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RESEARCH ARTICLE

Avatrombopag in immune thrombocytopenia: A real-world study of the Spanish ITP Group (GEPTI)

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[Correction added on 21 October 2024: The last name of the author, José-María Bastida has been corrected.]

Abstract

Avatrombopag is the newest thrombopoietin receptor agonist (TPO-RA) approved to treat immune thrombocytopenia (ITP). Real-world evidence regarding effectiveness/safety is limited. The Spanish ITP Group (GEPTI) performed a retrospective study with patients starting avatrombopag for the first time. A total of 268 ITP patients were recruited. The median (interquartile range [IQR]) follow-up time was 47.5 (30.4–58.9) weeks. Among the 193 patients with baseline platelet counts $<50 \times 10^9$/L, 174 (90.1%) of them achieved response (PC $\geq 50 \times 10^9$/L), and 113 (87.6%) of the 129 who persisted on avatrombopag at last visit had platelet levels above such threshold. Results were similar when only those patients switching to avatrombopag due to previous treatment failure were considered ($n = 104$). Patients reached response in 13 (7–21) days. Among patients with baseline levels $\geq 50 \times 10^9$/L,

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73/75 (97.3%) reported response, which was maintained by 53 (94.6%) of the 56 who continued on avatrombopag at the end of the study. Loss-of-response was always <10%. ITP duration did not influence response. Approximately 79% (34/43) of heavily pretreated (≥4 lines) patients with baseline platelet counts $<50 \times 10^9$/L switching after previous failure achieved PC $\geq 50 \times 10^9$/L. Previous use of eltrombopag and/or romiplostim did not influence response, regardless of whether previous TPO-RA(s) succeeded or failed. Avatrombopag allowed dose-reduction/suspension of corticosteroids in 40/50 (80.0%) patients with baseline platelet counts $<50 \times 10^9$/L. Overall, 40/268 (14.9%) thrombocytosis and 12/268 (4.5%) thromboembolic events were reported. Our real-world cohort supports the use of avatrombopag to manage ITP, regardless of disease severity and treatment history.

1 | INTRODUCTION

Thrombopoietin-receptor agonists (TPO-RAs) mimic the action of endogenous thrombopoietin,[1] and are accepted as long-term second-line therapy for immune thrombocytopenia (ITP) when corticosteroids alone are unable to achieve platelet recovery.[2] Eltrombopag and romiplostim have shown a favorable effectiveness/safety profile in numerous clinical trials and real-world studies, generally with durable platelet recoveries in more than 80% of treated patients, most of whom achieved levels $\geq 50 \times 10^9$/L during the first 2 weeks of treatment. Major safety concerns have not been reported, although the rate of thromboembolic events (TEVs) is in the range of 4–6%.[3–7] Avatrombopag is a newer, orally administered TPO-RA which was approved for the treatment of thrombocytopenia, initially in chronic liver disease and later in ITP.[8] Its convenient posology makes it an attractive choice for ITP patients. A pivotal trial addressing ITP management with avatrombopag yielded encouraging results, with an effectiveness comparable or superior to that of the other TPO-RAs, while no new adverse events (AEs) occurred.[9] However, the accumulated evidence is still lower than that gained with eltrombopag or romiplostim, especially in the real-world. Furthermore, the cohort sizes of the reported series, including those of trials, are rather small. For this reason, a group of researchers from the Spanish ITP Group (GEPTI) of the Spanish Society of Hematology and Hemotherapy (SEHH) combined their efforts to conduct a study in a cohort larger than those reported so far, to provide evidence that avatrombopag can be used in daily practice to provide TPO-RA therapy to ITP patients, especially those refractory to other treatments. Prior experience with eltrombopag, romiplostim and, more recently, avatrombopag, taught us that response to each TPO-RA may vary in and between patients, due to the differing molecular structures and mechanisms of action of these compounds.[10,11] For this reason, special attention was paid to the response to avatrombopag in patients previously treated with eltrombopag or romiplostim.

2 | METHODS

2.1 | Patients and study design

AVESPA was a nation-wide, multicenter, retrospective study performed by researchers from the GEPTI in ITP patients attending 28 Spanish hospitals (Figure S1). Recruitable patients were those with a confirmed diagnosis of ITP, regardless of severity and time of evolution, who started therapy with avatrombopag (Doptelet®, Sobi, Swedish Orphan Biovitrum, Stockholm, Sweden) for the first time, irrespective of the causes that led to switching from other treatments. The enrollment period covered from January 2022 to January 2024. Other inclusion criteria were: availability of complete clinical data; written informed consent. Patients were followed-up via regularly planned visits throughout the duration of the study, which ended in April 2024. The study was approved by the Medical Research Ethics Committee of every participating center. The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2 | Determinations

Primary effectiveness endpoint was response. Secondary endpoints were loss of response (LOR), response at the last follow-up visit, time to reach response, rescue requirement due to platelet drop or bleeding, World Health Organization (WHO) grade 2–4 bleeding rate, and dose-reduction/suspension of concomitant medications. Response was considered when platelet count reached $\geq 50 \times 10^9$/L. LOR was considered when platelet count dropped to $<30 \times 10^9$/L. The time between ITP diagnosis/first ITP treatment start and avatrombopag start was assessed.

Primary safety endpoints were rate of TEV, thrombocytosis, and AE-associated permanent discontinuation. Finally, persistence of treatment at follow-up end was determined.

2.3 | Statistical analysis

Discrete variables were summarized as numbers and percentages. Continuous variables were described by median (interquartile range [IQR]). The Mann–Whitney U-test was used to compare non-parametrically distributed continuous variables. Spearman's Rho coefficient was calculated to analyze the correlation between non-parametrically distributed variables. The Fisher's exact test was used to compare qualitative variables. Kaplan–Meier curves were plotted to describe the timing of platelet recovery upon avatrombopag exposure.

3 | RESULTS

A total of 268 patients were included. The flowchart diagram depicts the milestones on the patients' journey from ITP diagnosis until end of follow-up, with the focus on the phase corresponding to avatrombopag therapy. The main results at a glance are also provided (Figure S1).

