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A Phase 3, randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of avatrombopag for the treatment of children with immune thrombocytopenia (AVA-PED-301)

A Phase 3, randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of avatrombopag for the treatment of children with chronic immune thrombocytopenia (AVA-PED-301)

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Disclosures of Rachael Grace MD, MMSc

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Agios	X		X				
Novartis	X						
Sanofi			X				
Sobi	X		X				

Introduction

There is an **unmet need for new treatment options for children and adolescents with ITP**, given the difficult administration requirements and variable, transient responses, frequent relapses, and toxicities associated with existing therapies[1–4]

Current guidelines **recommend the use of TPO-RAs for children and adolescents with ITP** who do not respond to first-line treatment[5]

Avatrombopag, a TPO-RA, is approved for the **treatment of adults (≥18 years) with chronic ITP** with insufficient response to other treatments,[6] without food-type restrictions[7]

In a **Phase 3 study** in **adults** with **chronic ITP**, **treatment with avatrombopag** resulted in **significant improvements** in median cumulative number of weeks of **platelet response** (12.4 versus 0; p<0.0001) and **platelet response rate at day 8** (65.6% versus 0%; p<0.0001) compared with placebo[7]

Avatrombopag is **administered orally with food**, has **no significant hepatotoxicity**, and **a low immunogenicity risk**[a,6,7]

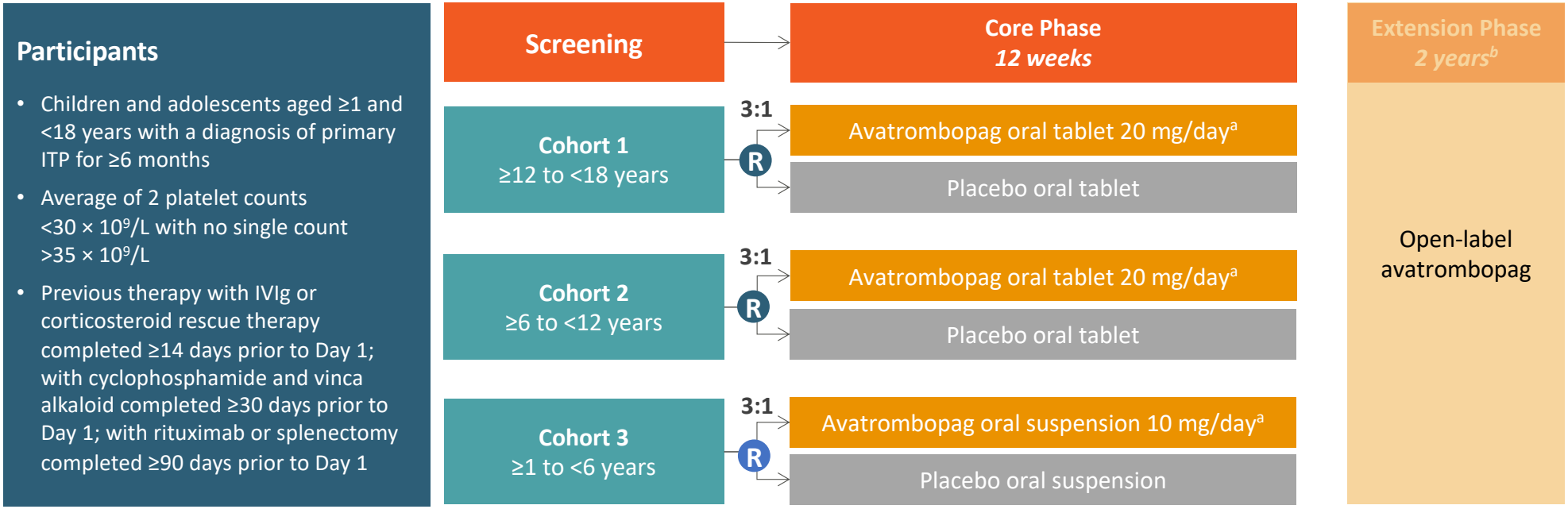
[a]As compared with parenterally administered agents.[6,7]

