21 August 2025
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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Revolade

Eltrombopag

Procedure no: EMA/PAM/0000274861

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	28 July 2025	29 July 2025
☐	CHMP comments	11 August 2025	11 August 2025
☐	Updated CHMP Rapporteur AR	14 August 2025	14 August 2025
☒	CHMP outcome	21 August 2025	21 August 2025

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List of abbreviations used in the text

AA	Aplastic anemia
AE	Adverse event
AESI	Adverse event of special interest
AKI	Acute kidney injury
ALG	Anti-lymphocyte immunoglobulin
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
ATG	Anti-thymocyte globulin
CHR	Chromosone
CR	Complete response
CsA	Cyclosporine A
CSR	Clinical study report
ECG	Electrocardiograms
EOT	End of treatment
GGT	Gamma-glutamyltransferase increased
G-CSF	Granulocyte colony-stimulating factor
h-ATG	Horse anti-thymocyte globulin
HSCT	Hematopoietic stem cell transplantation
IST	Immunosuppressive therapy
KM	Kaplan-Meier
LPLV	Last participant last visit
OS	Overall survival
PD	Protocol deviation
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
r-ATG	Rabbit anti-thymocyte globulin
RBC	Red blood cell
SAA	Severe aplastic anemia
SOC	System organ class
TPO-R	Thrombopoietin receptor
VSAA	Very severe aplastic anemia

1. Introduction

On 23 May 2025, the MAH submitted a completed paediatric study for Revolade, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

Study CETB115G2201 was an Interventional, non-randomized, open label, multi-center, Phase II study to assess the safety and efficacy of eltrombopag in combination with rabbit anti-thymocyte globulin (r-ATG) and cyclosporine A (CsA) in East-Asian patients with treatment naive severe aplastic anemia. Eight of the 36 total patients were children.

The critical expert overview presents paediatric data collected and reported from the final clinical study report for study CETB115G2201.

No changes to the paediatric information of the current EU Summary of Product Characteristics (SmPC) are proposed based on the results of this study.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that CETB115G2201 is a stand –alone study, which enrolled 36 total patients. Of them, 8 were paediatric patients under 18 yrs.

2.2. Information on the pharmaceutical formulation used in the study

Eltrombopag tablets were supplied to the Investigators by Novartis at dose strengths of 12.5 mg and 25 mg (for more information see Table 2, study treatment batch numbers in next section of this report).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- **Study G2201 (CETB115G2201; REACTS):** A non-randomized, open label, multi-center, Phase II study to assess the safety and efficacy of eltrombopag in combination with rabbit anti-thymocyte globulin (r-ATG) and cyclosporine A (CsA) in East-Asian patients with treatment naive severe aplastic anemia.

The clinical overview submitted by the company summarizes and discuss the results of the efficacy and safety for paediatric participants <18 years of age (N=8).

The results of the pharmacokinetics assessments involving paediatric participants are not within the scope of this report. In addition, efficacy and safety endpoints analysis that were not specifically conducted for the subgroup of paediatric participants <18 years of age but limited to only the overall population enrolled in the study are beyond the scope of the Company's report.