3.1 | Baseline features of the cohort

Table 1 summarizes the main hallmarks of the patients who were recruited. The median age was 59 years, and the proportion of female patients was slightly higher. The median ITP duration was 4.0 years. When the first dose of avatrombopag was administered, 193, 46, and 29 patients presented with severe, moderate, and mild ITP, respectively, and more than 75% of them had been diagnosed with ITP >12 months beforehand. More than 80% of patients were diagnosed with primary ITP. The median number of treatment lines previous to avatrombopag was 2. Nevertheless, 106 (40%) and 59 (22%) patients had used ≥3 and ≥4 different treatment lines, respectively. The main reasons for switching were largely LOR or low effectiveness of the previous therapy.

3.2 | Avatrombopag dose

The avatrombopag dose used varied throughout the different phases of the study. In those patients who persisted on avatrombopag at the end of the study, most of whom had achieved response long before, doses were generally lower than those used during the maintenance phase. Doses were lower in the group of patients who switched to avatrombopag for reasons other than urgent platelet count recovery due to LOR/low efficacy of the previous treatment. The last reported dose was <140 mg/week in 62% of them, while 67% of those who required rapid restoration of platelet counts when they switched to avatrombopag were using doses ≥140 mg/week at study end (Table S1).

3.3 | Effectiveness of avatrombopag

3.3.1 | Recovery from thrombocytopenia

Approximately 92% of patients in the whole cohort reached platelet counts ≥50 × 10^9/L during the follow-up period (Table 2). Considering the intention-to-treat population ($n = 268$), 84.4% of patients maintained values above ≥50 × 10^9/L at the last follow-up visit. When the analysis was limited to patients who were still on AVA at the last study visit ($n = 185$), 166 (89.8%) of them had a response, after a median (IQR) period of 46.7 (29.8–58.6) weeks (Figure 1A,B). Among patients with baseline platelet counts <50 × 10^9/L, results regarding response to treatment in the whole cohort and response at follow-up end in those still on avatrombopag therapy were essentially similar (Table 2, Figure 1C). When the analysis was further restricted to adult chronic ITP patients with baseline platelet counts <30 × 10^9/L, 74 out of 89 (83.1%) patients achieved levels ≥50 × 10^9/L. In this subgroup, 47 out of 57 (82.5%) patients who persisted on treatment at follow-up end had a response at the last follow-up visit.

The median (IQR) time for patients with baseline platelet counts <50 × 10^9/L to reach response was 13 (7–21) days. 55 out of 171 (32.2%) of them reached platelet counts ≥50 × 10^9/L in the first 8 days of treatment. Time to response was not influenced by age, and was not longer in older patients (Table S2). The effectiveness of avatrombopag did not decrease when the analysis was limited to patients who switched to avatrombopag because of LOR or low effectiveness of the previous therapy (Figure 1E). In this subgroup, the rate of response was not significantly influenced by stratifying ITP in newly diagnosed, persistent or chronic patients, although the proportion of patients unable to achieve platelet counts ≥50 × 10^9/L was slightly higher in those who had been diagnosed with ITP >12 months before initiating avatrombopag therapy (Table S3). Kaplan–Meier curves for the cumulative proportion of patients recovering platelet counts showed comparable time profiles both for this subgroup and the whole group of patients with baseline platelet counts <50 × 10^9/L (Figure 1D,F).

3.3.2 | Loss of response

Forty-two (15.7%) patients withdrew from treatment with avatrombopag because of LOR or no response (NR), 34 of whom had presented with baseline platelet counts <50 × 10^9/L. Only three of these patients resumed avatrombopag, two of whom had not responded by the end of follow-up. If we consider those patients who never discontinued avatrombopag treatment, LOR at follow-up end was reported by <5% of those who had previously reached response (Table 2).

TABLE 1 Baseline features of immune thrombocytopenia patients.

	Whole cohort $n = 268$	Patients with baseline platelet counts <50 × 10^9/L $n = 193$
Age at AVA start, years, median (IQR)	59.3 (42.3–73.0)	59.4 (45.8–71.9)
Sex, female, *n*/*N* (%)	155/268 (57.8)	106/193 (54.9)
ITP type[a]		
Primary, *n*/*N* (%)	227/266 (85.3)	161/192 (83.8)
Secondary, *n*/*N* (%)	39/266 (14.7)	31/192 (16.1)
ITP according to disease duration[a]		
Newly diagnosed (<3 mo), *n*/*N* (%)	24/266 (9.0)	20/191 (10.5)
Persistent (3–12 mo), *n*/*N* (%)	40/266 (15.0)	34/191 (17.8)
Chronic (>12 mo), *n*/*N* (%)	202/266 (75.9)	137/191 (71.7)
Time from ITP diagnosis to AVA start (weeks), median (IQR)	207.3 (39.1–462.0)	160.7 (23.2–498.1)
Number of treatment lines previous to AVA, median (IQR)	2 (1–3)	2 (1–4)
Corticosteroids, *n*/*N* (%)[b]	252/265 (95.1)	180/190 (94.7)
≥1 TPO-RA[c], *n*/*N* (%)	159/268 (59.3)	102/193 (52.8)
Intravenous immunoglobulins, *n*/*N* (%)[a]	131/266 (49.2)	98/191 (51.3)
Rituximab, *n*/*N* (%)[d]	40/267 (15.0)	33/192 (17.2)
Fostamatinib, *n*/*N* (%)[d]	39/267 (14.6)	36/192 (18.7)
Splenectomy, *n*/*N* (%)	35/268 (13.1)	30/193 (15.5)
≥2 concomitant treatments before starting AVA	125/268 (46.6)	101/193 (52.3)
Reason of switching to/starting AVA[a]		
Convenience posology, *n*/*N* (%)	39/266 (14.7)	9/191 (4.7)
Loss of response, *n*/*N* (%)	82/266 (30.8)	73/191 (38.2)
Low effectiveness/CTC-dependency, *n*/*N* (%)	96/266 (36.1)	74/191 (38.7)
AEs, *n*/*N* (%)	16/266 (6.0)	7/191 (3.7)
Preinvasive procedure, *n*/*N* (%)	4/266 (1.5)	4/191 (2.1)
Other/several, *n*/*N* (%)	26/266 (9.8)	21/191 (11.0)
n.a. (AVA was first line), *n*/*N* (%)	3/266 (1.1)	3/191 (1.6)

Abbreviations: AEs, adverse events; AVA, avatrombopag; CTC, corticosteroids; IQR, interquartile range; mo, months; n.a., not applicable; TPO-RA, thrombopoietin receptor agonist.
[a]Data of two patients missing.
[b]Data of three patients missing.
[c]Eltrombopag or/and romiplostim.
[d]Data of one patient missing.

