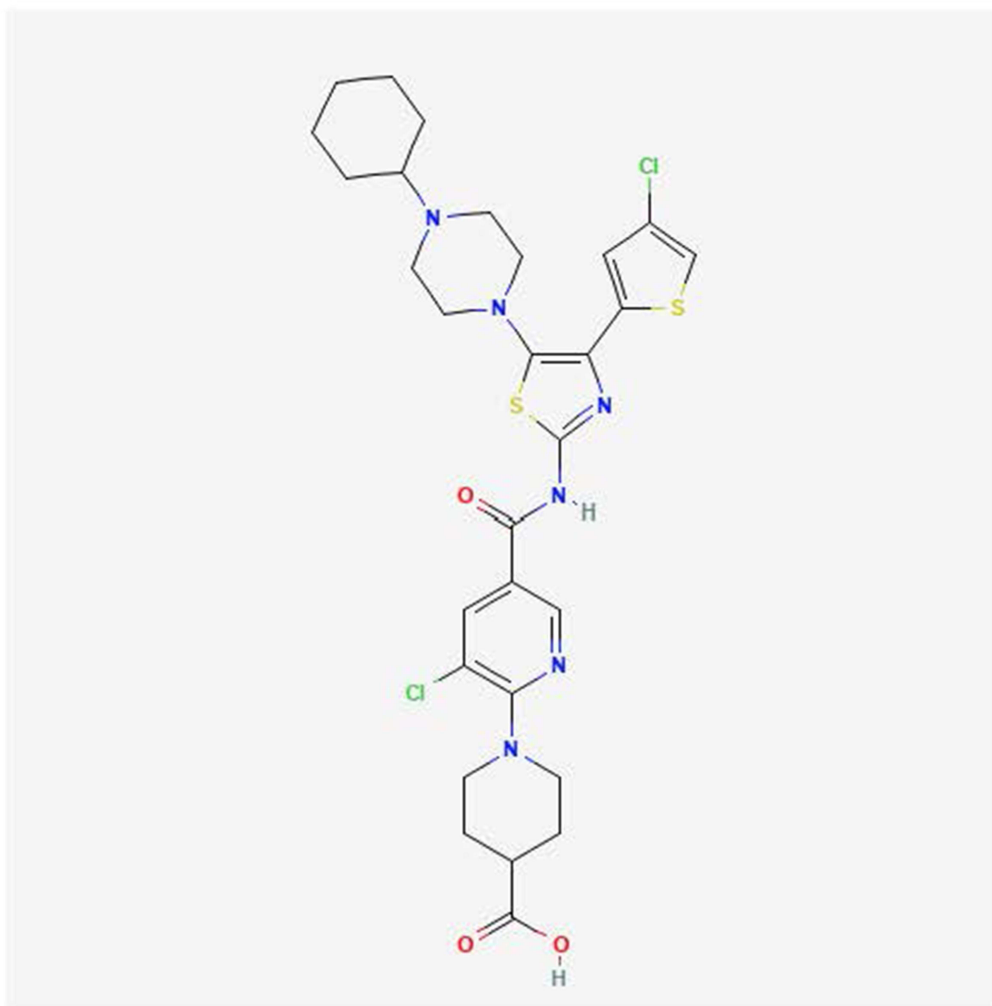


Figure 1 Chemical structure of avatrombopag (from PubChem) Avatrombopag (The international union of pure and applied chemistry (IUPAC) name is 1-[3-chloro-5-[[4-(4-chlorothiophen-2-yl)-5-(4-cyclohexylpiperazin-1-yl)-1,3-thiazol-2-yl]-1-carbamoyl]pyridin-2-yl]piperidine-4-carboxylic acid and molecular formula of C₂₉H₃₄Cl₂N₆O₃S₂) is a nonpeptide small molecule agonist of TPO-RA.

Pharmacodynamics

Early *in vitro* studies of avatrombopag (AKR-501), similar to eltrombopag, showed a highly species-specific activity, limited to humans and chimpanzees. The drug mimicked to some degree the effect of endogenous TPO and specifically stimulated megakaryocyte colony formation from human 34+ positive hematopoietic cells. Avatrombopag acts simultaneously with TPO without inhibiting TPO binding to the receptor.²⁶ In mice models transplanted with human fetal liver CD34+ cells, daily oral administration of avatrombopag led to a dose-dependent increase in platelet counts.²⁷ Later a randomized controlled trial in healthy Japanese and Caucasian individuals confirmed these observations showing that avatrombopag increased platelet counts in a dose-dependent fashion to maximum from baseline by day 11 and returned to baseline at around day 27²⁴ (Figure 2). In patients with liver disease it has been shown that avatrombopag increased platelet counts but did not result in platelet activation as opposite to TPO.²⁸