2.3.2. Clinical study

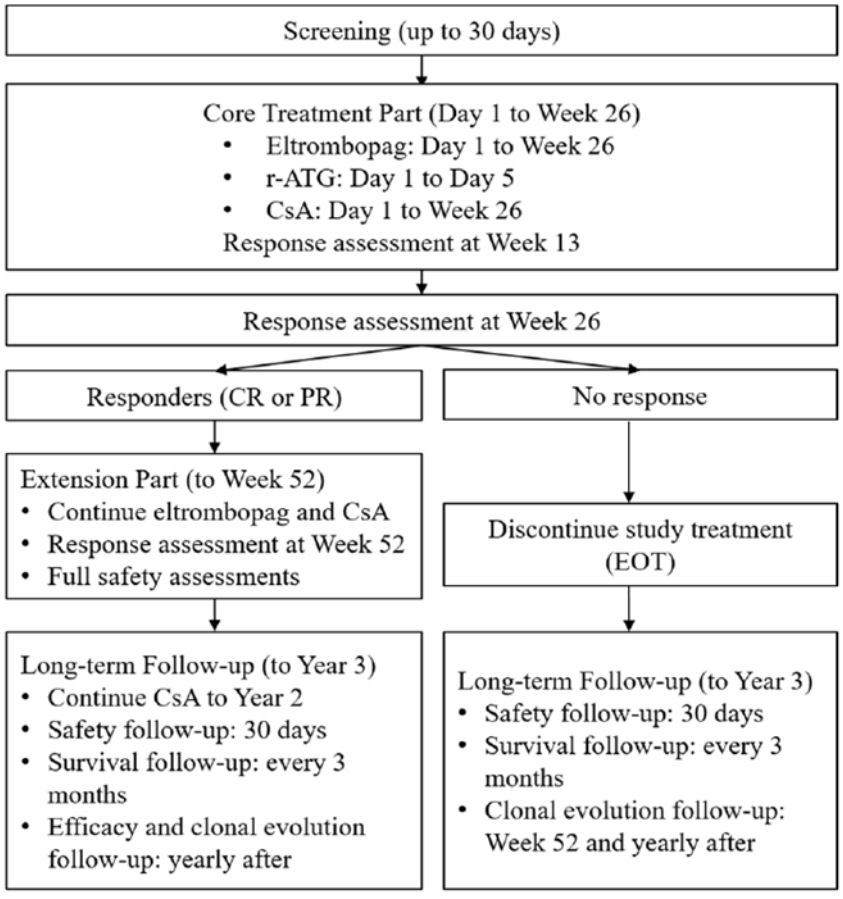
Clinical study number and title

Description

Study G2201 was a non-randomized, open label, single arm, multi-center, Phase II study. This study was designed to evaluate the efficacy and safety of eltrombopag when added to r-ATG and CsA in treatment-naive East-Asian adult and paediatric participants with SAA in Chinese Mainland, Japan, Korea, and Taiwan (Province of China). The study included 3 parts, a core treatment part from Day 1 to Week 26 (the time for primary endpoint assessment), an extension part up to Week 52 for responders (who met the CR or PR criteria at Week 26) and a long-term follow-up part for all participants enrolled.

Figure 1 represents the study design and Table 1 includes all details about study aim, objectives, rationale of study design, study population, inclusion/exclusion criteria, treatments and data analysis. Table 2 includes details about study treatment batch numbers.

Figure 1. Schematic of study design



Source: [Study G2201 Final analysis CSR-Figure 9-1]

Table 1. Summary of study design

Purpose	The purpose of this study was to evaluate the efficacy and safety of eltrombopag when added to r-ATG and CsA in treatment naive East-Asian adult and pediatric participants with SAA.	
	Objective(s)	**Endpoint(s)**
Primary	To evaluate the efficacy of eltrombopag in combination with r-ATG and CsA in terms of complete response rate at 6 months in East-Asian patients with treatment naive SAA.	CR rate at Week 26 (6 months) after starting the study treatment
Secondary	To evaluate complete response rate at 3, 12 months and yearly after	CR rate at Week 13 (3 months), Week 52 (12 months) and yearly after
	To evaluate overall response rate at 3, 6, 12 months and yearly after	Overall response (CR+PR) rate at Week 13 (3 months), Week 26 (6 months), Week 52 (12 months) and yearly after
	To evaluate duration of response	Time from the date of the start of response to the date of relapse or death, whichever occurs first at any time during the study
	To evaluate overall survival	Time from the date of first dose of study treatment to the date of death Overall survival rate at Week 26, Week 52 and yearly after
	To evaluate the need for transfusion (packed RBC units and platelet units)	Time from the most recent transfusion to Week 13 and Week 26* Proportion of participants who become (platelet/RBC) transfusion independent
	To evaluate safety and tolerability of eltrombopag in combination with r-ATG and CsA	Frequency and severity of AEs, SAEs, vital signs, electrocardiogram and laboratory abnormalities
	To evaluate clonal evolution	Time from the date of first dose of study treatment to the date of first occurrence of any of the clonal evolution events up to year 3.
	To determine the pharmacokinetics of eltrombopag in East-Asian treatment naive SAA patients*	Plasma PK parameters and trough concentration of eltrombopag at steady state
Study design	Non-randomized, open label, single arm, multi-center, Phase II study	
Rationale	SAA is a life-threatening bone marrow failure disorder characterized by pancytopenia and hypocellular bone marrow. Despite its rare incidence in the West, SAA is more prevalent in densely populated areas in East-Asia. IST, comprising r-ATG and CsA, is the first-line treatment for SAA patients who are ineligible for HSCT in East-Asian countries. However, incomplete responses, relapses, and primary refractoriness limit the success of IST and highlights the unmet medical need to improve outcomes following first-line IST in East-Asian patients. Eltrombopag, an oral thrombopoietin receptor agonist, has been reported to improve hematological response with an acceptable safety profile, in a phase I/II study (Study number: CETB115AUS01T), where eltrombopag was administered concurrently with h-ATG and CsA in IST naive SAA patients and in another phase II study (Study number: CETB115E1202) where eltrombopag was administered in combination with r-ATG and CsA in Japanese patients with moderate or more severe aplastic anemia who have not received prior ATG/ALG-based IST. Therefore, it is expected that a favorable benefit/risk profile can be derived from the use of eltrombopag in combination with r-ATG and CsA in the treatment of East-Asian treatment naive SAA patients.	
Study population	East-Asian adult and pediatric participants (≥ 6 years old) with treatment-naive SAA who lacked a suitable matched sibling marrow donor or were not allogeneic transplantation candidates due to participant choice, advanced age, or infeasibility of transplantation.	

