23 April 2026
EMADOC-1700519818-2802866
Human Medicines Division

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

Ultomiris

Ravulizumab

Procedure no: EMA/PAM/0000316561

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	2 February 2026	5 February 2026
☐	CHMP comments	16 February 2026	N/A
☐	Updated CHMP Rapporteur AR	19 February 2026	N/A
☐	CHMP outcome	26 February 2026	26 February 2026
☐	Submission of responses	24 March 2026	24 March 2026
☐	Restart date	25 March 2026	25 March 2026
☐	CHMP Rapporteur AR	8 April 2026	9 April 2026
☐	CHMP comments	13 April 2026	N/A
☐	Updated CHMP Rapporteur AR	16 April 2026	N/A
☒	CHMP outcome	23 April 2026	23 April 2026

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1. Introduction

On 27 November 2025, the MAH submitted a completed paediatric study for Ultomiris (ravulizumab), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measures.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Ravulizumab is a recombinant humanized monoclonal antibody, highly selective for binding to human complement component C5, and a potent antagonist of terminal complement activity. Ravulizumab is approved in the European Union for the treatment of Paroxysmal Nocturnal Haemoglobinuria (PNH), atypical Haemolytic Uremic Syndrome (aHUS), generalised Myasthenia Gravis (gMG) and Neuromyelitis Optica Spectrum Disorder (NMOSD).

The MAH stated that study ALXN1210-TMA-314 is part of an ongoing clinical development program in investigating the use of ravulizumab for the treatment of paediatric and adult patients with Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplantation (HSCT).

The MAH is also conducting Study ALXN1210-TMA-313, a Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicentre Study of Ravulizumab in Adult and Adolescent Participants who have TMA after HSCT. A line listing of all the studies included in the development program is included below:

Table 1. Studies included in the development program

Study title	Study number	Date of completion	Date of submission of final study report
A Phase 3, Open-label, Single-Arm, Multicenter Study of Ravulizumab in Addition to Best Supportive Care in Pediatric Participants (from 1 month to <18 years of age) with Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplantation (HSCT)	ALXN1210-TMA-314	27-May-2025	By 27-Nov-2025
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Ravulizumab in Adult and Adolescent Participants who have Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplant (HSCT)	ALXN1210-TMA-313	Primary evaluation period completed on 19 Sep 2025, follow up period ongoing	Within 6 months of last patient last visit in accordance with Art 46 of European Paediatric Regulation

2.2. Information on the pharmaceutical formulation used in the study

Ravulizumab is approved in the European Union for intravenous infusion administration as a concentrate for solution for infusion (300 mg/30 mL; 1,100 mg/11 mL; 300 mg/3 mL) containing 300 mg, or 1,100 mg of ravulizumab.

The formulation used in study ALXN1210-TMA-314 is the 300 mg/30 mL vial (10 mg/ml concentrated solution).

Participants received body weight-based dosages of ravulizumab IV for 26 weeks during the Treatment Period; loading doses on Days 1, 5, and 10 followed by maintenance dosing on Day 15 and Q8W thereafter for participants weighing [redacted], or Q4W for participants weighing [redacted]. All participants received BSC for the duration of the study.

Table 2. Ravulizumab body weight-based dosage regimen

Weight	Loading Phase Doses			Maintenance Doses
	Day 1	Day 5	Day 10	Starting Day 15
5 to < 10kg	600mg	300mg	300mg	400mg q4w[a]
10 to < 20kg	600mg	300mg	300mg	800mg q4w[a]
20 to < 30kg	900mg	300mg	300mg	2100mg q8w
30 to < 40kg	1200mg	300mg	300mg	2700mg q8w
40 to < 60kg	2400mg	600mg	600mg	3000mg q8w
60 to < 100kg	2700mg	900mg	900mg	3300mg q8w
≥100kg	3000mg	900mg	900mg	3600mg q8w

[redacted]

[a]Following a DCA (dose simulation exercise) after the first 10 participants (including at least 3 participants [redacted]) received body weight-based ravulizumab, maintenance doses for participants in the weight ranges [redacted] and [redacted] were increased from [redacted] to 400 mg q4w and from [redacted] to 800 mg q4w, respectively.

Body weight-based supplemental doses of ravulizumab were allowed during the Treatment Period, following administration of the first maintenance dose on Day 15 for participants who [redacted] and for participants who demonstrated clinical worsening.

Table 3. Timing of supplemental dosing

Weight	Timing of Assessment for [redacted] Supplemental Dose
[redacted]	2 weeks (± 3 days) after each maintenance dose (ie, Days 29, 57, 85, 113, 141, and 169)[a]
	4 weeks (± 3 days) after each maintenance dose (ie, Days 43, 99, and 155)[a]
	4 weeks (± 3 days) after each maintenance dose (ie, Days 43, 99, and 155)[a]

[a] The supplemental dose must have been administered within the same window noted above for each weight categories. If supplemental dosing was required at the same time as a scheduled study visit, the dosing could take place at that visit.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- ALXN1210-TMA-314: A Phase 3, Open-label, Single Arm, Multicentre Study of Ravulizumab in Addition to Best Supportive Care in Paediatric Participants (from 1 month to <18 years of age) with Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplantation (HSCT).

2.3.2. Clinical study

ALXN1210-TMA-314

Description

Study ALXN1210-TMA-314 was an open-label, single arm, multicentre study conducted to evaluate the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of ravulizumab in addition to best supportive care (BSC) in paediatric participants (from 1 month to < 18 years of age) with HSCT-TMA.

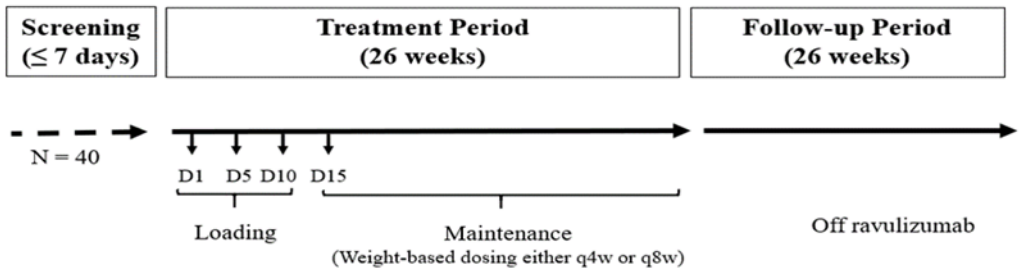
The first patient was enrolled on 07 Dec 2020 and the last patient's final study visit occurred on 27 May 2025. The release date of the CSR was 31 Oct 2025.

The study planned to enrol approximately 40 participants (a minimum of 5 participants ≥ 28 days to < 2 years of age, 10 participants ≥ 2 years to < 12 years of age, and 10 participants ≥ 12 years to < 18 years of age were planned to be enrolled), with at least 35 participants evaluable for the primary analysis.

Participants received body weight-based dosages of ravulizumab intravenously (IV) (see Figure 1) for 26 weeks during the Treatment Period; loading doses on Days 1, 5, and 10 followed by maintenance dosing on Day 15 and once every 8 weeks (q8w) thereafter for participants weighing [redacted], or once every 4 weeks (q4w) for participants weighing [redacted]. All participants received BSC for the duration of the study.

After completion of the 26-week Treatment Period, all participants entered the 26-week Follow up Period and remained in the study for 26 weeks without further ravulizumab administration. In the case of clinical need for extended treatment (eg, TMA response late in the 26-week Treatment Period), the Investigator and the Alexion Medical Monitor may have mutually agreed on additional dosing into the Follow-up Period based on the body weight-based dosage regimen.

Figure 1. Study Schema



	Loading			Maintenance
5 to < 10 kg	D1 = 600 mg	D5 = 300 mg	D10 = 300 mg	400 mg q4w
10 to < 20 kg	D1 = 600 mg	D5 = 300 mg	D10 = 300 mg	800 mg q4w
20 to < 30 kg	D1 = 900 mg	D5 = 300 mg	D10 = 300 mg	2100 mg q8w
30 to < 40 kg	D1 = 1200 mg	D5 = 300 mg	D10 = 300 mg	2700 mg q8w
40 to < 60 kg	D1 = 2400 mg	D5 = 600 mg	D10 = 600 mg	3000 mg q8w
60 to < 100 kg	D1 = 2700 mg	D5 = 900 mg	D10 = 900 mg	3300 mg q8w
≥ 100 kg	D1 = 3000 mg	D5 = 900 mg	D10 = 900 mg	3600 mg q8w

Source: Appendix 16.1.1, Protocol Figure 1

Dose Justification

Prior to initiation of the ALXN1210-TMA-313 or ALXN1210-TMA-314 studies, ravulizumab clinical data were not available in patients with HSCT-TMA. Studies of eculizumab in patients with severe HSCT-TMA indicated the need for higher and more frequent doses in this population than the currently approved eculizumab dosing regimen. The need for larger and more frequent doses is believed to be due to

greater circulating C5 caused by the severe and continuous endothelial damage leading to complement activation, as well as more frequent bleeding events necessitating [redacted] and resulting in faster eculizumab clearance.

The objective for dose selection in this complement-amplified population is to ensure immediate, complete, and sustained terminal complement inhibition. Using the final aHUS population PK model, simulations were conducted assuming similar ravulizumab clearance changes as seen with eculizumab over the first few weeks of treatment. The initial dosing regimen was predicted to maintain ravulizumab drug concentrations above the target PK threshold to ensure immediate, complete, and sustained terminal complement inhibition.

Given the large safety margin for ravulizumab observed in the PNH and aHUS programs to date, the focus of dose selection was to ensure sufficient ravulizumab plasma concentrations to sustain complete suppression of serum free C5 at all times. To accomplish this, modelling and simulation were employed using both ravulizumab data and data from experience with eculizumab in patients with HSCT-TMA.

The adequacy of the initial dose regimen and supplemental dosing regimen was confirmed using PK/PD data from 10 participants of ALXN1210-TMA-314. After the first 10 participants (including at least 3 participants [redacted]) received body weight-based initial dose, a preliminary PK/PD dose confirmation analysis (DCA) was conducted. This DCA confirmed that the initial ravulizumab dosage regimen and [redacted]supplemental dosing achieved and maintained complete terminal complement inhibition throughout the dosing interval. However, based on this DCA, only maintenance doses for participants in the weight ranges [redacted] kg and [redacted] kg were increased from [redacted] to 400 mg q4w and from [redacted] to 800 mg q4w, respectively.

Methods

Study participants

Main **inclusion criteria**:

1. Participant must be ≥ 28 days of age up to < 18 years of age at the time of signing the informed consent or assent form.
2. Paediatric participants who received HSCT within the past 12 months at the time of Screening.
3. Participants must have HSCT-TMA that persists for at least 72 hours after initial management of any triggering agent/condition (including withdrawal or dose reduction of the triggering agent [e.g., CNIs]; treatment of any underlying infection; or treatment of underlying GVHD).
4. A TMA diagnosis, based on meeting all of the following criteria during the Screening Period and/or ≤ 14 days prior to the Screening Period:
    a. De novo thrombocytopenia or transfusion refractoriness, defined as the presence of one or more of the following 3 conditions:
        i. Reduction in platelet count ≥ 50% from pre-TMA value
        ii. Platelet count ≤ 50000/mm^3
        iii. Increased platelet transfusion dependence as shown by a rise of less than 10 × 10^9/L 24 hours post-transfusion
    b. Any one of the following markers of haemolysis:

i. LDH > ULN for age

ii. Presence of schistocytes ≥ 2 HPF or ≥ 1% in peripheral blood smear

c. Proteinuria on spot urinalysis where proteinuria is defined as protein/creatinine ratio ≥ 1 mg/mg.

d. De novo anaemia OR the presence of hypertension, where:

i. De novo anaemia is defined as the presence of any one of the following 3 conditions: 1) A new decline in haemoglobin to ≤ 10 g/dL; 2) A > 1.5 g/dL drop in haemoglobin over any 14 day period; or 3) An increased transfusion dependence, defined as the need to administer transfusions in order to maintain haemoglobin at the clinically determined transfusion threshold;

ii. Hypertension is defined as the presence of any one of the following 3 conditions: 1) Systolic or diastolic blood pressure that is ≥ 95th percentile for age, sex, and height on 2 consecutive measurements taken at least 1 minute apart; 2) Requirement for new antihypertensive medication after HSCT (for a participant not on antihypertensive medication prior to HSCT); or 3) For participants with underlying hypertensive disease, a change in their antihypertensive regimen or the addition of new antihypertensive agents required to treat hypertension.

5. Body weight ≥ 5 kg at Screening or ≤ 7 days prior to the start of the Screening Period (date of consent).

6. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

7. Participants must be vaccinated against meningococcal infections if clinically feasible, according to national guidelines and recommendations for immune reconstitution after HSCT (if national guidelines and recommendations are not available, international guidelines or institutional guidelines must instead be followed). Participants must be revaccinated against Haemophilus influenzae type b (Hib) and Streptococcus pneumoniae if clinically feasible, according to institutional guidelines for immune reconstitution after HSCT. All participants should be administered coverage with prophylactic antibiotics according to institutional post-transplant infection prophylaxis guidance including coverage against N meningitidis for at least 2 weeks after meningococcal vaccination. Participants who cannot receive meningococcal vaccine should receive antibiotic prophylaxis coverage against N meningitidis the entire Treatment Period and for 8 months following the final dose of ravulizumab.

8. Participants or their legally authorized representative must be capable of giving signed informed consent or assent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent or assent form and in this protocol.

Main **exclusion criteria**:

1. Known familial or acquired ADAMTS13 deficiency (activity < 5%).

2. Known Shiga toxin-related haemolytic uremic syndrome (ST-HUS) as demonstrated by a positive test for Shiga toxin or culture of Shiga toxin-producing bacteria.

3. Positive direct Coombs test result which in the judgment of the Investigator is indicative of a clinically significant immune-mediated haemolysis not due to TMA.
4. Clinical diagnosis of disseminated intravascular coagulation (DIC) in the judgment of the Investigator, utilizing the ISTH scoring criteria.
5. Known bone marrow/graft failure for the current HSCT.
6. Diagnosis of venoocclusive disease (VOD), unresolved at the time of Screening, according to the EBMT criteria.
7. HIV infection evidenced by a positive HIV-1 or HIV-2 antibody titer. A documented negative HIV-1/HIV-2 test within 6 months prior to Screening is acceptable to confirm eligibility.
8. Unresolved meningococcal disease.
9. Presence of sepsis requiring vasopressor support within 7 days prior to enrolment.
10. Pregnancy or breastfeeding.
11. Hypersensitivity to murine proteins or to 1 of the excipients of ravulizumab.
12. Any ongoing or history of medical or psychological conditions unrelated to HSCT-TMA that, in the opinion of the Investigator or Alexion Medical Monitor, could increase the risk to the participant by participating in the study or confound the outcome of the study. This includes, but is not limited to, major cardiac, pulmonary, renal, endocrine, or hepatic disease (e.g., active hepatitis).
13. Respiratory failure from any cause requiring mechanical ventilation (including intubation, bilevel positive airway pressure [BiPAP], or continuous positive airway pressure [CPAP]) within 72 hours prior to enrolment.
14. Previously or currently treated with a complement inhibitor.
15. Participation in an interventional treatment study of any therapy (approved or unapproved) being evaluated for TMA within 30 days before Day 1 in this study or within 5 half-lives of that interventional treatment, whichever is greater.

Treatments

Participants received body weight-based dosages of ravulizumab IV for 26 weeks during the Treatment Period; loading doses on Days 1, 5, and 10 followed by maintenance dosing on Day 15 and q8w thereafter for participants weighing [redacted] kg, or q4w for participants weighing [redacted] kg. All participants received BSC for the duration of the study.