There are no studies in ITP patients directly comparing the potency of avatrombopag to romiplostim and eltrombopag. However, based on indirect comparison of all three TPO- RAs from phase 1 studies in healthy individuals, presented by Kuter,²⁹ it seems that romiplostim is more potent after a single dose administration than a single dose administration

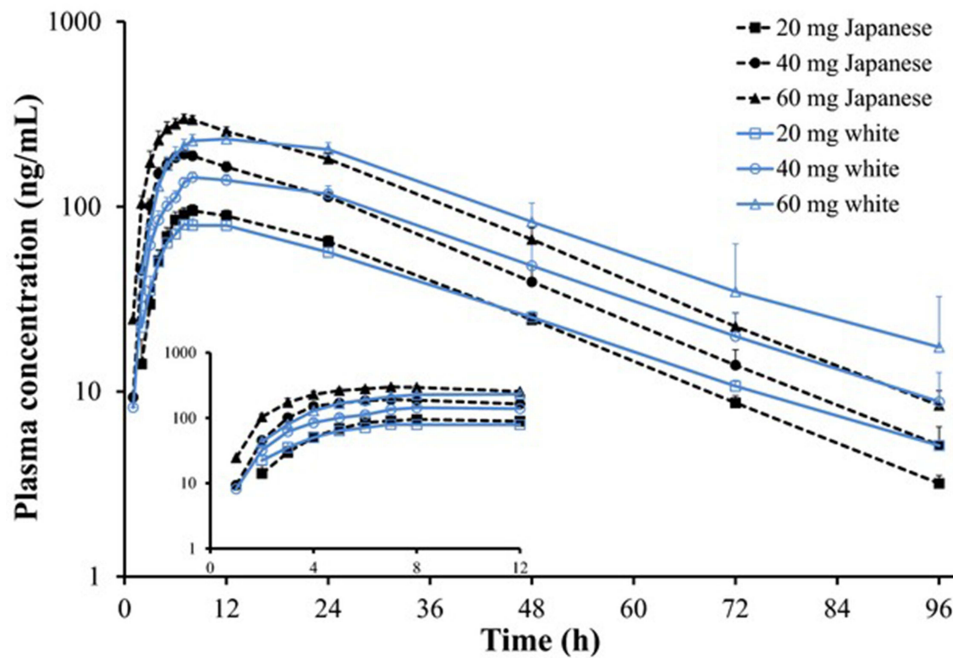


Figure 2 Mean (+SE) plasma avatrombopag concentration-time profile following single oral doses of 20, 40, and 60 mg under fed conditions in Japanese black dot line) and white (solid blue line) subjects. Semi-log scale. Reprinted from Nomoto M, Pastino G, Rege B, Aluri J, Ferry J, Han D. Pharmacokinetics, Pharmacodynamics, Pharmacogenomics, Safety, and Tolerability of Avatrombopag in Healthy Japanese and White Subjects. *Clin Pharmacol Drug Dev.* 2018;7:188–195. © 2017, The American College of Clinical Pharmacology.²⁴

Abbreviation: SE, standard error.

of avatrombopag. The data on single-dose administration is not available for eltrombopag, but the latter seems less potent than avatrombopag with multiple-dose administrations.

Overview of pharmacodynamics and pharmacokinetics is provided in [Table 2](#).

Efficacy of Avatrombopag in Adult ITP Patients

To date, there have been two randomized controlled trials of avatrombopag in the adult ITP population.

The first trial was a Phase II, double-blind, randomized dose-ranging, placebo-controlled parallel-group study.³⁰ Those who completed this trial were eligible to continue further in the extension study (study 004, NTC00625443).

This study included 64 patients in 19 centers across the US. The main criteria were the age of 18 years or older with a diagnosis of ITP of 3 months or longer, failure to respond, or relapse after at least one line of therapy. A platelet count of $<30 \times 10^9/L$ was required for inclusion, whereas those on steroid therapy must have had platelet counts $<50 \times 10^9/L$. Splenectomized patients were eligible for inclusion only if splenectomy was carried out over four weeks prior to the randomization. Patients randomly received either a once-daily fixed-dose of avatrombopag (2.5 mg, 5 mg, 10 mg, or 20 mg) or placebo and received treatment for 28 days.