Table 2. Study treatment batch numbers

Investigational/ combination drug (name and strength)	Pharmaceutical dosage form and route of administration	Supply Type	Batch numbers
Eltrombopag (ETB115) 25 mg	Tablet for oral use	Open label participant packs; bottles	2038615, 2039746, 2041381, 2043431
Eltrombopag (ETB115) 12.5 mg	Tablet for oral use	Open label participant packs; bottles	2038616, 2039747
r-ATG 25 mg	Sterile lyophilized powder in 10 mL vials for intravenous use	Open label participant packs; vials	AW0153, OW0727, AW4319, 9W2783
CsA 25 mg	Capsule for oral use	Open label participant packs; blisters	KK8384, KX3464, LB3249, LE3766
CsA 5.0 g/50 mL*	Solution for oral use	Open label participant packs; bottles	China: Not available Other countries: Local supply

*The CsA solution from Sandoz is not available in China
Source: Appendix 16.1.1-Protocol-Table 6-1, Appendix 16.1.6

Results

Recruitment and baseline data

Overall, 36 participants were enrolled and treated in the study and of them, 8 participants were paediatric participants of <18 years of age. Among the 8 paediatric participants, there were 4 participants each in the 6-11 years and 12-17 years age group, respectively (Table 3).

Table 3. Subject disposition by age subgroup < 18 years (n=8). FAS

	All Subjects n (%)
Core Treatment Part	
Completed	7 (87.5)
Non responders at Week 26	1 (12.5)
Responders (CR or PR) at Week 26	6 (75.0)
Discontinued prematurely	1 (12.5)
Reason for discontinuation	
New therapy for study indication	1 (12.5)
Subjects who entered Extension Part	
Completed	6 (75.0)
Ongoing	0
Discontinued prematurely	0
Reason for discontinuation	

Core Treatment Part : Study Day 1 to Week 26.
Extension Treatment Part : Study Week 26 to Week 52.
Long-term Follow-up : Study End of Treatment to Year 3.
- 4 subjects completed the core treatment part, but they didn't enter the extension part since they were assessed as nor responder at week 26, as per protocol.

Out of 8 participants, 7 (87.5%) completed the core treatment part at Week 26 (Responders = 6 participants; non responders = 1 participant). 1 participant (12.5%) discontinued the study treatment and subsequently initiated a new therapy for the disease. A total of 6 participants (75.0%), completed the extension treatment phase (Week 52). Of the 7 participants (87.5%), who entered the long-term follow-up, 1 participant discontinued from the study due to guardian decision.

The median age in the 6-11 years age group (n=4) was 11 years (min-max: 9-11) and the majority of them were female (3 participants). There were 3 Japanese participants and 1 Chinese participant. The median weight of the participants was 33.2 kg (min-max: 27.6-42.4) [Study G2201 Primary analysis CSR-Table 14.1-2.1.1]. Three participants had SAA and 1 participant had VSAA. Four participants required platelet transfusion, and 3 participants required RBC transfusion due to their underlying disease. Median baseline values of platelet count, hemoglobin, absolute neutrophil count, and absolute reticulocyte count were 55.0 × 109/L, 90.0 g/L, 0.3 × 109/L, and 45 × 109/L, respectively [Study G2201 Primary analysis CSRTable 14.1-2.2.1].

The median age in the 12-17 years age group (n=4) was 16 years (min-max: 15-17) and the majority of them were female (3 participants). There were 2 Japanese participants and 2 Chinese participants. The median weight of the participants was 51.0 kg (min-max: 45.8-99.0) [Study G2201 Primary analysis CSR-Table 14.1-2.1.1]. Two participants had SAA and 2 participants had VSAA. Three participants required platelet transfusion, and 3 participants required RBC transfusion due to their underlying disease. Median baseline values of platelet count, hemoglobin, absolute neutrophil count, and absolute reticulocyte count were 25.0 × 109/L, 66.5 g/L, 0.2 × 109/L, and 7.1 × 109/L, respectively [Study G2201 Primary analysis CSRTable 14.1-2.2.1].

In participants <18 years (N=8), the median duration of exposure for eltrombopag was 327.5 days (min-max: 115-365 days) and the median dose intensity was 37.5 mg/day (min-max: 33.3-75.0 mg/day). Seven participants (87.5%) were exposed to eltrombopag for a duration of > 6-12 months and remaining 1 participant (12.5%) for a period 137 days [Study G2201 Final analysis CSR-Table 14.3-1.1p] [Study G2201 Final analysis CSR-Listing 16.2.5-1.1].