1. Grace R, et al. *Am J Hematol*. 2018;93:882–8; 2. Cooper N, Cine DB. *Haematologica*. 2019;104:2132-4; 3. Kruse C et al. *Ann Blood*. 2021;6:9; 4. Platelet Disorder Support Association 2020. https://pdsa.org/voice-of-the-patient; Accessed June 03, 2024; 5. Neunert C, et al. *Blood Adv*. 2019;3:3829–66; 6. United States Food and Drug Administration. Doptelet (avatrombopag) Prescribing Information. Last updated in 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210238s006lbl.pdf. Accessed June 2024; 7. Jurczak W, et al. *Br J Haematol*. 2018;183:479–490.

ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

Study Design

Phase 3, randomized (3:1), double-blind, placebo-controlled trial of avatrombopag (NCT04516967)



[a]Patients in cohorts 1 and 2 received avatrombopag or placebo as an oral tablet (starting dose 20 mg/day); patients in cohort 3 received avatrombopag or placebo as a capsule with powder for oral suspension (starting dose 10 mg/day); doses were titrated to maintain a platelet count ≥50 and ≤150 × 10^9/L. [b]Patients completing the core phase, or without treatment effect at the maximum dose of blinded study drug, could enroll into the open-label extension phase for up to 2 years.

Patients were assigned to age cohorts in a 2:2:1 ratio. Participating sites were in France, Germany, Hungary, Poland, Russia, Turkey, Ukraine, UK, and the US.[1]

1. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT04516967. Accessed May 24, 2024.

ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; R, randomization.

Endpoints

Primary efficacy endpoint

Durable platelet response: proportion of patients achieving **at least 6 out of 8 weekly platelet counts ≥50 × 10^9/L during the last 8 weeks of the 12-week core-phase treatment period** in the absence of rescue therapy

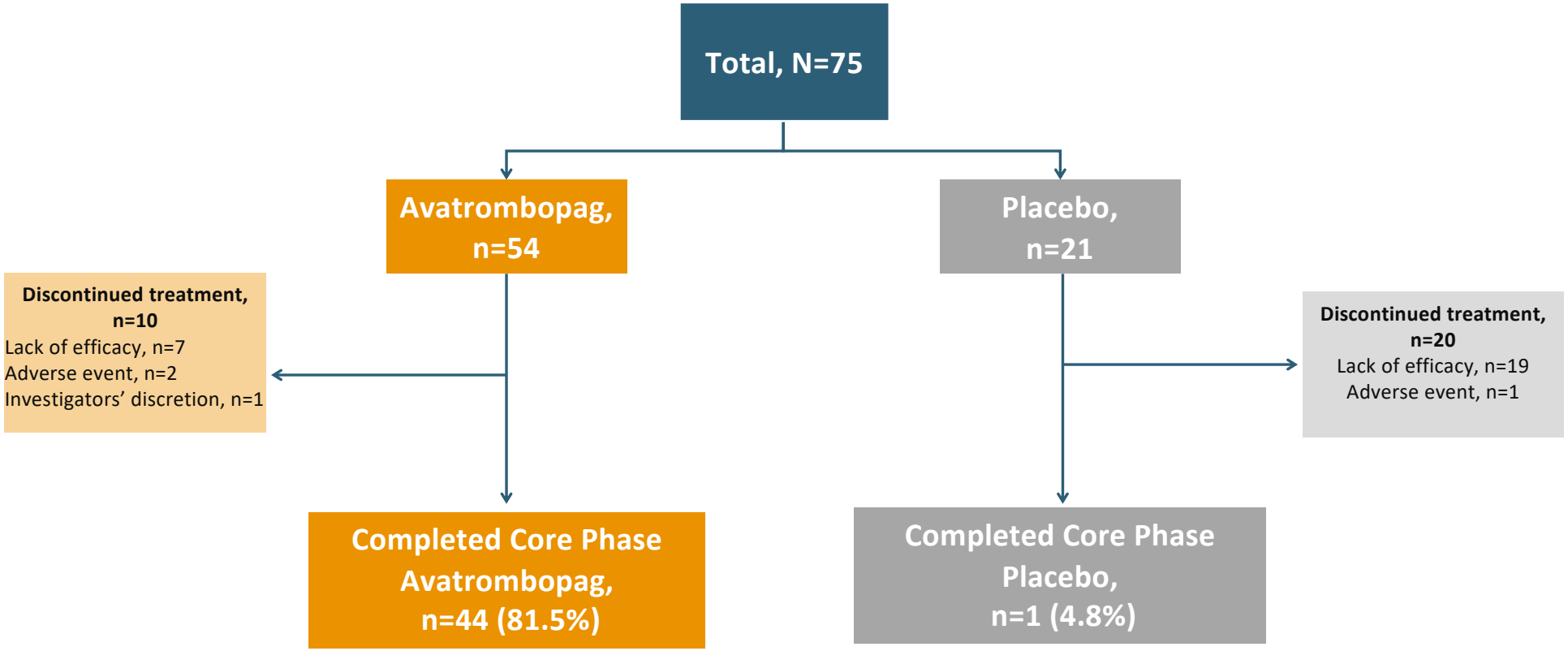
Alternative primary efficacy endpoint[a]