No changes in concomitant medications were allowed during the study, and administration of rescue medication led to the withdrawal. During this study, patients received treatment on an empty stomach due to a lack of the results from the food studies at that time. The primary endpoint was response rates, defined as the proportion of subjects who achieved platelet counts $\geq 50 \times 10^9/L$ and a minimum increase of $20 \times 10^9/L$ above baseline at day 28. Response rates for the various avatrombopag groups were: 13% (2.5 mg), 53% (5 mg), 50% (10 mg) and 80% (20 mg) as compared to 0% in the placebo group. Like for the phase I studies, there was a dose-dependent response with regards to median platelet count.

Response rate for avatrombopag and placebo cohorts and median platelet count over time by treatment group in the randomized study is shown in [Figure 3](#).

Table 2 Pharmacokinetic and Pharmacodynamics of TPO-RAs Used in Treatment of ITP

Parameter	Romiplostim (Subcutaneous)	Eltrombopag	Avatrombopag
Onset of action	Onset: 4–9 days Peak effect: day 12–16	Onset of action: within 1 to 2 weeks	Onset: 3–5 days Peak effect: after 10–13 days
Duration (platelet counts return to baseline)	By day 28	1–2 weeks after last dose	Platelet count gradually returns to baseline values
Protein binding		>99%	>96%
Time to peak, plasma	14 hours (range:7–50 hours)	2–6 hours	5–6 hours; delayed up to 2 hours if administered with high-fat or low-fat meal (compared to fasting)
Half-life elimination	Median: 3.5 days (range: 1–34 days)	~26–35 hours in ITP patients	~19 hours
Metabolism	Not available	Hepatic	Hepatic
Route of excretion	Partly dependent on binding to c-Mpl-receptors	Feces (59%, ~20% as unchanged drug); urine (31%, as metabolites)	Feces (88%; 34% as unchanged drug); urine (6%)
Drug interactions	May diminish the therapeutic effect of Fc Receptor-Binding Agents	Polyvalent cations (chelation): must not be taken within 4 hours of any medications or products containing polyvalent cations. Transporters: Substrates of OATP1B1 or BCRP: use with caution and monitor closely	Moderate or strong dual inhibitors of CYP2C9 and CYP3A4: reduce recommended starting dose of avatrombopag Moderate or strong dual inducers of CYP2C9 and CYP3A4: increase recommended starting dose of avatrombopag

Abbreviations: ITP, immune thrombocytopenia; TPO-RAs, thrombopoietin receptor agonists; OATP1B1, organic anion transport proteins 1b1; BCRP, human breast cancer resistance protein; CYP2C9, cytochrome P450 family 2 subfamily C member 9; CYP3A4, cytochrome P450 family 3 subfamily A member 4.

Fifty-three patients completed this trial were available for the 24 weeks extension period after day 28. The extension part of the study aimed to assess participants with durable response defined as platelet counts responses at $\geq 75\%$ of measurements over the last 14 weeks of the study and had a minimum of 3 platelet counts measurements. The main objective was to assess the safety and tolerability of avatrombopag. Twenty-five responders at day 28 continued in the extension study, receiving the same dose of avatrombopag /placebo for 24 weeks. Non-responders (28 patients) started an open-label treatment with avatrombopag at a starting dose of 10 mg, which could be increased to a maximum of 40 mg/daily to maintain platelet counts of $> 50 \times 10^9/L$. Overall, twenty-eight patients (53%) achieved a durable response. 40 (76%) achieved an overall response, defined as a durable or a transient platelet response. Ten out of 28 non-responders from the main study (36%) demonstrated durable responses in the extension study. Subgroups analyses showed that patients with platelet counts $> 15 \times 10^9/l$ at baseline and unsplenectomized were more likely to achieve durable responses. However, the number of patients in this sub-analysis was too small to make definite conclusions.

Twenty-four participants in the extension study (45%) used steroids at the entry. Of these, 13 participants had a $\geq 50\%$ steroid dose reduction, and 8 stopped steroids. In addition, the proportion of the subjects with bleeding episodes in both the randomized and the extension part of the study was reduced by week 14.

