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Human Medicines Division

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

Soliris

Eculizumab

Procedure no: EMA/PAM/0000314962

Note

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

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1. Introduction

Soliris (eculizumab) was initially approved in the EU for the treatment of paroxysmal nocturnal haemoglobinuria (PNH) in 2007. An extension of the therapeutic indication was approved in the EU for inclusion of treatment of atypical haemolytic uremic syndrome (aHUS) in adult and paediatric patients on 24 Nov 2011 (EMEA/H/C/000791/II/027). Efficacy and safety data for this indication were later updated within procedures EMEA/H/C/000791/II/0058/G, EMEA/H/C/000791/II/0071/G and EMEA/H/C/000791/II/0102. The currently authorised indications for Soliris and date of approval can be found in Table 1 Table 2below.

Table 1. Dates of Approval of Soliris by Indication in EU

Product	Indication	Date of EU Approval (EC Decision)
Soliris	PNH	20 Jun 2007
	aHUS	24 Nov 2011
	gMG	14 Aug 2017
	NMOSD	26 Aug 2019

On 18 November 2025, the MAH submitted a completed paediatric study (Study ECU-aHUS-302, completion date 7 May 2025) for Soliris, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure(s).

2. Scientific discussion

2.1. Information on the development program

The MAH presents an addendum to the original Clinical Overview for eculizumab (Soliris®)

This addendum updates the results from Study ECU-aHUS-302, which was a post-approval commitment study, agreed to as a condition for approval in China. Eculizumab is approved in China for the treatment of aHUS in children and adults. The therapeutic efficacy and safety of eculizumab was demonstrated in 3 global pivotal clinical studies conducted at study sites outside of China for registration.

The purpose of this commitment study was to assess the efficacy and safety of eculizumab in participants with aHUS in China.

The MAH stated that Study ECU-aHUS-302 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Table 2. Study Intervention

Study Intervention Name	Eculizumab		
Type	Monoclonal antibody		
Dose Formulation	Sterile liquid		
Unit Dose Strength(s)	300 mg/30 mL (10 mg/mL) as a clear, colorless solution in a single-dose vial		
Dosage Level(s)	Dosing is based on body weight as follows:		
	Body weight	Induction	Maintenance
	≥ 40 kg	900 mg weekly × 4 doses	1200 mg at Day 29; then 1200 mg every 2 weeks
	30 to < 40 kg	600 mg weekly × 2 doses	900 mg at Day 15; then 900 mg every 2 weeks
	20 to < 30 kg	600 mg weekly × 2 doses	600 mg at Day 15; then 600 mg every 2 weeks
	10 to < 20 kg	600 mg weekly × 1 dose	300 mg at Day 8; then 300 mg every 2 weeks
	5 to < 10 kg	300 mg weekly × 1 dose	300 mg at Day 8; then 300 mg every 3 weeks
Route of Administration	Intravenous infusion		
Use	Experimental		
IMP and NIMP	IMP		
Sourcing	Provided centrally by Alexion or contracted manufacturing organization		
Packaging and Labeling	Eculizumab will be provided in glass vials and stoppered with a butyl rubber stopper with an aluminum overseal and a flip-off cap. Eculizumab will be supplied in kits and labeled as required per country requirement.		

Abbreviations: IMP = investigational medicinal product; NIMP = non-investigational medicinal product

After dilution, the final concentration of the solution to be infused is 5 mg/ml.

No specific paediatric formulation is available nor required.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study ECU-aHUS-302, a Prospective, Single-Arm, Multicenter Study to Evaluate the Efficacy, Safety, Pharmacokinetics, Pharmacodynamics, and Immunogenicity of Eculizumab in Complement Inhibitor Treatment-Naïve Pediatric and Adult Participants with Atypical Hemolytic Uremic Syndrome (aHUS) in China.

2.3.2. Clinical study

Study ECU-aHUS-302

Methods

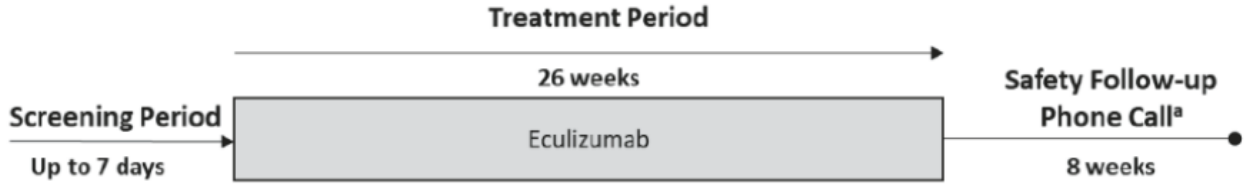
Study ECU-aHUS-302 was a Phase 3b, open-label, single-arm, multicenter study designed to evaluate the efficacy, safety, PK, PD, and immunogenicity of eculizumab in complement inhibitor treatment-naïve pediatric and adult participants with aHUS in China.

