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RESEARCH ARTICLE

Sustained response off-treatment in eltrombopag-treated adult patients with ITP who are refractory or relapsed after first-line steroids: Primary, final, and ad-hoc analyses of the Phase II TAPER trial

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Abstract

Immune thrombocytopenia (ITP) is characterized by reduced platelet count due to increased destruction and is categorized according to the time following diagnosis (newly diagnosed, persistent, chronic). First-line corticosteroid therapy is associated with transient response, high relapse rates, and considerable toxicity. TAPER (NCT03524612) is a Phase II, prospective, single-arm trial investigating whether eltrombopag can induce a sustained response off-treatment (SRoT) in adult patients with ITP after first-line corticosteroid failure. This study defines SRoT as an off-treatment period wherein platelet count remains above 30×10^9/L in the absence of bleeding or rescue therapy. The primary endpoint was the proportion of patients who achieved SRoT until Month 12, which was 30.5% ($n = 32/105$; $p < .0001$ testing hypothesis H1: proportion >15%) following eltrombopag tapering and discontinuation,

and median SRoT duration was ~8 months until Month 12. Median platelet count increased within 1 month of treatment and remained elevated until Month 12. Quality of life improved within 3 months and was maintained. Headache (21%) was the most common adverse event. None of the 4 deaths reported were considered treatment-related. In summary, ~one-third of patients achieved SRoT until Month 12 following eltrombopag tapering and discontinuation. An ad-hoc early-use analysis, stratified by ITP duration at baseline, assessed initial hematologic responses and safety. Results suggest that eltrombopag has similar efficacy in newly diagnosed and later stages of ITP. In follow-up until Month 24, a median SRoT duration of ~22 months was observed ($n = 20$). The safety profile was comparable across analyses and ITP duration groups and aligned with its well-established safety profile.

1 | INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by reduced platelet count (<100 × 10^9/L) and increased bleeding risk in the absence of other causes. It is categorized by disease duration from diagnosis as newly diagnosed ITP (ndITP; <3 months), persistent ITP (pITP; 3–12 months), and chronic ITP (cITP; >12 months).[1,2] The fundamental treatment goal for patients with ITP is to reduce bleeding by attaining a sustained hemostatic platelet count.[3] Corticosteroids (CSs) are the standard initial first-line treatments for primary ITP. Although initially effective, the response is often transient. CS use is associated with considerable toxicity and with high relapse rates.[3–5] Patients who do not respond to, or relapse after, first-line CS use require second-line treatments, such as thrombopoietin receptor agonists (TPO-RAs), rituximab, fostamatinib, or splenectomy.[3] In addition, treatments that achieve a treatment-free state with no further risk of bleeding and a reduction in the burden of treatment are needed.

Eltrombopag is a small-molecule TPO-RA indicated in the United States for the treatment of patients aged 1 year and above with pITP or cITP who have had an insufficient response to CSs, immunoglobulins, or splenectomy.[6] In the European Union, it is approved for use in adult patients with primary ITP (irrespective of time since diagnosis) who are refractory to other treatments, as well as for pediatric patients aged 1 year and above with primary ITP lasting 6 months or longer from diagnosis, and who are refractory to other treatments (e.g., corticosteroids, immunoglobulins).[7] There is evidence that a proportion of patients treated with TPO-RAs (i.e., eltrombopag, romiplostim) can achieve sustained responses that are maintained after TPO-RA tapering and discontinuation; however, much of the data are retrospective, with a few prospective and real-world observational studies investigating sustained response off-treatment (SRoT) having been conducted.[8–11] SRoT is an emerging treatment goal, with existing studies utilizing different thresholds for the components of SRoT, for example, platelet counts, and duration required to consider the response to be "off-treatment."[8,9,11]

Results from one recent Phase II trial confirm that short-term (24 weeks) exposure to eltrombopag can induce SRoT, defined as platelet count ≥30 × 10^9/L and at least a two-fold increase from the baseline count for at least 6 months following treatment discontinuation, in adult patients with ITP that is relapsed/refractory to first-line CS therapy.[9] Previously published data from real-world clinical practice also suggest that eltrombopag is as effective and well tolerated in the early stages of ITP as it is in cITP.[12,13]

We aimed to determine whether eltrombopag can induce SRoT in adult patients with ITP following CS failure. Here, we report the results of the 12-month TAPER primary analysis, follow-up analysis, and the results of an ad-hoc early-use analysis. The latter ad-hoc early-use analysis is by time since ITP diagnosis that assessed the efficacy during the first 2 months (while the majority of patients were expected to still be on study drug) and the safety of eltrombopag until the primary analysis cutoff date.

2 | METHODS

TAPER (NCT03524612) is a Phase II, prospective, single-arm trial designed to determine whether eltrombopag can induce a SRoT in patients with ITP after first-line CS failure.[14] Eligible patients included adults (≥18 years) with ITP who did not respond to or had relapsed after initial CS therapy, with platelet counts <30 × 10^9/L and assessed as needing treatment (Figure S1A). The starting dose of eltrombopag was 50 mg/day (25 mg/day for Asian patients; 12.5 mg/day for Japanese patients in Japan), which could be increased up to 75 mg/day (50 mg/day in Japan) if needed, to achieve a complete response (CR).