Response by the end of the study was maintained by 92% of patients who switched to avatrombopag even though their baseline platelet counts did not suggest that there was a risk of bleeding. This proportion increased to 95% in those who persisted on avatrombopag use at the last study visit (Table S4).

3.3.3 | Rescue requirement and bleeding events

Sixty-five (26%) patients who had achieved response required rescue therapy due to acute platelet drop and/or rebleeding (Figure 1G). Eight patients, seven of whom had baseline platelet counts <50 × 10^9/L, experienced a grade 2–4 bleeding episode while on treatment with avatrombopag, none of which was fatal (Table 2, Figure 1H).

3.3.4 | Durability of response

Among the 99 patients with baseline platelet counts <50 × 10^9/L who switched to avatrombopag due to previous treatment failure, achieved a response, and persisted on treatment at the end of follow-up, 91 (91.9%) maintained response at this date, and 70 (70.7%) did not require rescue throughout the entire follow-up period (53.7 [28.7–61.2] weeks).

TABLE 2 Effectiveness of treatment with avatrombopag.

	Whole cohort $n = 268$	Patients with baseline platelet counts $<50 \times 10^9$/L $n = 193$
Follow-up since AVA start (weeks), median (IQR)	47.5 (30.4–58.9)	49.0 (32.4–60.4)
Response (≥50 × 10^9/L)		
Yes, *n*/*N* (%)	247/268 (92.2)	174/193 (90.1)
No, *n*/*N* (%)	21/268 (7.8)	19/193 (9.8)
Days to response, median (IQR)	n.a.	13 (7–21)
LOR at the end of follow-up, *n*/*N* (%)[a]	6/179 (3.3)	6/123 (4.9)
Rescue therapy required after response, *n*/*N* (%)[b]	65/247 (26.3)	49/174 (28.2)
Bleeding grade 2–4 while on AVA, *n*/*N* (%)	8/268 (3.0)	7/193 (3.6)

Abbreviations: AVA, avatrombopag; IQR, interquartile range; LOR, loss of response; n.a., not applicable.

[a]Patients who achieved response and continued with AVA by the end of follow-up were considered for calculations. Loss of response was considered when platelet count dropped to <30 × 10^9/L at the end of follow-up (last visit) in those patients who had previously achieved response.

[b]Rescue therapy required due to thrombocytopenia or rebleeding.

3.4 | Factors influencing response to avatrombopag

3.4.1 | Among patients with baseline platelet counts <50 × 10^9/L switching due to failure of previous treatment

Age and sex

In this subgroup ($n = 147$), age and sex did not influence response to avatrombopag:

- There was no correlation between age at avatrombopag start and either response achieved (Rho = 0.080, $p = .334$) or response at the end of the study in those patients who did not suspend avatrombopag treatment (Rho = 0.112, $p = .260$, $n = 104$).
- Response was achieved by 62 out of 68 (91.2%) men and 72 out of 79 (91.1%) women, $p = 1.000$, and, when the analysis was only performed with those patients who had not suspended avatrombopag by the end of the study, response was reported in 42 out of 47 men and 49 out of 57 women ($p = .768$).

Number of previous treatment lines

A significant, inverse correlation was observed between the number of previous treatment lines and response achieved (Rho = −0.273, $p < .001$). Accordingly, the proportion of patients reaching response decreased as the number of previous treatment lines increased (Figure 2A), and was significantly higher when patients had received <4 treatment lines (Figure 2B). Nevertheless, avatrombopag benefited more than 70% of heavily pretreated patients, since response was achieved by up to 82.1% and 73.3% of those patients who had previously used 4 or >4 treatment lines, respectively.

Previous experience with thrombopoietin-receptor agonists

In order to ascertain whether a previous failure of another TPO-RA, either eltrombopag or romiplostim, or both, might be associated with subsequent worse response to avatrombopag, we limited the analysis to those patients who had previously been treated with two different lines of therapy ($n = 42$), and stratified them in two subgroups according to whether they had or had not used at least one TPO-RA. By doing this, we would prevent the number of previous treatment lines from interfering with the analysis. Response was essentially similar regardless of the previous use of eltrombopag and/or romiplostim, with 90.5% and 95.2% of patients with or without previous experience with TPO-RA, respectively, achieving platelet counts ≥50 × 10^9/L ($p = 1.000$) (Figure 2C). When all patients with previous experience with TPO-RAs were grouped, response to avatrombopag was worse than that observed in those who had never used these drugs (Table S5). Nevertheless, the number of previous lines of therapy was significantly higher in the former group (4.0 [2.5–4.0], $n = 85$ vs. 1.0 [1.0–2.0], $n = 62$, $p < .001$). Furthermore, even among those who had used both eltrombopag and romiplostim ($n = 50$), response to avatrombopag was achieved in 84.0% of cases, and platelet counts were maintained ≥50 × 10^9/L by 80.0% of them in the event that avatrombopag was being used at the last follow-up visit ($n = 35$).

When considering those patients who had used eltrombopag ($n = 8$), romiplostim ($n = 1$), or both ($n = 1$) and switched to avatrombopag because of reasons other than previous treatment failure, nine and one of them achieved CR and response, respectively.

3.4.2 | Among patients with baseline platelet counts <50 × 10^9/L switching for reasons other than previous treatment failure

When the reason for starting avatrombopag treatment was not related to failure of previous lines of therapy but to the patient's choice, AEs or other causes, 22 out of 23 (95.7%) patients achieved platelet levels ≥50 × 10^9/L (Figure 2D).