The median duration of exposure for CsA was 729.0 days (min-max: 142-752 days) and the median dose intensity was 214.1 mg/day (min-max: 140.1-229.4 mg/day). Three participants (37.5%) each were exposed to CsA for a duration of > 18 - 24 months and > 24 - 36 months respectively. One participant (12.5%) each were exposed to CsA for a duration of 3 - 6 months and > 6 - 12 months respectively [Study G2201 Final analysis CSR-Table 14.3-1.2p]. The median duration of exposure for r-ATG was 5.0 days (min-max: 5-5 days) and the median dose intensity was 134.8 mg/day (min-max: 85.0-300.0 mg/day) [Study G2201 Final analysis CSRTable 14.3-1.3p].

There was a total of 6 dose adjustments in participants <18 years of age, of which, 3 participants had at least 1 dose adjustment. The reasons for dose adjustment were adverse event (n=1), disease improvement under study (n=1) and physician decision (n=1). There was a total of 4 dose interruptions, of which 3 participants had at least one interruption. The most common reason for dose interruptions was adverse event (n=2) [Study G2201 Final analysis CSRTable 14.3-1.4p].

Efficacy results

The standard criteria of CR as assessed by the Investigator was met by 2 participants (25.0%) at Week 26, of which, 1 participant each, was from 6-11 years and 12-17 years age group respectively [Study G2201 Primary analysis CSR-Table 11-2].

Table 11-2 Hematological response assessed by Investigator by assessment time (FAS)

Assessment time Response	All participants N=36 n (%)	95% CI [1]
Week 13, total n	36	
Complete Response (CR)	2 (5.6)	
Partial Response (PR)	22 (61.1)	
No response/missed response	12 (33.3)	
Relapsed	0	
Overall Response Rate (ORR: CR+PR)	24 (66.7)	(49.0, 81.4)
Week 26, total n	36	
Complete Response (CR)	6 (16.7)	
Partial Response (PR)	22 (61.1)	
No response/missed response	8 (22.2)	
Relapsed	0	
Overall Response Rate (ORR: CR+PR)	28 (77.8)	(60.8, 89.9)
Week 52, total n	36	
Complete Response (CR)	11 (30.6)	
Partial Response (PR)	13 (36.1)	
No response/missed response	11 (30.6)	
Relapsed	1 (2.8)	
Overall Response Rate (ORR: CR+PR)	24 (66.7)	(49.0, 81.4)
Year 2, total n	36	
Complete Response (CR)	11 (30.6)	
Partial Response (PR)	7 (19.4)	
No response/missed response	16 (44.4)	
Relapsed [2]	2 (5.6)	
Overall Response Rate (ORR: CR+PR)	18 (50.0)	(32.9, 67.1)
Year 3, total n	36	
Complete Response (CR)	11 (30.6)	
Partial Response (PR)	4 (11.1)	
No response/missed response	19 (52.8)	
Relapsed [2]	2 (5.6)	
Overall Response Rate (ORR: CR+PR)	15 (41.7)	(25.5, 59.2)

"n" is the number of participants who reached the assessment time or withdrew earlier. It is denominator for percentage (%) calculation.
[1] 95% confidence interval (CI) based on Clopper and Pearson (1934) binomial 95% exact method.
[2] Three relapses reported by Year 2 and Year 3: the additional third participant had 'relapsed' information reported in the response assessment eCRF's 'other' field instead of 'response' field (due to uncertain date of relapse).
Source: Table 14.2-1.3

Supportive analysis that was derived programmatically was conducted for a more stringent definition of CR at Week 26 meeting all the criteria defined in [Study G2201 Final analysis CSR-Appendix 16.1.9-Section 2.5.5]. 1 participant from the 12-17 years subgroup met the stringent criteria of CR at Week 26 [Study G2201 Primary analysis CSR-Table 14.2-1.4.1].

Complete response rate at Week 13, Week 26, Week 52 and yearly after

The standard criteria of CR as assessed by the Investigator was met by [Study G2201 Final analysis CSR-Table 14.2-1.2p]:
- 1 participant (12.5%) (95% CI: 0.3, 52.7) at Week 13
- 2 participants (25.0%) (95% CI: 3.2, 65.1) at Week 26
- 4 participants (50.0%) (95% CI: 15.7, 84.3) at Week 52
- 4 participants (50.0%) (95% CI: 15.7, 84.3) at Year 2
- 5 participants (62.5%) (95% CI: 24.5, 91.5) at Year 3

Table 14.2-1.2p. Study G2201 Final analysis

Complete Response assessed by Investigator by assessment time by Age subgroup
Full Analysis Set