The primary endpoint was the proportion of patients with SRoT until Month 12, which was defined as the completion of a series of steps (Figure S1A). For step 1, patients had to achieve a CR (i.e., platelet count ≥100 × 10^9/L). In step 2, patients then had to maintain a stable platelet count (i.e., no counts <70 × 10^9/L) for 2 months. If a patient failed to maintain their response for 2 months and thus did not meet the criterion for step 2, they had to re-qualify for step 1 to proceed. For example, if a patient achieved a platelet count of 100 × 10^9/L on 50 mg eltrombopag and their platelet count subsequently dropped below 70 × 10^9/L, the protocol allowed for the dose to be increased to re-qualify for step 1. However, if rescue medication was required, the patient would not be considered for a

SRoT until Month 12. To achieve step 3, eltrombopag treatment had to be tapered and discontinued, and patients were required to maintain platelet counts ≥30 × 10^9/L in the absence of bleeding events and without any rescue therapy. Step 4 was the maintenance of platelet counts ≥30 × 10^9/L following discontinuation of eltrombopag, with no bleeding or use of rescue therapy by Month 12. A binomial test for one proportion, H0: $p = .15$ vs. H1: $p > .15$ at the one-sided 5% alpha level, was performed. Patients eligible for tapering off eltrombopag had an individualized duration of tapering dependent upon their starting dose of eltrombopag and their response. Dose was reduced by 25 mg every 2 weeks if the platelet counts were considered stable, with dosing at 25 mg carried out on alternate days for the last 2 weeks until fully discontinued (Table S1). Tapering for patients with Asian ancestry was done in 12.5 mg decrements every second week due to the reduced starting dose in this population.

Among patients who tapered and discontinued eltrombopag, only those who maintained a response until Month 12 were followed for an additional year. Secondary outcomes included SRoT duration, platelet count changes from baseline, changes in health-related quality of life, and safety outcomes. Health-related quality of life changes were assessed over time: the fatigue subscale of Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue), the Functional Assessment of Cancer Therapy–Thrombocytopenia 6-Item Version (FACT-Th6) scale, and the Short-Form 36 item version 2 (SF-36v2) scale were used.

Visits were scheduled weekly in the first 9 weeks of the study, then biweekly up to Month 12, and every 3 months from Month 12 to Month 24. Data from scheduled visits up to Month 12 (for the primary endpoint) and from scheduled and unscheduled visits during follow-up (from Month 12 and Month 24) are presented here. Primary analysis and ad-hoc early use analysis data cutoff date: October 22, 2021; final analysis data cutoff date: October 03, 2022; first patient first visit: November 02, 2018; last patient last visit: October 03, 2022.

This trial was conducted in accordance with the International Council for Harmonization harmonized tripartite guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki.

2.1 | Eltrombopag in earlier stages of ITP: An ad-hoc early-use analysis of data from the TAPER trial

An ad-hoc early-use analysis, stratified by ITP duration, assessing initial responses to eltrombopag therapy was conducted (using the primary analysis cutoff date: October 22, 2021). Patients were grouped according to time since ITP diagnosis at baseline (<3, 3 to <6, 6 to ≤12, and >12 months). The main analysis of hematologic response (i.e., percentage of patients with platelet count thresholds of ≥30, ≥50, and ≥100 × 10^9/L achieved at least once without rescue therapy) was restricted to data from the first 2 months (Week 9 Day 1). This was because the majority of patients were expected to still be on treatment at that time point. For other efficacy endpoints, data up to Month 6 were used. Safety endpoints included all data up to and including the primary analysis cutoff date.

3 | RESULTS

3.1 | Baseline characteristics and treatment exposure

Overall, 105 patients were enrolled; 69 patients completed the 12-month treatment period, and 36 patients discontinued treatment early. The most common reasons for treatment discontinuation were physician decision (all due to lack of efficacy, $n = 12$) and adverse events (AEs; $n = 10$) (Figure S1B). Patients had a median (range) age of 46.0 (18–88) years, 61% were female, and the median (range) time since diagnosis of ITP to first eltrombopag dose was 102 (7–5008) days (Table S2). In the first 12 months, the median (range) duration of exposure to eltrombopag was 5.6 (0.3–12.5) months, and the median (range) eltrombopag dose for all patients was 57.1 (18–74) mg/day, inclusive of the dose reduction period. The median (range) dose for the 32 patients who achieved SRoT until Month 12 was 37.0 (18–66) mg/day, and 63.8 (19–74) mg/day for the 73 remaining patients who were not able to attain and/or maintain SRoT until Month 12.

3.2 | Primary analysis results

3.2.1 | Efficacy outcomes

Overall, 89/105 patients (84.8%) achieved step 1 of the primary endpoint criteria, that is, platelet count ≥100 × 10^9/L at least once (CR) (Table S1). Sixty-four patients (61.0%) achieved step 2, maintaining a platelet count ≥70 × 10^9/L for 2 months after CR. Step 3 (eltrombopag tapering and discontinuation) was achieved in 44 patients (41.9%). The primary endpoint (step 4) was met, with 32 patients (30.5% [95% confidence interval, 21.9–40.2]; $p < .0001$ [H1: $p > 15\%$; alpha: 0.05]) able to maintain platelet counts ≥30 × 10^9/L after treatment discontinuation in the absence of bleeding events and without any rescue therapy by Month 12 (Figure 1A). Among the 44 patients who tapered and discontinued eltrombopag (step 3), a total of 32 patients (72.7%) attained SRoT until Month 12. Figure 2 portrays step achievement and duration over time for all patients. Of the 32 patients achieving SRoT until Month 12, 18 (56.3%) maintained an off-treatment platelet level ≥ 100 × 10^9/L for at least 6 months after tapering. The platelet count threshold to be maintained after treatment discontinuation until Month 12 in this study was set at ≥30 × 10^9/L. Interestingly, when applying the more stringent thresholds of ≥50 × 10^9/L or ≥ 100 × 10^9/L, a significant proportion of patients still achieve SRoT (22.9% (24/105) and 14.3% (15/105), respectively).