All patients who had used eltrombopag ($n = 8$), romiplostim ($n = 1$), or both ($n = 1$), achieved response.

3.5 | Influence of age on decision to start treatment with avatrombopag

When patients with baseline platelet counts <50 × 10^9/L who switched to avatrombopag due to previous treatment failure were stratified according to being older or younger than 65 years, a major

significant difference could be observed in the time that elapsed between ITP diagnosis and the start of avatrombopag therapy, which was notably later in younger patients (Figure S3A). Accordingly, the time between the start of the first treatment and the start of avatrombopag was shorter in patients ≥65 years (Figure S3B).

3.6 | Influence of avatrombopag on concomitant treatments

Up to 40% of patients in the whole cohort, and 45% in the group of patients with baseline platelet counts <50 × 10^9/L, initially received

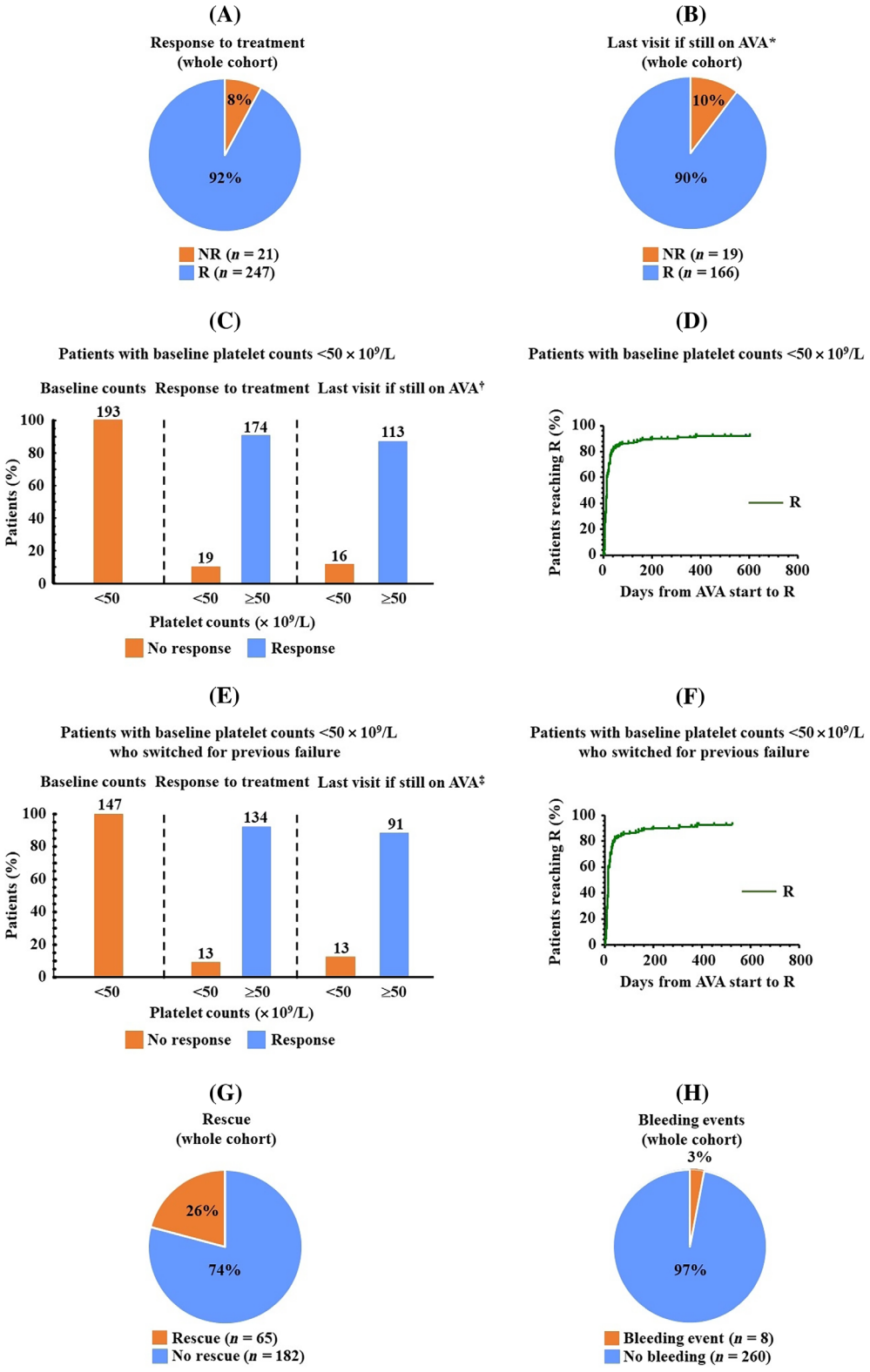

FIGURE 1 Legend on next page.

other treatments, especially corticosteroids, concomitantly with avatrombopag. These were dose reduced/suspended in 79% and 80% of cases, respectively. Less frequent medications such as fostamatinib, intravenous immunoglobulins, or mycophenolate mofetil were also dose reduced/suspended in around 20–30% of cases (Table S6, Figure S4).

3.7 | Safety of avatrombopag

The main reported AEs are summarized in Figure 2E and Table S7. Forty out of 268 (14.9%) patients discontinued treatment after reaching platelet counts >400 $\times$ 10^9/L, although only nine of them did not resume avatrombopag once the normal range of platelet count was restored. Twelve cases of thrombosis were documented, none of which was fatal. ITP secondary to antiphospholipid syndrome (APS) was found in two cases, one of whom was also diagnosed with systemic lupus erythematosus. They had acute myocardial infarction (AMI) and chronic inferior vena cava (IVC) thrombosis, respectively. This finding is in line with the recommendation that TPO-RAs should not be administered to patients with established thrombotic risk factors.[2] Three patients (two ischemic stroke patients and one pulmonary thromboembolism patient [PTE]) had previously developed thrombocytosis. The other events were ischemic stroke (three), PTE (two), peripheral artery disease (one), and AMI (one). Four patients resumed treatment before the last study visit.