Platelet response: proportion of patients for whom **at least 2 consecutive platelet assessments were ≥50 × 10^9/L over the 12-week core-phase treatment period** in the absence of rescue therapy

Secondary efficacy endpoints

- Percentage of weeks that patients have a platelet count ≥50 × 10^9/L during 12 weeks of treatment in the core phase in the absence of rescue therapy
- Percentage of weeks that patients have a platelet count ≥50 × 10^9/L and ≤150 × 10^9/L, during 12 weeks of treatment in the core phase in the absence of rescue therapy
- Platelet response at Day 8 (defined by the proportion of patients with a platelet count ≥50 × 10^9/L at Day 8, in the absence of rescue therapy)
- Proportion of patients who require rescue therapy during 12 weeks of treatment in the core phase
- Incidence and severity of bleeding symptoms associated with ITP measured using the WHO Bleeding Scale

Patient disposition



Baseline demographics and clinical characteristics

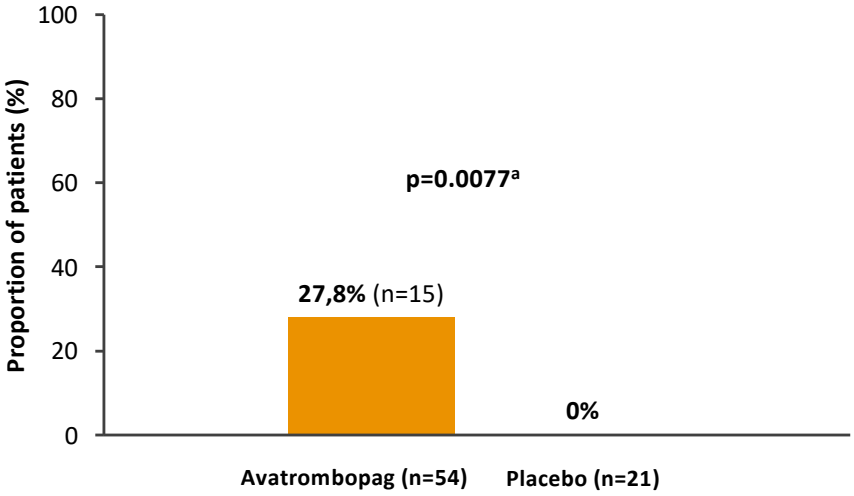
	Avatrombopag (n=54)	Placebo (n=21)
Female, n (%)	24 (44.4)	12 (57.1)
Age, years (mean ± SD)	8.9 ± 4.4	9.9 ± 4.1
Race, n (%)		
White	48 (88.9)	15 (71.4)
Asian	3 (5.6)	1 (4.8)
Platelet count ≤15 × 10^9/L, n (%)	45 (83.3)	17 (81.0)
Platelet count (mean ± SD)	12.0 ± 6.8	11.2 ± 6.6
Bruising or bleeding, n (%)	39 (72.2)	16 (76.2)
WHO bleeding scale for the 7 days prior to baseline, n (%)		
Grade 1	36 (66.7)	14 (66.7)
Grade 2	3 (5.6)	2 (9.5)
Time from primary ITP diagnosis to first dose, weeks (mean ± SD)	202 ± 164	225 ± 181
≥3 previous ITP medications received since diagnosis, n (%)	37 (68.5)	14 (66.7)
Prior TPO-RA use, n (%)	40 (74.1)	15 (71.4)
Prior TPO-RA response, n (%)	17 (42.5)	3 (20.0)
Previous platelet transfusion, n (%)	11 (20.4)	1 (4.8)
Splenectomy, n (%)	2 (3.7)	2 (9.5)