Of the 12/44 patients who tapered and discontinued eltrombopag but experienced a subsequent relapse (platelet count <30 × 10^9/L), eltrombopag was restarted in 8 of these patients. Platelet counts in 7 patients subsequently increased above the 30 × 10^9/L threshold. The remaining 5 patients did not restart eltrombopag therapy because of recovery of response without treatment, ongoing bleeding events, completion of the study, or discontinuation due to AEs.

The median (interquartile range [IQR]) time from the first eltrombopag dose to step 1 (CR) was 15.0 (9.0–29.0) days ($n/N = 89/105$).

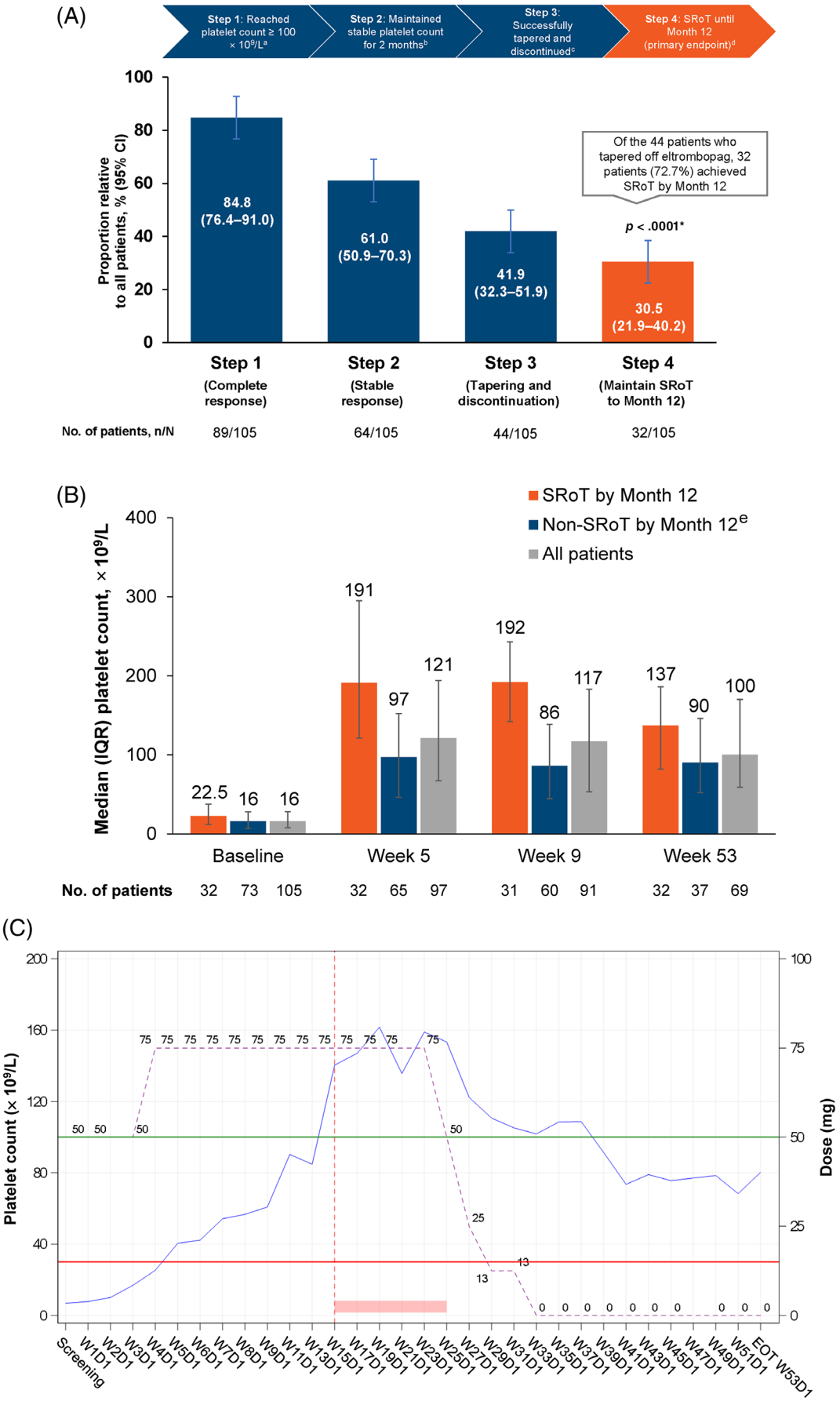

FIGURE 1 Legend on next page.

The median (IQR) tapering time from step 2 to step 3 for the 44 patients who discontinued eltrombopag was 25.0 (1.0–69.5) days. For the 32 patients who attained SRoT until Month 12, the tapering time was 21.0 (1.0–70.5) days. SRoT was maintained from the last dose of eltrombopag to Month 12 for a median duration of 33.3 (IQR: 25.7–45.3) weeks.

The median (IQR) absolute and relative increase in platelet counts from baseline to Month 12 was 77.0×10^9/L (35.0–145.0) and 493.1% (108.6–945.5), respectively. The median platelet count increased within 1 month of exposure to eltrombopag, with median (IQR) absolute and relative increase from baseline at Month 1 of 96.0×10^9/L (34.0–174.0) and 491.3% (207.2–1085.7), respectively (Figure 1B). For patients who attained SRoT, the median (IQR) absolute and relative increase in platelet counts from baseline at Month 12 was 90.6×10^9/L (46.0–163.0) and 498.4% (111.8–914.7), respectively. For patients who did not attain SRoT, the median (IQR) absolute and relative increase in platelet counts from baseline at Month 12 was 56.0×10^9/L (29.0–122.0) and 436.4% (96.4–1016.7), respectively. A patient profile plot of one patient who attained SRoT until Month 12 is presented in Figure 1C.