The results presented in the report cover the study period from 14 Jul 2023 (first participant first visit) to 07 May 2025 (last participant last visit; clinical data lock date of 04 Jun 2025).

The study consisted of the following periods (up to 35 weeks in total):

- Screening Period: up to 7 days
- Treatment Period: 26 weeks
- Safety Follow-up Phone Call: 8 weeks

Figure 1. Study Schema



The 8-week Safety Follow-up Phone Call was required only for:

1. Participants who discontinued eculizumab treatment during the study
2. Participants who did not receive continued access to eculizumab after completing study treatment.

After providing informed consent/assent, participants were to be screened for eligibility for the study during the 7-day Screening Period. If all inclusion criteria and none of the exclusion criteria were met, participants were enrolled and vaccinated against N meningitidis if not already vaccinated within the period of active coverage specified by the vaccine manufacturer. Participants who were vaccinated less than 14 days prior to receiving the first dose of eculizumab would receive treatment with appropriate antibiotics until 14 days after the vaccination.

Study participants

Inclusion criteria

Participants were eligible to be included in the study only if all of the following criteria were met:

- **Age:**
  1. Participants of any age weighing ≥5 kg.
- **Type of Patient and Disease Characteristics**
  2. Complement treatment naïve with evidence of thrombotic microangiopathy (TMA), including thrombocytopenia, evidence of haemolysis, and kidney injury, based on the following laboratory findings:
     a. Platelet count < 150000/µL during the Screening Period or within 28 days prior to the start of the Screening Period, **and**
     b. Lactate dehydrogenase (LDH) ≥1.5 × upper limit of normal (ULN) during the Screening Period or within 28 days prior to the start of the Screening Period, and hemoglobin ≤ lower limit of normal (LLN) for age and gender during the Screening Period or ≤28 days prior to the start of the Screening Period, **and**
     c. Serum creatinine level ≥ ULN in adults (≥18 years of age), or ≥97.5th percentile for

age at Screening in children (< 18 years of age) (participants who require dialysis for < 3 months are also eligible)

3. Among participants with a kidney transplant:
   a. Known history of aHUS prior to current kidney transplant, **or**
   b. If no known history of aHUS, persistent evidence of TMA at least 4 days after modifying the immunosuppressive regimen (eg, suspending or reducing the dose) of calcineurin inhibitor (CNI; eg, cyclosporine, tacrolimus) or mammalian target of rapamycin inhibitor (mTORi; eg, sirolimus, everolimus)
4. Among participants with onset of TMA postpartum, persistent evidence of TMA for > 3 days after the day of childbirth.
5. Participants must be vaccinated at least 14 days prior to receiving the first dose of eculizumab or be vaccinated and receive treatment with appropriate antibiotics until 14 days after the vaccination, to reduce the risk of meningococcal infection (N meningitidis).
6. Participants < 18 years of age must have been vaccinated against Haemophilus influenzae type b (Hib) and Streptococcus pneumoniae according to local vaccination schedule guidelines.
7. In participants receiving treatment with medications known to cause TMA, persistent evidence of TMA at least 4 days after modifying the excluded medication (eg, gemcitabine, calcineurin inhibitor [CNI; eg, cyclosporine, tacrolimus], or mammalian target of rapamycin inhibitor [mTORi; eg, sirolimus, everolimus]).

- **Weight**

8. Body weight ≥ 5 kg.

- **Sex**

9. Male and/or female.
10. Female participants of childbearing potential and male participants must follow protocol-specified contraception guidance.

Exclusion criteria

Participants were excluded from the study if any of the following criteria were met:

- **Medical conditions**

1. Known familial or acquired ADAMTS13 deficiency (activity < 5%).
2. Shiga toxin-related haemolytic uremic syndrome (ST-HUS) as demonstrated by local guidelines.
3. Positive direct Coombs test which, in the judgement of the Investigator, is indicative of a clinically significant immune-mediated haemolysis not due to aHUS.
4. Known human immunodeficiency virus (HIV) infection.
5. Unresolved meningococcal disease.
6. Confirmed diagnosis of ongoing sepsis defined as positive blood cultures within 7 days prior to the start of Screening and untreated with antibiotics.