ITP, immune thrombocytopenia; N, total number of patients; n, number of patients; SD, standard deviation; TPO-RA, thrombopoietin receptor agonist; WHO, World Health Organization.

Primary efficacy endpoints: platelet response

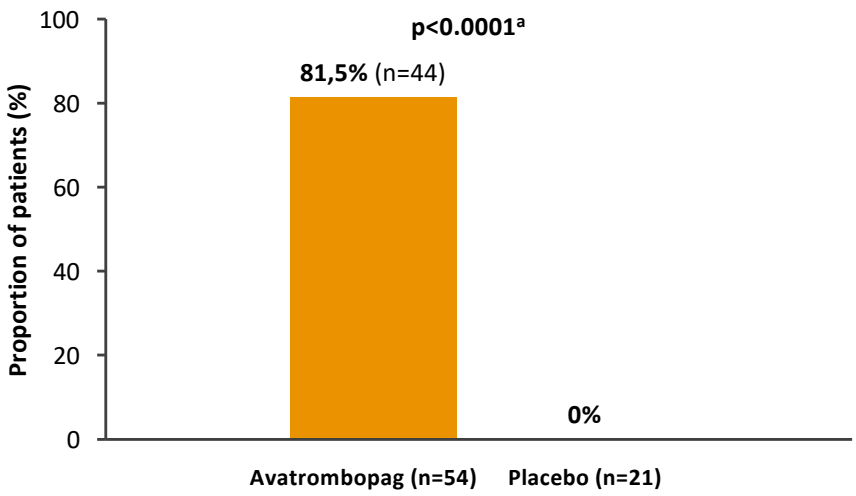
Primary efficacy endpoint

Durable platelet response: proportion of patients achieving **at least 6 out of 8 weekly platelet counts ≥50 × 10^9/L during the last 8 weeks of the 12-week core-phase treatment period** in the absence of rescue therapy