The proportion of patients who attained SRoT until Month 12 is also presented by the time since initial diagnosis and showed a similar proportion of patients who were able to complete steps 1–3, regardless of the stage of disease (differences <15%). Among the four groups of patients with different times since diagnosis, the numerically highest proportion of patients who completed step 4 were newly diagnosed patients (<3 months; [18/51; 35.3%]) (Table S3).

In addition, univariate and multivariate logistic regression models (using binary and continuous covariates) were explored to assess predictive factors of SRoT until Month 12. The candidate covariates were time since ITP diagnosis to first dose, age, gender, baseline platelet count, baseline neutrophils, baseline body mass index, time to achieve first CR (end of step 1), and platelet count at start of first tapering (end of step 2). Of these, none could be identified as a significant predictive factor. This may be due to small sample size (Table S4).

3.2.2 | Patient-reported quality of life outcomes

The mean (standard deviation [SD]) FACIT-Fatigue score increased from the baseline score of 34.5 (10.9) to 40.7 (8.1) at Month 3. The increase in FACIT-Fatigue score was maintained over time, with a score of 43.1 (7.0) assessed at Month 12. These improvements from baseline correspond to a mean (SD) point increase in score of 5.2 (9.7) at Month 3 and 7.6 (9.2) at Month 12. A difference in FACIT-Fatigue score of at least 3.0 points is considered to be the minimal important difference (MID).[15] Similar changes from baseline were observed regardless of the SRoT status until Month 12 (Figure S2A). Similar results were also reported for the mean (SD) FACT-Th6 score, which increased from 12.9 (6.3) at baseline to 17.1 (5.0) at Month 3 (mean [SD] change from baseline of 3.9 [5.1]; MID for FACT-Th6 score: 3.0 points[15]) (Figure S2B). There were also increases in both the SF-36v2 mental and physical component scores, maintained over time in both patients with and without SRoT until Month 12 (Figure S2C).

3.3 | Follow-up analysis results

Out of the 32 patients who achieved SRoT until Month 12, 31 patients entered the 1-year follow-up period as per protocol. One patient who achieved SRoT until Month 12 did not enter the second-year follow-up due to patient decision. Twenty-eight patients completed the second-year follow-up, and 3 patients discontinued (one was lost to follow-up, one was due to physician decision and one was due to patient decision). Although only SRoT until Month 12 patients were to enter the follow-up per protocol, 7 nonresponders continued into follow-up due to investigator decision and treatment supply.

Overall, out of the 105 patients in the study, 20 patients (19.0%, 95% CI 12.0–27.9) maintained SRoT until Month 24. As defined per protocol, these 20 patients achieved SRoT until Month 12, entered the second-year follow-up, and maintained platelet count $\geq 30 \times 10^9$/L in the absence of bleeding AEs or use of any rescue therapy from Month 12 to Month 24 (Figure 2). For these 20 patients, at the time of final analysis, the median duration of SRoT after tapering off eltrombopag was 88.6 weeks (approximately 22 months). The median (IQR) absolute and relative increase in platelet counts from baseline to Month 24 for patients who attained SRoT until Month 12 (i.e., those who met the primary endpoint) was 126.0×10^9/L (55.0–174.0) and 525.0% (84.6–985.7), respectively.

Patient-reported outcome scores were also increased from baseline to Month 24 in all patients. The increase in FACIT-Fatigue score was maintained over time, with a mean (SD) score of 42.6 (10.0) assessed at Month 24 (Figure S2A). This improvement from baseline corresponds to a mean (SD) point increase in score of 8.7 (10.6) at

FIGURE 1 (A) SRoT until Month 12 (primary endpoint; cutoff date: October 22, 2021), (B) SRoT status by visit, and (C) Patient profile plot of a patient who attained SRoT until Month 12. The Clopper–Pearson test was used for testing whether the proportion of patients who attained SRoT until Month 12 was greater than 0.15. CI and *p* values are reported. One-sided *p* value is <.001*. *N* indicates the total number of patients in the trial, and *n* indicates the number of patients who achieve each specific step. *Indicates statistical significance (one-sided) at the 0.05 level. [a]Patients who reached platelet count $\geq 100 \times 10^9$/L at least once (step 1). [b]Patients who maintained stable platelet count for 2 months after reaching 100×10^9/L (no counts $<70 \times 10^9$/L) (step 2). [c]Patients who were able to be tapered off the drug until treatment discontinuation, maintaining platelet count $\geq 30 \times 10^9$/L in the absence of bleeding AEs or use of any rescue therapy (step 3). [d]Patients who attained SRoT until Month 12, maintaining platelet count $\geq 30 \times 10^9$/L in the absence of bleeding AEs or use of any rescue therapy (step 4). [e]Patients who were not able to attain and/or maintain SRoT until Month 12. AE, adverse event; CI, confidence interval; D, day; EOT, end of treatment; IQR, interquartile range; SRoT, sustained response off-treatment; W, week. [Color figure can be viewed at wileyonlinelibrary.com]