7. Presence or suspicion of active and untreated systemic infection that, in the opinion of the Investigator, confounds an accurate diagnosis of aHUS or impedes the ability to manage the aHUS disease.
8. Heart, lung, small bowel, pancreas, or liver transplant.
9. Among participants with a kidney transplant, acute kidney dysfunction within 4 weeks of transplant consistent with the diagnosis of acute antibody-mediated rejection according to Banff 2013 criteria.
10. Among participants without a kidney transplant, history of kidney disease other than aHUS, such as:
    a. Known kidney biopsy finding suggestive of underlying disease other than aHUS
    b. Known kidney ultrasound finding consistent with an alternative diagnosis to aHUS (eg, small kidneys for age)
    c. Known family history and/or genetic diagnosis of noncomplement-mediated genetic renal disease (eg, focal segmental glomerulosclerosis)
11. Identified drug exposure-related HUS.
12. History of malignancy within 5 years of Screening with the exception of a nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
13. Bone marrow transplant/hematopoietic stem cell transplant within 6 months prior to the start of Screening.
14. HUS related to vitamin B12 deficiency.
15. HUS related to known genetic defects of cobalamin C metabolism.
16. Known systemic sclerosis (scleroderma), systemic lupus erythematosus, or antiphospholipid antibody positivity or syndrome.
17. Chronic dialysis (defined as dialysis on a regular basis as renal replacement therapy for ESKD for >3 months).
18. Prior use of eculizumab or other complement inhibitors.
19. Use of tranexamic acid within 7 days prior to the start of Screening.

- **Prior/Concomitant therapy**

20. Receiving plasma exchange/plasma infusion ≤ 28 days prior to the start of Screening.
21. Receiving other immunosuppressive therapies such as steroids, mTORi (eg, sirolimus, everolimus), CNI (eg, cyclosporine or tacrolimus) are excluded unless:
    a. Part of an established post-transplant antirejection regimen, **or**
    b. Participant has confirmed anticomplement factor antibodies requiring immunosuppressive therapy, **or**
    c. Steroids are being used for a condition other than aHUS (eg, asthma), **or**
    d. Participant is experiencing an acute aHUS relapse immediately after transplant.

22. Receiving chronic intravenous immunoglobulin (IVIg) within 8 weeks prior to the start of Screening, unless for unrelated medical condition (eg, hypogammaglobinemia); or chronic rituximab therapy within 12 weeks prior to the start of Screening.

23. Received vasopressors or inotropes within 7 days prior to Screening.

- **Other Exclusions**

24. Hypersensitivity to any excipient in eculizumab, including hypersensitivity to murine proteins.

25. Pregnant, breastfeeding, or intending to conceive during the course of the study.

26. Any medical or psychological condition that, in the opinion of the Investigator, could increase the risk to the participant by participating in the study or confound the outcome of the study.

Laboratory results for Exclusion Criterion 1 and/or Exclusion Criterion 2 may not be available prior to first dose. Later results for Exclusion Criterion 1 and/or Exclusion Criterion 2 could lead to discontinuation of study intervention and replacement of the participant.

Treatments

Eculizumab was administered by IV infusion according to body weight as described in the table below:

Table 3. Eculizumab Induction and Maintenance Dosing by Weight Cohort

Body Weight	Induction	Maintenance
≥ 40 kg	900 mg weekly × 4 doses	1200 mg at Day 29; then 1200 mg every 2 weeks
30 to < 40 kg	600 mg weekly × 2 doses	900 mg at Day 15; then 900 mg every 2 weeks
20 to < 30 kg	600 mg weekly × 2 doses	600 mg at Day 15; then 600 mg every 2 weeks
10 to < 20 kg	600 mg weekly × 1 dose	300 mg at Day 8; then 300 mg every 2 weeks
5 to < 10 kg	300 mg weekly × 1 dose	300 mg at Day 8; then 300 mg every 3 weeks

Note: Participants were weighed at each study visit as eculizumab dosing was based on the weight assessment.