Age: <18 years (N=8)

	All Subjects
Subjects who reached the week 13 visit or withdrew earlier	8
Complete response (CR) -n (%)	1 (12.5)
95% CI [1]	(0.3, 52.7)
Subjects who reached the week 26 visit or withdrew earlier	8
Complete response (CR) -n (%)	2 (25.0)
95% CI [1]	(3.2, 65.1)
Subjects who reached the week 52 visit or withdrew earlier	8
Complete response (CR) -n (%)	4 (50.0)
95% CI [1]	(15.7, 84.3)
Subjects who reached the year 2 visit or withdrew earlier	8
Complete response (CR) -n (%)	4 (50.0)
95% CI [1]	(15.7, 84.3)
Subjects who reached the year 3 visit or withdrew earlier	8
Complete response (CR) -n (%)	5 (62.5)
95% CI [1]	(24.5, 91.5)

The denominator for % calculation of CR was the number of subjects who reached the assessment visit or withdrew earlier.
[1] 95% confidence interval (CI) based on Clopper and Pearson binomial 95% exact method.

Overall response rate (CR+PR) at Week 13, Week 26, Week 52 and yearly after

Overall hematologic response rate (CR+PR), as assessed by the Investigator, was observed in:

- 6 participants (75.0%) (95% CI: 34.9, 96.8) at Week 13
- 6 participants (75.0%) (95% CI: 34.9, 96.8) at Week 26
- 6 participants (75.0%) (95% CI: 34.9, 96.8) at Week 52
- 5 participants (62.5%) (95% CI: 24.5, 91.5) at Year 2
- 6 participants (75.0%) (95% CI: 34.9, 96.8) at Year 3

[Study G2201 Final analysis CSR-Table 14.2-1.3p]:

There was no relapse reported at any time during the study.

Table 14.2-1.3p. Overall haematological response rate at week 52, year 2 and year 3 in paediatric patients.

Hematological Response assessed by Investigator by assessment time by age subgroup
Full Analysis Set

Age: <18 years (N=8)

Assessment time Response	All Subjects n(%)	 95% CI [1]
Week 52, total n	8	
Complete Response (CR)	4 (50.0)	
Partial Response (PR)	2 (25.0)	
No Response (NR)	2 (25.0)	
Relapse	0	
Overall Response Rate (ORR: CR+PR)	6 (75.0)	(34.9, 96.8)
Year 2, total n	8	
Complete Response (CR)	4 (50.0)	
Partial Response (PR)	1 (12.5)	
No Response (NR)	3 (37.5)	
Relapse	0	
Overall Response Rate (ORR: CR+PR)	5 (62.5)	(24.5, 91.5)
Year 3, total n	8	
Complete Response (CR)	5 (62.5)	
Partial Response (PR)	1 (12.5)	
No Response (NR)	2 (25.0)	
Relapse	0	
Overall Response Rate (ORR: CR+PR)	6 (75.0)	(34.9, 96.8)

"n" is the number of subjects who reached the assessment time or withdrew earlier. It is denominator for percentage (%) calculation.
[1] 95% confidence interval (CI) based on Clopper and Pearson binomial 95% exact method.

Duration of response

The median duration of CR (derived programmatically) for the 4 participants who were complete responders at any time during the study was not evaluable. All 4 participants who were complete responders at Week 52 were still responding without any documented relapses at Year 3 [Study G2201 Final analysis CSR-Table 14.2-2.1p].

The median duration of overall response (derived programmatically) for the 6 participants who were overall responders at any time during the study was not achieved from the analysis. 4/6 participants were still responding at last contact with study (either at Year 3 visit or last contact before discontinuation), and 2/6 participants were considered relapsed programmatically as they showed no hematological response. The KM estimated probability of relapse-free time at 30 months was 66.7% (95% CI: 19.5, 90.4) [Study G2201 Final analysis CSR-Table 14.2-2.2p].

Even though 2 participants showed no hematological response (identified as relapsed programmatically), these participants were assessed as PR at Week 26 by Investigators [Study G2201 Final analysis CSR-Listing 16.2.6-1.2] [Study G2201 Final analysis CSRListing 16.2.8-1.1].

