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DRUG PROFILE

Avatrombopag for the treatment of immune thrombocytopenia

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ABSTRACT

Introduction: Thrombopoietin-receptor agonists (TPO-RAs) are the only American Society of Hematology (ASH) guideline-advocated, second-line treatment for immune thrombocytopenia (ITP) that have been validated by randomized, controlled trials with a placebo comparator. Avatrombopag is a new candidate in this class that has been investigated as a treatment option for the treatment of ITP.

Areas covered: In this Drug Profile, we provide a review of the clinical data of avatrombopag, which was approved in May 2018 by the United States Food and Drug Administration (FDA) for the treatment of thrombocytopenia in patients with chronic liver disease undergoing an invasive procedure, and an opinion of its potential place in the current evidence-based ITP treatment landscape.

Expert commentary: Avatrombopag induces doubling of platelet counts, increasing them to above 50 X 10^9/L, and prevents the need for platelet transfusions while minimizing the need for rescue medications. Treatment-emergent adverse events (TEAEs) are comparable to placebo. Oral delivery, a 5-day dosing schedule and good tolerability (<1% discontinuation rate) with no clinically significant hepatoxicity make it a promising entrant as a potential second-line treatment for ITP. Further, data from a phase 3 study in patients with ITP supports its utility in the treatment of patients with ITP.

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1. Introduction

Primary immune thrombocytopenia (ITP) is an immune-mediated acquired thrombocytopenia defined as a transient or persistent decrease of the platelet count <100 X 10^9/L in the absence of other causes of thrombocytopenia. ITP is caused by a complex array of abnormalities, including antiplatelet antibodies that increase platelet clearance, impaired platelet production, T-cell mediated platelet destruction, and defective cellular immunity [1–5]. While ITP may be asymptomatic in many patients, it is associated with an increased risk of bleeding, which may lead to fatal hemorrhage in patients with a low platelet count of <30 X 10^9/L [6]. When ITP is a result of a known underlying disorder such as autoimmune disease, human immunodeficiency virus, *Helicobacter pylori*, or immune dysregulation syndromes, it is called secondary ITP [1,2]. A majority (about 80%) of adults have primary ITP [2].

In 2009, the International ITP Working Group (IWG) published a new standardized definition for the common abbreviation, ITP, as immune thrombocytopenia (neither idiopathic nor purpura), and also eliminated the term 'acute' from ITP. The IWG defined ITP as newly diagnosed if it is <3 months in duration, persistent if it is between 3 to 12 months in duration, and chronic if it is >12 months in duration. Refractory ITP was defined as the presence of severe ITP after splenectomy [2].

The incidence of ITP is estimated to be around 3.3/100,000 adults per year, while the prevalence is about 9.5/100,000 adults [7]. Results based on data from a UK General Practice Research database revealed that the overall average incidence rate for women was 4.4/100,000 adults per year, a number that was significantly higher than that noted for men (3.4/100,000 adults per year). Men seem to have a bimodal distribution for age-specific incidence of ITP, peaking at under 18 years and then between ages 75 to 84 years. The incidence rates for women were constant from childhood until around 60 years of age, after which they increased with age [7]. Results from a meta-analysis based on two large studies concluded that adults with ITP have a 60% higher risk of thromboembolism [8].

Our understanding of the pathophysiology of primary ITP has continued to evolve, and it is now considered an acquired immune disorder with the etiology of the thrombocytopenia being multifactorial and variable in different patients, including the development of pathologic platelet autoantibodies, impaired megakaryocytopoiesis, and T-cell mediated destruction of platelets [3–5]. In approximately 60–75% of patients with ITP, autoantibodies directed against platelet GPIIb/IIIa or GPIb/IX GP complexes can be identified, with many of the remaining patients having autoantibodies directed against other membrane glycoproteins, including GPV, GPIa/IIa, or GPIV. These autoantibody-coated platelets induce Fc receptor-mediated phagocytosis by mononuclear macrophages, primarily in the spleen. In addition to peripheral platelet destruction, impaired thrombopoiesis contributes to the thrombocytopenia in patients with ITP, with a failure of bone marrow megakaryocytes to increase platelet production and a lack of a compensatory increase in endogenous thrombopoietin (TPO).

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1.1. Treatment guidelines

The American Society of Hematology (ASH) and International Consensus Report published guidelines for the diagnosis and treatment of ITP in 2011 and 2010, respectively; updated guidelines to include newer treatment options are expected in 2018. While the role of newer drugs, including thrombopoietin-receptor agonists (TPO-RAs), is likely to expand as clinical evidence accumulates, the guidelines firmly establish the role of conventional treatments in the management of thrombocytopenia [9,10]. According to the ASH guidelines, as well as the International Consensus Report, first-line treatments for ITP in adults include corticosteroids such as prednisone and dexamethasone, intravenous immunoglobulin (IVIg), and anti-D (RhO) immunoglobulin [9–11]. The ASH guidelines suggest first-line treatments should be administered for newly diagnosed patients with a platelet count <30 X 10^9/L, although the initiation of treatment for ITP also depends on bleeding manifestations and other associated risk factors such as age or hypertension [10,11]. Other treatment recommendations include longer courses over shorter courses of corticosteroids or IVIg as first-line treatment. IVIg in combination with corticosteroids is proposed as an option if a rapid increase in platelet count is required, and the use of either IVIg or anti-D immunoglobulin when corticosteroids are contraindicated [10,11]. For adults, the ASH guidelines recommend splenectomy or TPO-RAs (in cases where splenectomy is contraindicated or not preferred) as second-line treatments. Third-line treatments include TPO-RAs or rituximab [10,11].

The International Consensus Report recommends second-line treatment in adults to include splenectomy, azathioprine, cyclosporine A, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, rituximab, and TPO-RAs eltrombopag (Promacta/Revolade) and romiplostim (Nplate) [9]. The ASH guidelines no longer recommend alternative immunosuppressive agents, such as azathioprine or cyclosporine, as there is insufficient data to support their use [10]. However, as a second-line approach, the ASH guidelines recommend splenectomy for patients who have failed corticosteroid therapy, and TPO-RAs for patients at risk for bleeding who relapse after a splenectomy or in whom a splenectomy is contraindicated, and for those who have failed at least one other therapy (either corticosteroids or IVIg) [10].

New to the 2011 updated ASH guidelines is the suggested use of rituximab for patients at risk of bleeding, who have failed at least one line of therapy, including corticosteroids, IVIg, or splenectomy [10]. However, these guidelines were published when only two TPO-RAs, eltrombopag and romiplostim, were available in the market. Since then, there has been an abundant gathering of data on the efficacy and safety of long-term use of romiplostim and eltrombopag [12–14]. Further, some studies have also shown that a small number of patients with ITP have gone into extended remission after being treated with these agents [15–18], and that baseline TPO concentrations may predict which patients would respond to treatment with a TPO-RA [19]. As such, the use of TPO-RAs has increased, leading to an overall lowering of the rates of splenectomy (<25%) as second-line treatment, and an increase in the usage of TPO-RAs and other agents as second- and third-line treatments [20].

Most recently, phase 3 data on avatrombopag as a potential treatment for chronic ITP has been published (Jurczak et al. 2018), and a new drug application (NDA) is under review by the FDA for this indication [21]. In addition, the guidelines were published prior to the newly approved spleen tyrosine kinase (Syk) inhibitor, fostamatinib (Tavalisse), that has been approved for the treatment of ITP [22]. This review is an overview of the clinical data on avatrombopag and provides an opinion on its potential place in the ITP treatment landscape if approved.