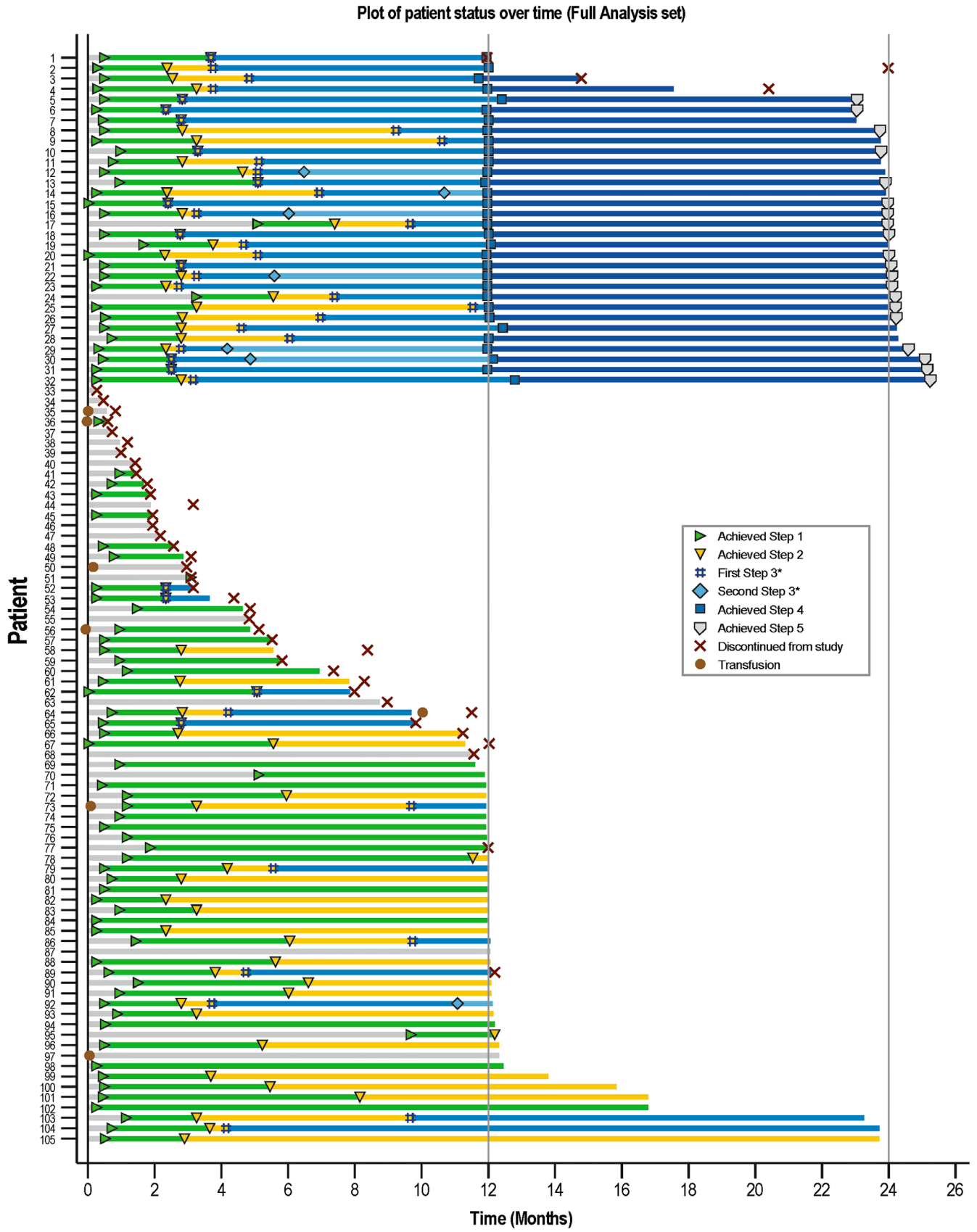

FIGURE 2 Step achievement and duration over time for all patients until Month 24. Each horizontal line represents a patient, each step achievement is marked by an icon (step 1, green triangle; step 2, yellow triangle; first step 3; blue hash; second step 3, blue diamond; step 4; blue square; step 5, gray shield) and corresponding color change for visualization. Platelet transfusion and study discontinuation are denoted with a red circle and red cross, respectively. Patients not indicated as discontinued early are completers. [Color figure can be viewed at wileyonlinelibrary.com]

Month 24. An increase from baseline was observed at Month 24 regardless of whether a patient achieved SRoT until Month 12, with a median increase of 6 and 17 points for SRoT and non-SRoT, respectively. Similar results were also reported in all patients for the FACT-Th6 score, with a mean (SD) increased from baseline to Month 24 of 7.1 (7.0) (Figure S2B). Increases in the SF-36v2 mental and physical component scores were maintained to Month 24 (Figure S2C).

3.4 | Safety analysis

For the final analysis, 94/105 patients (89.5%) experienced an AE, with 33 patients (31.4%) experiencing grade ≥3 AEs. The most common all-grade AEs were headache (21.9% of patients), thrombocytopenia (16.2%), and petechiae (11.4%) (Table S5). Treatment-related AEs were observed in 39 patients (37.1%), with 7 patients (6.7%) reporting a grade ≥3 event (Table 1). There were 5 treatment-related serious AEs (Table 1), namely intentional product misuse, thrombosis of the left saphenous vein, infectious diarrhea secondary to eltrombopag, deep vein thrombosis (DVT), and pulmonary embolism. Dose adjustment/interruption caused by all-grade AEs was recorded in 28 patients (26.7%). AEs of special interest were reported in 27 patients (25.7%), with 7 of these (6.7%) being grade ≥3.

Hepatotoxic events of special interest were recorded in 19 (18.1%) patients (Table S5). These events resulted in a dose interruption in 5 patients and were deemed to be treatment-related in 13 patients. One patient (1.0%) had a grade ≥3 event of increased blood bilirubin; this was initially reported as being treatment-related. However, the patient was subsequently confirmed by genetic analysis to have Gilbert's syndrome, a condition characterized by abnormal bilirubin processing, and the event was subsequently re-classified as not being treatment-related. Seven patients who experienced hepatoxic events achieved SRoT at month 12.