Table 14.2-2.1p (Page 1 of 4)
Duration of Complete Response by Age subgroup
Full Analysis Set

Age: <18 years (N=8)

	All Subjects
Number of complete responders at any time	4
Relapsed	0
Still responding	4 (100)
Ongoing	4 (100)
Lost to follow-up	0
Duration of complete response in months - Percentiles (95% CI) [1]	
25th	NE (NE, NE)
50th	NE (NE, NE)
75th	NE (NE, NE)
Relapse-free probability estimates (95% CI) [2]	
6 Months	100 (100, 100)
12 Months	100 (100, 100)
18 Months	100 (100, 100)
24 Months	100 (100, 100)
30 Months	100 (100, 100)
36 Months	NE (NE, NE)

[1] Percentiles with 95% CIs are calculated from PROC LIFETEST output using method of Brookmeyer and Crowley.
[2] Relapse-free probability estimate is the estimated probability that a patient will remain relapse-free up to the specified time point.
- Relapse-free probability estimates are obtained from the Kaplan-Meier survival estimates.Greenwood formula is used for CIs of KM estimates, where the log-log link function is used .
- NE = Not estimable
- Relapse: Relapse specifically refers to the loss of Complete Response
- Ongoing: Patients remained CR at the last planned investigator assessment (Year 3)
- Lost to Follow-up: Patients remained CR without further investigator assessment due to premature discontinuation or lost to follow-up before Year 3.

Overall survival

There were no deaths reported during the study. The median duration of OS was not evaluable from the KM analysis. The KM estimated probability of survival at 36 months was 100.0% (95% CI: 100.0, 100.0) [Study G2201 Final analysis CSR-Table 14.2-2.3p].

Transfusion-free interval (packed RBC and platelet) before Week 13 and Week 26

The median RBC transfusion-free interval was 26.0 days (min-max: 4-92 days) before Week 13 and 117.0 days (min-max: 14-183 days) before Week 26 [Study G2201 Primary analysis CSRTable-14.2-2.4.1]. The median platelet transfusion-free interval was 26.5 days (min-max: 2-66 days) before Week 13 and 131.0 days (min-max: 6-157 days) before Week 26 [Study G2201 Primary analysis CSR-Table-14.2-2.4.1].

Proportion of participants who become (packed RBC/platelet) transfusion independent

RBC transfusion independent

Out of 6 participants who had transfusion dependency at baseline, 4 participants achieved transfusion independence post-baseline (transfusion free for a period of at least 56 days) [Study G2201 Final analysis CSR-Table 14.2-2.8p].

The proportion of RBC transfusion dependent participants at baseline, showing ≥ 50% transfusion decrease or becoming transfusion free increased from 2 participants at Week 13 to 4 participants at Week 26 and remained at 4 participants for Week 52, Week 104 and Week 156 respectively [Study G2201 Final analysis CSR-Table 14.2-2.6p].

Platelet transfusion independent

Out of 7 participants who had transfusion dependency at baseline, 5 participants achieved transfusion independence post-baseline (transfusion free for a period of at least 28 days) [Study G2201 Final analysis CSR-Table 14.2-2.7p].

The proportion of participants (who were platelet transfusion dependent at baseline) showing a transfusion decrease (or free) was 6 participants at Week 13, 6 participants at Week 26, 5 participants at Week 52, 4 participants at Week 104 and 5 participants at Week 156 [Study G2201 Final analysis CSR-Table 14.2-2.5p].

The proportion of platelet transfusion dependent participants showing a ≥ 50% transfusion reduction compared to baseline was 3 participants at Week 13, 6 participants at Week 26, 5 participants at Week 52, 4 participants at Week 104 and 5 participants at Week 156 [Study G2201 Final analysis CSR-Table 14.2-2.5p].

Changes in platelet count, hemoglobin, and neutrophil count in absence of transfusion and changes in reticulocyte count from baseline

An improvement in platelet count (in the absence of platelet transfusion), hemoglobin levels (in the absence of RBC transfusion), neutrophil count (in the absence of G-CSF) and reticulocyte count was observed for all participants (n=8) at Week 13 compared to baseline. The trend continued at Week 26, Week 52 and during long term follow-up (Year 2 and Year 3 respectively).

Median platelet count increased from 42.5 × 109/L at baseline to 58.0 × 109/L, 86.5 × 109/L, 133.5 × 109/L, 148.0 × 109/L, and 148.5 × 109/L at Week 13, Week 26, Week 52, Year 2, and Year 3 respectively [Study G2201 Final analysis CSR-Table 14.2-2.12p].

Median hemoglobin increased from 78.0 g/L at baseline to 91.0 g/L, 112.5 g/L, 110.5 g/L, 124.0 g/L, and 136.0 g/L at Week 13, Week 26, Week 52, Year 2, and Year 3 respectively [Study G2201 Final analysis CSR-Table 14.2-2.13p].

Median neutrophil count increased from 0.3 × 109/L at baseline to 1.1 × 109/L, 1.7 × 109/L, 1.9 × 109/L, 2.2 × 109/L, and 2.8 × 109/L at Week 13, Week 26, Week 52, Year 2 and Year 3 respectively [Study G2201 Final analysis CSR-Table 14.2-2.14p].