The second study was a 6-month multicenter, randomized double-blinded, parallel-group Phase III trial with an open-label extension phase.³¹ The trial took place in 27 sites in Australia and New Zealand, Africa, Asia, and Europe. The study evaluated the efficacy and safety of daily dose of avatrombopag in chronic ITP patients. The main inclusion criteria

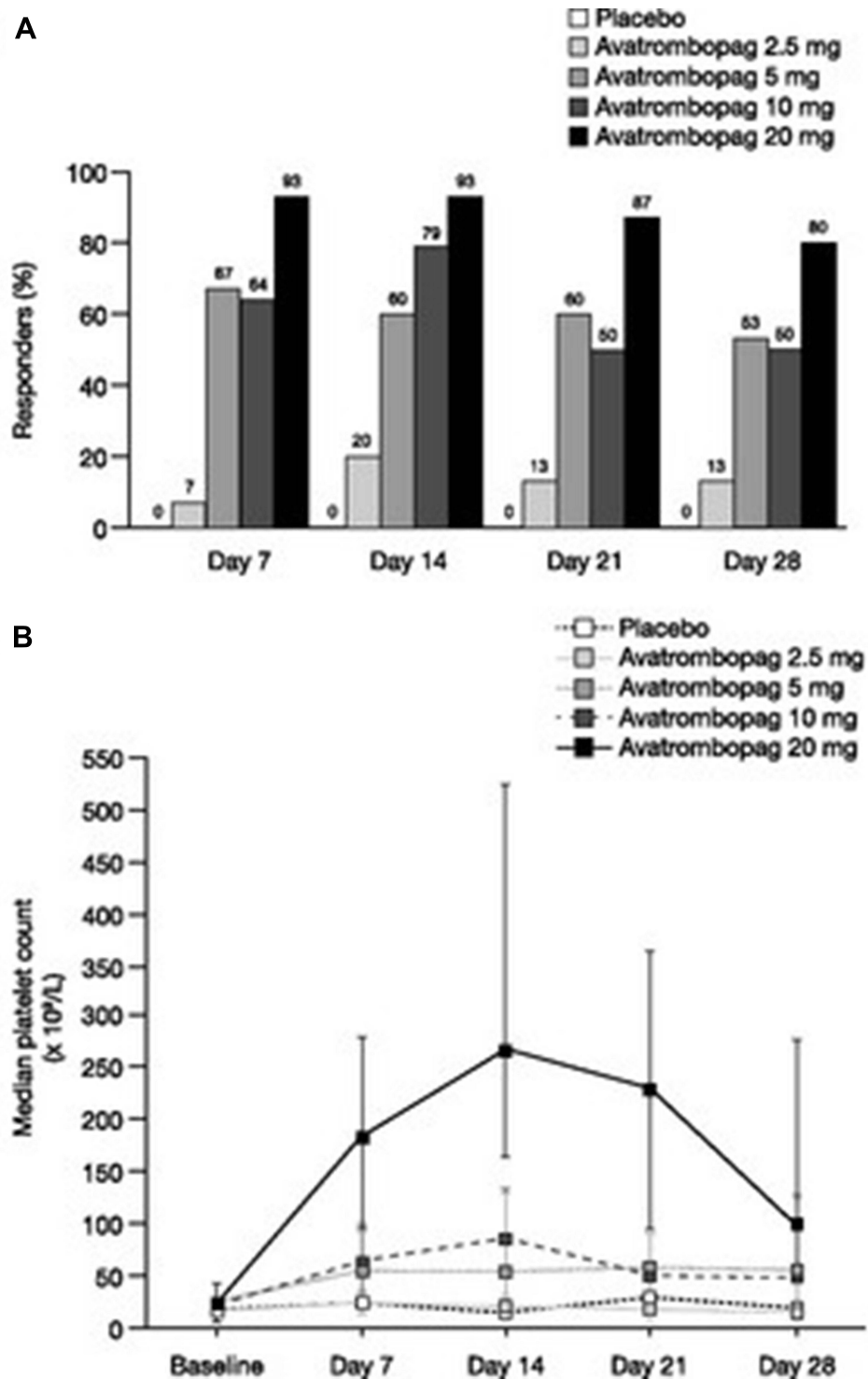


Figure 3 Response rate for avatrombopag and placebo cohorts and median [Q1, Q3] PC over time by treatment group in the randomized study. Response rate (proportion of subjects who achieved $PC \geq 50 \times 10^9/L$ and minimum PC increase of $20 \times 10^9/L$ above baseline) at each time point for avatrombopag and placebo cohorts (**A**) and median [Q1, Q3] platelet count over time by treatment group (**B**) in the randomized study (LOCF). For each median (second quartile) PC presented in panel B, error bars denote the first (lower value of bar) and third (upper value of bar) quartiles. LOCF, the last observation carried forward. Reprinted from *Blood*, 123, Bussel JB, Kuter DJ, Aledort LM et al. A randomized trial of avatrombopag, an investigational thrombopoietin-receptor agonist, in persistent and chronic immune thrombocytopenia. 3887–3894, Copyright 2014, with permission from Elsevier.³⁰