Objective(s), Endpoints and Estimands

Table 4. Mapping of Objectives to Estimands and Endpoints

Objectives	Estimands and Endpoints
Primary	
To assess the efficacy of eculizumab in the treatment of participants with aHUS	• Population: Participants in the FAS (defined in Section 9.3). • Variable: Complete TMA Response during the 26-week Treatment Period (Section 3.1). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All participants who meet response criteria after ICE1 or ICE2 will be considered as nonresponders thereafter. • Summary measure: The proportion of complete TMA responders overall along with 95% CIs.

Secondary	
To characterize the safety and tolerability of eculizumab in participants with aHUS	• Population: Participants in the Safety Set (defined in Section 9.3). • Variable: Incidence of TEAEs and SAEs (Section 3.2). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention; o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be included. • Summary measure: Number and percentage of participants with TEAEs and SAEs and number of events by System Organ Class and Preferred Term.
To characterize the pharmacokinetics of eculizumab in participants with aHUS	• Population: Participants in the PK Analysis Set (defined in Section 9.3). • Variable: Serum eculizumab concentrations over time (Section 3.2). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. • Summary measure: Serum eculizumab concentrations at all available study visits.
To characterize the pharmacodynamics of eculizumab in participants with aHUS	• Population: Participants in the PD Analysis Set (defined in Section 9.3). • Variable: Mean change in serum free and total complement component 5 concentrations over time (Section 3.2). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. • Summary measure: Mean change in serum free and total complement component 5 concentrations from baseline over time at all study visits.

Objectives	Estimands and Endpoints
To characterize the immunogenicity of eculizumab in participants with aHUS	• Population: Participants in the Safety Set (defined in Section 9.3). • Variable: Proportion of participants who develop ADA and neutralizing antibodies (Section 3.2). • Treatment: Eculizumab • ICE: o ICE1: premature discontinuation of study intervention o ICE2: initiation of disallowed therapy or medicine All data after ICE1 or ICE2 will be used. • Summary measure: Proportion of participants at all study visits with ADA positive and neutralizing antibody titers.
Additional Secondary	
To evaluate the efficacy of eculizumab and characterize TMA by additional measures	• Time to Complete TMA Response • Dialysis requirement status over time • Observed value and change from baseline in estimated glomerular filtration rate (eGFR) at all scheduled visits • Chronic kidney disease (CKD) stage classified as improved, stable (no change), or worsened at all scheduled visits compared to baseline • Observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin) at all scheduled visits • Increase in hemoglobin of ≥ 20 g/L from baseline through Week 26
To characterize the safety profile of eculizumab by additional safety measures	• Changes from baseline in vital signs and laboratory parameters at scheduled visits

Abbreviations: ADA = antidrug antibody; aHUS = atypical hemolytic uremic syndrome; CI = confidence interval; FAS = Full Analysis Set; ICE = intercurrent event; LDH = lactate dehydrogenase; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TMA = thrombotic microangiopathy

Results

Participant disposition and protocol deviations

A total of 28 participants diagnosed with aHUS were screened in this study and of these, 3 participants failed the screening process. Twenty-five participants were assigned and received eculizumab treatment.

Table 5. Disposition

	Eculizumab n (%)
Participants screened	28
Participants screened failure	3
Participants assigned	25
Participants assigned, not treated	0
Participants started treatment	25 (100)
Participants completed treatment	22 (88.0)
Participants discontinued treatment	3 (12.0)
Development of study specific discontinuation criteria	1 (4.0)
Other[a]	2 (8.0)
Participants completed study	22 (88.0)

	Eculizumab n (%)
Participants withdrawn from study	3 (12.0)

Note: Participants screened were those who signed informed consent/assent.
Participants assigned were those who passed Screening and were eligible for the study.
Percentages were based on the number of participants who started treatment.
[a] The reasons for treatment discontinuation were the Sponsor's request and participant's parental decision.
Source: Table 14.1.1

Protocol Deviations

Important protocol deviations were reported in 11 (44.0%) participants, and the majority of important protocol deviation related to inclusion criteria (10 out of 11 participants) which was mainly due to Chinese vaccination guidelines on meningococcal vaccination and the local clinical practice on Hib vaccination.

The participants with the important protocol deviations related to vaccination received prophylactic antibiotic treatment to prevent infection, and none of these participants developed the corresponding infection.

Table 6. Important Protocol Deviations (Safety Set)

	Eculizumab N = 25 n (%)
Participants with at least 1 important protocol deviation	11 (44.0)
Inclusion criteria	10 (40.0)
Exclusion criteria	1 (4.0)
IP deviation	1 (4.0)
Excluded medication taken	1 (4.0)
Deviations related to study procedure	1 (4.0)
Other important protocol deviations	1 (4.0)

Note: The same participant might have more than 1 important protocol deviation.