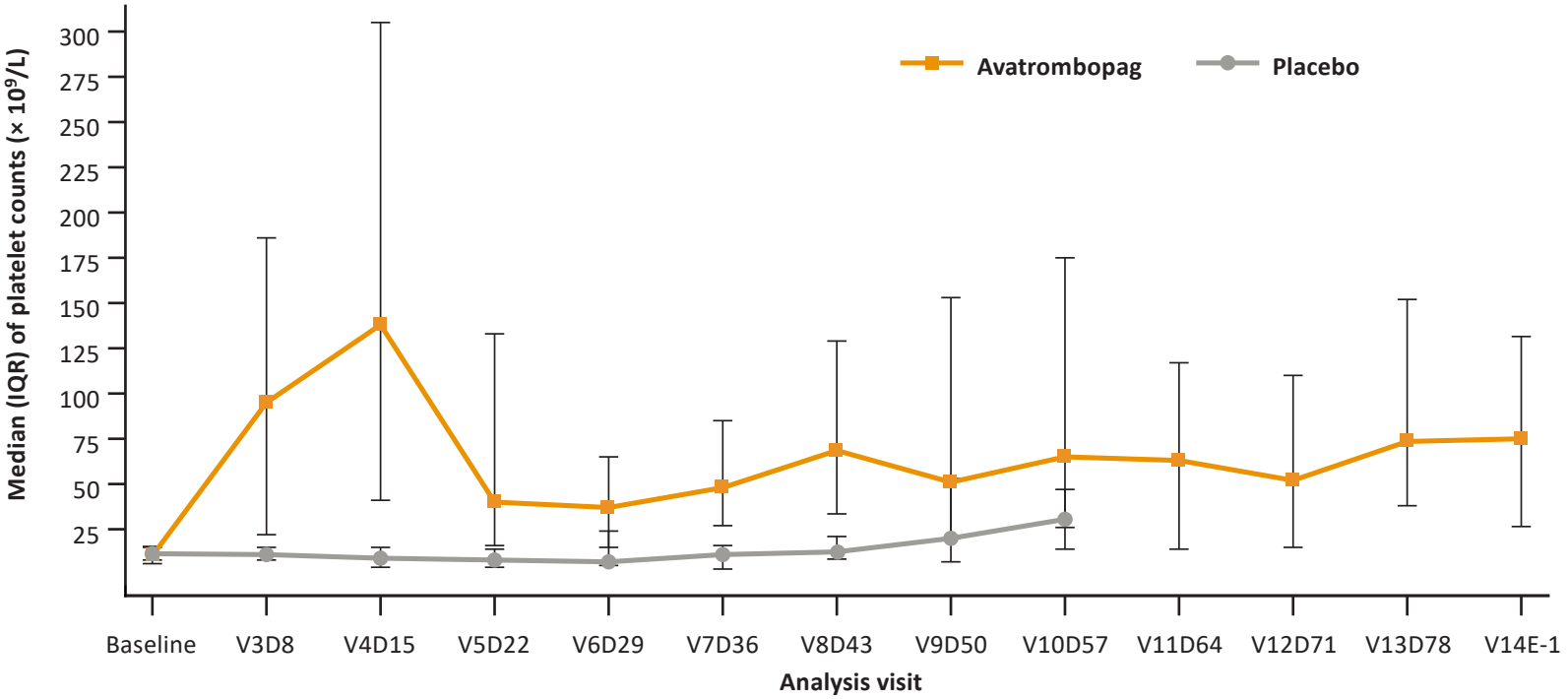
Alternative primary efficacy endpoint

Platelet response: proportion of patients for whom **at least 2 consecutive platelet assessments were ≥50 × 10^9/L over the 12-week core-phase treatment period** in the absence of rescue therapy



Full analysis set. [a]Cochran-Mantel-Haenszel test

Median platelet in the absence of rescue therapy in core phase

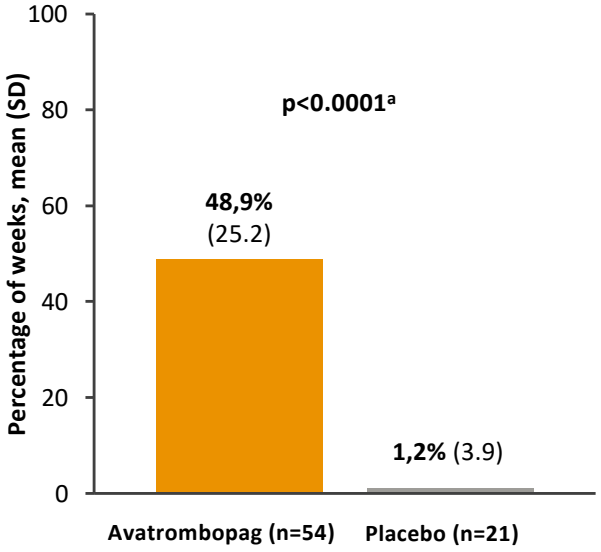


	Baseline	V3D8	V4D15	V5D22	V6D29	V7D36	V8D43	V9D50	V10D57	V11D64	V12D71	V13D78	V14E-1
Avatrombopag	54	51	51	49	49	49	48	47	47	47	46	44	44
Placebo	21	18	17	15	13	11	8	3	2				