Abbreviation: PC, platelet count.

were age 18 or older, with a chronic primary ITP (at least 12 months of duration) and persistent platelet counts lower than $30 \times 10^9/L$, patients could be included regardless of their splenectomy status. At least one previous treatment line for ITP therapy should have been received. In addition, the patient must have had an initial response to at least one therapy or have had a bone marrow examination within three years before inclusion to rule out other causes of thrombocytopenia. Forty-nine patients were stratified according to their platelet counts, splenectomy status, and use of concomitant medication. They were randomly assigned to receive either avatrombopag 20 mg daily or placebo treatment (double-blinded randomization 2:1). The dose could be titrated to a maximum of 40 mg to a minimum of 5 mg with the goal for platelet counts of between 50 and $150 \times 10^9/L$. In a core study, a dose reduction in concomitant medication was allowed until week 18, while the primary endpoint was evaluated during the maintenance phase (weeks 18–26). The primary endpoint, cumulative number of weeks with platelet counts of at least $50 \times 10^9/L$ in the absence of rescue therapy, was significantly longer with avatrombopag (mean 12 in the avatrombopag group and 0.1 weeks in the placebo group, $p < 0.0001$). In addition, patients in the avatrombopag group had a 66.8% platelet response on day 8 compared to no response in the placebo group. Furthermore, 33% of the patients were able to reduce their concomitant therapy compared to none in a placebo group. However, statistical significance was not reached due to the low number of participants.

The patients who discontinued the core study due to lack of response and patients who continued the core study throughout the maintenance phase were invited for enrollment into a 90-week extension period followed by the 4 weeks tapering period and 4 weeks observational period. The main goal in the extension period was to study the long-term safety and efficacy assessed by the bleeding rate, platelet counts response rate and use of rescue therapy. A short overview of both studies is provided in [Table 3](#).

The incidence of bleeding events was lower in the avatrombopag group when adjusted to the longer mean exposure time. Most bleeding events in both groups were grade 1 except two grade 2 and one grade 3 bleeding events observed in the avatrombopag treated group.

Quality of life (HQoL) was evaluated neither in phase II nor phase III study.

One phase III study aimed to evaluate the efficacy of avatrombopag versus eltrombopag (NCT01433978) was terminated early due to significant enrollment challenges.

There is also an ongoing phase III study (NCT04516967) is aimed to evaluate the efficacy of the drug in the pediatric population (children ≥ 6 months).

A Phase IV study to evaluate HQoL and the safety of avatrombopag after switching from other TPO-RAs (NCT04638829) is ongoing. Another real-world effectiveness study of avatrombopag in the ITP patient population (NCT04943042) is planned.

Safety of Avatrombopag in ITP Clinical Trials

Based on phase II and III trials, avatrombopag appeared to be generally safe and showed a favorable side effect profile in the ITP population.

In a phase II study,³⁰ the most frequent adverse events (AEs) were epistaxis, headache, fatigue, and confusion. There were no differences in the rate of occurrence of AEs in avatrombopag and placebo groups during the randomized part of the study. All AEs, except increased platelet count above the desired level, were dose-independent. Increased platelet count was reported in 7 patients during the entire study resulting in permanent drug discontinuation in 5.

Recurrence of thrombocytopenia after discontinuation of avatrombopag (defined as a drop in platelet counts $< 10 \times 10^9/L$) occurred in 14% of individuals during the follow-up period, most of this occurred during week 2.

In total, five thromboembolic events occurred in 6% (4 patients) during the phase II study, with one participant experiencing two different thromboembolic events. Those events were iliac DVT, superficial thrombophlebitis, myocardial infarction, stroke, and retinal artery occlusion. Two of these events resulted in permanent study drug discontinuation. There were additional risk factors of thrombosis in three of the participants.

There was some transient liver function tests elevation with two grade 2 or 3 events in study subjects, but with no dose-dependent trends.