Ravulizumab body weight-based dosage regimen is explained in Table 2.

Body weight-based supplemental doses of ravulizumab were allowed during the Treatment Period following administration of the first maintenance dose on Day 15 for participants following [redacted] and for participants who demonstrated clinical worsening. Timing of supplemental dosing is included in Table 3.

Objective(s)

Primary objective:

To assess the efficacy of ravulizumab plus BSC in the treatment of paediatric participants with HSCT-TMA.

Secondary efficacy objectives:

- To characterize TMA response after treatment with ravulizumab
- To assess improvement in organ dysfunction
- To assess TMA relapse
- To assess overall survival
- To assess non-relapse mortality

Pharmacokinetics and Pharmacodynamics objectives:

To assess PK/PD of ravulizumab in paediatric participants with HSCT-TMA.

Safety Objectives:

To characterize the safety profile of ravulizumab plus BSC in paediatric participants with HSCT-TMA.

Exploratory objectives:

- To assess biomarkers in paediatric participants with HSCT-TMA
- To assess improvement in QoL patient-reported outcomes in paediatric participants with HSCT-TMA
- To describe health resource utilization in paediatric participants with HSCT-TMA
- To assess complement pathway genetic mutations in paediatric participants with HSCT-TMA

Outcomes/endpoints

Table 4. Study ALXN1210-TMA-314 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of ravulizumab plus BSC in the treatment of paediatric participants with HSCT-TMA	• TMA response during the 26-week Treatment Period
Secondary	
To characterize TMA response after treatment with ravulizumab	• Time to TMA response during the 26-week Treatment Period • TMA response and time to response for each individual component of TMA response during the 26-week Treatment Period • Hematologic response during the 26-week Treatment Period • Time to hematologic response during the 26-week Treatment Period • Haemoglobin response during the 26-week Treatment Period • Platelet response during the 26-week Treatment Period • Partial response during the 26-week Treatment Period • Loss of TMA response during the 26-week Treatment Period • Duration of TMA response during the 26-week Treatment Period and through 52 weeks • Changes from baseline during the 26-week Treatment Period and through 52 weeks in the following: – Haptoglobin – Platelets – LDH – Haemoglobin • [redacted] during the 26-week Treatment Period
To assess improvement in organ dysfunction	• Change from baseline in TMA-associated organ dysfunction in renal system, cardiovascular system, pulmonary system, CNS, and GI system through 26 weeks and 52 weeks
To assess TMA relapse	• TMA relapse during the Follow-up Period

Objectives	Endpoints
To assess OS	• OS by Day 100, 26 weeks, and 52 weeks
To assess non-relapse mortality	• Non-relapse mortality by Day 100, during the 26-week Treatment Period, and through 52 weeks
Pharmacokinetics and Pharmacodynamics	
To assess PK/PD of ravulizumab in paediatric participants with HSCT-TMA	• Serum concentrations of ravulizumab over time • Changes in serum free C5 concentrations over time • Changes in serum total C5 concentrations over time
Safety	
To characterize the safety profile of ravulizumab plus BSC in paediatric participants with HSCT-TMA	• Incidence of treatment-emergent AEs and treatment-emergent SAEs • Changes from baseline in vital signs and laboratory parameters • Incidence of ADAs and assessment of immunogenicity

Abbreviations: ADA = antidrug antibody; AE = adverse event; BSC = best standard of care; CNS = central nervous system; GI = gastrointestinal; HSCT-TMA = thrombotic microangiopathy post hematopoietic stem cell transplant; LDH = lactate dehydrogenase; OS = overall survival; PD = pharmacodynamics; PK = pharmacokinetics; SAE = serious adverse event; TMA = thrombotic microangiopathy

Definition of endpoints:

TMA response: For TMA response participants must have met each response criterion of the following table, with each parameter meeting the requirement at 2 separate assessments obtained at least 24 hours apart, and any measurement in between.

		TMA Response Parameter
TMA response	Hematologic response	If baseline platelet count ≤ 50000/mm^3, all of the following criteria must be met: • Absolute platelet count > 50000/mm^3 without platelet transfusion support during the prior 7 days If baseline platelet count > 50000/mm^3, all of the following criteria must be met: • ≥ 50% increase in platelet count compared to baseline value without platelet transfusion support during the prior 7 days
		Normalization of LDH and absence of schistocytes[a]
	Renal response	At least 50% reduction of proteinuria from baseline

[a] Schistocytes of ≤ 1% or a result of "none" should be considered the "absence of schistocytes" in alignment with the International Council for Standardization in Hematology recommendations for schistocyte counting (Zini, 2021).

[redacted], participants must [redacted] response criterion [redacted] at 2 separate assessments obtained at least 24 hours apart, and any measurement in between.

[redacted]	[redacted]	If baseline platelet count ≤ 50000/mm^3, the following criteria must be met: • Absolute platelet count > 50000/mm^3 without platelet transfusion support during the prior 7 days If baseline platelet count > 50000/mm^3, the following criteria must be met: • ≥ 50% increase in platelet count compared to baseline value without platelet transfusion support during the prior 7 days
	[redacted]	[redacted]
	Renal response	At least 50% reduction of proteinuria from baseline

[a] [redacted]s" in alignment with the International Council for Standardization in Hematology recommendations for [redacted]

Haematological response: The predetermined criteria for hematologic response were the criteria considered as "Hematologic response" inside the TMA Response criteria.

Haemoglobin response: Defined as the ability to maintain haemoglobin ≥ 10 g/dL without RBC transfusion support. The criterion must be met at 2 separate assessments obtained at least 24 hours apart, and any measurement in between, and without RBC transfusion support during the prior 7 days.

Platelet response: Is defined according to the following criteria:

If baseline platelet counts <50000/mm^3, all of the following criteria must be met:

- Absolute platelet count > 50000/mm^3 without platelet transfusion support during the prior 7 days.

If baseline platelet count > 50000/mm^3, all of the following criteria must be met:

- ≥ 50% increase in platelet count compared to baseline value without platelet transfusion support during the prior 7 days.

Participants must have met each response criterion, with each parameter meeting the requirement at 2 separate assessments obtained at least 24 hours apart, and any measurement in between.

Partial response: Partial response was considered when the participant meets ≥ 1, but not all, criteria for TMA response.

Loss of TMA response: For participants that met the criteria for TMA response during the 26-week Treatment Period, loss of TMA response is defined as when the participant fails to meet the criteria for one or more components of TMA response at a subsequent visit during the 26-week Treatment Period. At least one parameter must fail to meet the response criteria at 2 separate assessments obtained at least 24 hours apart, and any measurement in between.

TMA Relapse: For participants that met the criteria for TMA response during the 26-week Treatment Period, TMA relapse was defined as evidence of worsening hematologic and renal dysfunction due to TMA during the post-treatment Follow-up Period that required treatment intervention, as determined by the Investigator.

Non-relapse mortality: A participant's death due to any cause during the study, except for death due to underlying disease progression or relapse.

Sample size

Approximately 40 participants were expected to be enrolled in this study, with at least 35 participants evaluable for the primary analysis. This sample size was deemed appropriate to provide complete safety information and the necessary precision level for the planned estimation. Assuming a proportion of participants achieving TMA response of 50%, 40 participants would yield a 95% CI for the proportion of response with a half-width of approximately 16%.

Randomisation and blinding (masking)

This was an open-label, single-arm study of ravulizumab treatment in paediatric patients with TMA after HSCT.

Statistical Methods

The population for the analyses of the study were:

- **Safety Set:** All participants who sign the informed consent and receive at least 1 dose of ravulizumab
- **Full Analysis Set:** All participants who sign the informed consent and receive at least 1 dose of ravulizumab, excluding participants who enrol prior to availability of ST-HUS and ADAMTS13 laboratory results and are subsequently found to be ineligible after enrolment.
- **Pharmacokinetic and Pharmacodynamic Analysis Set:** All participants who sign the informed consent and receive at least 1 dose of ravulizumab and who have evaluable pharmacokinetic or pharmacodynamic data.

The statistical analyses were then performed as follows:

- Efficacy analyses were performed on the FAS.
- The primary efficacy endpoint analysis, as well as selected secondary endpoint analyses, were performed on the Per Protocol Set.
- Safety analyses were performed on the Safety Set.
- Pharmacokinetic and PD analyses were performed on the PK and PD Analysis Set.

Conduct of the study

Protocol amendments

Since the original protocol (dated 25 Mar 2020), 3 global protocol amendments and 5 country-specific amendments have been made for this study. Substantial changes in the conduct of the study are summarized in Table 5.

Table 5. Summary of Protocol Changes

Amendment Number	Summary of Key Changes in the Amendment
Amendment 4.0 (Global) 02 Sep 2024	This amendment incorporated new secondary endpoints of [redacted] OS by Day 100, and non-relapse mortality by Day 100. These endpoints were added based on feedback from the healthcare providers as these data were considered clinically meaningful in this patient population and would support the assessment of the efficacy of ravulizumab in participants with

Amendment Number	Summary of Key Changes in the Amendment
	HSCT-TMA. Other updates in this amendment included: • Modifications from non-substantial Protocol Amendment 3.1, dated 27 Sep 2023 which was released to sites within the EU to address the requirements for transitioning a clinical study under the EU CTR. These changes were also communicated to non-EU sites through Administrative Change Letter 9 (dated 29 Feb 2024). • Updates from Administrative Change Letters 7, 8, and 10 (dated 04 May 2023, 08 Jun 2023, and 21 May 2024, respectively), which were released after Protocol Amendment 3. • Clarifications on other protocol requirements, including but not limited to assessment of acute GVHD status, pregnancy testing, handling of participants with subsequent HSCT. • Addition of text and medical literature references to support the statement that participants with HSCT-TMA were anticipated to experience more bleeding events and require [redacted] than participants with other approved indications for ravulizumab, with respect to the dose confirmation analysis. • The option to perform an interim analysis was introduced. This interim analysis would not impact the progression of the study.
Amendment 3.1 (EU) 27 Sep 2023	This non-substantial amendment addressed the requirements for transitioning a clinical study under the EU CTR. Further modifications included non-substantial changes, minor corrections, and harmonized terminology.
Amendment 3 (Global) 08 Feb 2023	This amendment incorporated the revised dose regimen following the prespecified DCA.
Amendment 2.2 (UK) 13 Apr 2022	In this amendment, revisions were made upon MHRA request to remove the option for Investigators in the UK to enroll participants prior to availability of local or central laboratory results from the ST-HUS screen and ADAMTS13 test and update the requirements for pregnancy exposure/lactation mitigations.
Amendment 2.1 (Not implemented) (UK) 04 Mar 2022	This amendment included changes to the dosing schedules and instructions for supplemental dosing and removal of the requirement for supplemental dosing after platelet transfusion, as done in Protocol Amendment 2, but any changes in Protocol Amendment 2 that were not related to the supplemental dosage regimen were removed.
Amendment 2 (Global) 03 Dec 2021	This amendment was done to allow for participants to be enrolled based on local laboratory assessments to align with current practice patterns for management of TMA patients, update eligibility criteria, and modify the supplemental dosing regimen and requirements.
Amendment 1.1 (UK)	This amendment was done to include COVID-19 risk assessment and COVID-19 vaccine risk assessment language.

Amendment Number	Summary of Key Changes in the Amendment
03 Jun 2021	
Amendment 1 (UK) 29 Sep 2020	This amendment was done to conform with The Medicines for Human Use (Clinical Trials) Regulations 2004 S.I. 2002/1031 as requested by the MHRA.
Original protocol 25 Mar 2020	Not applicable.

Protocol deviations

Table 6. Important Protocol Deviations – All Enrolled Participants

Deviation Category	Ravulizumab (N = 41) n (%)
At least one important protocol deviation	35 (85.4)
Laboratory assessment	17 (41.5)
Safety reporting	17 (41.5)
Investigational product	13 (31.7)
Informed consent	10 (24.4)
Study procedures/tests	8 (19.5)
Eligibility and entry criteria	2 (4.9)
Concomitant medication	1 (2.4)

Note: Percentages were based on the treatment group population and could add to more than 100% if a participant had more than one deviation.
Source: Table 14.1.2.1, Listing 16.2.2.3

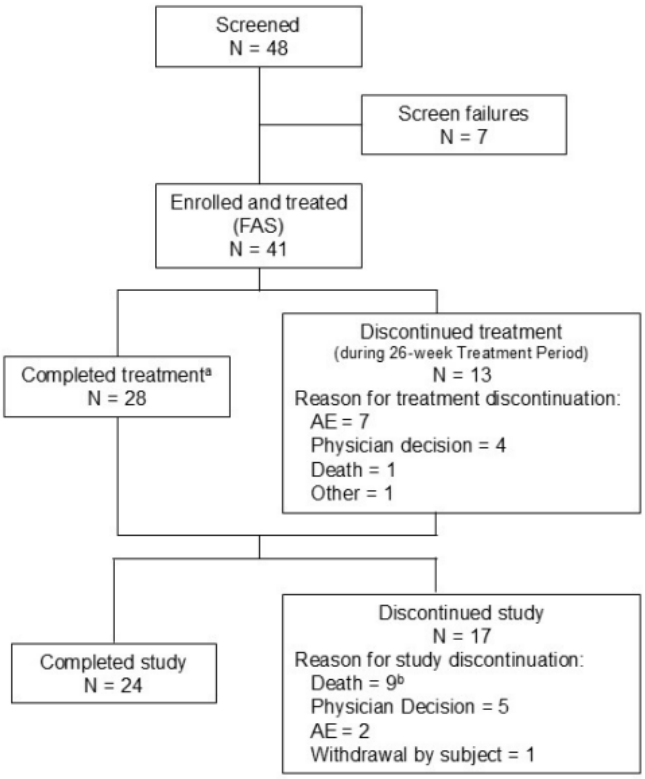
Study site visits were impacted for 2 participants due to COVID-19 (Listing 16.2.2.3).

No important protocol deviations were considered to have impacted the reliability of the study data.

Results

Participant flow

Figure 2. Participant flow



[a] Treatment refers to administration of ravulizumab.
[b] Includes the participant who discontinued study treatment due to death. Two additional deaths occurred after the participants were discontinued from the study. The 2 additional deaths are included in Listing 16.2.7.2 and the OS analysis.

A total of 48 participants were screened, and 41 (85.4%) participants were enrolled in the study. Ravulizumab study treatment was completed by 28 (68.3%) of 41 enrolled participants, while study treatment was discontinued for 13 (31.7%) of 41 participants. Overall, 24 (58.5%) of 41 participants completed the study. At total of 17 (41.5%) of 41 participants discontinued from the study over 52 weeks: Of the 13 participants who discontinued from study treatment, 12 participants also discontinued from the study during the 26-week Treatment Period, while 1 participant remained on the study to complete the Week 26 visit; and 5 of 17 participants discontinued from the study during the 26-week Follow-up period (Table 7).