Forty-seven (17.5%) patients reported mild and transitory AEs, especially cephalea (26) and arthralgia (11). 12 (4.5%) patients permanently discontinued avatrombopag due to adverse events other than thrombocytosis (Figure 2F). A total of 172 out of 268 (64.2%) patients never experienced AEs while on treatment with avatrombopag.

3.8 | Persistence in treatment

A total of 185 (69.0%) patients were still on avatrombopag treatment when they attended the last visit, 67% of whom were using doses ≤140 mg/week. Doses of 280 mg/week were being used by only 20%. The main reason for permanent discontinuation was no response to treatment, reported in 38 (14.2%) cases, 32 of whom corresponded to patients with baseline platelet counts <50 $\times$ 10^9/L. Eight out of the nine patients who permanently withdrew treatment because of thrombocytosis belonged to this group. Seven patients had died by the end of study. Causes were always unrelated to treatment (Figure 2F, Table S7).

4 | DISCUSSION

This study provides real-world evidence on the effectiveness and safety of avatrombopag to manage ITP in a large cohort of patients who were followed-up for a longer period than most other studies addressing the same topic. We found that more than 90% of patients achieved platelet counts ≥50 $\times$ 10^9/L while on treatment with avatrombopag. Approximately 90% of those who persisted on avatrombopag at the last visit maintained platelet counts ≥50 $\times$ 10^9/L. Interestingly, the effectiveness of avatrombopag did not decrease notably when the analysis was limited to patients with baseline platelet counts <50 $\times$ 10^9/L, even when switching was due to failure of the previous treatment. Effectiveness was slightly, nonsignificantly, lower in chronic ITP patients, where, in any case, response was close to 90%, as was observed in previous reports.[12] Taken together, our results are in line with those previously found in smaller cohorts.[13–15] Platelet count recovered fast upon treatment, since the median time for patients with baseline platelet counts <50 $\times$ 10^9/L to reach response was below 15 days. Response was slightly faster in the pivotal trial, where 56% of patients recovered platelet counts in the first 8 days with avatrombopag, although response was considered with platelet counts ≥30 $\times$ 10^9/L.[9]

The number of patients who experienced LOR was never above 5%, after a median follow-up slightly longer than that of the extension of the pivotal trial, where results regarding durability of response were similar.[16] Rescue therapies were required by less than 30% of those patients who achieved response with avatrombopag. These figures parallel those seen in the aforementioned real-world study, where rescue was required by 34% of patients, although during a much shorter follow-up period.[15] In the pivotal trial, rescue was required by 22% of patients after 18–30 weeks.[9] The rate of bleeding events of grade ≥2

FIGURE 1 Effectiveness of avatrombopag. Response to treatment was calculated in the whole cohort ($n = 268$) (A) and response at the last follow-up visit was assessed in those patients who were still on avatrombopag at this date ($n = 185$) (B). The proportion of patients categorized according to response achieved (middle) and response at last visit if still on avatrombopag treatment (right) was calculated for the group of patients with baseline platelet counts <50 $\times$ 10^9/L ($n = 193$) (C) and for those patients with platelet counts <50 $\times$ 10^9/L who switched to AVA because of failure of previous treatment due to either LOR or low effectiveness ($n = 147$) (E). The number of patients is indicated for each condition. Data for four (C) and one (E) patients at last visit are missing. Kaplan–Meier curves were constructed according to time elapsed from AVA start to the time required to achieve response (≥50 $\times$ 10^9/L) in the whole cohort (D) and in patients who changed to AVA due to previous treatment failure (F). Tick marks indicate patients whose data were censored by the time of last follow-up date. The proportions of patients in the whole cohort who had achieved response ($n = 247$) and subsequently required rescue due to drop in platelet counts or bleeding (G), and patients in the whole cohort who had at least one bleeding event of grade ≥2 according to the WHO scale throughout the follow-up period (H), were also determined. The number of patients in each category is indicated in the legends. R corresponds to platelet counts ≥50 $\times$ 10^9/L. *Follow-up: 47 (30–59) weeks, median (IQR). †Follow-up: 49 (33–59) weeks, median (IQR). ‡Follow-up: 50 (33–60) weeks, median (IQR). AVA, avatrombopag; IQR, interquartile range; LOR, loss of response; NR, no response; R, response; WHO, World Health Organization. [Color figure can be viewed at wileyonlinelibrary.com]