2. Avatrombopag in the treatment of ITP

2.1. Market overview

Conventional, current second- and third-line treatments play an important role in the management of chronic ITP, but they also have certain drawbacks that may be addressed by newer treatments. The only non-pharmacological option, splenectomy, is invasive in nature and associated with an increased risk of infections, including septicemia, which has been reduced with pre-splenectomy vaccinations; it is also associated with an increased risk of vascular complications from venous thromboembolism. Response to splenectomy is unpredictable with a durable response rate of 50% to 70%, although autologous platelet scintigraphy may prove to be a useful predictor of which patients will respond to splenectomy [23,24]. Since the arrival of TPO-RAs, fewer patients undergo splenectomy in daily practice and are directed to treatment with TPO-RAs instead, more broadly than the recommendations of the ASH guidelines [20,25].

The guideline-recommended, second-line pharmacological agents for the treatment of chronic ITP include rituximab and the TPO-RAs, romiplostim and eltrombopag [10]. However, the first randomized, placebo-controlled study that assessed the long-term efficacy of rituximab (off-label use) as a second-line treatment for ITP in adults concluded that rituximab did not significantly reduce the rate of long-term treatment failure when compared with placebo beyond 78 weeks of use. There was a small (10%) number of rituximab-treated patients who had a sustained response, but the study was not adequately powered to observe a statistically significant difference [26]. Based on Kaplan-Meier estimates, the cumulative incidence of overall response and complete response at 78 weeks was 81% versus 73% (P = 0.15) and 58% versus 50% (P = 0.12) for rituximab and placebo, respectively [26].

In contrast, TPO-RAs have demonstrated a favorable safety profile and high efficacy (unequivocally over 70% of the response rate) [27]. Safety concerns include increased risk of portal vein thrombosis in patients with chronic liver disease (CLD) for romiplostim, and an increased risk of thrombotic/thromboembolic events as well as severe and potentially life-threatening hepatotoxicity for eltrombopag for which it carries a boxed safety warning. Additionally, eltrombopag use has important dietary restrictions that potentially affect its efficacy and require patient education and effort to increase compliance [12,21].

There are new TPO-RAs in various stages of development that may offer advantages over current therapies or serve as alternatives to conventional treatment. These include avatrombopag, lusutrombopag, and hetrombopag, the former two having recently been approved by the FDA for the treatment of thrombocytopenia in patients with CLD undergoing a procedure [28]. Avatrombopag has also completed a phase III study in patients with ITP, and a supplemental NDA (sNDA) for this indication is under review by FDA; phase II development of lusutrombopag for ITP was terminated. Hetrombopag is a small-molecule, non-peptide TPO-RA with a mechanism of action similar to eltrombopag, but with an *in vivo* pharmacological effect that is 8 to 10 times that of eltrombopag [29]. A phase I study demonstrated that hetrombopag is safe and well tolerated in healthy subjects and can be a potential candidate for the treatment of patients with chronic ITP [29]. It is currently starting phase III trials for the treatment of ITP [29].

In addition to the TPO-RAs, there is a new class of drugs now available for the treatment of ITP [30]. It includes fostamatinib, the newly approved spleen tyrosine kinase (Syk) inhibitor that targets the Syk-mediated pathway of platelet destruction, which has now been approved for the treatment of ITP. Results from two phase III randomized, placebo-controlled trials in patients with chronic ITP, showed that stable responses (defined as platelet counts ≥50 X 10^9/L at ≥4 of 6 biweekly visits without the need for rescue therapy) occurred in 18% of patients on fostamatinib compared with 2% on placebo [30]. The most common adverse events (AEs) reported included diarrhea, hypertension, nausea, and transaminase elevation [30].

2.2. Introduction to avatrombopag

2.2.1. Chemistry

Avatrombopag (chemical name: 4-piperidinecarboxylic acid, 1-[3-chloro-5-[[[4-(4-chloro-2thienyl)-5-(4-cyclohexyl-1-piperazinyl)-2-thiazolyl]amino]carbonyl]-2-pyridinyl],-(2Z)-2-butenedioate) is an orally administered, small molecular TPO-RA with a molecular weight of 765.73 that acts by mimicking the biological effect of TPO *in vitro* and *in vivo* [31,32] (Figure 1). Additionally, the binding site of avatrombopag on the TPO receptor is unique from the binding site of endogenous TPO, enabling avatrombopag to not block the binding of native TPO and have an additive effect with endogenous TPO on platelet production [31,33]. It is available as an immediate-release, 20-mg tablet that is taken orally with food once daily for five consecutive days for patients with thrombocytopenia and CLD, based on patients' baseline platelet count (40 or 60 mg for 5 days), and is started 10 to 13 days prior to the scheduled procedure. In patients with ITP, chronic dosing of avatrombopag was initiated with a 20-mg daily starting dose, which was then subsequently titrated based on platelet counts from 5 to 40 mg [6,31].

2.2.2. Pharmacokinetics and metabolism

Once-daily dosing of avatrombopag was established from two double-blind, dose-rising, placebo-controlled phase 1 studies (single-dose study and multiple ascending-dose study) in which avatrombopag demonstrated dose-proportional pharmacokinetics (PKs) as well as a dose-independent half-life of 18 to 21 h [34]. In the multiple-dose study (starting dose of 3 mg followed by doses of 10, 20, 50, or 100 mg for 14 days), avatrombopag was measurable in plasma 0.25 to 1 h after initial and repeat dose administration with maximum concentrations observed 4.5 to 6 h after initial (day 1) and final (day 14) dose administration. C_{max} and area under the curve (AUC) increased in a dose-proportional manner following avatrombopag administration on days 1 and 14. The median T_{max} was around 6 h, while the mean $t_{1/2}$ ranged from 18 to 21 h [34].

Absorption was unaffected by food, and C_{max} and AUC were not affected when avatrombopag was taken with a low-fat or high-fat meal, while the T_{max} was delayed by 0 to 2 h. Avatrombopag is more than 96% bound to human plasma proteins and has a mean plasma elimination half-life of 19 h with a clearance of 6.9 L/hour [31]. Avatrombopag is metabolized by cytochrome P450 2C9 and 3A4. Figure 2 shows the mean maximum change from baseline platelet count with single (Figure 2(a,b)) and multiple (Figure 2(c,d)) doses of avatrombopag, as well as the maximum platelet count rise above baseline compared with the C_{max}. The PKs of avatrombopag were similar in both healthy subjects and those with CLD [31].

2.2.3. Pharmacodynamics

In vitro studies have shown that avatrombopag stimulates the proliferation of human c-Mpl-Ba/F3 cells (with an EC50 value

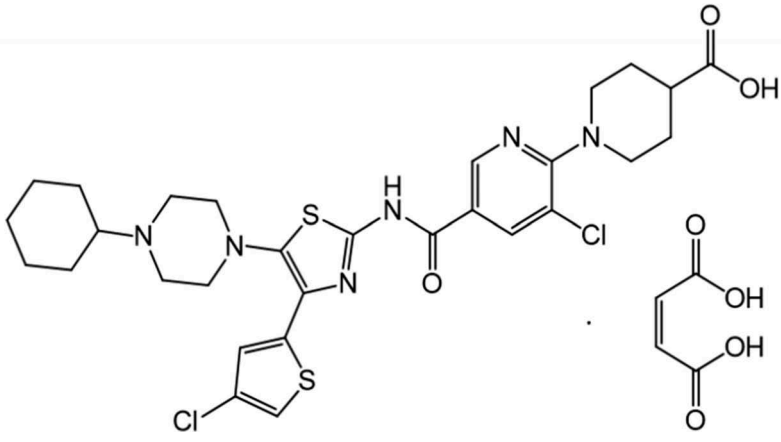

Figure 1. Chemical structure of avatrombopag. Retrieved from Doptelet [package insert]. Durham, NC: Dova Pharmaceuticals Inc; 2018 [31].