Table 7. Study Disposition – All Screened Participants

Category	Total n (%)
Screened	48
Screen failures	7 (14.6)
All enrolled participants	41
Treated (Safety Set)	41 (100)
Not treated	0
Completed scheduled study treatment during 26-week Treatment Period	28 (68.3)
Discontinued from study treatment	13 (31.7)
Reason for study treatment discontinuation:	
Adverse event	7 (17.1)
Death	1 (2.4)
Physician decision [a]	4 (9.8)
Other	1 (2.4)
Completed 52-week study	24 (58.5)
Discontinued from study (discontinued during entire study period)	17 (41.5)
Reason for study discontinuation:	
Adverse event	2 (4.9)
Death [b]	9 (22.0)
Physician decision	5 (12.2)
Withdrawal by participant	1 (2.4)
Discontinued study during 26-week Treatment Period	12 (29.3)
Reason for study discontinuation:	
Adverse event	2 (4.9)
Death	5 (12.2)
Physician decision [a]	4 (9.8)
Withdrawal by participant	1 (2.4)
Discontinued study during 26-week Follow-up Period (Week 26 through Week 52)	5 (12.2)
Reason for study discontinuation:	
Death	4 (9.8)
Physician decision [c]	1 (2.4)

Note: Percentages are based on the number enrolled. Percentages for screen failures are based on number screened.
[a] Two participants were discontinued due to TMA improvement, 1 participant changed to treatment with eculizumab, and 1 participant was discontinued because the need for additional dosing could not be confirmed by the central laboratory (Listing 16.2.1.2.1.1).
[b] Includes the participant who discontinued study treatment due to death. Two additional deaths occurred after the participants were discontinued from the study. The 2 additional deaths are included in Listing 16.2.7.2 and the OS analysis.
[c] Participant was discontinued because participant was transferred to new hospital trust (Listing 16.2.1.2.2.1).
Source: Table 14.1.1.1, Table 14.1.2.5, Listing 16.2.1.2.1.1, Listing 16.2.1.2.2.1

No participant discontinued from the study or died due to COVID-19.

Recruitment/Number analysed

The study was initiated at 68 sites globally. Participants were enrolled in 24 sites (participants were screened at 26 sites) across 7 countries (Israel, Italy, Japan, South Korea, Spain, UK, and USA).

Baseline data

Demographic characteristics:

Overall, 21 (51.2%) of 41 participants in the FAS were female, and the median (min, max) age was 6.0 years (0, 17) at Screening. Most participants were White (n = 22 [53.7%]) and 8 (19.5%) participants were Japanese. A total of 14 (34.1%) of 41 participants had GVHD at Baseline, including 8 (19.5%) of 41 participants with Grades I and II and 6 (14.6%) of 41 participants with Grades III and IV.

Table 8. Demographics and Baseline Characteristics – Full Analysis Set

Category	Ravulizumab (N=41)
Sex, n (%)	
N	41
Male	20 (48.8)
Female	21 (51.2)
Race, n (%) [a]	
N	41
White	22 (53.7)
Black or African American	2 (4.9)
Japanese	8 (19.5)
Korean	2 (4.9)
Other Asian	1 (2.4)
Other	6 (14.6)
Age at Screening (years)	
N	41
Mean (SD)	7.6 (5.57)
Median	6.0
Min, max	0, 17
Age at Screening category (years), n (%)	
N	41
28 days to <2 years	7 (17.1)
2 to <6 years	12 (29.3)
6 to <12 years	10 (24.4)
12 to <18 years	12 (29.3)
Baseline weight category (kg), n (%)	
N	41
5 to <10	5 (12.2)
10 to <20	15 (36.6)
20 to <30	4 (9.8)
30 to <40	3 (7.3)
40 to <60	8 (19.5)
60 to <100	6 (14.6)
Geographical region, n (%)	
N	41

Category	Ravulizumab (N=41)
Japan	8 (19.5)
Rest of World	33 (80.5)
Acute GVHD Grade, n (%)	
N	41
No Acute GVHD	27 (65.9)
Acute Grade I-II	8 (19.5)
Acute Grade III-IV	6 (14.6)

Percentages were based on number of participants with nonmissing values in each group.
[a] Multiple races could have been selected.
Source: Table 14.1.4.3

Baseline disease and transplant parameters:

- Median (min, max) time from TMA diagnosis to enrolment was 6.0 (0, 27) days. The majority of participants (90.2%) received acute GVHD prophylaxis (one or more of the following: cyclosporine, mycophenolate mofetil, tacrolimus, cyclophosphamide, corticosteroids, methotrexate, abatacept, sirolimus) at study entry.
- Of the 41 participants, 3 (7.3%) participants were transplanted with autologous and 13 (31.7%) and 25 (61.0%) participants were transplanted with allogeneic related or allogenic unrelated stem cells, respectively.
- Two (4.9%) of 41 participants received dialysis within 5 days of Baseline.
- During the Screening Period, 26 (63.4%) of 41 participants had a platelet transfusion and 21 (51.2%) of 41 participants had pRBC transfusions
- At baseline, 32 (78.0%) of 41 participants had a Urine Protein-to-Creatinine Ratio ≥ 1.0 mg/mg. The median (min, max) UPCR was 2.500 mg/mg (0.24, 29.87).
- Cardiopulmonary signs and symptoms were observed in 29 (70.7%) of 41 participants at Baseline. Among the 29 participants with cardiopulmonary symptoms, the highest proportion was hypertension in 22 (75.9%) participants followed by pericardial effusion in 9 (31.0%) participants (Table 14.1.3.1.2). In addition to the 22 participants with hypertension, another 11 participants had an ongoing medical history of hypertension but were not reported with symptoms at Baseline because they were receiving anti-hypertensive treatment.
- Approximately half of the participants (19 [46.3%] of 41) were reported with GI symptoms, including 2 participants with GI bleeding.
- CNS involvement at baseline was observed in 3 (7.3%) of 41 participants (Table 14.1.3.1.2). There were no cases of PRES.
- The median (min, max) eGFR at baseline was 114.1 mL/min/1.73 m2 (17, 304).
- The median (min, max) haemoglobin level was lower than the normal reference ranges (age-specific) at 8.95 g/dL (5.9, 10.9).
- At baseline, 8 (21.6%) of 41 participants had LDH levels > 2 × ULN. The median (min, max) LDH was above the normal reference ranges (age-specific) at 571.0 U/L (193, 1260).
- At baseline, 11 (26.8%) of 41 participants had platelet counts below 20 × 109 /L and 27 (65.9%) of 41 participants had a platelet count of ≤ 50 × 109 /L. The median (min, max) platelet count was 38000.0/mm3 (4000, 120000).

- Nine (22.0%) of 41 participants had schistocytes present.

Table 9. Disease and Transplant Characteristics and Baseline Organ Dysfunction – Full Analysis Set

HSCT Category	Ravulizumab (N=41) n (%)
Time from TMA diagnosis to enrollment (days)	
N	41
Mean (SD)	6.9 (5.27)
Median	6.0
Min, max	0, 27
Transplant indication for current HSCT	
N	41
Malignancy	9 (22.0)
Hematologic malignancy	18 (43.9)
Non-malignancy	14 (34.1)
Donor type of current HSCT	
N	41
Autologous	3 (7.3)
Allogeneic related	13 (31.7)
Allogeneic unrelated	25 (61.0)
HSCT preparative regimen for current HSCT	
N	41
Yes [a]	40 (97.6)
Myeloablative	28 (70.0)
Non-myeloablative	3 (7.5)
Reduced intensity	6 (15.0)
No	1 (2.4)
Irradiation for current HSCT	
N	41
Yes	14 (34.1)
Total body	13 (92.9)
Total lymphoid or nodal regions	1 (7.1)
No	27 (65.9)

Time from current HSCT to TMA diagnosis (days)	
N	41
Mean (SD)	74.4 (55.34)
Median	57.0
Min, max	3, 240
Number of prior HSCTs per participant	
N	41
0	33 (80.5)
1	6 (14.6)
2	2 (4.9)
>2	0
Acute GVHD prophylaxis at baseline	
N	41
Yes	37 (90.2)
No	4 (9.8)

HSCT Category	**Ravulizumab (N=41) n (%)**
Engraftment achieved at baseline	
N	41
Yes	37 (90.2)
No	4 (9.8)
Initial hematopoietic recovery at baseline [b]	
N	41
Yes	38 (92.7)
No	3 (7.3)
Platelet count at baseline (/mm^3)	
N	41
Mean (SD)	46975.6 (29248.49)
Median	38000.0
Min, max	4000, 120000
Platelet count $\geq 20 \times 10^9$/L at baseline	
N	41
Yes	30 (73.2)
No	11 (26.8)
Platelet count $\leq 50 \times 10^9$/L at baseline	
N	41
Yes	27 (65.9)
No	14 (34.1)
LDH scale factor (Result/ULN)	
N	37
Mean (SD)	1.61 (0.780)
Median	1.50
Min, max	0.4, 4.4
LDH > 2 × ULN at baseline	
N	37
Yes	8 (21.6)
No	29 (78.4)

HSCT Category	Ravulizumab (N=41) n (%)
UPCR (mg/mg creatinine)	
N	41
Mean (SD)	5.477 (6.6345)
Median	2.500
Min, Max	0.24, 29.87
UPCR at baseline ≥ 1 mg/mg [c]	
N	41
Yes	32 (78.0)
No	9 (22.0)
Hemoglobin (g/dL) at baseline	
N	34
Mean (SD)	8.90 (1.149)
Median	8.95
Min, max	5.9, 10.9
Schistocytes present at baseline	
N	41
Yes	9 (22.0)
No	14 (34.1)
Missing	18 (43.9)
Cardiopulmonary symptoms at baseline	
N	41
Yes	29 (70.7)
No	12 (29.3)
CNS involvement at baseline	
N	41
Yes	3 (7.3)
No	38 (92.7)
Presence of PRES at baseline	
N	41
No	41 (100.0)

HSCT Category	Ravulizumab (N=41) n (%)
Gastrointestinal involvement at baseline	
N	41
Yes	19 (46.3)
No	22 (53.7)
Dialysis within 5 days of baseline	
N	41
Yes	2 (4.9)
No	39 (95.1)

Note: Percentages are based on number of participants with nonmissing values in each group. Proteinuria is defined as a protein/creatinine ratio ≥ 0.5 mg/mg.
[a] Multiple responses may be checked per participant. Three participants did not have any regimen reported.
[b] Defined as absolute neutrophil count ≥ 500/mm^3 and sustained for 3 laboratory values.
[c] UPCR of ≥ 1 mg/mg was an eligibility criterion at Screening and not a requirement at Baseline.
Source: Table 14.1.3.1.3, Table 14.1.3.1.2, Listing 16.2.4.2.1.3, Listing 16.2.4.2.2.3, Listing 16.2.4.3.2, Listing 16.2.4.4.1.2, Listing 16.2.4.4.2.2

Additional information on demographics and baseline characteristics and disease and transplant characteristics is provided in Table 14.1.3.1.2, Table 14.1.3.1.4, Table 14.1.4.2, and Table 14.1.4.4.

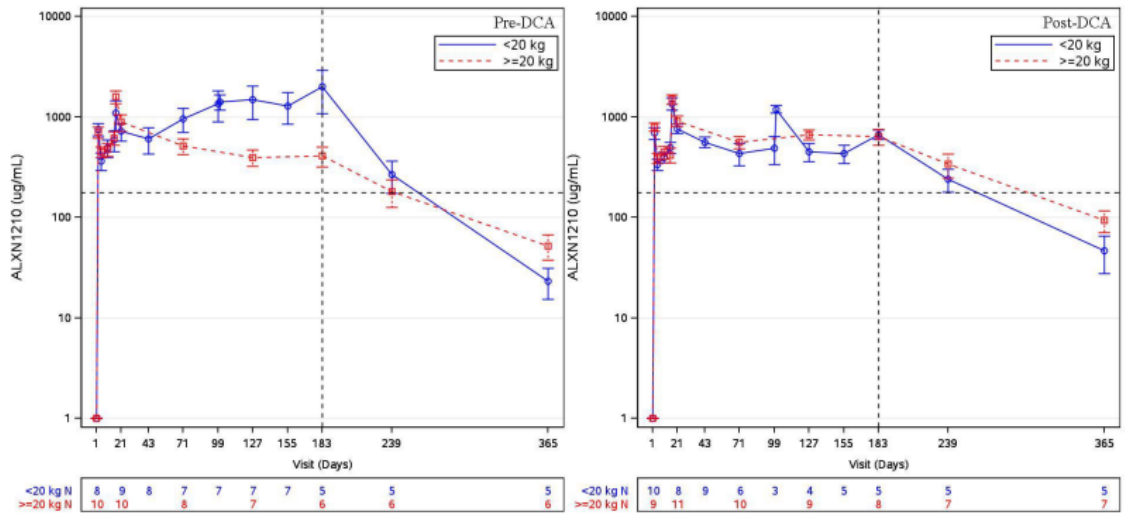
Clinical Pharmacology results

Pharmacokinetics

During the 26-week Treatment Period, the mean ravulizumab serum concentrations were maintained above 175 µg/mL, the target PK threshold. Following the last scheduled dose [redacted] during the 26-week Treatment Period, mean ravulizumab serum concentrations continued to be above the PK threshold up to and including the initial Follow-up Visit (Day 239).

All individual serum ravulizumab concentrations were maintained above the 175 µg/mL threshold, except for transient excursions below this threshold in 7 of 40 participants (excluding 3 participants who missed their regular dosing). [redacted] Of these 7 participants, 5 excursions occurred pre-dose confirmation analysis (DCA). Post-DCA, only 2 participants experienced excursions, each minor in extent (Cmin values of 144 µg/mL and 164 µg/mL). PK profiles were less variable post-DCA relative to pre-DCA, which may reflect the impact of revised dosage regimen implemented post-DCA.

Figure 3. Mean (±SE) Serum Ravulizumab Concentrations (µg/mL) Over Time and by Baseline Body Weight Stratified by Dose Confirmation Analysis Using Semi-log Scale (PK/PD Analysis Set)



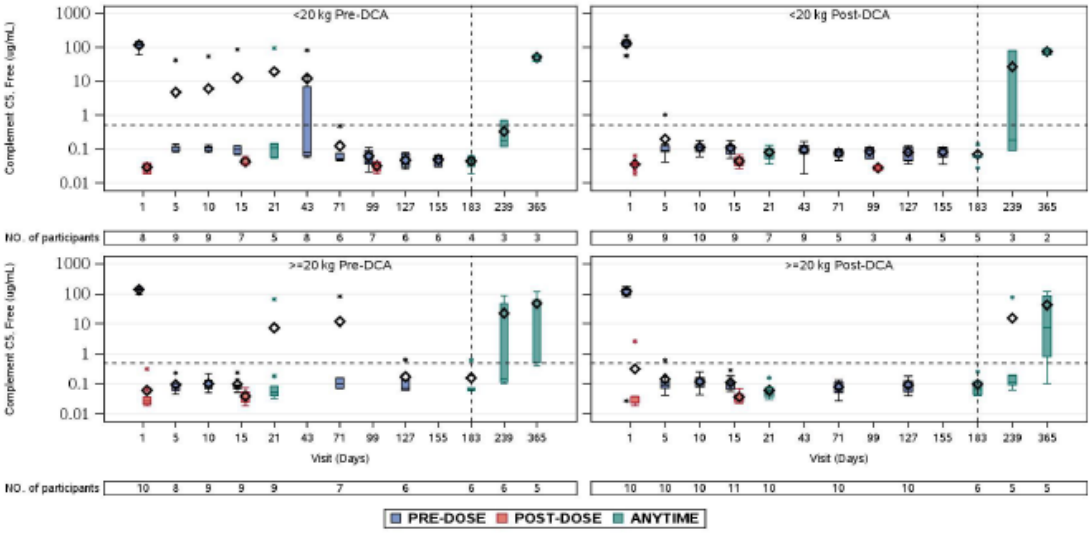
Note: ALXN1210 = ravulizumab.
Dashed horizontal line at 175 µg/mL indicates a level of immediate, complete, sustained inhibition. Mean (± SE) are displayed.
Doses were administered on Days 1, 5, 10, 15, 43, 71, 99, 127, 155 (for participants < 20 kg at Baseline) or Days 1, 5, 10, 15, 71, 127 (for participants ≥ 20 kg at Baseline). Peak and trough samples were collected on Days 1 and 15 for all participants, and on Day 99 for participants < 20 kg on Day 1. Trough samples were collected for all other times.
For timepoints with predose and postdose samples, the predose N is displayed.
Due to the limited blood volume collected, the available samples were divided for PK and PD analyses, leading to reduced sample sizes (N values) for each assessment.