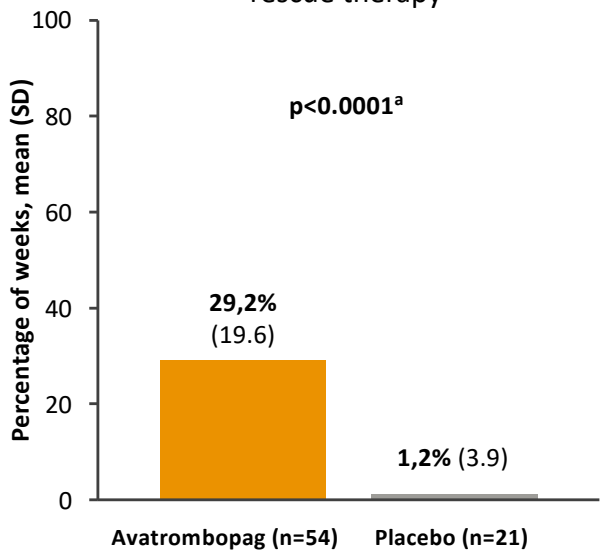
Full analysis set. D, day; E, extension; IQR; interquartile range; V, visit

Secondary efficacy endpoints

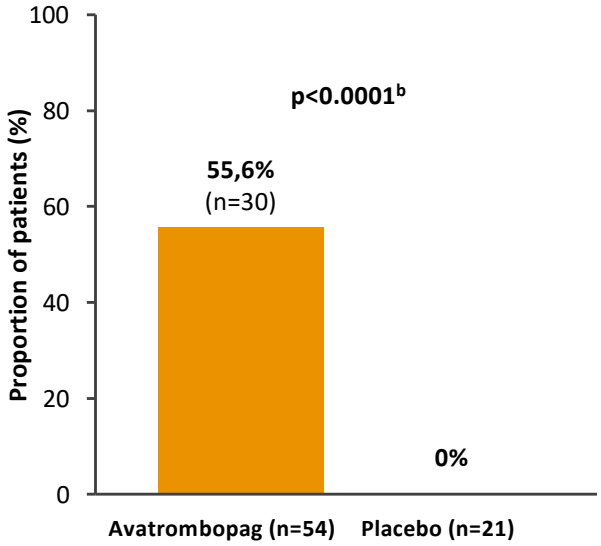
Percentage of weeks platelet count ≥50 × 10^9/L during 12 weeks of treatment in the absence of rescue therapy



Percentage of weeks platelet count between ≥50 × 10^9/L and ≤150 × 10^9/L, during 12 weeks of treatment in the absence of rescue therapy



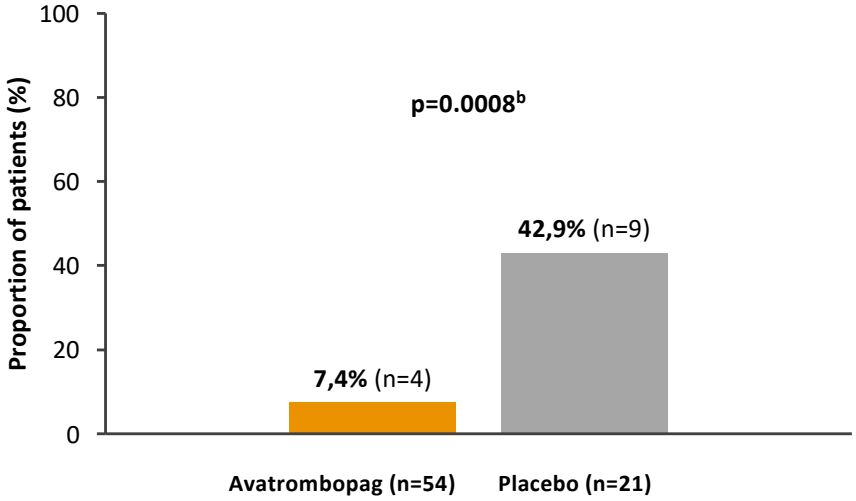
Platelet response at Day 8 Proportion of patients with a platelet count ≥50 × 10^9/L at Day 8 in the absence of rescue therapy