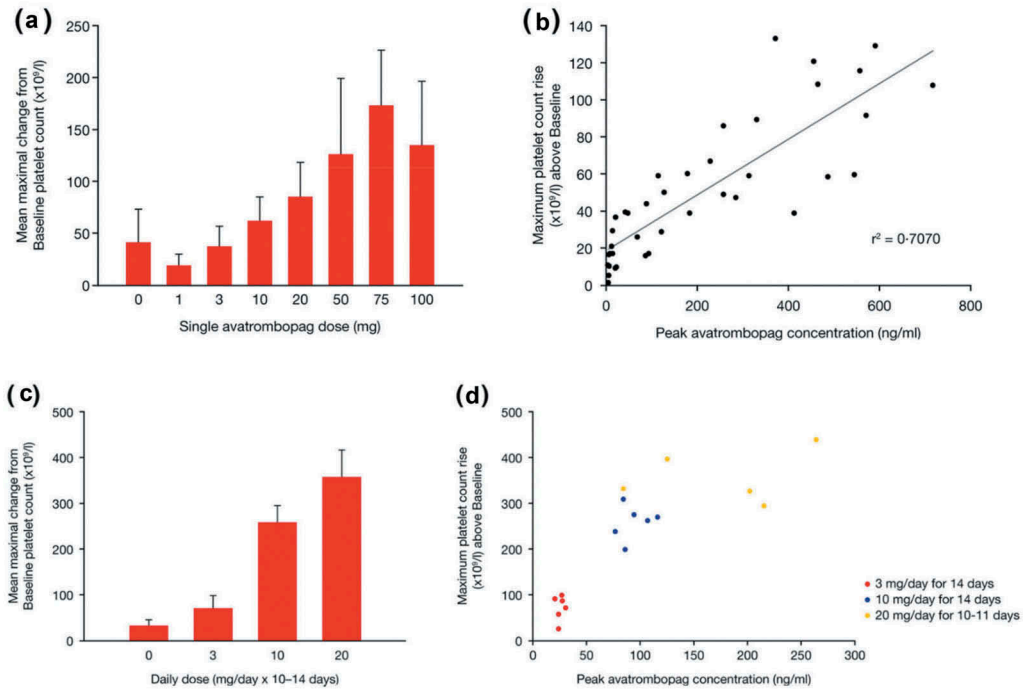

Figure 2. Pharmacokinetics of avatrombopag. Single-dose study (a) Mean maximum change (±SD) from baseline platelet count with single doses of avatrombopag, (b) Maximum platelet count rise (X 10^9/L) above baseline (C_{pmax}) compared with peak avatrombopag concentration (C_{max}). Multiple-dose study (c) Mean change (±SD) from baseline platelet counts by dose cohorts. (d) Maximum platelet count rise (X 10^9/L) above baseline (C_{pmax}) compared with peak avatrombopag concentration (C_{max}). Reprinted from [34].

of 3.3 ± 0.2 nmol/l) and promotes the megakaryocyte colony formation from human CD34+ cells (EC50 24.6 ± 7.8 nmol/l) [32]. These preclinical data predicted the therapeutic potential for the treatment of thrombocytopenia of various etiologies, including ITP.

In a phase I, multiple-dosing study, a small increase in platelet count occurred with the avatrombopag 3-mg dose, whereas significant increases were observed with the 10- and 20-mg doses at approximately 3 to 5 days after the start of avatrombopag when compared with placebo [34]. For all treatment cohorts (3 mg, 10 mg, and 20 mg), the maximum increases in platelet counts from baseline occurred at approximately 13 to 16 days and appeared to be dependent on dose, concentration, and duration of treatment. There was no change in mean platelet volume.

In a 28-day, phase II dose escalation study in patients with ITP (N = 64), a low (13%) platelet count response rate was observed with the avatrombopag 2.5-mg dose, whereas a statistically greater proportion of responses (80%) occurred with the 20-mg dose compared to placebo (0%), with most responses occurring by day 7 [6]. These results in patients with ITP are comparable to the data from the phase I multiple-dosing trial, which support the continued investigation of avatrombopag in patients with other etiologies of thrombocytopenia such as ITP [34]. In a phase II extension study for patients with ITP from the 28-day dose escalation study (N = 53), chronic avatrombopag dosing resulted in 76% of subjects having an overall platelet response, and 53% achieving a durable response, supporting the ability of avatrombopag to achieve and maintain clinically relevant platelet count increases in patients with ITP [6].

2.3. Clinical efficacy

2.3.1. Phase I studies

Dose selection for phase II and III efficacy trials was based on the results of two double-blind, dose-rising, placebo-controlled phase I studies [34]. These studies also provided extensive PK and pharmacodynamic (PD) data and an assessment of AEs of avatrombopag in healthy subjects aged 18 to 65 years with a platelet count between 150 and 300 X 10^9/L. Tested doses were 1, 3, 10, 20, 50, 75, or 100 mg for the single-ascending dose study, and 3, 10, 20, 50, or 100 mg for the multiple-ascending dose study. Dosing for the multiple-dose study was based on the safety and tolerability information from the single-dose study. The 50- and 100-mg dose cohorts were not populated as the 20-mg cohort subjects reached the pre-specified PD limit of platelet counts ≥500 X 10^9/L after 10 or 11 days of daily dosing.

Both phase I studies found that avatrombopag was well tolerated with no serious AEs (SAEs) or dose-limiting toxicities [34]. The peak concentration of avatrombopag increased proportionally to the dose, with a half-life of 18 to 21 h that supported once-daily dosing [34]. Platelet count increases were first observed 3 to 5 days after the first dose, and maximum changes were seen after 13 to 16 days. Platelet count increases for the 20 mg once-daily dose over 10 days resulted in a mean maximum platelet count of 372 X 10^9/L over baseline.

2.3.2. Phase II studies

A phase II study was conducted to evaluate the efficacy of avatrombopag in patients with ITP. This sequential, 4-week, double-blind, randomized, dose-ranging, placebo-controlled,

parallel group phase II study (Study 003 or NCT00441090) of avatrombopag with a 24-week open-label, follow-on extension study (Study 004 or NCT00625442) was conducted to assess the efficacy and safety of once-daily avatrombopag for the treatment of patients with a confirmed diagnosis of ITP [6]. Patients (N = 64) were given 2.5, 5, 10, or 20 mg avatrombopag or placebo once daily for 28 days. Responders at day 28 continued in the extension study taking the same daily dose of avatrombopag or placebo, whereas nonresponders were given 10 mg once daily in the extension study, with increases of up to 40 mg as needed to maintain a platelet count >50 X 10^9/L. The primary efficacy endpoint was the platelet count response rate, defined as the proportion of patients who achieved a platelet count ≥50 X 10^9/L and a minimum increase of 20 X 10^9/L above baseline at day 28. The objective of the extension study was to assess the safety and tolerability of avatrombopag for an additional period while assessing the proportion of patients with ITP who achieved a durable response. The drug was discontinued at the end of the extension study, followed by a 4-week follow-up period wherein platelet count was determined twice weekly at weeks 1 and 2, and then once weekly at weeks 3 and 4.

Patients in all the avatrombopag dose groups achieved a higher proportion of platelet count responders than patients in the placebo group (Figure 3(a)) [6]. Once-a-day 20-mg oral avatrombopag resulted in a significantly greater proportion of responses (80%; P = 0.0036) compared with placebo. A higher proportion of patients in this avatrombopag dose group doubled their platelet count compared with placebo (87% vs 20%, P = 0.0139). Results from the extension study (N = 53) were similar, with 76% and 53% of the patients with ITP achieving an overall response and durable response, respectively (Figure 3(b)). The response rates were higher in the extension study because of the ability to increase the doses. The mean and median final doses of avatrombopag at the end of the 24 weeks were 15 mg and 10 mg, respectively. The most common reported AEs seen in ≥10% of the patients who received avatrombopag in the randomized study were fatigue, headache, and epistaxis, while the only dose-related AE was an increased platelet count, reported by four patients in the 20-mg group, two of whom had to be discontinued from the study. The AE profile (e.g. thromboembolic events) was comparable to that reported in clinical trials of other TPO-RAs, and consistent with the entry criteria in other TPO-RA studies, patients at high risk of thrombosis were excluded from the clinical study.