Pharmacodynamics

Immediate and complete inhibition of serum C5 (terminal complement) was observed in both paediatric body weight categories (< 20 kg and ≥ 20 kg) (with median serum free C5 concentrations of < 0.5 µg/mL) by the end of the first ravulizumab infusion and was sustained throughout the entire 26-week Treatment Period. During the Follow-up Period, median serum free C5 concentrations increased and exceeded the ICS threshold.

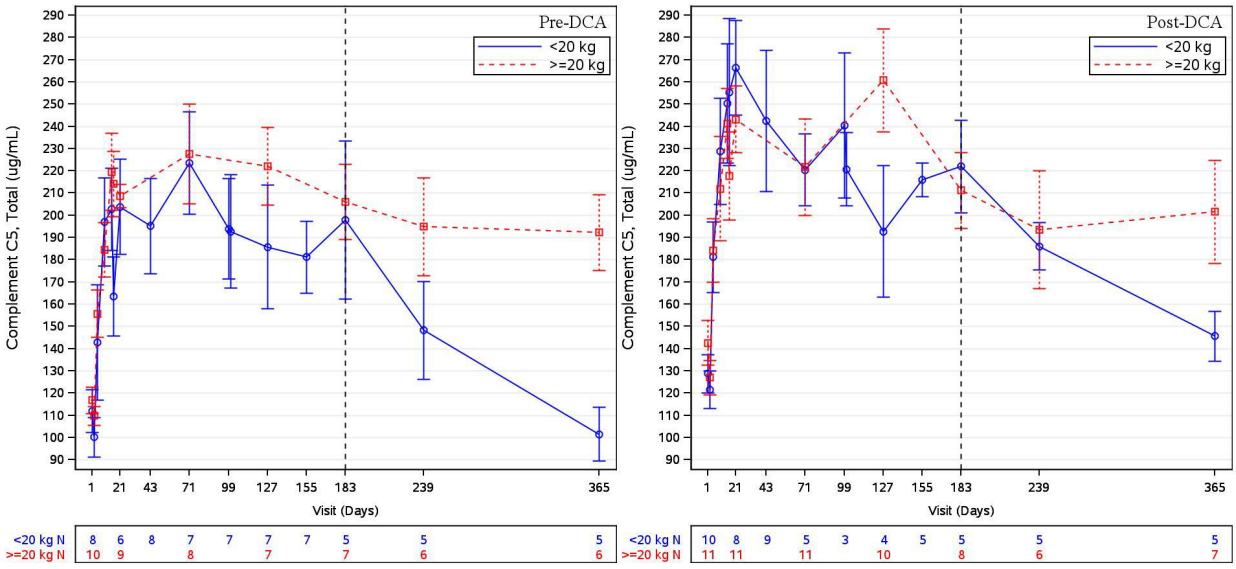
All individual serum free C5 concentrations remained below 0.5 µg/mL except for transient increase in serum free C5 in 6 of 40 participants (excluding 1 participant who missed regular dosing) which were associated with a combination of following clinical factors: [redacted] Of these 6 participants, 4 excursions occurred pre-DCA. Post-DCA, only 2 participants experienced excursions, each minor in extent (free C5 values of 1.03 µg/mL and 0.612 µg/mL). Notably, ravulizumab concentrations remained above 175 µg/mL in both cases. Free C5 concentrations profiles were less variable post-DCA relative to pre-DCA, as indicated by closer alignment of mean and median values post-DCA compared to pre-DCA. This consistency likely reflects the benefit of revised dosage regimen introduced with DCA.

Figure 4. Serum Free C5 Concentration (µg/mL) Over Time Stratified by Baseline Body Weight and Dose Confirmation Analysis Using Semi-Log Scale (PK/PD Analysis Set)



Note: NO. = number.
Dashed horizontal line at 0.5 ug/mL indicates a level of immediate, complete, and sustained inhibition.
The horizontal line in the middle of each box represents the median, the diamond indicates the mean, and the top and the bottom borders of the box mark the 25th and 75th percentiles. The whiskers represent the highest and lowest values within 1.5 times the IQR from the lower quartile and upper quartile. Outliers are represented by asterisk beyond the whiskers.
For timepoints with predose and postdose samples, the predose N is displayed.
Due to the limited blood volume collected, the available samples were divided for PK and PD analyses, leading to reduced sample sizes (N values) for each assessment.
Source: Figure 14.2.24.2.5.6

Figure 5. Mean (±SE) of Serum Total C5 Concentration (µg/mL) Over Time by Baseline Body Weight and Dose Confirmation Analysis Using Linear Scale (PK/PD Analysis Set)



Note: For timepoints with predose and postdose samples, the predose N is displayed. Due to the limited blood volume collected, the available samples were divided for PK and PD analyses, leading to reduced sample sizes (N values) for each assessment.
Source: Figure 14.2.24.2.6.6

Efficacy results

Efficacy analyses used the FAS comprising 41 evaluable participants.

Primary endpoint: TMA Response – 26 Weeks Treatment Period

During the 26-week Treatment Period, Complete TMA Response was observed in 7 (17.1%) of 41 participants (95% CI: 7.2, 32.1) in the FAS.

Individual TMA component response rates (LDH, platelet, and proteinuria response) were higher than the Complete TMA Response rate, ranging from 36.6% (15 of 41 Participants) for LDH and 58.5% (24 of 41 Participants) for platelet count. Individual component response during the 26-week Treatment Period can be found on Table 10:

Table 10. TMA Response and Individual Component Response During the 26-week Treatment Period using Composite Endpoint Strategy (Full Analysis Set)

Assessment	Ravulizumab (N=41)
TMA response during 26-week Treatment Period [a]	
Responders (n/m)	7/41
Percentage and 95% confidence interval	17.1 (7.2, 32.1)
Individual components of TMA response	
Platelet count	
Responders (n/m)	24/41
Percentage and 95% confidence interval	58.5 (42.1, 73.7)
LDH	
Responders (n/m)	15/41
Percentage and 95% confidence interval	36.6 (22.1, 53.1)
Proteinuria assessed by Protein/Creatinine ratio	
Responders (n/m)	22/41
Percentage and 95% confidence interval	53.7 (37.4, 69.3)

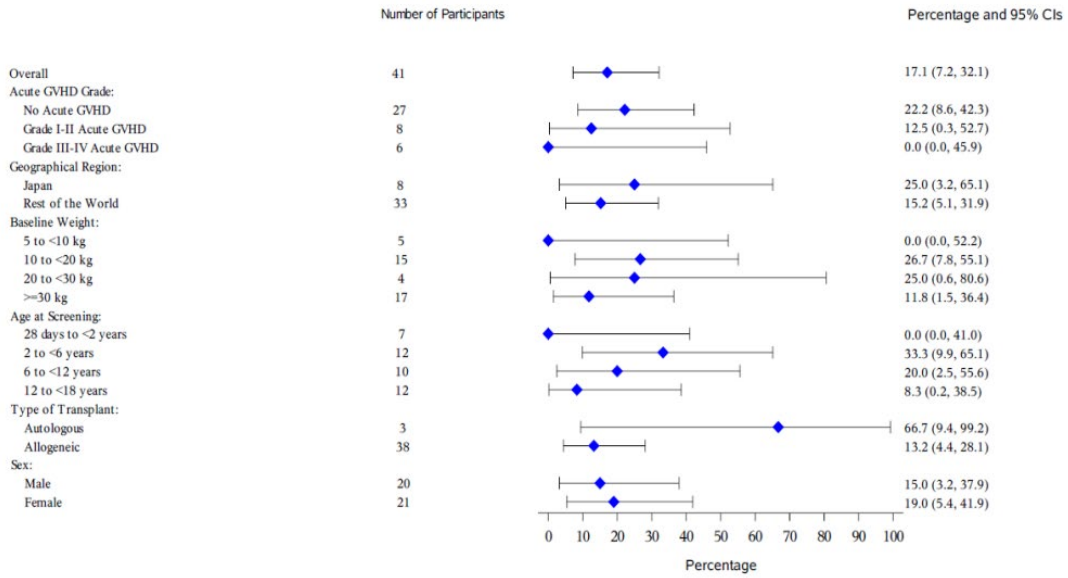
Note: n = number who meet criteria and have a confirmatory result, m = number in the population.
[a] TMA response required the following:
1) A platelet count ≥ 50000 mm^3 or ≥ 50% increase in platelet count (depending on baseline platelet count) without transfusion support during the prior 7 days.
2) LDH normalization and absence of schistocytes (Section 2.2).
3) Proteinuria, of at least 50% reduction in UPCR from Baseline. Participants must have met each TMA criterion at 2 separate assessments obtained at least 24 hours apart, with no criteria failures or more than 1 missed scheduled visit in between. Additionally, all intervals in which the criteria were met must overlap for at least 1 day. Participants with an intercurrent event as defined in the SAP prior to response were assigned as non-responders for this analysis.
95% CIs for the percentage were based on exact confidence limits using the Clopper-Pearson method.

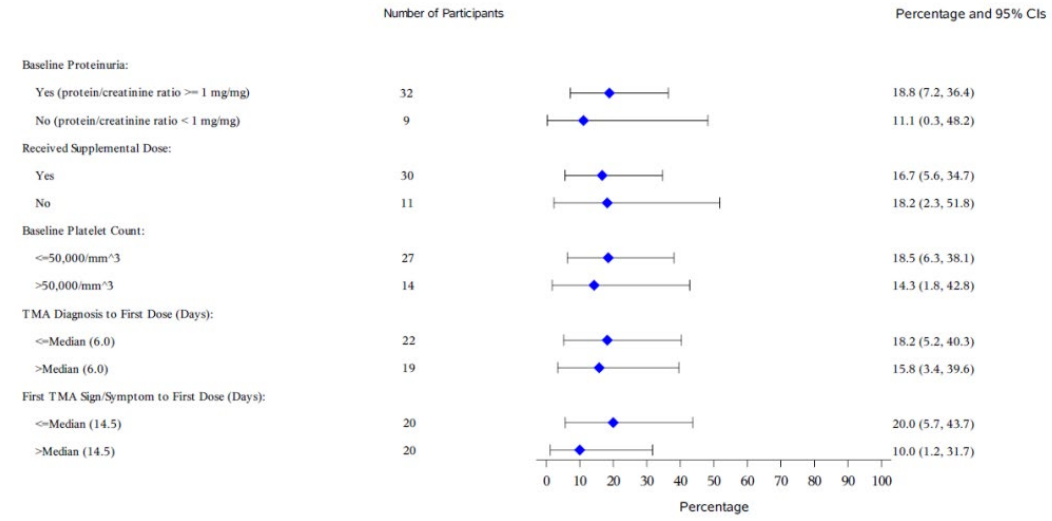
When haemoglobin response (≥10 g/dL without transfusion support) was incorporated as a criterion of complete TMA response, 5/41 participants (12.2%) achieved an Hb-inclusive complete TMA response, compared with 7/41 participants (17.1%) using the original three-component definition.

Subgroup analyses (primary endpoint):

Subgroup analyses were performed by acute GVHD grade, geographical region, baseline weight, age, type of transplant, sex, baseline proteinuria level, received supplemental dose (yes or no), baseline platelet count, time from TMA diagnosis to first dose, and time from first TMA sign/symptom to first dose. Given the small number of participants in each subgroup, no conclusions can be drawn.

Figure 6. Forest Plot of Percentage and 95% CI of Complete TMA Response (Overall and by Subgroups) During the 26-week Treatment Period using Composite Endpoint Strategy (Full Analysis Set)





Secondary endpoints:

Overall survival:

During the 26-week Follow-up Period, 5 participants died, including death cases from underlying disease. Of the 5 participants who died during the 26-week Treatment Period, 3 (7.3%) participants died within the first 100 days of treatment.

OS was 92.6% at Day 100, 87.2% at Week 26, and 73.4% at Week 52.

One additional participant died during the 26-week Treatment Period after receiving an additional HSCT; this participant is included in the efficacy analyses for OS, but the follow-up was censored at the time of the additional HSCT as specified in the study SAP.

Non-Relapse mortality:

Non-relapse mortality was defined as a participant's death due to any cause during the study, with the exception of death due to underlying disease (malignant or non-malignant reason for HSCT) for progression or relapse.

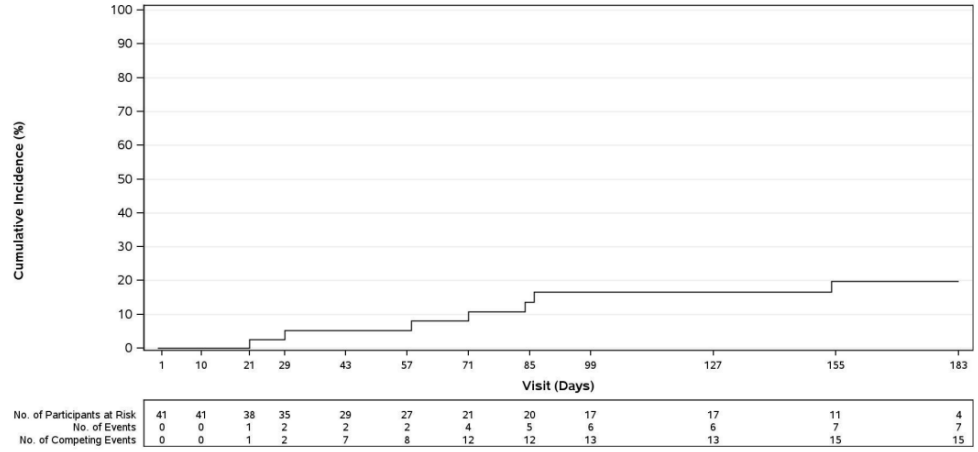
The cumulative incidence for non-relapse mortality was 12.8% (5 of 41 participants) at Week 26 and 18.4% (7 of 41 participants) at Week 52. All of the 5 participants who died during the 26-week Treatment Period, were non-relapse-related deaths, whereas 2 of the 5 participants who died during the 26-week Follow-Up Period (following period up to 52 weeks) were non-relapse-related deaths.

Time to TMA Response – 26 Weeks Treatment Period:

At Week 26, the cumulative incidence of Complete TMA Response was 0.198 (95% CI: 0.085, 0.346; KM estimate). The first Complete TMA Response occurred from Day 21 following the first dose of ravulizumab. The MAH did not provide the median time to TMA response for the FAS.

Cumulative incidence curve of time to TMA Response during the 26-week period can be found in Figure 7:

Figure 7. Cumulative Incidence Curve of Time to Complete TMA Response during the 26-week Treatment Period (Full Analysis Set)



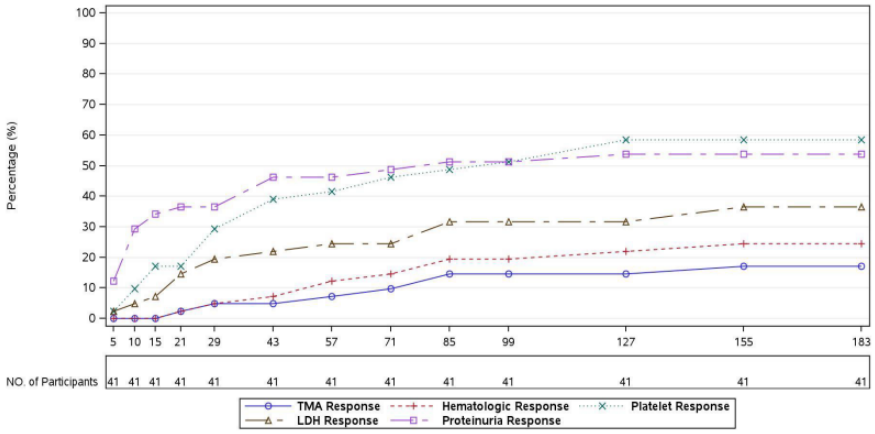
Note: Cumulative incidence was estimated using a competing risk analysis with time from Day 1 to first occurrence of response up to 26 weeks as the event of interest, and the last visit with all 3 TMA components available as censoring date. Death up to 26 weeks, additional HSCT up to 26 weeks, clinical worsening, and treatment discontinuation were considered competing risks.