In total, eight subjects (13%) had temporary discontinuation of the drug across the whole study due to AE. Most were due to an increase in platelet counts (5 patients), which was the only AE resulting in permanent treatment

Table 3 Efficacy of Avatrombopag in ITP in Phase II and III Trials

Study/Phase	Duration	Location	Number of Patients (n) Enrolled	Main Inclusion Criteria	Main Results
Bussel et al ³⁰ 2014 Phase II double-blind, randomized dose-ranging, placebo-controlled, parallel group study	Randomized study 28 days	US	Total (n= 64) - Placebo (n= 5) - 2.5 mg (n=15) - 5 mg (n=15) -10 mg (n=14) - 20 mg (n= 15)	<ul style="list-style-type: none"> • Age \geq18 years • ITP \geq3 month • Platelet counts $<30 \times 10^9/L$, or $< 50 \times 10^9/L$ if receiving steroids • Failure to respond \geq1 prior line of ITP therapy. 	Platelet response rate ^a : 0% placebo 13% at 2.5 mg avatrombopag 53% at 5 mg avatrombopag 50% at 10 mg avatrombopag 80% at 20 mg avatrombopag
	Extension part 24 weeks		Total (n=53) - Responders (n=25) - non-responders (n=28)	<ul style="list-style-type: none"> • completed treatment in the randomized part 	Overall response: 76% Durable response: 53% 13 out of 24 reduced steroid doses by \geq 50% 8 out of 24 discontinued steroids
Jurczak et al ³¹ , 2018 Phase III multicenter, randomized, double-blinded, parallel- group study	Core study 6 months	Asia, Australia, and New Zealand, Africa, Europe	Total (n =49) - placebo (n=17) - avatrombopag (n=32)	<ul style="list-style-type: none"> • age\geq18 years • ITP\geq12 months • platelet counts$<30 \times 10^9/L$ • \geq1 prior line of therapy. • Initial response to \geq1 prior line of therapy or bone marrow examination to rule out other causes of thrombocytopenia 	Duration of a platelet count $\geq 50 \times 10^9/L$ (avatrombopag/ placebo) Median: 12.4 vs 0.0 weeks Mean: 12.0 vs 0.0 weeks Durable response rate: 34.4% vs 0.0%
	Extension phase 90 weeks		Total (n=39)	<ul style="list-style-type: none"> • Completed maintenance in a core study or discontinued early due to lack of response • No safety or tolerability issues 	

Note: ^aPlatelet response: platelet count $\geq 50 \times 10^9/L$ at a given assessment time point.

Abbreviation: ITP, immune thrombocytopenia.

Table 4 Most Common and Severe (Grade 3 or 4) AEs During the Randomized and Extension Study (Total Number of Patients N=64)

AEs	Most Common AE (>10%)	Serious AEs N (%)
No of subjects with > 1 AE	64 (100)	26 (41)
Fatigue	24 (38)	2 (3)
Headache	21 (33)	1 (2)
Epistaxis	16 (25)	1 (2)
Contusion	13 (20)	0
Arthralgia	9 (14)	0
Diarrhea	9 (14)	1 (2)
Severe (<10x10 ⁹ /L) thrombocytopenia	9 (14)	8 (13)
Gingival bleeding	8 (13)	0
Back pain	7 (11)	1 (2)
Peripheral odema	7 (11)	1 (2)
Platelet count increase	7 (11)	7 (11)
Vomiting	7 (11)	2 (3)

Notes: Adapted with permission from Elsevier, from Bussel JB, Kuter DJ, Aledort LM et al. A randomized trial of avatrombopag, an investigational thrombopoietin-receptor agonist, in persistent and chronic immune thrombocytopenia. *Blood*. 123:3887–3894, copyright 2014, permission conveyed through Copyright Clearance Center, Inc.³⁰

Abbreviation: AE, adverse event.

discontinuation in > 1 patient. Permanent discontinuation of the treatment due to various reasons occurred in 10 patients (16%).

The most common and severe adverse events during the phase II trial are shown in Table 4.

During the core phase III study,³¹ the most common treatment-emergent adverse events (TEAE) were headache, contusion, upper respiratory tract infection, arthralgia, epistaxis, fatigue, gingival bleeding, and petechiae, these were higher in the avatrombopag group. However, when exposure-adjusted, the incidence rates were comparable or lower than in the placebo group. In the extension study, there were some additional AEs: hypertension, pharyngitis, and nasopharyngitis.

Adverse events of special interests (AESI) were reported only in the avatrombopag-treated group. In a core study, three patients (9, 4%) experienced thromboembolic events and one additional patient in an extension phase. Three of these patients had several additional risk factors. One patient had liver tests elevation, which was considered unrelated to the study drug treatment. Only one avatrombopag patient-reported bleeding event or recurrence of thrombocytopenia during the study period. No cases of gastric atrophy or bone marrow fibrosis were reported.