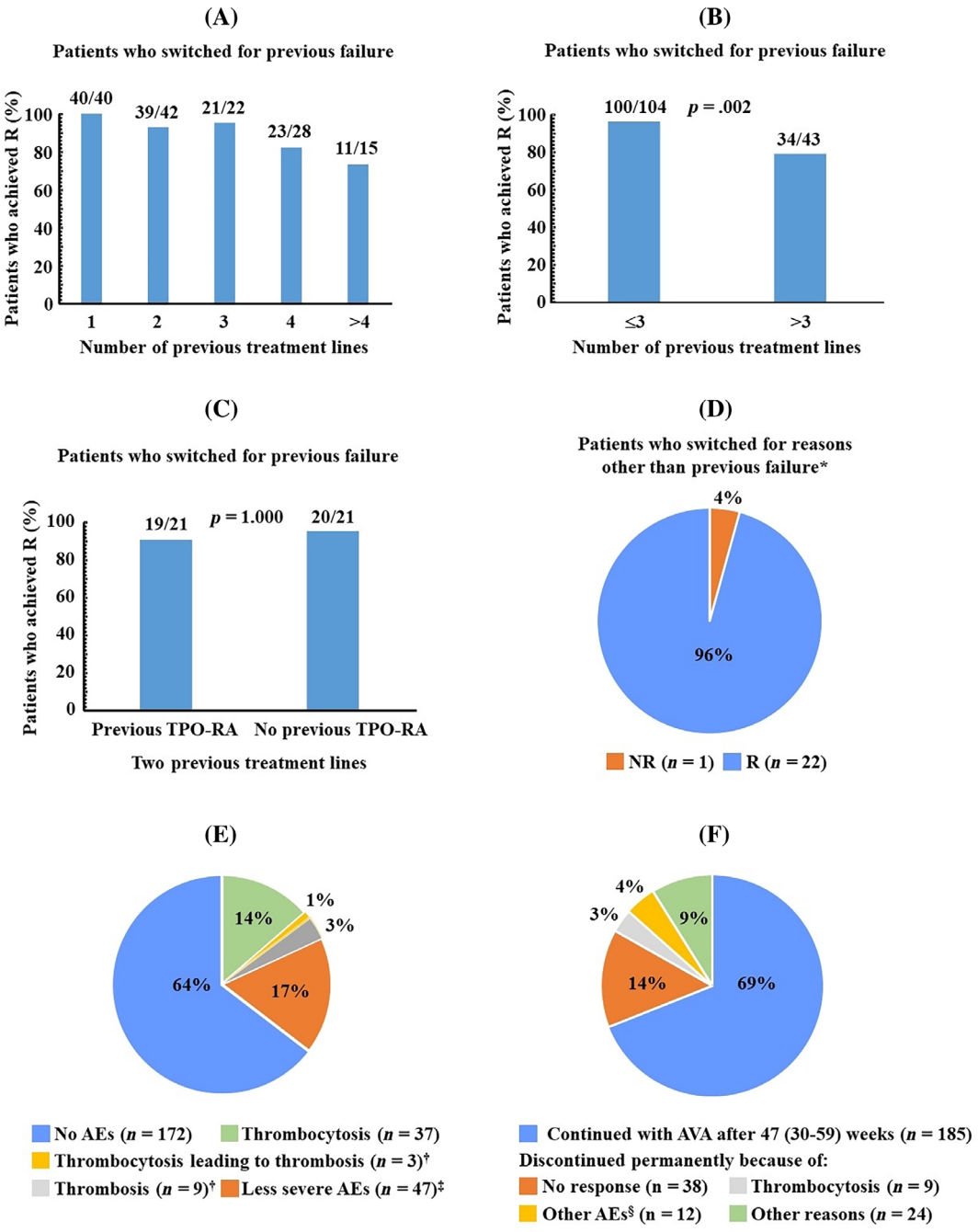

FIGURE 2 Response to avatrombopag according to reasons for switching, safety, and persistence on treatment. Response was assessed in patients with baseline platelet counts <50 × 10^9/L ($n = 193$) after switching to avatrombopag due to: failure of previous treatment according to the number of previous line therapies ($n = 147$) (A, B); failure of two previous treatment lines, when ≥1 of these was or was not another TPO-RA ($n = 42$) (C); reasons other than LOR or low effectiveness of previous treatment ($n = 23$) (D). The number of patients who achieved response and the total number of patients are indicated above the histograms (A, B, C). Safety of avatrombopag in the whole cohort ($n = 268$) was assessed by calculating the proportion of AEs while on treatment (E). The proportion of patients in the whole cohort who either were still on avatrombopag treatment or had discontinued it at the time of the last follow-up visit was calculated (data of six patients were missing) (F). Thrombocytosis was considered with platelet counts >400 × 10^9/L. *P* values correspond to the one-tailed (B) and two-tailed (C) Fisher's exact test. *Patients whose reasons for switching were not specified were not included in the analysis ($n = 23$). †Ischemic stroke (five), pulmonary thromboembolism (three), acute myocardial infarction (two), peripheral artery disease (one), chronic inferior vena cava thrombosis (one); none fatal. ‡Cephalea, arthralgia, asthenia, GI AEs, others. §Ischemic stroke (three), pulmonary thromboembolism (one), asthenia (one), asthenia and cephalea (one), red eye (one), arthralgia (one), acute myocardial infarction (one), photopsia (one), non-specified (two). AEs, adverse events; AVA, avatrombopag; GI, gastrointestinal; LOR, loss of response; NR, no response; R, response; TPO-RA, thrombopoietin receptor agonist. [Color figure can be viewed at wileyonlinelibrary.com]

in our study was lower than that reported in the pivotal trial,[9] with an incidence below 4% in patients whose baseline platelet counts were $<50 \times 10^9$/L.

The cohort size allowed us to perform analyses to identify variables potentially influencing treatment outcomes. Age and sex did not seem to bias response, although most patients were >18 years, which precluded assessment of effectiveness in the pediatric population. Not surprisingly, refractoriness to previous treatment lines did influence response. Nevertheless, the proportion of patients with baseline platelet counts $<50 \times 10^9$/L who switched to avatrombopag after at least four failed therapy lines and reached platelet counts $\geq 50 \times 10^9$/L was above 90%. This finding suggests that avatrombopag may be a suitable option for heavily pretreated patients.

Some reports described that switching from eltrombopag to romiplostim, or vice versa, could be useful in case of a first failure.[17,18] In this study, previous failure with eltrombopag and/or romiplostim did not substantially challenge platelet recovery with avatrombopag. When the analysis was restricted to patients who had tried two treatment lines before switching to avatrombopag, effectiveness did not decrease when one of these lines was another TPO-RA. In fact, response was achieved in more than 90% of cases. Unfortunately, this analysis could not be performed in patients with a larger number of previous therapies, since most of these cases had used eltrombopag and/or romiplostim, which precluded comparison against patients heavily pretreated but naïve to TPO-RAs. Nevertheless, even in the group of patients with baseline platelet counts $<50 \times 10^9$/L who switched due to previous failure and had previous experience with both eltrombopag and romiplostim, platelet counts $\geq 50 \times 10^9$/L were reached by 84% of them, and were maintained above concerning levels at follow-up end in 80% of those who did not discontinue avatrombopag throughout the study. Our results are in line with those of Al-Samkari et al., who found that 12 out of 14 patients who had switched to avatrombopag due to eltrombopag or romiplostim failure achieved response, which was maintained during more than 80% of their time on treatment.[19,20] Therefore, avatrombopag emerges as a valid alternative to deliver TPO-RA-based therapy in case of previous failure of eltrombopag and/or romiplostim. Regarding those patients where eltrombopag had previously achieved good responses, our results suggest that switching to avatrombopag should not compromise response.