Thromboembolic events of special interest were recorded in 6 (5.7%) patients, with 4 (3.8%) of these having a grade ≥3 event. These events included DVT seen in 3 (2.9%) patients (2 patients with a grade ≥3 event), and cerebral thrombosis (which was a sinus thrombosis), cerebrovascular accident, pulmonary embolism, and superficial vein thrombosis, each recorded in 1 (1.0%) patient (Table S5). Four of these thromboembolic events were deemed to be treatment-related, including 2 patients with grade 3 DVT, one of whom experienced two events: a pulmonary embolism and a superficial vein thrombosis. Further information on each of the thromboembolic events of special interest is reported in Table S6.

Four deaths (3.8%) were reported during the trial, and none were considered treatment-related. Three of these deaths occurred on treatment; these were recorded as a central nervous system hemorrhage ($n = 1$), intracranial hemorrhage ($n = 1$), and metastases to peritoneum ($n = 1$) (Table 1). One death (malignant neoplasm) occurred 238 days after the last dose. In the patient who died following the central nervous system hemorrhage, the platelet count at the last visit (3 days) before death was 1×10^9/L; in the patient who died following intracranial hemorrhage, the last platelet count (7 days) before death was 2×10^9/L. In both patients who suffered hemorrhage, tapering of eltrombopag had not occurred. No deaths occurred in the second year of follow-up.

Bleeding events according to the World Health Organization (WHO) bleeding scale (grade 1 to 4) decreased in the first 12 months. The proportion of patients with grade 1 bleeding events decreased from baseline (34.3%) to 4.8% (Month 9 to Month 12), and grade 2 bleeding events decreased from 4.8% to 0% in the same period. No grade 3 bleeding events were recorded after baseline. By the end of treatment visit, 58 patients (55.2%) had experienced no bleeding, 7 patients (6.7%) had experienced grade 1 (mild) blood loss, and 1 patient each (1.6%) had experienced grade 2 (moderate), grade 3 (gross), or grade 4 (debilitating) blood loss. One (1.6%) patient had a WHO grade 4 bleeding event (Month 9 to Month 12); (Figure S3A).

TABLE 1 Overview of AEs and deaths until Month 24.[a]

Overview of AEs (safety set)[b]	All patients ($N = 105$)	
Category	All grades, *n* (%)	Grade ≥3, *n* (%)
AEs	94 (89.5)	33 (31.4)
Treatment-related	39 (37.1)	7 (6.7)
SAEs	21 (20.0)	21 (20.0)
Treatment-related	5 (4.8)	5 (4.8)
Fatal SAEs	3 (2.9)	3 (2.9)
Treatment-related	0	0
AEs leading to discontinuation	10 (9.5)	5 (4.8)
Treatment-related	5 (4.8)	2 (1.9)
AEs leading to dose adjustment/interruption	27 (25.7)	13 (12.4)
Treatment-related	12 (11.4)	3 (2.9)
AEs of special interest	27 (25.7)	7 (6.7)
Treatment-related	15 (14.3)	3 (2.9)

On-treatment deaths (safety set)[c]	All patients ($N = 105$)
Category: preferred term	*n* (%)
On-treatment deaths	3 (2.9)
CNS hemorrhage[d]	1 (1.0)
Intracranial hemorrhage[e]	1 (1.0)
Metastases to peritoneum	1 (1.0)

Note: Numbers (*n*) represent counts of patients.
Abbreviations: AE, adverse event; CNS, central nervous system; CTCAE, common terminology criteria for adverse events; MedDRA, medical dictionary for regulatory activities; SAE, serious adverse event.
[a]Final analysis cutoff date, October 03, 2022.
[b]Patient with multiple severity grades for an AE is only counted under the maximum grade. MedDRA version 24.1, CTCAE version 4.03.
[c]On-treatment = ongoing patients until cutoff date. For patients who discontinue and complete, it is until the last nonzero dose +30 days.
[d]Platelet count at the last assessment visit before death (3 days) was 1×10^9/L.
[e]Platelet count at the last assessment visit before death (7 days) was 2×10^9/L.

A similar pattern of changes in the proportions of patients with WHO bleeding events was seen in patients with and without SRoT (Figure S3B,C).

3.5 | Ad-hoc early-use analysis results

All 105 patients were included in the ad-hoc analysis (Table S2). The proportions of patients with platelet counts equal to or above the specified response thresholds (i.e., ≥30, ≥50, and ≥ 100 × 10^9/L) were comparable across the time-since-ITP-diagnosis groups (<3, 3 to <6, 6 to ≤12, and >12 months), ranging from 72.2% to 100% (Figure 3). The median (IQR) increase in platelet count to Week 9 Day 1 was 97.5 × 10^9/L (35.0–163.0) (Figure S4). Median time to a platelet count of ≥50 × 10^9/L was also comparable across groups, ranging from 8 to 19 days.

Grade 1 to 4 WHO bleeding events also decreased in the first 6 months across all time-since-ITP-diagnosis groups. From baseline to Week 27 Day 1, the proportion of patients with grade 1 bleeding events changed from 52.9% to 3.3% in the <3 months group, from 38.1% to 5.9% in the 3 to <6 months group, from 44.4% to 0% in the 6 to ≤12 months group, and from 20.0% to 10.0% in the >12 months group. Over the same period, the percentage of patients with grade 2 bleeding events changed from between 4.8% and 9.8% at baseline to 0% at Week 27 Day 1 across all time-since-ITP-diagnosis groups. There were no WHO grade 3 or 4 bleeding events recorded during this first 6-month period (Figure S5).