Median absolute reticulocyte count increased from 11.5 × 109/L at baseline to 82.3 × 109/L, 48.0 × 109/L, 51.7 × 109/L, 64.7 × 109/L, and 72.5 × 109/L at Week 13, Week 26, Week 52, Year 2 and Year 3 respectively [Study G2201 Final analysis CSR-Table 14.2-2.15p].

Safety results

Overview of adverse events

An overview of the adverse events is presented in Table 4.

Category	All Subjects N=8 All grades n (%)	Grade >=3 n (%)
Adverse events	8 (100)	5 (62.5)
Suspected to be related to eltrombopag	7 (87.5)	4 (50.0)
Suspected to be related to study treatment	8 (100)	5 (62.5)
SAEs	3 (37.5)	3 (37.5)
Suspected to be related to eltrombopag	1 (12.5)	1 (12.5)
Suspected to be related to study treatment	2 (25.0)	2 (25.0)
Fatal SAEs	0	0
AEs leading to discontinuation	0	0
AEs leading to dose adjustment/interruption	6 (75.0)	2 (25.0)
Suspected to be related to eltrombopag	2 (25.0)	0
Suspected to be related to study treatment	6 (75.0)	1 (12.5)
AEs requiring additional therapy	8 (100)	5 (62.5)
Suspected to be related to eltrombopag	4 (50.0)	2 (25.0)
Suspected to be related to study treatment	8 (100)	5 (62.5)

Numbers (n) represent counts of subjects.
AEs occurring during treatment or within 30 days of the last dose of eltrombopag are summarized.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 27.1, CTCAE version 4.03.
Source: [Study G2201 Final analysis CSR-Table 14.3.1-1.1p]

Analysis of adverse events

The most reported AEs by PT (> 30% of participants) were constipation, stomatitis, pyrexia and ALT increased (each in 4 participants, 50.0%). This was followed by vomiting, hypertension, hyperuricaemia and febrile neutropenia (each in 3 participants, 37.5%). The most reported ≥ Grade 3 AEs by PT (≥ 25% of participants) were febrile neutropenia (3 participants, 37.5%) followed by ALT increased and serum sickness (each in 2 participants, 25.0%) [Study G2201 Final analysis CSR-Table 14.3.1-1.2p].

All participants (n=8) experienced at least one on-treatment AE in the first 30 days of eltrombopag treatment; there was no trend of increasing frequency observed with any of the reported AEs over time (time period of onset includes > 30 to ≤ 90 days, > 90 to ≤ 180 days, > 180 to ≤ 360 days) [Study G2201 Final analysis CSR-Table 14.3.1-1.2.2p].

The most reported AEs (≥ 25.0% of participants) suspected by the Investigator to be related to study treatment (study treatment included any of the following: eltrombopag, r-ATG, CsA, or combination of these drugs up to the end of Year 2) were ALT increased and hyperuricaemia, (each in 3 participants, 37.5%). This was followed by febrile neutropenia, vomiting, serum sickness, hypersensitivity, pyrexia, cytomegalovirus infection reactivation, renal impairment and hypertension (each in 2 participants, 25.0%). The most reported ≥ Grade 3 AEs suspected by the Investigator to be related to study treatment were febrile neutropenia and serum sickness, (each in 2 participants, 25.0%) [Study G2201 Final analysis CSR-Table 14.3.1-1.4p].

The most reported AEs (≥ 25.0% of participants) suspected by the Investigator to be related to eltrombopag were ALT increased (3 participants, 37.5%) and hyperuricaemia (2 participants, 25.0%). AEs (≥ Grade 3) suspected by the Investigator to be related to eltrombopag were ALT increased, blood alkaline phosphatase increased, lipase increased and hyperuricaemia (each in 1 participant, 12.5%) [Study G2201 Final analysis CSR-Table 14.3.1-1.4.3p].

Death

There were no deaths reported during the study [Study G2201 Final analysis CSR-Listing 16.2.7-1.3].

Serious adverse events

The reported SAEs by PT were herpes zoster, sepsis, hyperuricemia (each in 1 participant, 12.5%) for both all grades and ≥ Grade 3, respectively [Study G2201 Final analysis CSR-Table 14.3.1-1.5p].

Among the reported SAEs, hyperuricaemia was suspected by the investigator to be related to eltrombopag. As of the LPLV date (06-Dec-2024), the reported SAEs were recovered/resolved in all the participants [Study G2201 Final analysis CSR-Listing 16.2.7-1.1].

Adverse events leading to discontinuation

There were no AEs reported that led to discontinuation of participants [Study G2201 Final analysis CSR- Table 14.3.1-1.6p].