Based on the positive results from this study that support the use of once-daily oral avatrombopag in patients with ITP, a phase III trial for avatrombopag was designed to demonstrate the superiority of avatrombopag over placebo in increasing and maintaining platelet count in patients with chronic ITP within a target range of 50 to 150 X 10^9/L over a 6-month period, as well as to study the safety and efficacy of long-term treatment with avatrombopag [21].

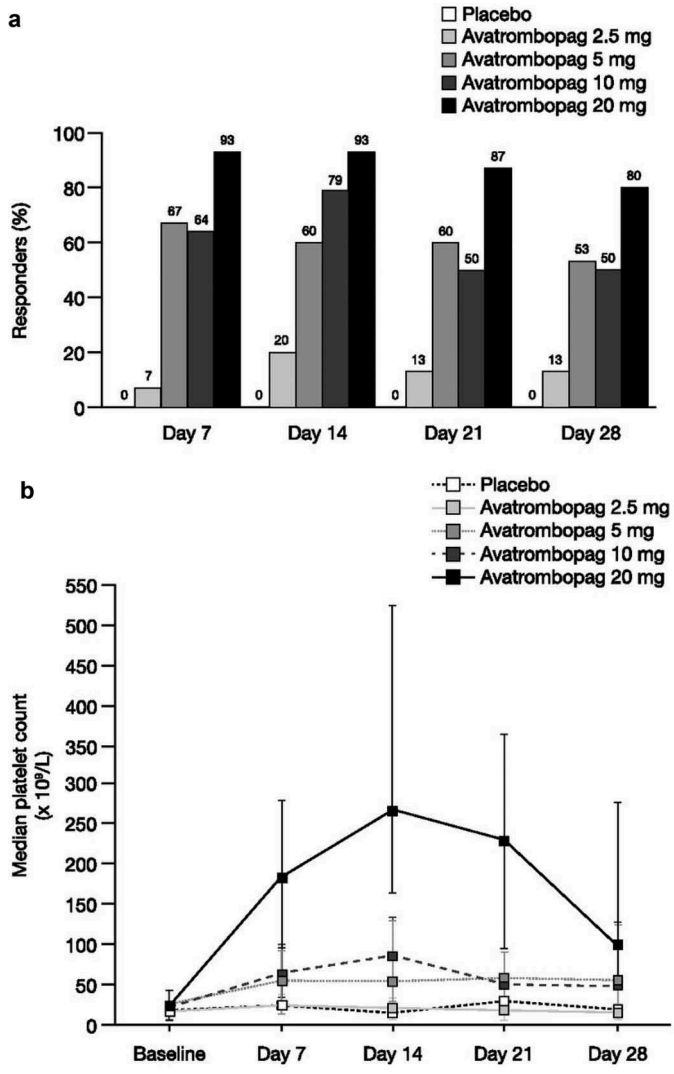

Figure 3. (a) Response rate for avatrombopag and placebo cohorts over time in phase II randomized study in patients with ITP. Response rate defined as the proportion of patients who achieved platelet counts ≥50 X 10^9/L and a minimum platelet count increase of 20 X 10^9/L above baseline at each time point. (b) Median platelet count over time by treatment group. For each median platelet count, error bars denote the first and third quartiles. Reprinted from [6] with permission of the American Society of Hematology.

2.4. Phase III studies

2.4.1. NCT01438840

The efficacy of avatrombopag in the treatment of ITP was further assessed in phase III multicenter, randomized, double-blind, parallel-group, placebo-controlled study (NCT01438840) in patients with ITP (*N* = 49) and an average of two platelet counts <30 X 10^9/L [21]. In addition to the core study, where efficacy was evaluated over a 6-month period, the trial included an open-label extension phase (*N* = 39) of up to 76 weeks designed to further evaluate the safety of chronic treatment [21]. Patients in the core study received either 20 mg avatrombopag or placebo, once daily. The study permitted the up or down titration of the dose to a minimum of 5 mg and a maximum of 40 mg according to prespecified protocols. The primary efficacy endpoint was the cumulative number of weeks of platelet response defined as a platelet count ≥50 X 10^9/L without the need for rescue therapy, over 6 months of treatment with avatrombopag. The efficacy and safety endpoints in the extension phase were assessed by measuring platelet response rate, bleeding, and the use of rescue therapy.

Avatrombopag was found to be superior to placebo in the median cumulative number of weeks of platelet response (12.4 vs. 0.0 weeks, Table 1), and more patients in the

avatrombopag group (65.6%) had a platelet response at day 8 compared with patients in the placebo group (0.0%) [21]. Patients treated with avatrombopag also had a significantly longer duration with a platelet count ≥50 X 10^9/L and an absence of rescue therapy compared with patients treated with a placebo. The response rate was maintained through the extension phase at least until week 36.

Table 1. Summary of phase III core study (NCT01438840) efficacy endpoints in patients with chronic ITP. Adapted from [21].

	PBO (*N* = 17)	AVA (*N* = 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
Platelet count ≥50 X 10^9/L at day 8		
Yes (%, 95% CI)	0.0	65.6 (49.17, 82.08)
No (%)	100.0	34.4
Difference of response rate (95% CI)[a]		65.63 (49.17, 82.08)
p-Value of Fisher's exact test		<0.0001
Reduction in use of concomitant ITP medications from baseline		
	PBO (*n* = 7)	AVA (*n* = 15)
Yes (%, 95% CI)	0.0	33.3 (9.48, 57.19)
No (%)	100.0	66.7
Difference of rate of reduction (%, 95% CI)[b]		33.3 (9.48, 57.19)
p-value of Fisher's exact test		0.1348

AVA, avatrombopag; CI, confidence interval; FAS, full analysis set; ITP, immune thrombocytopenia; n, number of patients; PBO, placebo; SD, standard deviation.

[a]Difference of response rate is the difference of platelet response rate at day 8 of AVA and platelet response rate at day 8 of PBO.

[b]Difference of rate reduction is the difference of rate of reduction in the use of concomitant ITP medications from baseline of AVA and the rate of reduction in the use of concomitant ITP medications from baseline of PBO.

2.4.2. Summary of phase III trial efficacy results

Data from the NCT01438840 trial support the efficacy and safety of long-term exposure to avatrombopag for the treatment of thrombocytopenia in adult patients with chronic ITP [21]. A summary of the primary and secondary efficacy endpoint results from the NCT01438840 trial are presented in Table 1 and Figure 4 [21].

Data from two other phase 3 trials studying the efficacy and safety of avatrombopag (ADAPT-1 and ADAPT-2) show that avatrombopag can be used safely and effectively to treat patients with CLD and thrombocytopenia who are scheduled for a surgical procedure that requires platelet counts of at least 50 X 10^9/L [35].