Several meta-analyses suggested that avatrombopag may be superior to eltrombopag or romiplostim in terms of response and bleeding rate.[21–23] Collectively, our findings regarding effectiveness of avatrombopag are consistent with previous trial and real-world observations, and provide additional strength, derived from the follow-up duration and, especially, the number of enrolled patients, to consider avatrombopag as suitable to treat ITP. Finally, avatrombopag, in combination with fostamatinib, was successfully used in ITP patients refractory to multiple therapies.[24]

The median time that elapsed between either ITP diagnosis or first treatment start and administration of the first dose of avatrombopag was considerably shorter in patients older than 65 years, with a difference much >12 months. The explanation may lie in the fact that, in daily practice, glucocorticosteroid-based immunosuppression is considered as the first treatment line to manage ITP.[25] Indeed, duration of glucocorticosteroid therapy should be kept to a minimum in older patients to prevent severe infection, and this practice has gained further importance after the outbreak of COVID-19.[26] Furthermore, in the event that prednisone or dexamethasone does not succeed in normalizing platelet levels rapidly in those cases of older patients who are on long-term anticoagulation/antiaggregation, prompt switching to alternative second-line treatments, such as TPO-RAs, is highly advisable. The aim of this practice is to recover platelet counts as soon as possible and thus minimize bleeding risk while trying to avoid suspension of anticoagulant treatment, since thrombocytopenia does not protect against venous thromboembolism or stroke.[27,28] The fact that platelet response and time required to platelet recovery were unrelated to age in our adult ITP population and, therefore, were also good in elderly patients, further supports the early use of avatrombopag to normalize platelet counts. Furthermore, after starting avatrombopag, concomitant medications were reduced or suspended in more than 60% of those patients who were using additional therapies. This proportion increased up to 80% in the case of glucocorticoids. These data are in agreement with previous reports,[9,15] and reinforce the idea that avatrombopag may be suitable for fragile patients to avoid long immunosuppression periods.

The risk of TEVs has been described to increase 4–5 (venous) and 2 (arterial) fold with TPO-RA use, and this therapy is discouraged in patients with thrombotic risk factors.[29] A pooled analysis of clinical trials assessed an incidence of TEV of 6% with eltrombopag or romiplostim.[30] Regarding avatrombopag, the rate of TEVs was 9.4% during the core study.[9] In four pooled clinical trials, the rate was 7.0%.[31–34] There are few real-world series available addressing this occurrence. One TEV was documented in a cohort of 75 adult ITP patients treated with avatrombopag in a multicenter observational study.[12] In another cohort of 44 patients who had been treated with other TPO-RAs previously, one of them, who had a previous history of multiple venous thromboembolic events, developed a portal-vein thrombosis episode while on treatment with avatrombopag.[19] Finally, isolated cases have been described.[35] Our rate of TEVs during a follow-up period not shorter than those of the cited studies was 4.5%. In two cases, patients had APS, which further warns against use of TPO-RAs in patients with thrombotic risk factors. Although thrombotic events associated with TPO-RA can occur with low, normal, or high platelet counts,[30] three patients who had TEV had reported levels $>400 \times 10^9$/L. Thus, in the event of thrombocytosis, suspension of avatrombopag is recommended. Thrombocytosis was reported in 15% of patients, where AVA was suspended, although most of them resumed treatment later. Indeed, the dose had to be adjusted to prevent a new acute platelet rise. Thrombocytosis was more frequent in patients with baseline platelet counts $\geq 100 \times 10^9$/L, where the dose should be carefully adjusted when avatrombopag

therapy is considered. No other worrying AEs, either treatment-related or unrelated, were reported. The proportion of permanent discontinuations because of thrombocytosis, thrombosis or other AEs was half of that due to no response. Collectively, our real-world cohort supports that avatrombopag can be safely used to manage ITP, as previously suggested,[15,16] although alternative options such as fostamatinib are preferable in patients bearing thrombotic risk factors.[2]

Our study has limitations inherent to the retrospective nature of the study. The lack of regular monitoring of platelet counts precluded an accurate estimation of the time on response, although the data regarding proportion of patients with platelet counts ≥50 $\times$ 10^9/L in the last visit among those who persisted on treatment are encouraging. Finally, we were unable to assess sustained remission off-treatment (SROT), an aspect that should be addressed in future, prospective studies.

In summary, this large real-world group of ITP patients treated with avatrombopag allowed us to confirm previous observations derived from clinical trials and smaller real-world cohorts. Our findings support the idea that this easy-to-use TPO-RA is not inferior to its counterparts to manage ITP as second line of treatment, and might be considered as a first therapeutic alternative.

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DATA AVAILABILITY STATEMENT

Databases are available upon request to the corresponding author via e-mail.

PATIENT CONSENT STATEMENT

Written informed consent was one of the mandatory patient inclusion criteria. All patients whose data were included in the study signed written informed consent.

