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)

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Background and Objectives

- Avatrombopag (AVA) is an oral TPO-RA without food-type restrictions[1] widely approved for the treatment of adults with chronic ITP.
- The aim of this study is to assess the efficacy and safety of AVA in children and adolescents with ITP of ≥6 months with insufficient response to a previous treatment.

Methods

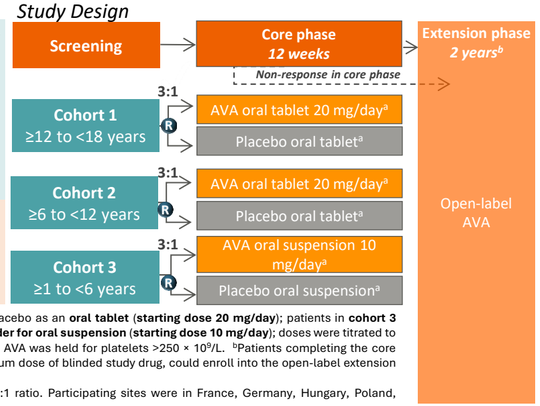
Multicenter Phase 3b Double-Blind Placebo- Controlled Trial (NCT04516967) [2]

Participants

- Subjects >1 to <18 years
- ITP of ≥6 months duration
- Insufficient response to previous treatment
- Mean platelet counts (PC) <30×10^9/L (from two PC during screening) with no single count PC >35×10^9/L.

- Secondary ITP
- Enrollment in another clinical study with any investigational drug or device within 30 days prior to this study

Study Design



[a]Patients in **cohorts 1 and 2** received AVA or placebo as an **oral tablet** (**starting dose 20 mg/day**); patients in **cohort 3** received AVA 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. AVA was held for platelets >250 × 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]

Primary 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 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 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

[a] An alternative primary efficacy endpoint was included to meet the requirements of the EU regulatory authorities.

RESULTS

Figure 1: Patient disposition

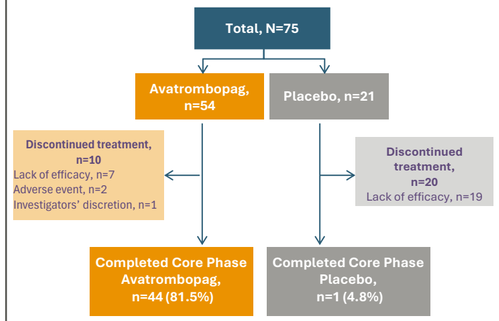
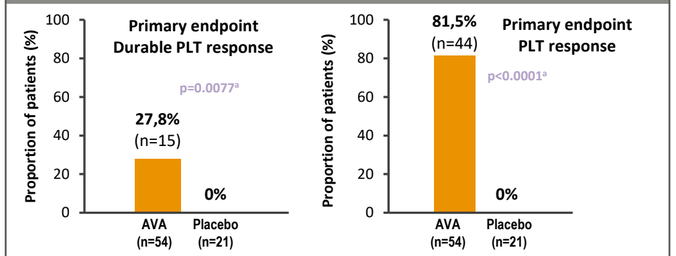


Table 1. Baseline demographics and clinical characteristics

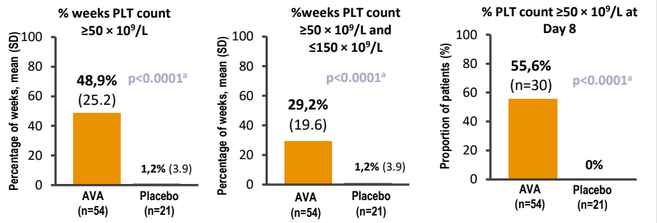
	AVA n = 54	Placebo n=21
Female, n (%)	24 (44.4)	12 (57.1)
Age, years (mean ± SD)	8.9 ± 4.4	9.9 ± 4.1
Race, n (%) White Asian	 48 (88.9) 3 (5.6)	 15 (71.4) 1 (4.8)
Platelet count ≤15 × 10^9/L, n (%)	45 (83.3)	17 (81.0)
Platelet count (mean ± SD)	12.0 ± 6.8	11.2 ± 6.6
Bruising or bleeding, n (%)	39 (72.2)	16 (76.2)
WHO bleeding scale for the 7 days prior to baseline, n (%) Grade 1 Grade 2	 36 (66.7) 3 (5.6)	 14 (66.7) 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)

Figure 2: Primary efficacy endpoints: platelet response (core phase)

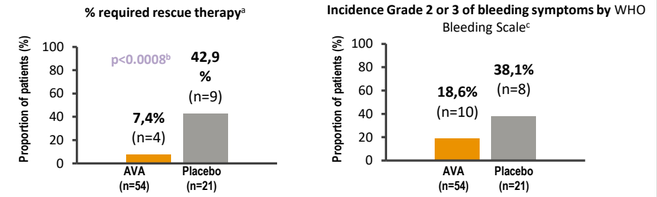


Full analysis set. [a]Cochran-Mantel-Haenszel test

Figure 3: Secondary efficacy endpoints (core phase)

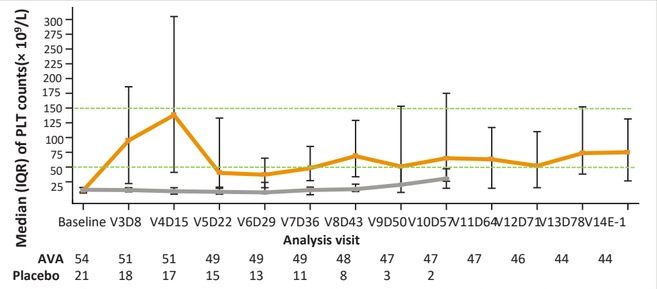


Full analysis set. [a]Non-parametric Wilcoxon rank sum test (continuous data); [b]Cochran-Mantel-Haenszel test (categorical data).



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.

Figure 4: Median platelet counts in the absence of rescue therapy (core phase)



Full analysis set. D, day; E, extension; IQR; interquartile range; V, visit. Dotted line: Target PLT count with AVA. AVA was held for platelets >250 ×10^9/L

Table 2: Safety (core phase)

	AVA n = 54	Placebo n=21
Median treatment duration, weeks	12	6
Any TEAE, n (%) Considered treatment-related by investigator[a]	50 (92.6) 7 (13.0)	16 (76.2) 1 (4.8)
TEAE leading to study drug being withdrawn, n (%)	2 (3.7)	1 (4.8)
Most frequent TEAEs by preferred term (≥15% of patients in either group), n (%)		
Petechiae	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 treatment-related adverse event reported in more than 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; N, total number of patients; n, number of patients; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- AVA resulted in significant improvements in the primary and secondary efficacy endpoints compared with placebo
- AVA was demonstrated to be an efficacious and well-tolerated oral TPO-RA in children and adolescents with ITP ≥6 months
- AVA may offer benefits in terms of monitoring and administration, including the absence of dietary restrictions and ease of oral dosing thereby potentially reducing treatment burden

References

1. Jurczak et al. Br J Haematol. 2018;183:479-90.
2. https://clinicaltrials.gov/study/NCT04516967. Accessed Sep 2024.

Acknowledgments

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Abbreviations

AE, adverse event; **AESI**, adverse event of special interest; **FAS**, full analysis set; **ITP**, immune thrombocytopenia; **IVIg**, intravenous immunoglobulin; **PC**, platelet count; **PLT**, platelet; **SAE**, serious adverse event; **SD**, standard deviation; **TEE**, thromboembolic event; **TPO-RA**, thrombopoietin receptor agonist; **WHO**, World Health Organization.

Disclosures

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