2.4.3. Safety and tolerability

Data gathered from the phase II studies in patients (*N* = 64) with ITP (NCT00441090 and NCT00625442) showed that the most common AEs occurring in >10% of subjects across both studies were fatigue, headache, epistaxis, and contusion [6]. The detailed safety profile of avatrombopag during the studies is outlined in Table 2. Four subjects had an increased platelet count and two of these subjects had to be taken off the study as their platelet counts were >500 X 10^9/L. In the combined studies, seven subjects had increased platelet counts, of which five subjects were taken off the study. Thromboembolic events were seen in 6% of the patients, of which two subjects were taken off the study. Recurrence of thrombocytopenia, defined as a platelet count that dropped

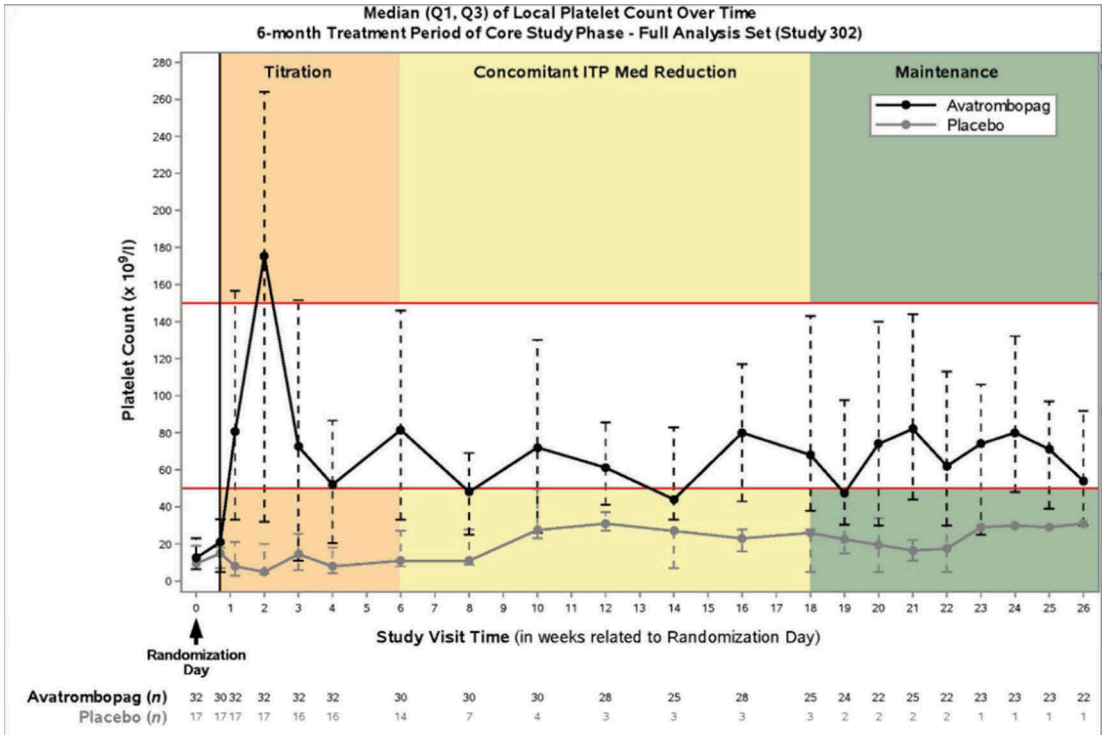

Figure 4. Phase III core study (NCT01438840) median platelet count over time in patients with chronic ITP. Reprinted from [21].

Table 2. Overall safety profile of avatrombopag and summary of most common AEs (occurring in more than 10% of the subjects in the combined avatrombopag treatment groups) during the randomized and extension phase II studies. Adapted from [6] with permission of the American Society of Hematology.

AE category[a]	Total number of subjects receiving avatrombopag (*N* = 64)
≥1 AE during treatment	64 (100)
Severe (grade 3–4) AEs	26 (41)
Suspected drug-related AEs[b]	42 (66)
SAEs	12 (19)
Serious TEAEs	4 (6)
Withdrawal of study drug due to AE	10 (16)
Dose interruption due to AE	8 (13)
Deaths	0

	Total number of subjects receiving avatrombopag (*N* = 64)		
AE	Any AE (Any grade)	Severe AE (Grade 3 or 4)	SAE
No. of subjects with ≥ 1 AE	64 (100)	26 (41)	12 (19)
Fatigue	24 (38)	2 (3)	0
Headache	21 (33)	1 (2)	0
Epistaxis	16 (25)	1 (2)	0
Contusion	13 (20)	0	0
Arthralgia	9 (14)	0	0
Diarrhea	9 (14)	1 (2)	1 (2)
Severe thrombocytopenia (platelets < 10 X 10^9/L)	9 (14)	8 (13)	5 (8)
Gingival bleeding	8 (13)	0	0
Back pain	7 (11)	1 (2)	1 (2)
Peripheral edema	7 (11)	1 (2)	0
Petechiae	7 (11)	0	0
Platelet count increased	7 (11)	7 (11)	0
Vomiting	7 (11)	2 (3)	2 (3)

AE, adverse event; *N*, number of patients; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Subjects may fall into >1 category.
[b]Related AEs include those whose relationship was categorized as possible or probable by the investigator.

below 10 X 10^9/L on discontinuation of avatrombopag, occurred in 14% of the patients who had received ≥10 mg doses of avatrombopag during the follow-up period. Bleeding events were reported in 67% of the subjects, of which the majority were mild or moderate in nature. No AEs regarding renal function were reported. While transient liver function changes were noted, no dose-related trends were observed. Treatment was well tolerated with eight subjects temporarily discontinuing the treatment as a result of an AE, of which five subjects discontinued due to an increased platelet count and three subjects due to grade 2 elevated alanine aminotransaminase (ALT) levels, grade 2 leukocytosis, and grade 3 cerebrovascular accident. Permanent discontinuation due to an AE occurred in 16% of the patients, four in the randomized study, and six in the extension study. An increased platelet count was the only AE that led to permanent discontinuation in more than one subject. Avatrombopag was well tolerated with low rates of AEs, SAEs, and drug discontinuations due to TEAEs. The rates of thromboembolic events (6.3%) or recurrence of thrombocytopenia seen with avatrombopag treatment were comparable to that seen in trials of other TPO-RAs. For example, the frequency of thromboembolic events in the long-term studies of romiplostim and eltrombopag was also 6%.

Further safety data were gathered from phase III trials in patients with ITP and CLD. The combined clinical safety data from the three phase III trials (NCT01438840, ADAPT-1, ADAPT-2) conducted to date on avatrombopag indicate that avatrombopag was well tolerated and its observed safety and tolerability profile are promising [21].

Results from the NCT01438840 trial (*N* = 49) show that the incidence of bleeding and the need for rescue therapy was not statistically different between the avatrombopag and placebo groups [21]. There were also no clinically important differences in the exposure-adjusted incidence rates of treatment-emergent AEs (TEAEs) and SAEs in both treatment groups (Table 3). While the overall incidence of TEAEs in the core study was higher in the avatrombopag group compared with the placebo group (96.9% vs. 58.8%, respectively), this higher incidence can probably be attributed to the greater mean (2.6 fold) and median (4.3 fold) duration of exposure. Importantly, there were no clinically important differences in the exposure-adjusted incidence rates of TEAEs (4.3% vs 6.6% per patient-

Table 3. Overview of TEAEs during the phase III core study (NCT01438840). Adapted from [21].