An overview of treatment-emergent adverse events grade 3–4 and serious adverse events in the phase III study is shown in Table 5.

No deaths were reported during the study period in any of the studies.

Labeled Indications and Practical Considerations

Avatrombopag is approved in the US and Europe for use for the following indications:

1. Treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia with insufficient response to a previous treatment.

Table 5 Treatment-Emergent AE Grade 3–4 and Serious AEs (Total Number of Patients N=47) in a Core Study± Extension Phase

AE	Incidence N (%)	Exposure Adjusted Incidence Rate
TEAE grade 3–4	14 (29.8)	0.7
SAE	15 (31.9)	0.7
Most frequent SAEs		
Headache	2 (4.3)	0.1
Vomiting	2 (4.3)	0.1
Platelet count decrease	2 (4.3)	0.1

Notes: Adapted from Jurczak W, Chojnowski K, Mayer J et al. Phase 3 randomised study of avatrombopag, a novel thrombopoietin receptor agonist for the treatment of chronic immune thrombocytopenia. *Br J Haematol*. 2018;183:479–490. © 2018 The Authors. *British Journal of Haematology* published by John Wiley & Sons Ltd and British Society for Haematology. Creative Commons license and disclaimer available from: <http://creativecommons.org/licenses/by/4.0/legalcode>³¹.

Abbreviations: AE, adverse event; SAE, serious adverse event; TEAE; treatment emergent adverse event.

Initial dosing is 20 mg once daily. Max dose is 40 mg daily. The dose must be adjusted in case of significant drug interactions

2. Treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure.

Treatments should start 10–13 days before the scheduled procedure. The procedure must be undergone 5–8 days after the last avatrombopag dose. Patients with platelet counts of 40–60x10⁹/L should take 40 mg avatrombopag once daily for 5 consecutive days; those with platelet counts <40x10⁹/L should take 60 mg avatrombopag for 5 consecutive days.

No dose adjustments due to drug interactions are required for this patient group.

Avatrombopag should be administered with food.

Management of Particular Populations

Patients with renal and hepatic impairment: there is no need for dose adjustments in patients with reduced renal function. Dialysis is not expected to enhance avatrombopag elimination.

Patients with hepatic impairment required no dose adjustment as hepatic impairment has no meaningful effect on pharmacokinetics.

Elderly: no dose adjustment is necessary compared to adult dosing.

Pediatric population: to date, there are no data on the safety and efficacy of avatrombopag in this population. A Phase 3 study with avatrombopag for the treatment of ITP in children ≥6 months is ongoing (NTC04516967).

Clinical Perspective in the Use of Avatrombopag

The development of TPO-RAs represents one of the major advances in the management of ITP during the last 15 years. Romiplostim and eltrombopag were first licensed for adult chronic ITP in 2008. However, their label has changed several times, and consequently, their use has gradually increased to become among the most widely used ITP treatment modalities in most countries.³² According to the updated ASH guidelines¹³ TPO-RA are now preferred over rituximab in patients who do not respond adequately or become dependent on corticosteroids.

In addition to their high and durable response rates, these agents have shown good safety profiles and high tolerability. Nevertheless, both romiplostim and eltrombopag have some drawbacks related to the safety profiles or mode of administration. Romiplostim is a parenteral medication with the potential of administering an incorrect dose. In addition, in the US, the drug is still administered by health care professionals, and as such, it places some restrictions on

a patient's life. Even in Europe, where the drug is licensed for self-treatment, around 2/3 of the patients may have difficulties self-administration and may require help from family members or health care professionals.³³

For eltrombopag, limitations are mainly due to dietary restrictions, which may affect the efficacy and impact compliance. In addition, its use is restricted in patients with liver disease due to its hepatotoxicity, and it also carries a Black Box Warning due to the risk of decompensation in patients with chronic hepatitis C treated with ribavirin and interferon. In patients without liver disease, its use requires frequent and regular monitoring of liver function particularly during the first year after its initiation where at least monthly blood tests are required.

Avatrombopag is administered orally, once a day, requiring no dietary restrictions which obviously present an advantage over the two other preparations. In contrast to eltrombopag, hepatic events have been observed in only 3% of avatrombopag treated patients with no documented increase in bilirubin of grade 2 or higher³⁴ representing another advantage over eltrombopag. The safety of avatrombopag has also been confirmed in patients with chronic liver disease.³⁵ That makes avatrombopag an attractive alternative in treating ITP patients with underlying liver disorders. Based on phase II and III studies and despite a limited number of patients, it seems that avatrombopag, like both romiplostim and eltrombopag, is an effective and safe treatment alternative in the adult ITP population. As with the other two TPO RAs, avatrombopag yields high response rates with an impressive rise in platelet counts to $>50 \times 10^9/L$ already at day 8 in 66% of the patients. However, there are no studies comparing these agents' relative efficacy and safety head-to-head.