TMA Response and Time to Response for Each Individual Component of TMA Response – 26 Weeks Treatment Period

During the 26-week Treatment Period, 24 (58.5%) of 41 participants showed a platelet response, 15 (36.6%) of 41 participants showed a LDH response and 22 (53.7%) of 41 participants showed a proteinuria response.

Cumulative complete TMA and hematologic response and individual components with confirmatory result over time are represented in the following figure:

Figure 8. Line Graph of Cumulative Complete TMA and Hematologic Response and Individual Components with Confirmatory Result Over Time Using Composite Endpoint Strategy (Full Analysis Set)



Note: Cumulative response is the number who meet criteria and have a confirmatory result out of the number in the FAS.
Participants with an intercurrent event as defined in the SAP prior to response were assigned as non-responders for this analysis.

Table 11. Cumulative TMA Response and Individual Component Response with a Confirmatory Result Over Time Using Composite Endpoint Strategy (Full Analysis Set)

Assessment	Parameter	Ravulizumab (N = 41)
Day 99	Complete TMA Response	
	Responders (n/m)	6/41
	Percentage and 95% CI	14.6 (5.6, 29.2)
	Individual components of TMA response	
	Platelet count	
	Responders (n/m)	21/41
	Percentage and 95% CI	51.2 (35.1, 67.1)
	LDH	
	Responders (n/m)	13/41
	Percentage and 95% CI	31.7 (18.1, 48.1)
	Protein/Creatinine ratio	
	Responders (n/m)	21/41
	Percentage and 95% CI	51.2 (35.1, 67.1)
Day 183	Complete TMA Response	
	Responders (n/m)	7/41
	Percentage and 95% CI	17.1 (7.2, 32.1)
	Individual components of TMA response	
	Platelet count	
	Responders (n/m)	24/41
	Percentage and 95% CI	58.5 (42.1, 73.7)
	LDH	
	Responders (n/m)	15/41
	Percentage and 95% CI	36.6 (22.1, 53.1)
	Protein/Creatinine ratio	
	Responders (n/m)	22/41
	Percentage and 95% CI	53.7 (37.4, 69.3)

Note: n = number who meet criteria and have a confirmatory result, m = number in the population.
Participants with an intercurrent event as defined in the SAP including clinical worsening, start of disallowed therapy, treatment discontinuation, additional HSCT, or death prior to response were assigned as non-responders for this analysis.
95% CIs for the percentage are based on exact confidence limits using the Clopper-Pearson method.
Source: Table 14.2.3.2.3, Listing 16.2.6.2.5.3, Listing 16.2.6.2.6.3

Hematologic response:

During the 26-week Treatment Period, 10 (24.4%) of 41 participants showed a hematologic response.

Table 12. Hematologic Response during the 26-week Treatment Period Using Composite Endpoint Strategy (Full Analysis Set)

Assessment	Ravulizumab (N = 41)
Hematologic response [a]	
Responders (n/m)	10/41
Percentage and 95% CI	24.4 (12.4, 40.3)

Note: n = number who meet criteria and have a confirmatory result, m = number in the population.
[a] Criteria for meeting hematologic response included platelet count and LDH and were defined fully in the SAP.
Participants with an intercurrent event as defined in the SAP prior to response were assigned as non-responders for this analysis.
95% CIs for the percentage are based on exact confidence limits using the Clopper-Pearson method.
Source: Table 14.2.3.1.3, Listing 16.2.6.2.1.3

Haemoglobin response:

The cumulative haemoglobin response rate was 41.5% (95% CI: 26.3, 57.9, 17 of 41 participants) at Week 26.

Table 13. Cumulative Haemoglobin Response Over Time Using Composite Endpoint Strategy (Full Analysis Set)

Visit	Hemoglobin Response	Ravulizumab (N = 41)
Day 99	Responders (n/m) Percentage and 95% CI	13/41 31.7 (18.1, 48.1)
Day 183	Responders (n/m) Percentage and 95% CI	17/41 41.5 (26.3, 57.9)

Note: n = number who meet criteria and have a confirmatory result, m = number in the population.
Hemoglobin response defined as hemoglobin ≥ 10 g/dL without receipt of transfusion during the prior 7 days. Participants must have met criterion at 2 separate assessments obtained at least 24 hours apart, with no criteria failures or more than 1 missed scheduled visit in between.
Participants with an intercurrent event as defined in the SAP prior to response were assigned as non-responders for this analysis.
95% CIs for the percentage were based on exact confidence limits using the Clopper-Pearson method.
Source: Table 14.2.5.2.1.3, Listing 16.2.6.2.6.3

Partial response:

During the 26-week Treatment Period, 22 (53.7%) of 41 participants had a partial TMA response and met 1 or 2 TMA response criteria. 29 (70.7%) of 41 participants met at least 1 TMA response criterion (including the 22 partial responders above and the 7 Complete TMA responders).

Loss of TMA response– 26 Weeks Treatment Period:

During the 26-week Treatment Period, 2 (28.6%) of 7 participants with a Complete TMA Response lost 1 or more TMA response components:

- One participant achieved Complete TMA Response on Day 58 and lost Complete TMA Response on Day 79 by loss of 3 TMA response components.
- One participant achieved Complete TMA Response on Day 71 and lost Complete TMA Response on Day 99 by loss of 1 TMA response component.

Duration of TMA response:

5 (71.4%) of the 7 complete responders maintained the Complete TMA Response through the Follow-up Period (52-weeks) and only 2 (28.6%) participants lost one or more components of their complete response during the 26-week Treatment Period.

For the entire study, through the Follow-up Period, no median time to loss of complete response or relapse was estimable; the estimated 25th percentile time to loss of response/relapse from TMA response was 29 days.

Table 14. Descriptive Summary of Duration of TMA Response Through 52 Weeks for Participants with TMA Response (Full Analysis Set)

Statistic	Ravulizumab (N = 41)
Loss of complete TMA response or TMA relapse	
TMA response	7
KM estimate and 95% CI for proportion of participants maintaining TMA response	0.714 (0.258, 0.920)
Number (%) with loss/relapse	2 (28.6)
Number (%) censored	5 (71.4)
Time to loss/relapse from TMA response	
25th percentile and 95% CI	29.0 (22.0, NA)
Median and 95% CI	NA (22.0, NA)
75th percentile and 95% CI	NA

Note: This analysis includes data for each participant after TMA response under the composite strategy through final follow-up. Time is calculated as the number of days from TMA response under the composite strategy to first loss of response or intercurrent event in the 26-week Treatment Period, or TMA relapse in the Follow-up Period. Participants with TMA response who did not experience these events were censored at their end of study date. Time statistics were based on KM estimates.
Source: Table 14.2.6.4.3, Listing 16.2.6.4.1.3, Listing 16.2.6.4.4.3

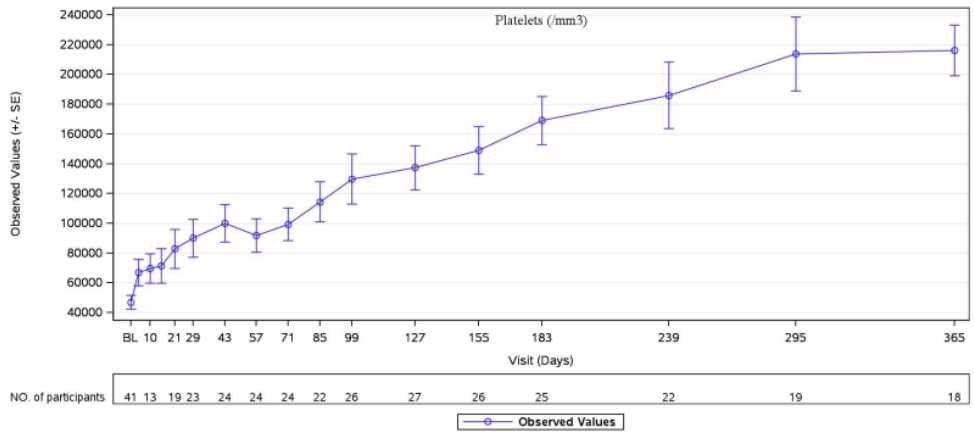
Changes from Baseline in Haptoglobin, Platelets, LDH, and Haemoglobin Over Time

- Mean (SD) **platelet count increased** from Baseline (46975.6 [29248.49] platelets/mm^3) by 118360.0 (79091.13) platelets/mm^3 for 25 evaluable participants at Week 26 and increased further by 163055.6 (61957.74) platelets/mm3 from Baseline for 18 evaluable participants at Week 52, resulting in a mean (SD) platelet count of 216000.00 (72209.66) platelets/mm3 at Week 52. In this study, the LLN for platelet count is 163000.
- Mean (SD) **LDH decreased** from Baseline (606.9 [274.50] U/L) by -337.0 (274.71) U/L for 25 evaluable participants at Week 26 and remained generally stable through Week 52 (change from Baseline: -317.8 [264.40] U/L) for 22 evaluable participants.
- Mean (SD) **haemoglobin increased** from Baseline (8.90 [1.149] g/dL) by 1.95 (2.117) g/dL for 20 evaluable participants at Week 26 and further increased from Baseline by a mean (SD) of 3.20 (2.563) g/dL for 14 evaluable participants and reached 12.02 (2.524) g/dL at Week 52.
- Mean (SD) **haptoglobin increased** from Baseline (0.482 [0.6771] g/L) by 0.643 (1.0160) g/L for 24 evaluable participants at Week 26 and remained generally stable through Week 52 (change from Baseline: 0.843 [1.0002] g/L) for 22 evaluable participants.

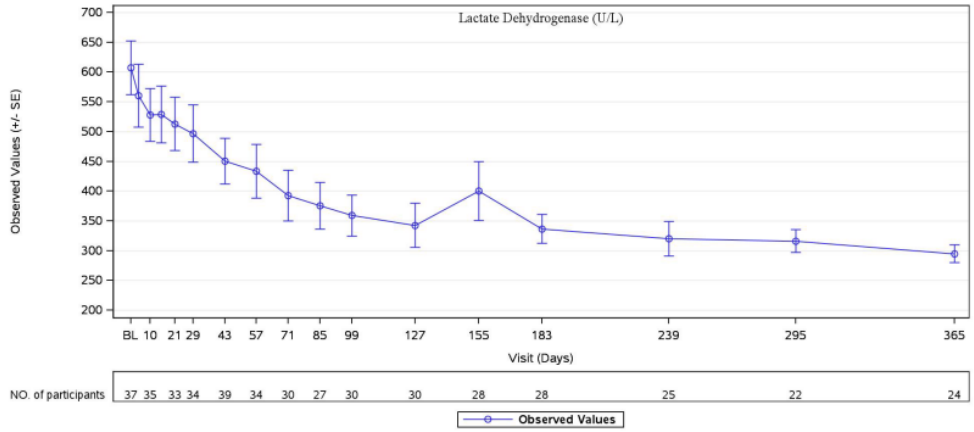
Line graphs of platelets, LDH, haemoglobin, and haptoglobin values for participants who completed the study are:

Figure 9. Secondary Efficacy – Line Graph of Hematologic Parameters Over Time (Full Analysis Set)

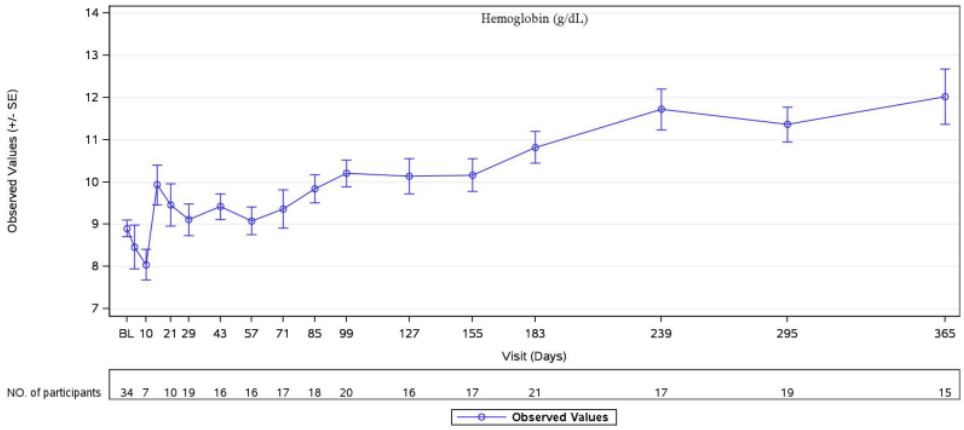
A



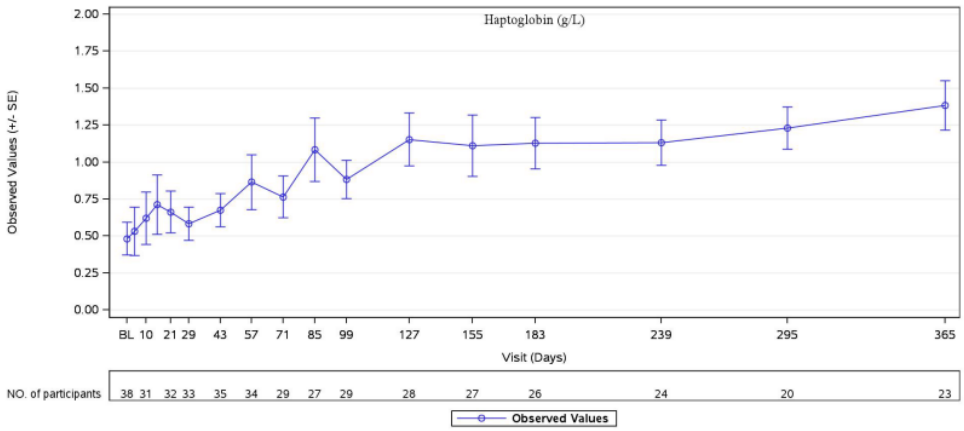
B



C



D



[redacted] – 26 Weeks Treatment Period:

Criteria for meeting [redacted] included [redacted].

During the 26-week Treatment Period [redacted] rate was 19.5% (8 of 41 participants).

Changes from Baseline in TMA-Associated Organ Dysfunction through 26 and 52 weeks

Renal system disfunction:

As previously mentioned, 22 out of 41 patients (53.7%) were considered as proteinuria responders (>50% reduction in UPCR from baseline) at week 26.

UPCR decreased from Baseline (mean [SD] 5.477 [6.6348] mg/mg) by -5.183 (6.5147) mg/mg for 21 evaluable participants at Week 26 and remained stable through Week 52 for 21 evaluable participants (change from Baseline: -4.217 [4.8705] mg/mg).