In the first 3 months of the trial, platelet transfusions were required in 4/51 (7.8%) patients in the ITP <3 months group and 1/18 (5.6%) patient in the 6 to ≤12 months group. One patient (2.0%) in the ITP <3 months group required a platelet transfusion at 3 to 6 months into the trial.

The proportions of patients who experienced an AE across the time-since-ITP-diagnosis groups were comparable, with the highest proportion of patients experiencing AEs grade ≥3 in the 3 to <6 months group(38.1%), whereas the lowest proportion of patients with AEs grade ≥3 was in the >12 months group (13.3%). The most common all-grade AEs (≥10%) in each group regardless of time since diagnoses were headache and thrombocytopenia (Table S7). There were 5 treatment-related serious AEs, of which 2 were cases of intentional product misuse and thrombosis of the left saphenous vein recorded in the <3 months group; the 3 cases of infectious diarrhea secondary to eltrombopag, DVT, and pulmonary embolism were recorded in the 6 to ≤12 months group.

Of the 4 deaths reported by the cutoff date, the central nervous system hemorrhage occurred in the <3 months group; the intracranial hemorrhage in the 3 to <6 months group; the metastases to peritoneum in the 6 to ≤12 months group; and the malignant neoplasm in the >12 months group.

4 | DISCUSSION

The results from this prospective, Phase II, single-arm trial indicated that, of the 105 patients, around one-third of patients achieved the primary efficacy endpoint of sustained response following eltrombopag tapering and discontinuation until Month 12 (30.5%), with median (IQR) SRoT duration until Month 12 of 33.3 (25.7–45.3) weeks (approximately 8 months). Additionally, in the second-year follow-up, 20 patients (19.0%) maintained SRoT at Month 24. These prospective data confirm that a substantial proportion of patients with ITP can successfully taper off eltrombopag treatment and maintain platelet counts ≥30 × 10^9/L up to Month 24 without bleeding events or the

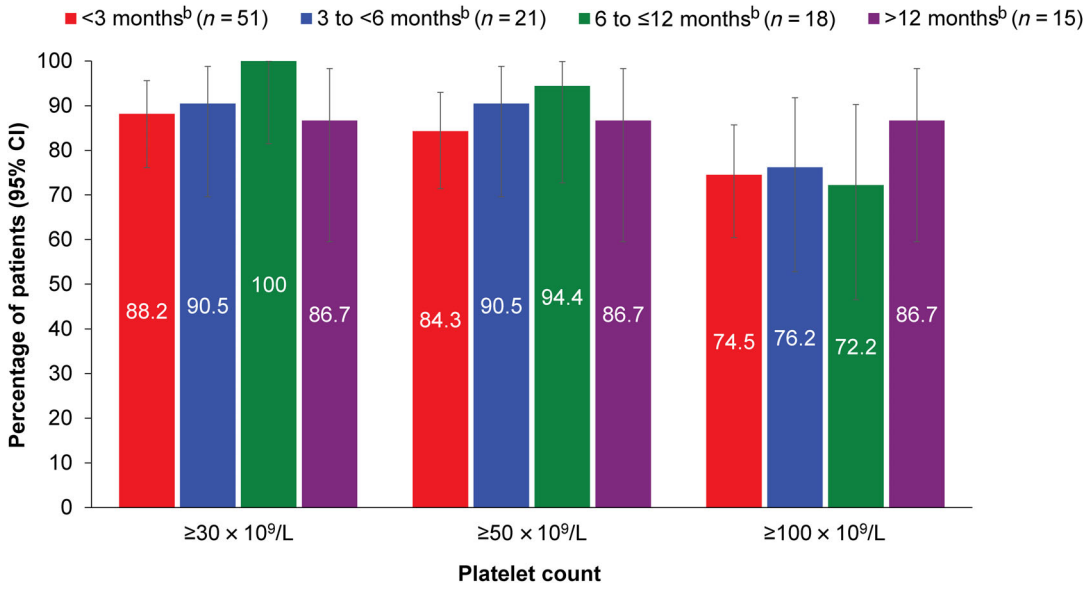

FIGURE 3 Hematologic response[a] by time since ITP diagnosis in the first 2 months of the TAPER trial (full analysis set). [a]The proportion of patients with platelet counts greater than or equal to the prespecified thresholds at least once by Week 9 Day 1. [b]Time since ITP diagnosis. CI, confidence interval; ITP, immune thrombocytopenia. [Color figure can be viewed at wileyonlinelibrary.com]

need for rescue therapy. In clinical practice, tapering off treatment holds several important benefits, including reducing the potential for treatment-related adverse events and ensuring that patients receive the lowest effective dose only for as long as required. As such, this is a step toward personalized medicine such that patients' specific needs are tailored to. Median platelet count was increased within 1 month of exposure to eltrombopag and remained elevated at 12 and 24 months, regardless of SRoT until Month 12 status. Patient-reported outcome measures also indicated that quality of life initially improved and was then maintained over time, regardless of eltrombopag tapering and discontinuation.

The bleeding events in all patients, assessed by the WHO bleeding scale (Grade 1 to 4), showed a decrease in the rate of bleeding over time by Month 12. This trend was observed in patients with and without SRoT until Month 12. In addition, similar trends in the decreased bleeding rates were observed in the ad-hoc analysis investigating the early response to eltrombopag in all ITP groups.

Eltrombopag was well tolerated, with no unexpected AEs and no deaths considered treatment-related. All-grade thromboembolic events were recorded in 5.7% of patients. However, all but one event (DVT) had resolved by Month 12. As a broad comparison, in their prospective Phase II trial of eltrombopag tapering and discontinuation, Lucchini et al. reported 3 (6%) cases of thrombosis (1 case of DVT and 2 of acute myocardial infarction).[9]

It was also encouraging to note that, of the 8 patients who restarted eltrombopag because of relapse following initial tapering and discontinuation, 7 subsequently showed a platelet response to re-treatment. This suggests that eltrombopag can be reinstated following discontinuation without significant difficulty.