Adverse events of special interest

Hepatotoxicity: Hepatotoxicity was reported in 7 participants (87.5%). The most reported hepatotoxicity related events (≥ 25% of participants) were ALT increased (4 participants, 50.0%) followed by AST increased, blood bilirubin increased, GGT increased (each in 2 participants, 25.0%).

Hyperbilirubinemia was reported in 1 participant (12.5%). Grade 3 hepatotoxicity related events were reported for 3 participants (37.5%) during the study. Hepatotoxicity related events that were suspected by the Investigator to be related to eltrombopag treatment were reported in 6 participants (75.0%). Eltrombopag treatment was interrupted in 2 participants (25.0%). 4 participants (50.0%) required additional medication/therapy due to these events. None of the reported hepatotoxicity related events were serious, fatal or led to eltrombopag withdrawal. As of the LPLV date (06-Dec-2024), the hepatotoxicity related events were recovered/resolved in 6 participants (75.0%) [Study G2201 Final analysis CSR-Table 14.3.1-3.1p].

Acute kidney injury: Acute kidney injury was reported in 5 participants (62.5%). The reported AKI related events were blood creatinine increased and renal impairment (each in 2 participants, 25.0%), followed by blood urea increased, acute kidney injury and renal failure (each in 1 participant, 12.5%).

None of the reported AKI related events were suspected by the Investigator to be related to eltrombopag treatment. None of the reported AKI related events were ≥ Grade 3, serious, fatal or led to eltrombopag withdrawal/interruption. Only 1 participant (12.5%) required additional medication/therapy due to these events. As of the LPLV date (06-Dec-2024), the AKI related events were resolved in all 5 participants (62.5%) [Study G2201 Final analysis CSR-Table 14.3.1-3.9p].

Thromboembolic events: There were no cases of thromboembolic events reported during the study [Study G2201 Final analysis CSR-Table 14.3.1-3.3p].

Clonal evolution/cytogenetic abnormality and haematological malignancy events

There was 1 clonal evolution/cytogenetic abnormality AESIs reported during the post-treatment follow-up period [Study G2201 Final analysis CSR -Listing 16.2.5-1.1], [Study G2201 Final analysis CSR-Listing 16.2.7-1.1], [Study G2201 Final analysis CSR-Listing 16.2.8-1.6], [Study G2201 Final analysis CSR-Listing 16.2.8-1.7]. The participant reported CHR8 abnormalities (in 3% of cells examined) at an unscheduled visit 187 days after last dose of eltrombopag.

Follow-up cytogenic FISH analysis reported normal CHR8 results; the reported cytogenic abnormality AE was reported as resolved after 16 days. There were no cases of haematological malignancies.

One participant reported cytogenetic abnormalities (as assessed by karyotype) that were not considered clinically significant and/or did not lead to clonal evolution/cytogenetic abnormality or hematological malignancy related events. The participant reported 46, XX, del(20q) in 1 out of 20 metaphases at Week 156 [Study G2201 Final analysis CSR-Listing 16.2.8-1.6].

Bone marrow fibrosis was reported in 1 participant at screening and Week 13 visit. However, there was no fibrosis observed at Week 26 [Study G2201 Final analysis CSR-Listing 16.2.8-1.5].

2.3.3. Discussion on clinical aspects

The MAH has provided limited data on long-term efficacy (up to week 26 for primary assessment and up to 3 years for secondary assessment) in 8 Asian paediatric participants with treatment-naïve severe

aplastic anaemia in study G2201. A CR rate of 12.5%, as observed by the Investigator at Week 13, improved to 25.0% at Week 26. The CR further improved and remained at 50.0% at Week 52 and Year 2. At Year 3, the CR rate was 62.5%. All 4 participants who were complete responders at any time were still responding without any documented relapses at Year 3. The overall haematological response rate as observed by the Investigator was consistent and remained at 75.0% from Week 13 up to Week 52 and at Year 3. The rate dropped to 62.5% at Year 2 alone.

Treatment with eltrombopag tended to prolong the transfusion-free interval of packed RBC and platelets and increased the proportion of paediatric participants who became packed RBC and platelet transfusion independent. An improvement relative to baseline was observed in Platelet, neutrophil and reticulocyte counts, and haemoglobin levels at Week 26, Week 52 and during long-term follow-up. However, the data are too scarce to draw any meaningful conclusion.

The safety profile of eltrombopag in paediatric participants was consistent with the established safety profile. No new safety signals were detected. There were no deaths reported during the study. The median duration of OS was not evaluable from the KM analysis. The KM estimated probability of survival at 36 months was 100.0% (95% CI: 100.0, 100.0)

Based on the final results of Study CETB115G2201, the benefit-risk profile of eltrombopag in the approved indications remains unchanged and no changes to the approved Summary of Characteristics are proposed.

The rapporteur agrees with the MAH that no further action is required.

3. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required.