At Baseline, mean eGFR was within the normal reference range (≥ 90 mL/min/1.73 m2) with a mean (SD) of 120.8 (62.55) mL/min/1.73 m^2. At Week 26, eGFR was 104.1 (61.07) mL/min/1.73 m2 for 26 evaluable participants and remained generally stable through Week 52 (107.1 [48.56] mL/min/1.73 m2) for 24 evaluable participants. The LS mean change (SE) at Week 26 was -6.3 (9.4) mL/min/1.73 m2, with 95% CI of (-24.9, 12.3).

Creatinine remained generally stable from Baseline (mean [SD] 0.6460 [0.7279] mg/dL) for 21 evaluable participants at Week 26 and through Week 52 for 21 evaluable participants.

At Baseline, 2 (4.9%) of 41 participants required dialysis. At Week 26, 4 of 30 (13.3%) participants required dialysis, and 1 (4.2%) of 24 participants at Week 52. A total of 9 (22.0%) of 41 participants required dialysis through Final Follow-up Period.

Among the seven participants who initiated dialysis during the study, only one achieved a partial TMA response.

Schistocytes:

The change in percentage of participants with schistocytes remained generally stable from Baseline (27 [65.8%] of 41 participants) to Week 26 (10 [34.5%] of 29 participants]) and through Week 52 (13 [54.2%] of 24 participants).

Cardiovascular and cardiopulmonary dysfunction:

Mean (SD) systolic blood pressure decreased from Baseline (114.0 [15.50] mm Hg) to 106.4 (14.58) mm Hg at Week 26 (30 evaluable participants) and remained stable through Week 52 (106.7 [15.55] mm Hg) for 23 evaluable participants.

Mean (SD) diastolic blood pressure decreased from Baseline (73.1 [14.02] mmHg) to 68.5 (12.69) mmHg at Week 26 (30 evaluable participants) and remained generally stable through Week 52 (67.7 [12.22] mm Hg) for 23 evaluable participants.

The percentage of participants with hypertension was 22 (55.0%) of 40 participants at Baseline, 6 (20.0%) of 30 participants at Week 26 and 5 (20.8%) of 24 participants at Week 52.

The percentage of participants with cardiopulmonary dysfunction at Baseline was (29 [70.7%] of 41 participants), 11 (36.7%) of 30 participants at Week 26 and 7 (29.2%) of 24 participants at week 52. Of the 12 participants without any cardiopulmonary dysfunction at Baseline, 6 (50%) participants experienced cardiopulmonary dysfunction during the 26-week. Among cardiopulmonary disfunction symptoms, the MAH included pulmonary hypertension, hypertension, pleural effusion, pulmonary edema, pericardial effusion, serositis, ventilatory or Respiratory Support, and other (no further specified).

CNS Dysfunction

Three (7.3%) of 41 participants showed CNS dysfunction at Baseline and 11 additional participants reported CNS dysfunctions through the 26-week Treatment Period and through Final Follow-up Period. At Week 26 and at Week 52, 3 (10.0%) of 30 participants and 2 (8.3%) of 24 participants showed CNS dysfunction, respectively. Of these 11 additional participants that presented CNS dysfunction during the follow-up, 8 achieved a partial TMA response.

GI System disfunction

The percentage of participants with any GI dysfunction was 19 (46.3%) of 41 participants at Baseline, 6 (20.0%) of 30 participants at Week 26 and 3 (12.5%) of 24 participants at Week 52.

Two (4.9%) of 41 participants showed GI bleeding at Baseline. While through Week 52 overall 8 (19.5%) of 41 participants experienced GI bleeding, 1 (3.3%) of 30 participants had GI bleeding at Week 26.

Other GI symptoms such as diarrhoea, abdominal pain or vomiting generally improved or remained stable.

TMA Relapse during the 26-week Follow-up Period:

No TMA relapse was observed during the 26-week Follow-up Period in the subgroup of those participants with TMA response (N = 7).

Safety results

Exposure

Table 15. Study Duration, Compliance, and Supplemental Dosing – Safety Set

Exposure Category	Ravulizumab (N=41)
Treatment Period duration (days)[a]	
N	41
Mean (SD)	155.3 (52.87)
Median	182.0
Min, max	20, 188
Number of scheduled infusions	
N	41
Mean (SD)	6.5 (1.89)
Median	6.0
Min, max	2, 9
Number of infusion interruptions, n (%)	
0	36 (87.8)
1	4 (9.8)
2	0
3	0
4	1 (2.4)
5+	0
Treatment compliance (%)	
N	41
Mean (SD)	97.34 (9.196)
Median	100.0
Min, max	50.0, 100.0
Supplemental dosing, n (%)	
Yes [b]	30 (73.2)
[redacted]	[redacted]
Clinical worsening	6 (14.6)
No	11 (26.8)

Adverse Events

Safety results for the 26-week Treatment Period and the 26-week Follow-up Period (52-Week) were analysed. Safety results are presented for the Safety Set (N = 41), which contains the same participants as the FAS.

Table 16. Overall Summary of TEAEs during the 26-week Treatment Period – Safety Set

	Ravulizumab (N = 41)	
Adverse Event Category	**n (%)**	**E**
TEAEs	41 (100)	860
Serious TEAEs	30 (73.2)	94
TEAEs leading to death	6 (14.6)	6

	Ravulizumab (N = 41)	
Adverse Event Category	**n (%)**	**E**
TEAEs leading to study discontinuation	2 (4.9)	2
TEAEs leading to study treatment discontinuation	7 (17.1)	8
Serious TEAEs leading to study treatment discontinuation	5 (12.2)	5
Drug-related TEAEs	8 (19.5)	14
Drug-related serious TEAEs	3 (7.3)	6
TEAEs by toxicity		
Grade 1	36 (87.8)	331
Grade 2	35 (85.4)	248
Grade 3	33 (80.5)	215
Grade 4	18 (43.9)	60
Grade 5	6 (14.6)	6

Note: A TEAE is any AE that starts between the start of the first infusion of ravulizumab and 8 months after the last infusion of ravulizumab, inclusive. For TEAE by toxicity grade, all events within each severity category were counted. If a participant had more than 1 occurrence of a TEAE, the participant was counted once for each level of severity reported. Only TEAEs starting prior to the end of the 26-week Treatment Period were included in this table.

Source: Table 14.3.1.2.1.2.2, Listing 16.2.7.1.1.2

Common Adverse Events

The most frequently reported TEAEs were in the following SOCs:

- Infections and infestations (102 events in 32 [78.0%] of the 41 participants)
- Gastrointestinal disorders (92 events in 28 [68.3%] of the 41 participants)
- Investigations (148 events in 24 [58.5%] of the 41 participants)
- Blood and lymphatic disorders (105 events in 15 [36.6%] of the 41 participants).

The most frequently reported TEAEs by PT (> 20% of the participants) were headache (n = 12; 29.3%), diarrhoea and pyrexia (both n = 11, 26.8%), and abdominal pain (n = 9, 22.0%).

Adverse Events by Severity

Thirty-three (80.5%) of 41 participants experienced TEAEs that were Grade 3 in severity (215 events), 18 (43.9%) of 41 participants experienced TEAEs that were Grade 4 in severity (60 events), and 6 (14.6%) of 41 participants experienced TEAEs that were Grade 5 in severity (6 events).

Treatment related TEAEs

During the 26-week Treatment Period, 8 (19.5%) of 41 participants experienced 14 TEAEs that were assessed as related to ravulizumab by the Investigator:

Table 17. Drug-Related TEAEs during the 26-week Treatment Period by MedDRA System Organ Class and Preferred Term (Safety Set)

	Ravulizumab (N = 41)	
System Organ Class Preferred Term	**n (%)**	**E**
Any drug-related TEAE	8 (19.5)	14
Cardiac disorders	1 (2.4)	1
Pericardial effusion	1 (2.4)	1
Hepatobiliary disorders	1 (2.4)	1
Venoocclusive liver disease	1 (2.4)	1
Immune system disorders	1 (2.4)	1
Hypersensitivity	1 (2.4)	1
Infections and infestations	2 (4.9)	2
Norovirus infection	1 (2.4)	1
Sepsis	1 (2.4)	1
Investigations	1 (2.4)	1
Urine output decreased	1 (2.4)	1
Musculoskeletal and connective tissue disorders	1 (2.4)	3
Soft tissue necrosis	1 (2.4)	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (2.4)	1
Pyogenic granuloma	1 (2.4)	1
Nervous system disorders	1 (2.4)	2
Partial seizures	1 (2.4)	1
Seizure	1 (2.4)	1
Skin and subcutaneous tissue disorders	1 (2.4)	2
Dry skin	1 (2.4)	2

Note: A TEAE is any AE that starts between the start of the first infusion of ravulizumab and 8 months after the last infusion of ravulizumab, inclusive. In summarizing n (%), if a participant had multiple events for a particular SOC or PT, they were counted only once for that SOC or PT. Only TEAEs starting prior to the end of the 26-week Treatment Period were included in this table, AEs were coded using MedDRA Version 28.0.
Source: Table 14.3.1.3.7.2.2, Listing 16.2.7.1.7.2

Deaths

During the 26-week Treatment Period, 6 (14.6%) of the 41 participants experienced TESAEs with an outcome of death. During the 26-week Follow-up Period, 4 (13.8%) of the 29 participants who entered the Follow-up Period experienced TESAEs with an outcome of death.

All TESAEs with an outcome of death were assessed as not related to ravulizumab by the Investigator except for 1 event of neuroblastoma (worsening of neuroblastoma). The Investigator assessed the

event as related due to the temporal association of ravulizumab treatment; however, concurrent progression of renal and respiratory failure were considered causal factors.

Table 18. Deaths Due to TEAEs by Study Period

TEAEs Leading to Death(N = 10)	Study Day (Day of Death)	Investigator Assessment of Relationship to Ravulizumab
Screening Period (no deaths)		
26-week Treatment Period (6 deaths)		
Multiple organ dysfunction syndrome	Day 41	Not related
Multiple organ dysfunction syndrome	Day 60	Not related
Septic shock	Day 63	Not related
Adenovirus infection	Day 92	Not related
Cardiac failure	Day 157	Not related
Mucormycosis	Day 167	Not related
26-week Follow-up Period (4 deaths)		
Neuroblastoma	Day 197	Related
Pseudomonas infection	Day 203	Not related
Cerebral haemorrhage	Day 256	Not related
Haemoperitoneum	Day 284	Not related

Note: Outcomes of death reported after study completion are only discussed within the Efficacy section.
Source: Table 14.1.2.5, Table 14.3.1.2.1.2.2, Table 14.3.1.2.1.3.2, Listing 16.2.7.2, Listing 16.2.7.1.4.2.

Serious Adverse Events

Serious TEAEs occurred in 30 (73.2%) out of 41 patients.

Table 19. TESAEs Occurring in ≥ 5% of Participants during the 26-week Treatment Period by MedDRA System Organ Class and Preferred Term (Safety Set)

	Ravulizumab (N = 41)	
System Organ Class Preferred Term	**n (%)**	**E**
Any serious TEAE	30 (73.2)	94
Blood and lymphatic system disorders	5 (12.2)	5
Febrile neutropenia	3 (7.3)	3
General disorders and administration site conditions	5 (12.2)	5
Multiple organ dysfunction syndrome	3 (7.3)	3
Nervous system disorders	7 (17.1)	10
Seizure	3 (7.3)	3

Note: A TEAE is any AE that starts between the start of the first infusion of ravulizumab and 8 months after the last infusion of ravulizumab, inclusive. In summarizing n (%), if a participant had multiple events for a particular SOC or PT, they were counted only once for that SOC or PT. Only TEAEs starting prior to the end of the treatment period are included in this table. AEs were coded using MedDRA Version 28.0.
Source: Table 14.3.1.3.2.2.2, Listing 16.2.7.1.2.2

Three participants (7.3%) experienced 6 TESAEs that were assessed as related to ravulizumab by the Investigator. These were:

- Soft tissue necrosis (2 events in 1 participant reported during the 26-week Treatment Period; the outcomes of the events were resolved with sequelae and resolving respectively).

- Seizure and partial seizures (2 events in 1 participant reported during the 26-week Treatment Period; the outcomes of the events were resolved).
- Sepsis and veno-occlusive liver disease (2 events in 1 participant reported during the 26-week Treatment Period; the outcomes of the events were resolved).

During the 26-week Follow-up Period, 2 (6.9%) of the 29 participants who entered the Follow-up Period experienced 2 TESAEs that were assessed as related to ravulizumab by the Investigator:

- Gonococcal infection (1 event in 1 participant; the outcome of the event was resolved).
- Neuroblastoma (1 event in 1 participant; the outcome of the event was death).

Adverse Events of Special Interest:

No meningococcal infections were reported during the 26-week Treatment Period and the 26-week Follow-up Period.

Discontinuations and/or Dose Modifications Due to TEAEs

During the 26-week Treatment Period, 7 (17.1%) of the 41 participants experienced 8 TEAEs leading to discontinuation of treatment with ravulizumab. All these events were considered not related to ravulizumab, except for 1 serious event (soft tissue necrosis) and 2 nonserious events (dry skin, urine output decreased). All TEAEs leading to dose discontinuation or modification are available in the following table:

Table 20. TEAEs Leading to Study Treatment Discontinuation by MedDRA System Organ Class and Preferred Term (Safety Set)

	Ravulizumab (N = 41)	
System Organ Class Preferred Term	**n (%)**	**E**
Any TEAE	7 (17.1)	8
Cardiac disorders	2 (4.9)	2
Arrhythmia	1 (2.4)	1
Pericardial effusion	1 (2.4)	1
General disorders and administration site conditions	1 (2.4)	1
Multiple organ dysfunction syndrome	1 (2.4)	1
Infections and infestations	2 (4.9)	2
Adenovirus infection	1 (2.4)	1
Mucormycosis	1 (2.4)	1
Investigations	1 (2.4)	1
Urine output decreased	1 (2.4)	1
Musculoskeletal and connective tissue disorders	1 (2.4)	1
Soft tissue necrosis	1 (2.4)	1
Skin and subcutaneous tissue disorders	1 (2.4)	1
Dry skin	1 (2.4)	1

Note: A TEAE is any AE that starts between the start of the first infusion of ravulizumab and 8 months after the last infusion of ravulizumab, inclusive. In summarizing n (%), if a participant had multiple events for a particular SOC or PT, they were counted only once for that SOC or PT. AEs were coded using MedDRA Version 28.0.

Other safety considerations:

During the 26-week Treatment Period, 6 participants experienced clinically significant changes in laboratory parameters reported as TESAEs; all the events were assessed as not related to ravulizumab by the Investigator.

During the 26-week Follow-up Period, 2 participants experienced clinically significant changes in laboratory parameters reported as TESAEs; all events were assessed as not related to ravulizumab by the Investigator.

During the 26-week Treatment Period and 26-week Follow-up Period, participants experienced fluctuations in vital signs, ECGs, and physical examinations, with no signals or concerns identified.

Two AEs of QT prolongation were reported. Both events were nonserious, concurrent with comorbid conditions, and assessed as not related to ravulizumab by the Investigator. No AEs of torsades de pointes were reported in the study. Two AEs of syncope were reported in the study, both events were assessed as not related to ravulizumab by the Investigator.

Biomarkers

The MAH studied plasma and urinary [redacted] levels. [redacted] concentration after allo-HSCT in children has been closely related to the occurrence of TMA after HSCT.

At Baseline, 18 (47.4%) of 38 participants tested had elevated plasma [redacted]evels (> 244 ng/Ml, a threshold previously identified in the literature) (median [IQR] = 240.4 (151.7) ng/mL) and at Week 26, [redacted] levels were observed in 9 (36.0%) of 25 participants (median [IQR] = 212.3 (123.7) ng/mL). At Week 52, at the end of the 26-week Follow-up Period, a continuous reduction in [redacted] levels were observed, also after treatment suspension: only 8 (36.4%) of 22 participants tested had [redacted] levels (median [IQR] = 223.3 (159.2) ng/mL).