	Core study				Core + extension phase	
	Incidence	Exposure-adjusted incidence rate[a]			Incidence	Exposure-adjusted incidence rate[a]
AE	PBO (*N* = 17) *N* (%)	AVA (*N* = 32) N (%)	PBO (*N* = 17) *N* (%)	AVA (*N* = 32) *N* (%)	AVA (*N* = 47) *N* (%)	AVA (*N* = 47) *N* (%)
TEAEs, *N* (%)	10 (58.8)	31 (96.9)	6.6	4.3	45 (95.7)	2.2
Treatment-related TEAEs,[b] *N* (%)	3 (17.6)	20 (62.5)	2.0	2.7	31 (66.0)	1.5
TEAEs with CTCAE Grade 3 or 4, *N* (%)	0	6 (18.8)	0	0.8	14 (29.8)	0.7
SAEs, *N* (%)	1 (5.9)	9 (28.1)	0.7	1.2	15 (31.9)	0.7
Deaths	0	0	0	0	0	0
Other SAEs	1 (5.9)	9 (28.1)	0.7	1.2	15 (31.9)	0.7
TEAEs leading to study-drug	0	5 (15.6)	0	0.7	11 (23.4)	0.5
Withdrawal	0	3 (9.4)	0	0.4	6 (12.8)	0.3
Dose increase	0	1 (3.1)	0	0.1	3 (6.4)	0.1
Dose reduction	0	1 (3.1)	0	0.1	2 (4.3)	0.1
Dose interruption	0	0	0	0	0	0

AE, adverse event; AVA, avatrombopag; CTCAE, Common Terminology Criteria for Adverse Events; N, number of patients; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Note: A TEAE is 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. For each row category, a patient with two or more AEs in that category is counted only once.
[a]Exposure-adjusted incidence rate = number of events/total patient-weeks exposure x 100%.
[b]Includes TEAEs considered by the investigator to be possibly or probably related to study drug or TEAEs with missing causality.

week, respectively). The same is true for the higher overall incidence of SAEs in the avatrombopag treatment group compared with the placebo treatment group (28.1% vs 5.9%), with comparable exposure-adjusted incidence rates for SAEs in the core study, 1.2% per patient-week and 0.7% per patient-week for the avatrombopag and placebo groups, respectively. There were no deaths reported during the study in either treatment group. Similar to the core study data, the exposure-adjusted incidence rates for all TEAEs were comparable for both treatment groups in the extension phase of the study.

Side effects commonly reported in the core study phase included headache, contusion, upper respiratory tract infection, arthralgia, epistaxis, fatigue, gingival bleeding, and petechiae, with exposure-adjusted incidence rates that were comparable with or lower than those noted for placebo (Table 4) [21]. Additional TEAEs noted in the open-label extension phase included a low incidence of thrombocytopenia, hypertension, pharyngitis, and nasopharyngitis, and additional SAEs noted included decreased thrombocytopenia/platelet counts. AEs of special interest (AESI) that were prospectively defined included the recurrence of thrombocytopenia (defined as a platelet count <10 X 10^9/L and >10 X 10^9/L below baseline), thromboembolic events, bleeding events (WHO Grade 3 or 4), neoplastic events, gastric atrophy events, bone marrow pathology, and clinically significant liver tests. No AESIs were reported in the placebo-treated group. No patients in the avatrombopag-treated group had gastric atrophy events or bone marrow pathology. One patient in this group had a Grade 3 increase in liver tests in the core study that returned to normal on continued avatrombopag dosing and that did not require dose adjustment or treatment; this event was deemed unrelated to the treatment with avatrombopag due to the past history of the patient, which included fatty liver, hepatitis, obesity, gallstones, past liver function test elevations, and alcohol usage. Recurrence of thrombocytopenia, neoplastic events, and bleeding was each reported in one subject treated with avatrombopag during the core study. Thromboembolic events were observed in three subjects during the core study and an additional patient in the open-label extension phase. Of these four subjects, three had multiple risk factors for thromboembolic disease and the thromboembolic events were associated with platelet counts between 39 and 271 X 10^9/L and avatrombopag doses between 10 and 40 mg.

The safety data gathered from the ADAPT-1 and ADAPT-2 trials in patients with CLD corroborate the safety and tolerability of avatrombopag.

2.5. Competitors of avatrombopag

A summary of the competitors for avatrombopag, once it is approved for the treatment of ITP, is included in Table 5. Less direct competitors (owing to their different mechanisms of action) would include fostamatinib, an oral kinase inhibitor, which was approved by the FDA in April 2018 for the treatment of chronic ITP in adults who have had an insufficient response to a previous treatment, and rozanolixizumab, a subcutaneously administered anti-neonatal Fc receptor recycling agent that is currently in phase II clinical testing [22,36].

2.6. Regulatory status

Avatrombopag received its first global approval on 21 May 2018, by the FDA for the treatment of thrombocytopenia in patients with chronic liver disease undergoing a procedure. A Marketing Authorization Application for use of avatrombopag

Table 4. Frequently reported TEAEs in the phase III core study (NCT01438840). Adapted from [21].

	Core study				Core + extension phase	
	Incidence		Exposure-adjusted incidence rate[a]		Incidence	Exposure-adjusted incidence rate[a]
	PBO (*N* = 17) *N* (%)	AVA (*N* = 32) *N* (%)	PBO (*N* = 17) %	AVA (*N* = 32) %	AVA (*N* = 47) *N* (%)	AVA (*N* = 47) %
Patients with any TEAE	10 (58.8)	31 (96.9)	6.6	4.3	45 (95.7)	2.2
Headache	2 (11.8)	12 (37.5)	1.3	1.6	14 (29.8)	0.7
Contusion	4 (23.5)	10 (31.3)	2.6	1.4	19 (40.4)	0.9
Upper respiratory tract infection	1 (5.9)	6 (18.8)	0.7	0.8	11 (23.4)	0.5
Arthralgia	0 (0)	4 (12.5)	0	0.5	5 (10.6)	0.2
Epistaxis	3 (17.6)	4 (12.5)	2.0	0.5	8 (17.0)	0.4
Fatigue	1 (5.9)	4 (12.5)	0.7	0.5	7 (14.9)	0.3
Gingival bleeding	0 (0)	4 (12.5)	0	0.5	8 (17.0)	0.4
Petechiae	1 (5.9)	4 (12.5)	0.7	0.5	7 (14.9)	0.3
Thrombocytopenia	0 (0)	2 (6.3)	0	0.3	9 (19.1)	0.4
Pharyngitis	1 (5.9)	0 (0)	0.7	0	6 (12.8)	0.3
Hypertension	1 (5.9)	2 (6.3)	0.7	0.3	5 (10.6)	0.2
Nasopharyngitis	0 (0)	3 (9.4)	0	0.4	5 (10.6)	0.2
Patients with any SAE	1 (5.9)	9 (28.1)	0.7	1.2	15 (31.9)	0.7
Headache	0 (0)	2 (6.3)	0	0.3	2 (4.3)	0.1
Vomiting	0	2 (6.3)	0	0.3	2 (4.3)	0.1
Platelet count decreased	0	1 (3.1)	0	0.1	2 (4.3)	0.1

AVA, avatrombopag; *N*, number of patients; PBO, placebo; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Note: A TEAE (during core study and extension phase) is 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. An SAE is defined as any untoward medical occurrence that at any dose resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability/incapacity, or caused a congenital anomaly/birth defect in the child of an exposed parent. Patients with ≥2 AEs in the same preferred terms were counted only once for that preferred term.

[a]Exposure-adjusted incidence rate = number of events/total patient-weeks exposure x 100%.

Table 5. Comparison between various second-line treatments for ITP. Adapted from [23] with permission of the American Society of Hematology.