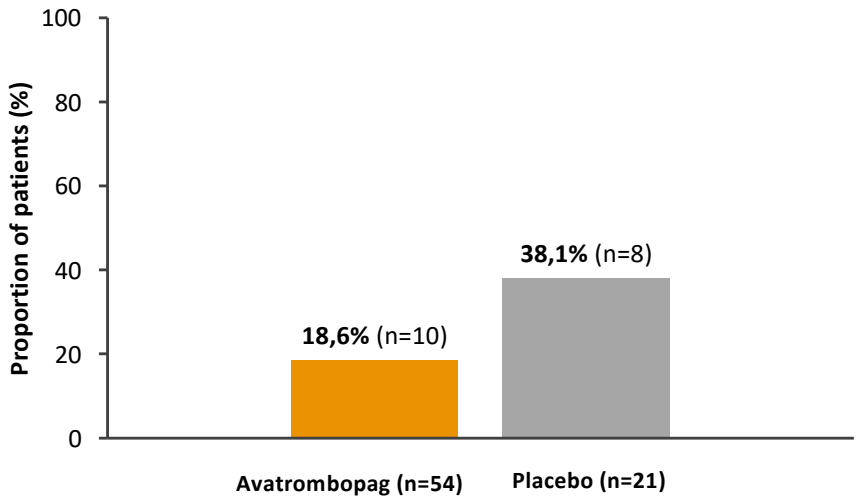
Full analysis set. [a]Non-parametric Wilcoxon rank sum test (continuous data); [b]Cochran-Mantel-Haenszel test (categorical data).

Secondary efficacy endpoints

Proportion of patients who required rescue therapy during 12 weeks of treatment[a]



Incidence of bleeding symptoms associated with ITP measured using the WHO Bleeding Scale (any bleeding event, WHO Grades 2 and 3)[c]



Full analysis set. [a]Rescue therapy use, ~50% corticosteroids/50% IVIg; no platelet transfusions; [b]Cochran-Mantel-Haenszel test; [c]P-value not available; data show the proportion of patients with the highest severity bleeding event that occurred after initiation of study drug.
ITP, immune thrombocytopenia, IVig, intravenous immunoglobulin; WHO, World Health Organization.

Safety

	Avatrombopag (n=54)	Placebo (N=21)
Median treatment duration, weeks	12	6
Any adverse event, n (%) Considered treatment-related by investigator[a]	50 (92.6%) 7 (13.0%)	16 (76.2%) 1 (4.8%)
Adverse event leading to study drug being withdrawn, n (%)	2 (3.7%)	1 (4.8%)
Most frequent adverse events (≥15% of patients in either group), n (%)		
Petachiae	14 (25.9%)	6 (28.6%)
Epistaxis	12 (22.2%)	4 (19.0%)
Ecchymosis (bruising)	10 (18.5%)	1 (4.8%)
Headache	10 (18.5%)	4 (19.0%)
Cough	9 (16.7%)	0
Pyrexia	9 (16.7%)	0
Serious adverse event[b], n (%)	5 (9.3%)	1 (4.8%)
Thromboembolic event, n	0	0
CTCAE grade ≥3 bleeding event, n	0	0
Deaths, n	0	0

[a]Headache was the only adverse event considered to be treatment-related by the investigator reported in ≥1 patient (n=4). [b]Two serious adverse events (headache, thrombocytosis) that occurred in one patient in the avatrombopag group were considered treatment-related by the investigator. CTCAE, Common Terminology Criteria for Adverse Events.

Conclusions

- Avatrombopag resulted in significant improvements in the primary efficacy endpoints of **durable platelet response** and **platelet response** compared with placebo
  - Secondary efficacy endpoints were also significantly improved with avatrombopag
- The **safety profile** in children was reassuring with no new safety signals

Avatrombopag may offer **benefits in terms of monitoring and administration**, including the absence of dietary restrictions and ease of oral dosing, thereby reducing treatment burden

Avatrombopag was demonstrated to be an **efficacious and well-tolerated oral TPO-RA for children and adolescents** aged ≥1 and <18 years with **persistent or chronic ITP (≥6 months)** who had an insufficient response to prior therapy

ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.