At Baseline, all 29 evaluable participants (100%) had [redacted] levels (> 2.53 ng/mg creatinine, threshold defined by Alexion using a self-defined cohort of normal paediatric donors) (median [IQR] = 97.2 (754.6) ng/mg creatinine) and at Week 26, [redacted] levels were elevated in 7 (36.8%) of 19 participants (median [IQR] = 1.31 (2.54) ng/mg creatinine). The strong reduction in urinary [redacted] levels observed at Week 26 was sustained also during the 26-week Follow-up Period. At Week 52, at the end of the Follow-up Period, only 4 (26.7%) of 15 participants tested had [redacted] levels (median [IQR] = 1.11 (2.62) ng/mg creatinine).

Immunogenicity

Nine (22.0%) of 41 participants had pre-existing immunoreactivity and none of them were treatment boosted. Three (7.3%) of 41 participants exhibited treatment-emergent ADA responses of which 1 was transient and 2 were indeterminate. One (2.4%) of 41 participants was positive for antidrug Nabs observed only on Day 365.

One participant exhibited a transient ADA response, testing ADA-positive only on Day 71 with a titer of < 1:1. Serum ravulizumab concentrations in this participant were below the established therapeutic PK threshold (> 175 µg/mL) on Days 10, 15, 43 and 71. As PK levels were already low prior to ADA detection, no clear association between ADA and reduced drug exposure could be established.

Overall, no apparent impact of ADA on PK, PD, efficacy and safety was observed.

2.3.3. Discussion on clinical aspects

The MAH submitted the final CSR for study ALXN1210-TMA-314 as part of this Article 46 procedure. ALXN1210-TMA-314 is part of an ongoing clinical development program investigating the use of

ravulizumab for the treatment of paediatric and adult patients with Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplantation (HSCT). This clinical trial was a Phase 3, Open-label, Single Arm, Multicentre Study of Ravulizumab in Addition to Best Supportive Care in Paediatric Participants (from 1 month to <18 years of age) with TMA after HSCT.

There is another Phase 3 study ongoing in adults and adolescents with TMA after HSCT (ALXN1210-TMA-314) for which the primary evaluation period was completed in September 2025.

Within this procedure, the MAH is not planning to update the SmPC.

Study design:

The main objective of the study was to evaluate the efficacy of ravulizumab in patients presenting with TMA after a HSCT. TMA represents a severe and potentially fatal post-transplant complication for which there are currently no approved therapies. Therefore, a significant unmet medical need exists in this clinical setting.

The study was planned to enrol approximately 40 paediatric patients (≥28 days of age up to <18 years). Participants should have HSCT-TMA that persists for at least 72 hours after initial management. The criteria for TMA diagnosis are adequately described in the inclusion criteria. Overall, the study population included in the trial is considered representative of the target patient population.

To evaluate their primary objective, the MAH used a composite endpoint of TMA response, which evaluated on the one hand, the haematological response using platelet counts, normalization of LDH and absence of schistocytes and, on the other hand, the renal response evaluating proteinuria reduction from baseline. The participants must have met each response criterion at 2 separate assessments obtained at least 24 hours apart. Even though this approach may seem reasonable, the MAH excluded the normalization of haemoglobin levels in the primary composite endpoint and, therefore, the overall response rate may be overestimated. It is noted, however, that the haemoglobin response was assessed in a secondary endpoint separately. The remaining secondary endpoints are deemed adequate.

Regarding the dosing strategy, the initial regimen was extrapolated from other ravulizumab indications and prior experience with eculizumab in TMA, where higher dosing requirements were anticipated in this clinical context. Subsequently, the MAH performed a Dose Confirmation Analysis (DCA) after the inclusion of the first 10 participants. Based on these findings, the maintenance dosage for paediatric patients in the [redacted]kg and [redacted]kg weight cohorts was properly adjusted. However, for the dosing regimens for the [redacted]kg or [redacted]kg patients ravulizumab was administered every 8 weeks and no dose adjustment was proposed. [redacted]

Clinical Pharmacology results:

The proposed loading and maintenance dosing regimens, following the adjustments made after the DCA, are considered adequate to maintain the PK threshold defined by the MAH of > 175 ug/ml.

Furthermore, considering the frequent requirement for [redacted]in patients with HSCT-TMA, the provision for supplemental dosing of ravulizumab is deemed clinically appropriate to [redacted]during such procedures. These PK findings are further supported by PD data demonstrating sustained terminal complement inhibition throughout the treatment period

Efficacy results

A total of 41 patients were enrolled in the trial. Given the small sample size and the single-arm study design, the efficacy outcomes should be interpreted with caution.

During the 26-week treatment period, 7 (17.1%) of 41 participants achieved a complete TMA response as defined by the MAH. Of these, 5 patients maintained the response through the 52-week follow-up, while 2 patients experienced a loss of response within the initial 26-week period. The TMA partial response was achieved by 22 (53.7%) participants. Haematological response was reported for 10 (24.4%) patients and haemoglobin response was considered for 17 (41.5%) of the participants. When haemoglobin response (≥10 g/dL without transfusion support) was incorporated as a criterion of complete TMA response, 5/41 participants (12.2%) achieved an Hb-inclusive complete TMA response, compared with 7/41 participants (17.1%) using the original three-component definition (platelets, LDH, proteinuria). This result is consistent with the expected lower responder rate when haemoglobin is added as a required component, given the multifactorial influences on haemoglobin levels in HSCT-TMA (inflammation, marrow suppression, transfusion burden, renal impairment). Overall, 29 participants (70.7%) met at least one TMA response criterion.

While subgroup analyses were performed for the primary endpoint, no conclusions can be drawn given the limited number of participants for each subgroup.

The OS rate at 100 days of the first dose was 92.6%, at 26 weeks it was 87.2 and in 52 weeks it was 73.4%.

The evaluation of TMA-associated organ dysfunction revealed concerning trends, particularly regarding renal and neurological system.

Mean eGFR show a slight deterioration during the follow-up. Most notably, the requirement for dialysis increased from 2 participants (4.9%) at baseline to 9 (22.0%) by the final follow-up period. Among the seven participants who initiated dialysis during the study, only one achieved a partial TMA response. While the size of this subgroup is very small, the distribution of clinical responses does not suggest that ravulizumab response is associated with worsening renal function leading to dialysis initiation. Rather, the need for dialysis probably reflects the disease course of HSCT-TMA and the heterogeneous baseline renal status of the enrolled population.

Three (7.3%) of 41 participants showed CNS dysfunction at baseline. This result worsened at the end of the 26-week treatment period, adding 11 additional participants (total of 14 participants [34.1%]). Of these eleven patients, eight achieved a partial TMA response, indicating that CNS involvement did not preclude clinical improvement according to the predefined response criteria of HSCT-TMA. It is noteworthy that in six of the eleven participants, at least one of the recorded CNS dysfunction AE was headache, a common symptom in this clinical context and not indicative of structural neurological injury. Nevertheless, more severe manifestations, including seizures, epilepsy, and PRES, were also reported among ravulizumab TMA partial responders. Given the diversity of CNS presentations and the absence of a comparator arm, it is difficult to isolate whether these events reflect the natural course of HSCT-TMA, comorbidities, concurrent medications, or a potential effect of ravulizumab. Other TMA-Associated Organ dysfunctions remained stable or exhibited a slight improvement.

Safety results:

During the 26-week period, all 41 participants (100%) experienced at least 1 TEAE with a cumulative total of 860 events. The majority of TEAEs were nonserious and Grade 1 or 2 in severity. Thirty-six (87.8%) of 41 participants experienced Grade 1 events and 35 (85.4%) of 41 participants experienced Grade 2 events.

Thirty (73.2%) of 41 participants experienced SAEs, most of which were not related to treatment with ravulizumab. Three (7.3%) of 41 participants experienced 6 SAEs that were assessed as related to ravulizumab by the Investigator, these were soft tissue necrosis (2 events in 1 participant), seizure and partial seizures (2 events in 1 participant) and Sepsis and veno-occlusive liver disease (2 events in 1 participant).

Six (14.6%) of 41 participants experienced TEAEs with an outcome of death. All TEAEs with an outcome of death were assessed as not related to ravulizumab by the Investigator except for 1 event of neuroblastoma (worsening of neuroblastoma).

The majority of TEAEs were not related to ravulizumab and did not result in discontinuation from the study or discontinuation of treatment with ravulizumab. There were 7 (17.1%) patients that discontinued treatment due to TEAEs, three of them considered related to ravulizumab (one SAE of soft tissue necrosis and 2 non-SAEs of dry skin and urine output decreased). No safety signals were identified from the subgroup analyses. No meningococcal infections were reported.

Overall, the observed safety profile of ravulizumab was in accordance with the previously known profile of the approved indications.

Other concerns:

According to the MAH, ALXN1210-TMA-314 is part of a broader clinical development program evaluating ravulizumab for the treatment of both paediatric and adult patients with HSCT-associated TMA. In parallel, the MAH is conducting study ALXN1210-TMA-313, a Phase 3, randomized, double-blind, placebo-controlled, multicentre trial. However, this second study focuses exclusively on adult and adolescent participants.

Given the limited number of patients enrolled in ALXN1210-TMA-314, its single-arm methodology, and that ALXN1210-TMA-313 clinical trial is restricted to adult and adolescent population, the overall benefit-risk balance of ravulizumab will likely still be uncertain in the paediatric population.

3. Rapporteur's overall conclusion and recommendation

Overall, the results provided in the final CSR for study ALXN1210-TMA-314 are deemed encouraging, particularly in light of the high unmet medical need for patients experiencing TMA following HSCT. No new concerns regarding the safety of ravulizumab have been identified.

However, ravulizumab does not hold an indication in TMA-HSCT, neither in adults nor in paediatric population. The MAH does not intend to apply for a regulatory status change at this time. Due to the limited number of patients included and the single-arm methodology employed in ALXN1210-TMA-314 clinical trial, the benefit-risk balance of ravulizumab in paediatric patients with TMA after HSCT is considered uncertain at this stage. This benefit-risk balance is likely to remain uncertain throughout the development program, as the ongoing Phase III ALXN1210-TMA-313 trial restricts enrolment to adult and adolescent participants.

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

None.

5. Assessment of the responses to Request for supplementary information

Question 1:

The MAH is requested to provide a comprehensive justification for the maintenance dosage modifications implemented for participants in the 5 < 10kg and 10 < 20kg weight cohorts following the DCA.

MAH's response:

The Dose Confirmation Analysis (DCA) confirmed the protocolized ravulizumab dosing regimen that provides complete, immediate, and sustained terminal complement inhibition in paediatric patients with HSCT-TMA (including those [redacted]kg) based on PKPD modelling and simulation predicting fewer PK excursions; its scope and dataset included [redacted] evaluable paediatric participants in TMA-314, and data from TMA-313 participants [redacted].

This protocolized ravulizumab dosing regimen obviates the need for therapeutic drug monitoring; ensures sustained terminal complement inhibition and addresses requirements for the vulnerable sub-population of patients where HSCT-TMA is complicated by bleeding and/or a [redacted].

The maintenance dose modifications implemented for participants in the 5 to <10 kg and 10 to <20 kg cohorts following the DCA in Study ALXN1210-TMA-314 are justified based on the observed PK/PD data and population pharmacokinetic (PopPK) modelling and simulation identifying a [redacted], and dose simulation demonstrating that the revised maintenance doses increase the likelihood of maintaining therapeutic ravulizumab exposure associated with complete terminal complement inhibition. The DCA for Study ALXN1210-TMA-314 is enclosed with this submission (Appendix dose confirmation analysis).

The protocol dosing strategy targeted immediate, complete, and sustained free C5 inhibition, supported by prior ravulizumab experience across indications where ravulizumab trough concentrations ≥175 µg/mL are associated with free C5 <0.5 µg/mL. In the ALXN1210-TMA-314 DCA, 2/9 participants demonstrated ravulizumab concentrations falling below 175 µg/mL with concomitant free C5 excursions above 0.5 µg/mL. These participants also had [redacted], consistent with the biologically plausible mechanism that [redacted] may be associated with [redacted] in HSCT-TMA, as also described for other C5 inhibitors used off-label in this condition discussed in the published literature (Jodele, 2016; Mizuno, 2022).

PopPK modelling (leveraging ALXN1210-TMA-314 with supportive data from ALXN1210-TMA-313) indicated higher PK variability in this paediatric HSCT-TMA population, with the [redacted] This was most relevant in participants [redacted] kg, in whom the margin to maintain the target trough across the q4w interval is smaller and the impact of [redacted] is proportionally greater.

To address the risk of sub-therapeutic exposure in the [redacted] kg cohorts while maintaining an acceptable exposure range, simulations (1,000 virtual patients per weight band) evaluated the probability of concentrations falling below 175 µg/mL under scenarios reflecting both [redacted] and a subgroup with [redacted] The analyses demonstrate that [redacted] (while maintaining the q4w interval) improves trough

coverage in the [redacted] kg cohorts, particularly [redacted], without producing exposures considered meaningfully higher than previously studied.

Accordingly, the revised maintenance dosing regimen (and aligned [redacted]) was implemented as follows (starting Day 15):

- 5 to <10 kg: maintenance dose increased from [redacted] to 400 mg q4w
- 10 to <20 kg: maintenance dose increased from [redacted] to 800 mg q4w

These adjustments were supported by simulation outputs showing higher predicted Cmin distributions under the revised dose regimen versus PA2, and a lower predicted proportion of participants experiencing concentrations below 175 µg/mL in the presence of [redacted] (e.g., at approximately [redacted], reductions were predicted from ~12% to 5.8% for 5 to <10 kg, and from ~7.2% to 3.0% for 10 to <20 kg; DCA report Figure 15). Importantly, predicted Cmax values under the revised regimen remained within the range considered consistent with prior ravulizumab experience, supporting a favourable exposure balance while improving trough coverage.

Overall, a model-based approach was applied to data gathered for a DCA assessment resulting in a quantitative characterization of exposure, which informed a dose adjust for patients [redacted] kg for both standard maintenance dosing and [redacted] supplemental dosing.

Assessment to MAH's response:

Data from literature indicates that paediatric HSCT-TMA patients treated with eculizumab may have a mixed response in bleeding and non-bleeding patients. The literature also suggests that increased drug clearance due to blood loss and transfusions may be one of the contributing factors. To confirm that dose regimens were appropriate, a dose confirmation analysis (DCA) was performed with ravulizumab PK/PD data from [redacted] paediatric patients from ALXN1210-TMA-314 study (The median age was 2.0 years (range 0–15)). Given the limited number of patients, [redacted] patients [redacted] from ALXN1210-TMA-313 study were also included in the analysis. All except one patient ([redacted], WT 55 kg) in ALXN1210-TMA-314 study weighed < 30 kg. The Applicant also indicates that paediatric patients in ALXN1210-TMA-314 appeared to have more frequent [redacted] as compared to the adult patients in ALXN1210-TMA-313, however, these results have not been included in the report. Observed data showed that [redacted] out of these [redacted] paediatric patients from ALXN1210-TMA-314 study had ravulizumab concentrations levels below 175ug/ml and free C5 concentrations above 0.5ug/ml, who weighed less than 30 kg and had frequent [redacted].