Therapy	Efficacy and response prediction	Safety	Contraindications	Mode of application and follow-up	ASH 2011 guidelines recommendation
Splenectomy	Highest cure rate Short-term response, 80% and long-term response 60–70% at 5–10 y Response hard to predict	Surgery-related mortality and morbidity Lifetime risk of infection Possible AEs such as venous thrombosis, pulmonary hypertension, etc.	Patients with co-morbid conditions that increase complication risk Relative: elderly patients over 60–70 years due to high complication rates, patients with immunodeficiency and secondary ITP	Invasive procedure	Well-established treatment Used as second-line after failure of steroids
Rituximab[a]	May be curative treatment Initial response in 50%–60% and sustained response 3–5 y in 20%	Infusion-related side effects Possible AEs such as increased risk of infection and viral reactivation	Pregnancy and lactation Active hepatitis B virus, clinically significant allergy	Weekly IV infusions for 4 weeks; CBC required, depending on response	Not approved for ITP, only off-label use
Romiplostim	A maintenance treatment 60%-80% achieve platelet elevation; sustained response in 70%-90% of those entering long-term studies	Headache, rebound TCP, weekly injection Possible AEs: bone marrow reticulin fibrosis, arterial and venous thrombosis, risk of malignancy	Pregnancy and lactation, myelodysplastic syndrome Relative: past history of venous or arterial thrombosis	Weekly subcutaneous infections Requires dose adjustment and regular CBC	FDA-approved treatment for chronic ITP Suggested as second- and third-line of treatment after failure of steroids and before splenectomy
Eltrombopag	A maintenance treatment 60%-80% achieve platelet elevation; sustained response in 70%-90% of those entering long-term studies	Headache, rebound TCP, elevated liver enzymes Possible AE: bone marrow reticulin fibrosis, arterial and venous thrombosis Boxed warning for hepatotoxicity and for use in patients with chronic hepatitis C	As with romiplostim Requires monitoring of liver tests but used successfully in large studies of patients with liver disease secondary to hepatitis C	Daily ingestions Taken on an empty stomach (1h before or 2 h after a meal) Requires dose adjustment and regular CBC and liver tests	FDA approved to treat adults and pediatric patients >1 y with chronic ITP and to treat patients with chronic hepatitis C to allow interferon-based treatment Suggested as second- and third-line of treatment after failure of steroids and before splenectomy
Avatrombopag [21,31]	A maintenance treatment Median cumulative number of weeks of platelet response was 12.4 65.6% achieve platelet response at day 8	Headache, contusion, upper respiratory tract infection, arthralgia, epistaxis, fatigue, gingival bleeding and petechiae Possible AE: Thrombotic/ thromboembolic complications may occur as with any other TPO-RA; monitor platelet counts and for thromboembolic events	None	Daily ingestions with food	FDA approved treatment for TCP in adult patients with chronic liver disease who are scheduled to undergo a procedure sNDA currently under review by FDA for the treatment of patients with ITP

AE, adverse event; ASH, American Society of Hematology; CBC, complete blood count; ITP, immune thrombocytopenia; TCP, thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.
[a]off-label indication.

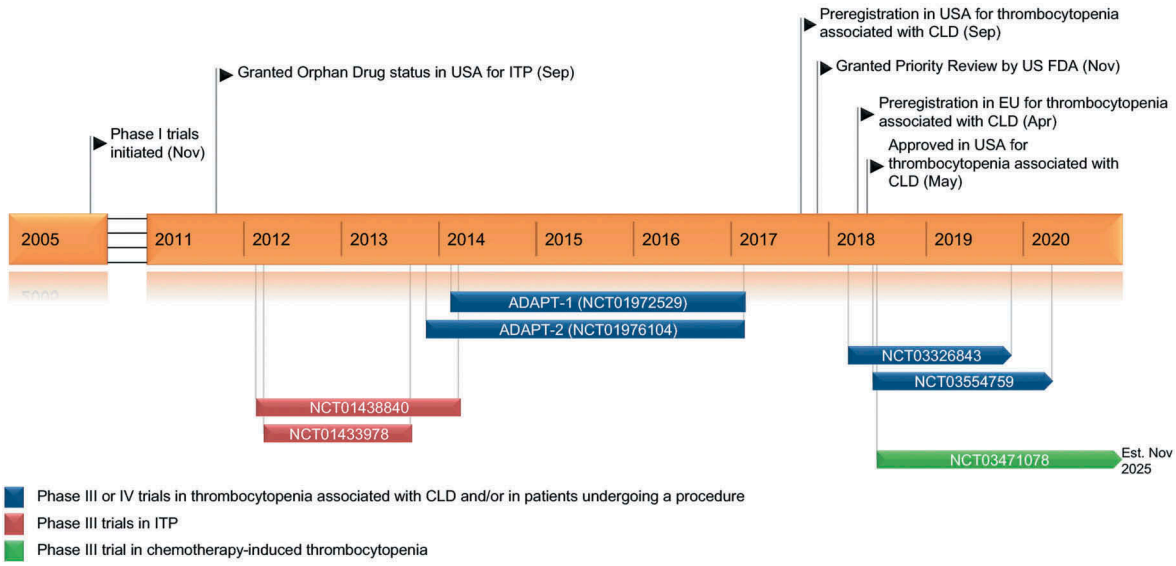

Figure 5. Key milestones in the development of avatrombopag. Reprinted from [37] with permission of Springer Nature.
CLD, chronic liver disease; ITP, immune thrombocytopenia.

for the same indication was submitted to the European Medicines Agency (EMA) in April 2018 and has been accepted for a Standard Review Assessment [37].

An sNDA was accepted for review by the FDA for the use of avatrombopag for the treatment of patients with ITP with the decision on the application expected by 30 June 2019.

Clinical development of avatrombopag in the treatment of other thrombocytopenic disorders, including chemotherapy-induced thrombocytopenia, is ongoing (Figure 5).

3. Conclusion

The data reviewed in this Drug Profile support the efficacy of long-term exposure to avatrombopag for the treatment of thrombocytopenia in adult patients with chronic ITP. Further, the platelet count response has been shown to be durable with chronic treatment, which is important for its use in patients with ITP [35].

Avatrombopag was also found to have acceptable exposure-adjusted safety and tolerability profile comparable to placebo with low incidences of the predefined AESIs, including WHO Grade ≥2 bleeding events, recurrence of thrombocytopenia and thromboembolic events; further, there was no evidence of hepatotoxicity. Therefore, avatrombopag, offers an attractive alternative to current TPO-RAs because of its oral availability, with absorption not affected by food and PK optimized with food without dietary restrictions, and lack of significant hepatotoxicity. It has the ability to increase and maintain platelet counts in the target range with chronic dosing, with acceptable safety and tolerability profile for the treatment of patients with chronic ITP.

4. Expert commentary

Since the development of ITP guidelines, the emerging data on various second-line therapies and the availability of newer therapies has resulted in increased use of pharmacological agents (especially TPO-RAs) and decreased rates of splenectomy. As continued TPO-RA treatment may be needed in order to maintain platelet response, the long-term tolerability of the treatment is important. In this regard, the EXTEND trial has provided long-term, follow-up data for eltrombopag in the treatment of patients with chronic ITP, demonstrating that it is not only efficacious but tolerable and safe in most patients [38]. Similarly, a pooled analysis of 13 clinical trials showed that the long-term romiplostim treatment (up to 5 years) is well tolerated [39].