These findings are consistent with those of other published studies of eltrombopag and romiplostim, which report SRoT in up to around one-third of patients.[8,9,11] Results from a previously reported prospective Phase II clinical trial investigating the activity of eltrombopag in adult patients with ndITP or pITP after first-line therapy showed that the proportion of patients achieving SRoT for at least 6 months was 25% (13/51 patients).[9] SRoT in this case was defined as a platelet count of $\geq 30 \times 10^9$/L and at least a 2-fold increase from baseline count at the end of treatment (Week 24), tapering and discontinuation (up to Week 32) of eltrombopag, and subsequent maintenance of response in the absence of bleeding and rescue therapy (an additional 24 weeks).[9] Additionally, romiplostim (TPO-RA) has been investigated in a single-arm Phase II trial to evaluate platelet response and ITP remission rates in adult patients with ndITP, where it showed 32% (24/75 patients) maintenance of platelet count $>50 \times 10^9$/L in patients not receiving any medication for 24 weeks.[8] As mentioned in the results, if the platelet count maintenance threshold in the present study had been set at $\geq 50 \times 10^9$/L after treatment discontinuation until Month 12 instead of $\geq 30 \times 10^9$/L, the proportion of patients attaining SRoT would have been 23%. A recent prospective multicenter interventional study assessed SRoT in patients with ITP following TPO-RA discontinuation. In contrast to TAPER, only patients who were in CR on TPO-RA treatment were enrolled, and the primary endpoint of SRoT was defined as maintenance of a platelet count $>30 \times 10^9$/L at Week 24, rather than Week 52. Out of 48 patients in this study, 27 achieved SRoT and 15 achieved sustained complete response off treatment (SCRoT) at Week 24, and 25 and 14 patients achieved SRoT and SCRoT, respectively, at Week 52. While these findings suggest potential strategies for patients who have already achieved CR, the differences in study design, endpoint definitions (i.e., SRoT), and patient population need to be taken into consideration in the context of the TAPER findings, and a direct comparison of these findings should be avoided. Tapering of an otherwise efficacious medicine may be potentially associated with risks, such as bleeding events. In keeping with the pathophysiology of bleeding events in ITP patients in general, bleeding events, which occurred in this study are likely related to low platelet counts. However, the etiology of bleeding events in ITP is known to have inherent inter-individual variability, as such it is difficult to state the cause of bleeding events in this population without specific investigations which were outside of the scope of this manuscript.

In terms of the investigation of early response to eltrombopag in ITP, the results we obtained indicate that eltrombopag induced comparable early rates of platelet response and reduced the frequency and severity of bleeding events in patients with ndITP, pITP, and cITP. We have not documented any trends toward a more favorable response or safety concerns regardless of time since ITP diagnosis to first dose, age, gender, baseline platelet count, baseline neutrophils, baseline body mass index, time to achieve a platelet count $\geq 100 \times 10^9$/L, and platelet count at the start of tapering. These results further build on the previously reported retrospective data that suggest the effectiveness and tolerable safety profile of eltrombopag in patients with ndITP, as well as pITP and cITP.[12,13]

One limitation of these analyses was the lack of a placebo/control arm. In addition, the trial enrolled a relatively small number of patients; however, despite these limitations, this is one of the first prospective trials looking at tapering and SRoT until Month 12 in adult patients with ITP using eltrombopag following CS failure. Of the 32 patients who had SRoT until Month 12, 20 had SRoT until Month 24. These data provide additional information on the durability of SRoT and the ability of eltrombopag to induce a sustained response in a substantial proportion of patients with ITP. Moreover, 8 out of the 12 patients who tapered off eltrombopag and experienced a subsequent relapse restarted the medication, with 7 subsequently showing a platelet response. This suggests that eltrombopag can be reinstated following discontinuation without significant difficulty. A larger body of data is also needed to determine the optimal platelet threshold count before tapering off to increase the likelihood of sustained response off treatment. One interesting finding from the present study was that, despite the initiation of tapering after a relatively short period of time at a high platelet count (i.e., $\geq 100 \times 10^9$/L at least once followed by $\geq 70 \times 10^9$/L for 2 months), the proportion of patients who attained SRoT until Month 12 and Month 24 was still approximately 30% and 20%, respectively; therefore, larger studies should also ascertain what is the optimal threshold duration as well as platelet count required for successful tapering and discontinuation. Finally, the natural history of the disease and heterogeneity of the patient population make it impossible to disprove the possibility of spontaneous remission, given the absence of a control arm in the

study. However, our findings provide valuable information on the ability of eltrombopag to induce a sustained response in a significant proportion of patients with ITP.

In summary, the TAPER trial indicates that a significant proportion of patients with ITP attained SRoT until Month 12 following tapering and discontinuation of eltrombopag. Furthermore, the ad-hoc analysis data suggest that eltrombopag is as effective and well tolerated in the early stages of ITP as it is in later stages of ITP. The safety profile was comparable across analyses and groups of ITP duration and was aligned with the well-established safety profile of eltrombopag.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design or analysis and interpretation of the data, drafting of the manuscript or revising it critically, and read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Novartis is committed to sharing with qualified external researchers' access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial, in line with applicable laws and regulations. This trial data availability is in accordance with the criteria and process described on www.clinicalstudydatarequest.com.

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SUPPORTING INFORMATION

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

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