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REFERENCES

1. Mingot-Castellano ME, Bastida JM, Caballero-Navarro G, et al. Novel therapies to address unmet needs in ITP. *Pharmaceuticals*. 2022; 15(7):779.
2. Mingot-Castellano ME, Canaro Hirnyk M, Sánchez-González B, et al. Recommendations for the clinical approach to immune thrombocytopenia: Spanish ITP working group (GEPTI). *J Clin Med*. 2023;12(20):6422.
3. Saleh MN, Bussel JB, Cheng G, et al. Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study. *Blood*. 2013;121(3): 537-545.
4. Kuter DJ, Bussel JB, Newland A, et al. Long-term treatment with romiplostim in patients with chronic immune thrombocytopenia: safety and efficacy. *Br J Haematol*. 2013;161(3):411-423.
5. Bidika E, Fayyaz H, Salib M, et al. Romiplostim and Eltrombopag in immune thrombocytopenia as a second-line treatment. *Cureus*. 2020; 12(8):e9920.
6. Moulis G, Germain J, Rueter M, et al. Eltrombopag in adult patients with immune thrombocytopenia in the real-world in France, including off-label use before 6 months of disease duration: the multicenter, prospective ELEXTRA study. *Am J Hematol*. 2022;97(2):E40-E44.
7. Chen F, McDonald V, Newland A. Experts' review: the emerging roles of romiplostim in immune thrombocytopenia (ITP). *Expert Opin Biol Ther*. 2021;21(11):1383-1393.
8. Shirley M. Avatrombopag: first global approval. *Drugs*. 2018;78(11): 1163-1168.
9. 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(3):479-490.
10. Kuter DJ. The structure, function, and clinical use of the thrombopoietin receptor agonist avatrombopag. *Blood Rev*. 2022;53:100909.
11. Al-Samkari H, Kuter DJ. Relative potency of the thrombopoietin receptor agonists eltrombopag, avatrombopag and romiplostim in a patient with chronic immune thrombocytopenia. *Br J Haematol*. 2018;183(2):168.
12. Virk ZM, Leaf RK, Kuter DJ, et al. Avatrombopag for adults with early versus chronic immune thrombocytopenia. *Am J Hematol*. 2024;99(2): 155-162.
13. Jain S, Gernsheimer T, Kolodny S, Bernheisel C, Vredenburg M, Panch SR. Additional efficacy analysis of avatrombopag phase III data for the treatment of adults with immune thrombocytopenia. *Platelets*. 2023;34(1):2195016.
14. Mei H, Zhou H, Hou M, et al. Avatrombopag for adult chronic primary immune thrombocytopenia: a randomized phase 3 trial in China. *Res Pract Thromb Haemost*. 2023;7(6):102158.
15. Oladapo A, Kolodny S, Vredenburg M, et al. Avatrombopag treatment response in patients with immune thrombocytopenia: the REAL-AVA 1.0 study. *Ther Adv Hematol*. 2023;14:20406207231179856.
16. Al-Samkari H, Nagalla S. Efficacy and safety evaluation of avatrombopag in immune thrombocytopenia: analyses of a phase III study and long-term extension. *Platelets*. 2022;33(2):257-264.
17. Khellaf M, Viallard JF, Hamidou M. A retrospective pilot evaluation of switching thrombopoietic receptor-agonists in immune thrombocytopenia. *Haematologica*. 2013;98(6):881-887.
18. Cantoni S, Carpenedo M, Mazzucconi MG. Alternate use of thrombopoietin receptor agonists in adult primary immune thrombocytopenia patients: a retrospective collaborative survey from Italian hematology centers. *Am J Hematol*. 2018;93(1):58-64.
19. Al-Samkari H, Jiang D, Gernsheimer T, et al. Adults with immune thrombocytopenia who switched to avatrombopag following prior treatment with eltrombopag or romiplostim: a multicentre US study. *Br J Haematol*. 2022;197(3):359-366.
20. Al-Samkari H, Jiang D, Gernsheimer T, et al. Durability of platelet response after switching to avatrombopag from eltrombopag or romiplostim in immune thrombocytopenia. *Res Pract Thromb Haemost*. 2023;7(3):100134.
21. Liu Y, Zhang HX, Su J, Geng QC, Lin X, Feng CX. Efficacy and incidence of TreatmentRelated adverse events of Thrombopoietin receptor agonists in adults with immune thrombocytopenia: a systematic review and network meta-analysis of randomized controlled study. *Acta Haematol*. 2023;146:173-184.
22. Deng J, Hu H, Huang F, et al. Comparative efficacy and safety of Thrombopoietin receptor agonists in adults with thrombocytopenia: a systematic review and network meta-analysis of randomized controlled trial. *Front Pharmacol*. 2021;12:704093.
23. Wojciechowski P, Wilson K, Nazir J, et al. Efficacy and safety of Avatrombopag in patients with chronic immune thrombocytopenia: a systematic literature review and network meta-analysis. *Adv Ther*. 2021; 38(6):3113-3128.
24. Mingot-Castellano ME, Bastida JM, Ghanima W, et al. Avatrombopag plus fostamatinib combination as treatment in patients with multirefractory immune thrombocytopenia. *Br J Haematol*. Published online June 19, 2024. doi:10.1111/bjh.19602
25. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. *Blood Adv*. 2019;3(22):3780-3817.
26. Mohan A, Iyer VA, Kumar D, Batra L, Dahiya P. Navigating the post-COVID-19 immunological era: understanding long COVID-19 and immune response. *Life*. 2023;13(11):2121.
27. Balitsky A, Arnold D. The use of anticoagulation in patients with thrombocytopenia. *The Hematologist*. 2018;15(3):15.
28. Thachil J, Carrier M, Lisman T. Anticoagulation in thrombocytopenic patients – time to rethink? *J Thromb Haemost*. 2022;20(9):1951-1956.
29. Rodeghiero F. ITP and thrombosis: an intriguing association. *Blood Adv*. 2017;1(24):2280.
30. Rodeghiero F, Stasi R, Giagounidis A, et al. Long-term safety and tolerability of romiplostim in patients with primary immune thrombocytopenia: a pooled analysis of 13 clinical trials. *Eur J Haematol*. 2013; 91(5):423-436.
31. Efficacy and safety of oral E5501 plus standard of care for the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (amendment 02). ClinicalTrials.gov identifier: NCT01438840. Accessed July 16, 2024. https://clinicaltrials.gov/study/NCT01438840?tab=results
32. 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*. 2014;123(25): 3887-3894.
33. ClinicalTrials.gov. Study of AKR-501 Tablets Taken Orally Once Daily for 28 Days in Patients with Chronic Idiopathic Thrombocytopenic Purpura (ITP). Accessed July 16, 2024. https://clinicaltrials.gov/ct2/show/NCT00441090
34. ClinicalTrials.gov. Phase 2, Parallel Group, Rollover Study of AKR-501 in Patients with Chronic ITP Who Completed 28 Days of Study Treatment in Protocol 501-CL-003. Accessed July 16, 2024. https://clinicaltrials.gov/study/NCT00625443

35. Abdelsamia M, Farid S, Dean S, Cataland SR. Thrombotic complications in immune thrombocytopenia patients treated with Avatrombopag. *Hematol Rep*. 2023;15(3):518-523.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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