However, each of these TPO-RAs have drawbacks. For instance, the dosing schedule of eltrombopag is not straightforward and requires strict dietary restrictions, which may affect its efficacy, and requires regular monitoring of blood counts. It also has a boxed warning for the risk of severe and potentially life-threatening hepatotoxicity, which requires monitoring of liver function, and restricts its dosing in patients with liver disease. Studies with eltrombopag in patients with ITP (Wong et al., 2017) and hepatitis C (Afdhal et al., 2014) have reported hepatobiliary changes in 15% and hyperbilirubinemia in 53–55% of the patients, respectively [38,40]. On the other hand, such hepatic events have been documented in only 3% of the patients with ITP treated with avatrombopag, and no avatrombopag-treated patients with ITP had an increase in bilirubin levels from baseline to CTCAE Grade 2 or higher [41]. In addition per the US prescribing information for eltrombopag, thromboembolic events were reported in 6% of the eltrombopag-treated patients versus 0% of the placebo-treated patients across seven clinical trials in patients with chronic ITP (eltrombopag, n = 763; placebo, n = 179) [12]. However, a recent meta-analysis of 15 randomized, controlled trials with the TPO-RAs in patients with ITP or CLD suggested the higher risk of thromboembolic events versus controls in that analysis may be driven by the patients with CLD [42]. While there are no randomized studies of the TPO-RAs that compared the incidence of thromboembolic events, data from the published phase III trials demonstrated

that avatrombopag results in an increase in platelet counts that is predictable and was not associated with a higher risk of thromboembolic events, making it a suitable candidate for use in the treatment of ITP. There is a low incidence of AESI reported in the avatrombopag phase III core study, with only one subject reporting a bleeding event or recurrence of thrombocytopenia. In the same trial, only three avatrombopag-treated patients had platelet counts ≥200 X 10^9/L, suggesting a decreased risk of thromboembolic events with the recommended avatrombopag dosage. In addition, analyses of platelet function following TPO-RAs showed no evidence of platelet activation or increased reactivity with avatrombopag or romiplostim; [43,44] eltrombopag treatment also did not result in platelet activation but showed a slight increase in platelet reactivity [45]. Overall, the platelet function data with the TPO-RAs suggest no increased risk of platelet aggregation.

In case of romiplostim, its parenteral mode of administration and the increased risk for development/progression of bone marrow reticulin fiber formation are of concern. Portal vein thrombosis events have also been reported in patients with CLD receiving romiplostim. Avatrombopag is an oral formulation whose absorption was not affected by food and PK was optimized with food without regard to food type, that has also been demonstrated to have an acceptable safety and tolerability profile without clinically significant hepatotoxicity.

Patients with CLD and thrombocytopenia are at increased risk of bleeding. This can lead to delays in necessary medical diagnostic or therapeutic procedures [35]. While platelet transfusion is an option in these patients, the decision to undergo transfusion can be a complicated one. Firstly, consensus guidelines for physicians related to platelet transfusion in patients with CLD prior to an elective procedure are lacking [46,47]. The guidelines merely state that platelet count trigger levels of >50 X 10^9/L for most major surgeries and >20 X 10^9/L for minor surgeries, and that patients at a higher risk of bleeding (e.g. liver disease) must have higher trigger levels, leaving the choice up to the physician. Secondly, the use of platelet transfusions can be complicated due to various reasons, including its varied efficacy, the possibility of fatal complications such as sepsis, and the development of refractoriness in patients that can prevent further platelet transfusions, the last of which can lead to decreased survival, prolonged hospital stays, and increased health-care costs [46,47]. Moreover chronically, there is a shortage of platelets due to the decline in blood collection and increased utilization [48]. Avatrombopag has been approved as an alternative to platelet transfusions in patients with CLD in order to minimize bleeding and improve clinical outcomes [35].

In a clinical setting, individual patient risk factors must be considered when evaluating the risk of thrombosis attributed to the use of TPO-RAs [39]. However, the positive benefit-risk profile of avatrombopag offers physicians the opportunity to change the standard of care for the treatment of thrombocytopenia in patients with ITP.

5. Five-year view

Both treatment guidelines for ITP recommend a monotherapeutic approach to its treatment. However, there is increasing evidence that a more intensive therapeutic regimen that can address multiple disease mechanisms simultaneously may improve response to chronic and refractory ITP. The future of first-line treatment of ITP, therefore, may lie in the use of combination therapies. A prospective study of patients with ITP demonstrated that the addition of rituximab to dexamethasone improves patient outcomes and yields sustained response rates compared with dexamethasone alone [49]. Similar findings were reported by Zaja et al., who found that a combination of rituximab and dexamethasone results in sustained response rates in 63% of the patients compared with 36% of the patients treated with dexamethasone alone [50]. Another study reported response rates in 60% of the patients treated with a short duration triple therapy (28 days) of low-dose rituximab, and high-dose dexamethasone and cyclosporine with prolonged remissions of more than 7 months without further therapy [51]; although it must be noted that the sample size was small, limiting the interpretation of this study. The addition of TPO-RAs to ITP treatment regimens can, therefore, increase response rates, help to decrease the dosage of immunosuppressive treatments, and improve mortality and morbidity [52,53].

Currently, all international guidelines (ASH, International Consensus, French, German, Norwegian, British, and Swedish) recommend splenectomy as second-line therapy after steroids, although the French and German guidelines indicate that rituximab and TPO mimetics can be considered in some patients [23]. The indefinite duration of treatment with TPO mimetics is a major drawback in their use and increases the cost of managing ITP. However, there are various studies that suggest that TPO-RAs may induce self-tolerance and normalize the increased destruction of platelets, allowing for treatment-free remissions in some patients [15–18,52]. With the continued development of innovative drug classes, pharmacological interventions are likely to displace splenectomies and become the preferred second-line choice of treatment.

6. Information resources

In this review, the present literature was taken into consideration. Publications were identified by PubMed using the following search criteria: 'ITP, avatrombopag, TPO-R agonists, ITP guidelines for diagnosis and treatment, clinical trials, efficacy and safety data.' More information about avatrombopag is available at https://dova.com/, US FDA (https://usfda.gov), and ClinicalTrials.gov.

Details on the clinical trials reviewed in the present Drug Profile are available in publications on individual trials: phase I trials, phase II trials, core and extended phase III trial (ClinicalTrials.gov identifier NCT01438840), ADAPT-1 and ADAPT-2 (ClinicalTrials.gov identifiers NCT01972529 and NCT01976104, respectively) [6,21,34,41]. The most recent updated guidelines for the diagnosis and treatment of ITP are published by the American Society of Hematology (2011; to be updated in 2018) and the International Consensus Report (2010) [9,10]. Guidelines on platelet transfusions are published by the American Association of Blood Banks (AABB)

(2015) and the American Society of Hematology ASH (2007) [46,47].

Key issues

- Avatrombopag is an orally administered TPO-R agonist that has been developed to provide a predictable increase in platelet counts as an alternative to other TPO-RAs.
- Avatrombopag absorption is not affected by food and its PK is optimized with food, eliminating the need for strict dietary restrictions.
- Avatrombopag is the first TPO-RA to be approved for the treatment of thrombocytopenia in adult patients with CLD who are scheduled for a medical procedure.
- Results from a phase III clinical study conclude that avatrombopag is significantly superior to placebo in increasing platelet counts in patients with chronic ITP over a 6-month period.
- Compared with placebo, avatrombopag treatment resulted in a median of 12.4 cumulative weeks of platelet response during the core phase 3 ITP study and was also shown to be superior to placebo (0 weeks).
- Avatrombopag is well tolerated and has an exposure-adjusted safety profile comparable to that of placebo, when it comes to the type, incidence, and severity of AEs.
- Avatrombopag has no clinically significant impact on renal and liver function. Only 3% of the patients with ITP experienced hepatic events with avatrombopag in a phase II trial, and no avatrombopag-treated patients with ITP had an increase in bilirubin levels from baseline to CTCAE Grade 2 or higher.
- The magnitude and duration of the increase in platelet count following acute treatment with avatrombopag are predictable and of short duration, peaking at days 5 to 8 after the last dose and allowing for a 4-day procedure window (days 10–14) after the first dose. The predictable increase in platelet count with avatrombopag reduces the risk of thromboembolic events typically seen with TPO-RAs.
- Chronic avatrombopag dosing resulted in durable platelet responses and maintained clinically relevant platelet count increases in patients with ITP.
- Avatrombopag is available as a 20 mg tablet to be taken with food once daily for 5 consecutive days, 10 to 13 days before a scheduled procedure for patients with CLD, or chronically with titrated dosing for patients with ITP.

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