The previously developed paediatric aHUS population PK model was applied to this HSCT-TMA PK dataset. The PK parameters and associated inter-individual variability were re-estimated. At a structural level, ravulizumab PK was described using a 2-compartment model with standard allometric scaling on V, Vp and CL, Q and RBC transfusion as a covariate on CL. Structural model parameters were estimated with relatively good precision (RSE <20%). The model included moderate IIV on CL (39.2%) and Vc (29.9%). Overall, VPC and GOF show acceptable description of the experimental data. Importantly, the relative standard errors (RSEs) for the structural parameters are below 20%, indicating adequate parameter precision despite the sparse data. Therefore, the observed discrepancies likely reflect sparse data and limited parameter identifiability rather than fundamental structural misspecification of the model.

Then a model-based approach was conducted to evaluate the adequacy of the current dosing regimen and higher doses (RDR) assuming different [redacted] in 22% of the simulated population. The overall simulation strategy is endorsed, since stratified analysis for each body-weight cohort was assumed. Similarly, different [redacted] were considered [redacted] in order to

reflect [redacted] conditions. The simulations suggested that patients with WT[redacted], would benefit from a [redacted] dose, keeping more patients above the threshold, while not reaching significantly higher maximum concentration (Cmax) than previously studied. The results were reported for Cmax and Cmin, stratified by body-weight cohort. Although the proportion of patients below 175ug/ml for the RDR dosing regimen was not reported, the MAH provided the 95% PI for Cmax and Cmin. For paediatric patients [redacted]kg and [redacted]kg with [redacted], the 95% PI for Cmin is above the 175 ug/ml threshold. However, when [redacted] were assumed, the Cmin ranges from 129 to 1390 and 169 to 961 ug/ml for paediatric patients [redacted]kg and [redacted]kg, respectively. Although we do not know the percentage of patients below the efficacy threshold (175 ug/ml), this proportion is surely lower than 5-10% of simulated patients. Therefore, we consider that the RDR proposal is coherent and appropriate.

However, for the dosing regimens for the [redacted]kg or [redacted]kg patients administered every 8 weeks, no dose adjustment is proposed. The applicant argues that the available data for this group are limited and that increasing the dose would carry a risk of overdosing these patients. Additionally, it remains to be clarified whether these patients are also more likely to experience a higher number of [redacted] than adult patients and could therefore benefit from an increased dose, which would require using a 4-week regimen. [redacted]

Conclusion

Issue solved.

Question 2:

The MAH should submit an analysis of the complete TMA response rate that incorporates haemoglobin response as a mandatory criterion, to better assess the efficacy of ravulizumab.

MAH's response:

In line with the agency's request, Alexion has performed an analysis of the complete TMA response that includes the haemoglobin response criterion (Table 2). The results showed that 5/41 patients achieved this amended TMA response. The estimated response rate was 12.2% with a 95% confidence interval of 4.1% to 26.2%.

Table 2: Amended Complete TMA Response and Individual Component Response During the 26-week Treatment Period using Composite Endpoint Strategy (Full Analysis Set)

Assessment	Amended Complete TMA response	Protocol Complete TMA response
Amended Complete TMA response during 26-week Treatment Period [a]		
Responders (n/m)	5/41	7/41
Percentage and 95% confidence interval	12.2 (4.1, 26.2)	17.1 (7.2, 32.1)
Individual components of TMA response		
Platelet count		
Responders (n/m)	24/41	24/41
Percentage and 95% confidence interval	58.5 (42.1, 73.7)	58.5 (42.1, 73.7)
LDH		
Responders (n/m)	15/41	15/41
Percentage and 95% confidence interval	36.6 (22.1, 53.1)	36.6 (22.1, 53.1)
Proteinuria assessed by Protein/Creatinine ratio		
Responders (n/m)	22/41	22/41
Percentage and 95% confidence interval	53.7 (37.4, 69.3)	53.7 (37.4, 69.3)
Hemoglobin		
Responders (n/m)	17/41	N/A
Percentage and 95% confidence interval	41.5 (26.3, 57.9)	

Note: n = number who meet criteria and have a confirmatory result, m = number in the population.
[a] Amended TMA response required the following:
1) A platelet count ≥ 50000 mm^3 or ≥ 50% increase in platelet count (depending on baseline platelet count) without transfusion support during the prior 7 days.
2) LDH normalization and absence of schistocytes.
3) Proteinuria, of at least 50% reduction in UPCR from Baseline.
4) Hemoglobin response defined as hemoglobin ≥10 g/dL without receipt of transfusion during the prior 7 days.
Participants must have met each TMA criterion at 2 separate assessments obtained at least 24 hours apart, with no criteria failures or more than 1 missed scheduled visit in between. Additionally, all intervals in which the criteria were met must overlap for at least 1 day. Participants with an intercurrent event as defined in the SAP prior to response were assigned as non-responders for this analysis.
95% CIs for the percentage were based on exact confidence limits using the Clopper-Pearson method.

Assessment to MAH's response:

The MAH has provided comprehensive data on Hb response, including an amended analysis in which Hb ≥10 g/dL (without transfusion support) was incorporated as a mandatory criterion within the definition of complete TMA response. In this amended analysis, 5/41 participants (12.2%) achieved an Hb-inclusive complete TMA response, compared with 7/41 participants (17.1%) using the original three-component definition (platelets, LDH, proteinuria). This result is consistent with the expected lower responder rate when haemoglobin is added as a required component, given the multifactorial influences on Hb in HSCT-TMA (inflammation, marrow suppression, transfusion burden, renal impairment) as recognized by the MAH.

The MAH appropriately acknowledges the limitations of haemoglobin as a marker of microangiopathy activity, particularly its delayed kinetics and the strong confounding from transfusion practices. Nonetheless, the recent consensus mentioned by the MAH (Schoettler et al., 2025) also recognises haemoglobin as a relevant component for assessing treatment response in TMA after hematopoietic cell transplantation, especially when integrated with other organ-specific parameters and hematologic markers.

As expected, incorporating haemoglobin leads to a smaller proportion of responders. However, given the very limited number of participants and the heterogeneity of clinical profiles, no firm conclusions can be drawn regarding the complete haematological response rates achieved by the participants due to the effect of ravulizumab.

Conclusion

Issue solved.

Question 3:

The MAH is requested to provide further discussion regarding the impact of ravulizumab on renal and CNS. This should include specific information on the incidence of dialysis requirements and the progression of CNS dysfunction, categorized by responder status to better characterize the drug's influence on organ-specific morbidity.

MAH's response:

Renal function:

In ALXN1210-TMA-314, treatment with ravulizumab resulted in mean UPCR improvement from a median of 2.5 mg/mg at baseline (n=41) to 0.43 mg/mg at week 26 (n=21) and 0.24 mg/mg at week 52 (n=21), which represents normalization.

Dialysis:

A total of 9/41 patients received dialysis treatment during the 52-week study (8 haemodialysis/continuous venovenous hemofiltration, 1 peritoneal dialysis)

- 2/41 patients were on dialysis at baseline; 1 died at Day 41 and the other survived and had a complete TMA response
- 7 patients started dialysis during the 52-week study period; 6/7 of these patients died; the surviving patient had partial TMA response (platelet and LDH responses)

Table 3: Characteristics of patients receiving dialysis treatment during the 52-week study

Age (years), sex	Dialysis Details	Relevant Medical History	Survival Status Cause of Death, if Deceased	TMA Response Complete	Partial	Hematologic
Dialysis at Baseline						
[redacted]	Hemodialysis D-5 to D4	Ongoing AKI stage 3 acute kidney failure	Deceased D41 Multi-organ failure secondary to a pulmonary TMA	N	N	N
[redacted]	Peritoneal dialysis D-7 ongoing	Ongoing kidney dysfunction and renal tubular acidosis	Completed Study	Y D86	Platelet D16 UPCR D44 LDH D86	Y D86
Dialysis Started During the Study						
[redacted]	Hemofiltration D17 to D27, Hemodialysis D28 to D140	Acute renal failure (dates unknown) Ongoing AKI – probably drug induced	Deceased D203 Underlying disease progression	N	N	N
[redacted]	Hemodialysis D21 ongoing	Ongoing dysplastic left kidney Previous hemofiltration (dates unknown)	Discontinued D287*	N	Platelet D127 LDH D185	N

[redacted]		Renal impairment pre-HSCT				
	Hemodialysis D87 to D92	-	Deceased D92 Hypoxic respiratory failure underlying cause: disseminated adenovirus	N	N	N
	Hemodialysis D26 to D156	-	Deceased D157 Heart failure	N	N	N
	Continuous veno-venous hemofiltration D46 ongoing	Diuresis (resolved Day 44)	Deceased D63 Septic shock – unknown pathogen	N	N	N
	Hemodialysis D23 to D197	Ongoing hematuria and renal failure	Deceased D197 Underlying disease progression	N	N	N
	Hemodialysis D54 to D284	Ongoing renal failure	Deceased D284 Circulatory insufficiency due to intraperitoneal hemorrhage	N	N	N

*Patient was discontinued from the study due to moving to a hospital that was not involved in the study.

CNS Dysfunction

As per the study protocol, symptoms of CNS dysfunction were defined as the presence of posterior reversible encephalopathy syndrome (PRES), headache, confusion, visual, loss, seizures, and "other" (defined by the investigator).

CNS dysfunction was reported in 7.3% (3/41) of participants at baseline; and an additional 11/38 (28.9%) participants without symptoms at baseline reported CNS dysfunction after study entry, with resolution in the majority of cases. CNS dysfunction was reported in 10.0% (3/30) of participants at the end of the primary treatment period (at week 26). Due to the small sample size of participants experiencing CNS dysfunction, no meaningful conclusions can be made.

At baseline, 3/41 patients were reported with any CNS dysfunction: 1 headache, 2 'other' (recent cerebral bleed, sedated for ventilation, and persistent abnormalities in pons; neurological injury causing increased secretions).

Symptoms of CNS dysfunction were reported at any time through final follow-up of the study in 14/41 patients.

Table 4: Characteristics of patients with CNS dysfunction during the study period

Age (years), sex	CNS Dysfunction	Survival Status	TMA Response		
			Complete	Partial	Hematologic
CNS Dysfunction at Baseline					
[redacted]	Headache, D1 Visual loss, D99 Other – blurring of vision – secondary to uveitis glaucoma, D365	Completed Study	N	Y Platelet D85	N
[redacted]	Other - recent cerebral bleed. Sedated for ventilation, Screening, and D1 Other – right intraventricular bleeding, D5 Other – previous cerebral bleed, D15 Confusion, D21, D57 Other – hemiparesis left-related to medical history, D57, D85, D99 Visual loss, D183 Other – upper and lower limb weakness – longstanding; no clinical change, D239	Discontinued D287*	N	Y LDH D85 Platelet D127	N
[redacted]	Other - persistent abnormalities in pons; neurologic injury causing increased secretions, Screening ongoing Other - persistent abnormalities in pons; neurologic injury causing increased secretions, D5, D10. Added: abnormal mentation (clinched fists, clonus at ankles) suggestive of neurological injury, D15, D29; improving at D21 Other – limbic encephalitis; concern of HHV-6 in brain, persistent abnormalities in pons; neurologic injury causing increased secretions. Abnormal mentation suggestive of neurological injury, D43 Other - abnormal mentation (clinched fists, clonus at ankles) suggestive of neurological injury at D57; Pons abnormalities almost resolved at D57	Deceased D63 Septic shock	N	N	N
CNS Dysfunction Started During the Study					
[redacted]	Other – intermittent headache, D127, D239 Other – difficulty concentrating, D239	Completed Study	N	Y UPCR D9 Platelet D15	N
[redacted]	Other – bilateral hyporeactive mydriasis, D5, D10, D15	Deceased D41 Multi-organ failure	N	N	N

[redacted]	Other – second episode of bilaterial mydriasis, D21, D29	secondary to a pulmonary TMA			
	Headache, D57	Deceased D203 Underlying disease progression	N	N	N
	Other – neurological changes, D85, D127	Completed Study	N	Y UPCR D10 Platelet D125	N
	Headache, D183	Completed Study	N	Y Platelet D10 UPCR D127	N
	Headache, D15, D29-126, D183, D239 PRES, D5-99	Deceased D256 Underlying disease progression	N	Y UPCR D13	N
	Headache, D22	Deceased D192 Septic shock which progressed to multiple organ failure, ARDS, and bleeding diathesis leading to death	N	N	N
	Headache, D56	Deceased D167 Mucormycosis	N	Y LDH D28	N
	Seizures, D10, D15 Other - motor weakness present; limited movement of upper extremity; delayed milestones, D43; improving at D71 Other – motor weakness, D239	Completed Study	N	Y UPCR D21 Platelet D44 LDH D56	Y D56
	Headache, D21, D365	Completed Study	N	Y UPCR D9 Platelet D29	N
	Headache, D10	Completed Study	N	Y UPCR D9 Platelet D29	N

*Patient was discontinued from the study due to moving to a hospital that was not involved in the study.

Assessment to MAH's response:

The MAH has provided additional information regarding the incidence and evolution of renal and CNS dysfunction in participants enrolled in ALXN1210-TMA-314. Based on the data submitted, no clear signal suggesting that ravulizumab contributes to renal or CNS deterioration can be identified, although

the interpretation remains inherently limited by the single-arm design of the study and the small number of participants.

Dialysis:

Among the seven participants who initiated dialysis during the study, only one achieved a partial TMA response. While the size of this subgroup is very small, the distribution of clinical responses does not suggest that ravulizumab is associated with worsening renal function leading to dialysis initiation. Rather, the need for dialysis likely reflects the underlying severity of HSCT-TMA and the heterogeneous baseline renal status of the enrolled population.

CNS dysfunction:

A total of eleven participants experienced CNS dysfunction during the study. Of these, eight achieved a partial TMA response, indicating that CNS involvement did not preclude clinical improvement according to the predefined response criteria. It is noteworthy that in six of the eleven participants, at least one recorded CNS dysfunction consisted of headache, a common symptom in this clinical context and not indicative of structural neurological injury. Nevertheless, more severe manifestations, including seizures, epilepsy, and PRES, were also reported among TMA partial responders. Given the diversity of CNS presentations and the absence of a comparator arm, it is difficult to isolate whether these events reflect the natural course of HSCT-TMA, comorbidities, concurrent medications, or a potential effect of ravulizumab.

Overall considerations:

The small number of participants included in the ALXN1210-TMA-314 study, the broad heterogeneity of clinical presentations, and the open-label, single-arm design significantly limit the interpretability of the findings regarding the efficacy and safety of ravulizumab in paediatric patients with HSCT-TMA. At present, the available evidence does not indicate that ravulizumab contributes to renal deterioration or CNS morbidity. Additional data is expected to further characterise the efficacy and organ-specific safety profile of ravulizumab in HSCT-TMA in future studies. The MAH is conducting the ALXN1210-TMA-313 clinical trial, which focuses on adolescent and adult patients but does not include paediatric patients from 1 month to 18 years of age. Therefore, its ability to clarify the specific contribution of ravulizumab to organ outcomes in the paediatric population will remain limited.

Conclusion

Issue solved.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Ultomiris Active substance: ravulizumab

Study title	Study number	Date of completion	Date of submission of final study report
A Phase 3, Open-label, Single-Arm, Multicenter Study of Ravulizumab in Addition to Best Supportive Care in Pediatric Participants (from 1 month to <18 years of age) with Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplantation (HSCT)	ALXN1210-TMA-314	27-May-2025	By 27-Nov-2025
A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Ravulizumab in Adult and Adolescent Participants who have Thrombotic Microangiopathy (TMA) after Hematopoietic Stem Cell Transplant (HSCT)	ALXN1210-TMA-313	Primary evaluation period completed on 19 Sep 2025, follow up period ongoing	Within 6 months of last patient last visit in accordance with Art 46 of European Paediatric Regulation