The main limitation of avatrombopag is currently the limited safety data available. One worrying signal is the rates of thromboembolic events observed in phase II and III studies of avatrombopag, which seems higher than that reported for the two other TPO agonists. That may be due to the low number of patients, but this issue should be carefully accessed in further trials. Until more data is available, a vigilant approach has to be adopted particularly concerning those at high risk for thromboembolism, eg patients with multiple risk factors for TE.

In general, the number of patients included in both studies is relatively small and more data is required to affirm the safety of this agent. Hopefully, the ongoing studies, including phase IV study of the effectiveness and safety of avatrombopag in the ITP population, will bridge some of the current knowledge gaps with avatrombopag (NCT04943042).

Currently, avatrombopag is licensed for adult patients with chronic ITP ie ITP > 12 months since diagnosis. We do not believe that this label will be changed before more data on safety and efficacy of avatrombopag is available. Since the romiplostim and eltrombopag are currently licensed for ITP of less than one year, this means that most patients will start on these preparations first. However, if a patient fails to respond or loses response to one or both thrombopoietic agents and has chronic ITP, switching to avatrombopag is often effective and should be attempted. Several publications demonstrate the efficacy of switching between TPO-RAs when switching was conducted either due to the lack of efficacy, adverse events or platelets fluctuations.³⁶ However, available data applies and supports first and foremost switching between romiplostim and eltrombopag. There is very limited experience regarding switching to avatrombopag from the two other TPO RAs. Al-Samkari et al reported data on 45 heavily pretreated ITP switched from romiplostim or eltrombopag to avatrombopag. The reasons for switching were inconvenience (51%), ineffectiveness (31%), or adverse events (18%). In patients switched due to ineffectiveness, the median platelet count on avatrombopag was $114 \times 10^9/L$ compared to $28 \times 10^9/L$ before the switch. Of 19 patients who used concomitant steroids, 12 (63%) discontinued steroids, and 32% reduced dose.³⁷ There is also an ongoing study on safety and treatment satisfaction after switching to avatrombopag from other TPO-RAs (NCT04638829). In our practice, we switch to avatrombopag in those who have failed or lost response to any of the two other TPO-RA.

There is no reason to believe that avatrombopag would have different safety or efficacy profiles if used at an earlier stage, eg during the persistent phase of ITP or even in the newly diagnosed ITP after the failure of corticosteroids. In fact, according to the international consensus report, it is enlisted among the subsequent therapies with robust evidence, thus allowing for use at an earlier stage.¹⁴ Restrictions imposed by local regulatory authorities, reimbursement bodies, and national guidelines will be determinant in that regard.³⁸

Generally, we recommend administration of avatrombopag according to the label. Only in an exceptional case we deviate from that eg, if no other treatment is available or if the patient prefers oral medication but cannot take

eltrombopag because of drug interaction or expected difficulty because of dietary restrictions. However, when the patient can be offered any of the three available agents, our practice is to let the patient decide after presenting the three options with their pros and cons. Despite the limited evidence on safety as the main limitation, the patients frequently choose avatrombopag because of the ease of administration. Once the response is achieved, the dose should be adjusted to the lowest to maintain platelet count $50\text{--}150 \times 10^9/\text{L}$ according to the schedule recommended by the manufacturer. Not infrequently, we manage to reduce the dose to every second or third day, which may substantially reduce the cost of treatment.

In contrast, for patients who do not respond to 20 mg daily within a week or two, a dose increment to 40 mg is recommended. If no response is achieved within 6 weeks, it is unlikely that the patient will respond to avatrombopag monotherapy. In this case, one should either switch to another TPO-RA or different treatment or combine avatrombopag with an immunosuppressive agent, like prednisolone or mycophenolate mofetil.³⁹ We usually add a small dose of prednisolone (2.5–5 mg) first if satisfactory results are not achieved. This combination often results in response.³⁸

To summarize, avatrombopag seems to be a valuable addition to the TPO treatment specter, but further studies are needed to affirm the efficacy, safety, and effect on HQoL. Considering apparent low toxicity demonstrated in studies and ease of administration, avatrombopag has the potential to become a TPO agonist of choice for many patients with ITP.

Disclosure

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