Analysis Sets

Table 7. Analysis Sets

	Eculizumab n
Screened Set	28
Safety Set	25
Excluded from Safety Set	3
Not treated	3
FAS	25
Excluded from FAS	3
Not treated	3

PK Analysis Set	25
Excluded from PK Analysis Set	3
Not treated	3
PD Analysis Set	25
Excluded from PD Analysis Set	3
Not treated	3
Per-Protocol Set	23
Excluded from Per-Protocol Set	2
Excluded medications taken	1
Exclusion criteria deviations	1

Note: The same participant could have been excluded from an analysis set for more than 1 reason.

Baseline data

Table 8. Demographics and Baseline Characteristics (Full Analysis Set)

	Statistic	Eculizumab N = 25
Age at first infusion (years)		
	n	25
	Mean	23.40
	SD	15.95

Age group at first infusion (years)		
Birth to < 2 years	n (%)	2 (8.0)
2 to < 6 years	n (%)	0
6 to < 12 years	n (%)	7 (28.0)
12 to < 18 years	n (%)	2 (8.0)
≥ 18 years	n (%)	14 (56.0)
Sex		
Male	n (%)	19 (76.0)
Female	n (%)	6 (24.0)
Race		
Asian	n (%)	25 (100)
Ethnicity		
Not Hispanic or Latino	n (%)	24 (96.0)
Missing	n (%)	1 (4.0)
Height at first infusion (cm)		
	n	25
	Mean	152.42
	SD	31.86
	Min	68.0
	Median	164.00
	Max	193.0
Weight at first infusion (kg)		
	n	25
	Mean	58.616
	SD	31.050
Weight group at first infusion (kg)		
≥ 5 to < 10 kg	n (%)	0
≥ 10 to < 20 kg	n (%)	2 (8.0)
≥ 20 to < 30 kg	n (%)	5 (20.0)
≥ 30 to < 40 kg	n (%)	1 (4.0)
≥ 40 kg	n (%)	17 (68.0)

Table 9. Disease Characteristics at Baseline (FAS)

	Statistic	Eculizumab N = 25
Age at first aHUS symptoms (years)		
	n	25
	Mean	23.19
	SD	16.04
	Min	0.8
	Median	23.80
	Max	58.9
Age at aHUS diagnosis (years)		
	n	25
	Mean	23.35
	SD	15.94
	Min	0.8
	Median	23.80
	Max	58.9
ADAMTS-13 (% activity)		
≥ 5%	n (%)	21 (84.0)
< 5%	n (%)	0
Missing	n (%)	4 (16.0)
Participant with plasma exchange/infusion, related to the current TMA, and prior to the first dose of study drug		
Yes	n (%)	17 (68.0)
No	n (%)	8 (32.0)
Participants with kidney dialysis, within 5 days prior to the first dose of study drug		
Yes	n (%)	11 (44.0)
No	n (%)	14 (56.0)
Whether the dialysis is of regular or not[a]		
Yes	n (%)	8 (72.7)
No	n (%)	3 (27.3)

Note: Pre-treatment plasma exchange/infusion is defined as plasma exchange/infusion prior to the first infusion of study drug. Participants could have been counted in multiple types of plasma exchange/infusion.
Pre-treatment kidney dialysis is defined as dialysis within 5 days prior to the first dose of study drug.
[a]Percentages were based on the number of participants with kidney dialysis within 5 days prior to the first dose of study drug.

Number analysed

PK Results

A summary and a box-plot (linear scale) of serum concentration of eculizumab over time are presented below:

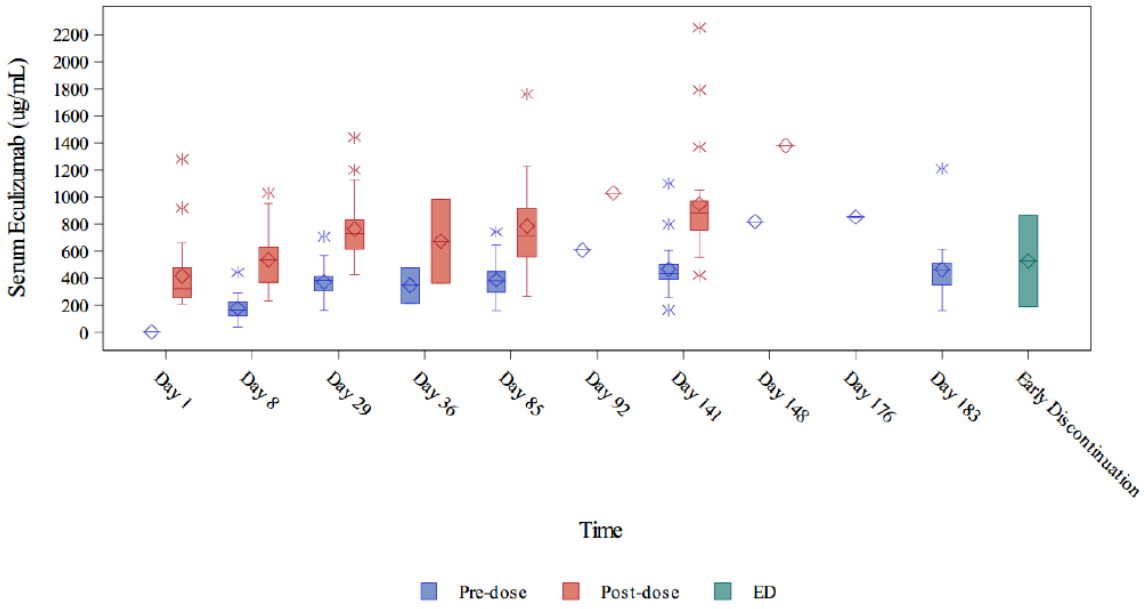
Table 10. Serum Concentrations (µg/mL) of Eculizumab Over Time (PK Analysis Set)

Timepoint		n	N < LLOQ	Arithmetic Mean	Arithmetic SD	Geometric Mean	GeoCV%	Min	Median	Max
Day 1	Pre-dose	25	25	4.690	0.000	4.690	0.00	4.69	4.690	4.69
	Post-dose	25	0	418.280	243.157	373.423	47.59	210.00	326.000	1280.00
Day 8	Pre-dose	24	0	179.725	93.463	153.190	69.69	38.40	169.500	444.00
	Post-dose	24	0	536.792	214.260	498.262	41.18	234.00	538.000	1030.00
Day 29	Pre-dose	21	0	374.905	128.560	353.726	36.96	167.00	385.000	709.00
	Post-dose	21	0	763.905	254.460	727.862	32.22	430.00	734.000	1440.00
Day 36	Pre-dose	2	0	349.000	186.676	323.074	NC	217.00	349.000	481.00
	Post-dose	2	0	676.000	436.992	601.245	NC	367.00	676.000	985.00
Day 85	Pre-dose	21	0	389.667	153.207	360.070	43.89	165.00	383.000	744.00
	Post-dose	21	0	786.524	325.937	728.624	42.04	272.00	711.000	1760.00
Day 92	Pre-dose	1	0	608.000	NC	608.000	NC	608.00	608.000	608.00
	Post-dose	1	0	1030.000	NC	1030.000	NC	1030.00	1030.000	1030.00
Day 141	Pre-dose	21	0	467.571	197.216	433.737	41.32	166.00	436.000	1100.00
	Post-dose	21	0	949.810	415.483	883.675	38.74	423.00	886.000	2250.00
Day 148	Pre-dose	1	0	821.000	NC	821.000	NC	821.00	821.000	821.00
	Post-dose	1	0	1380.000	NC	1380.000	NC	1380.00	1380.000	1380.00
Day 176	Pre-dose	1	0	853.000	NC	853.000	NC	853.00	853.000	853.00
Day 183	Pre-dose	21	0	465.810	200.163	434.739	38.66	164.00	462.000	1210.00
ED		2	0	529.000	479.418	406.103	NC	190.00	529.000	868.00

The geometric mean concentrations of eculizumab at pre-dose visits (excluding Day 1) range from 153.190 to 853.000 µg/mL. The geometric mean concentrations of eculizumab at post-dose visits range from 498.262 to 1380.000 µg/mL (excluding Day 1).

All the serum concentrations of eculizumab after first dose were higher than 50 µg/mL, except for 3 pre-dose samples from Participants (at Day 9 (one) and Day 8 (the other two). These 3 participants did not receive plasma exchange/infusion during the study.

Figure 2. Box-plot of Serum Concentration (µg/mL) of Eculizumab Over Time (Linear Scale) (PK Analysis Set)



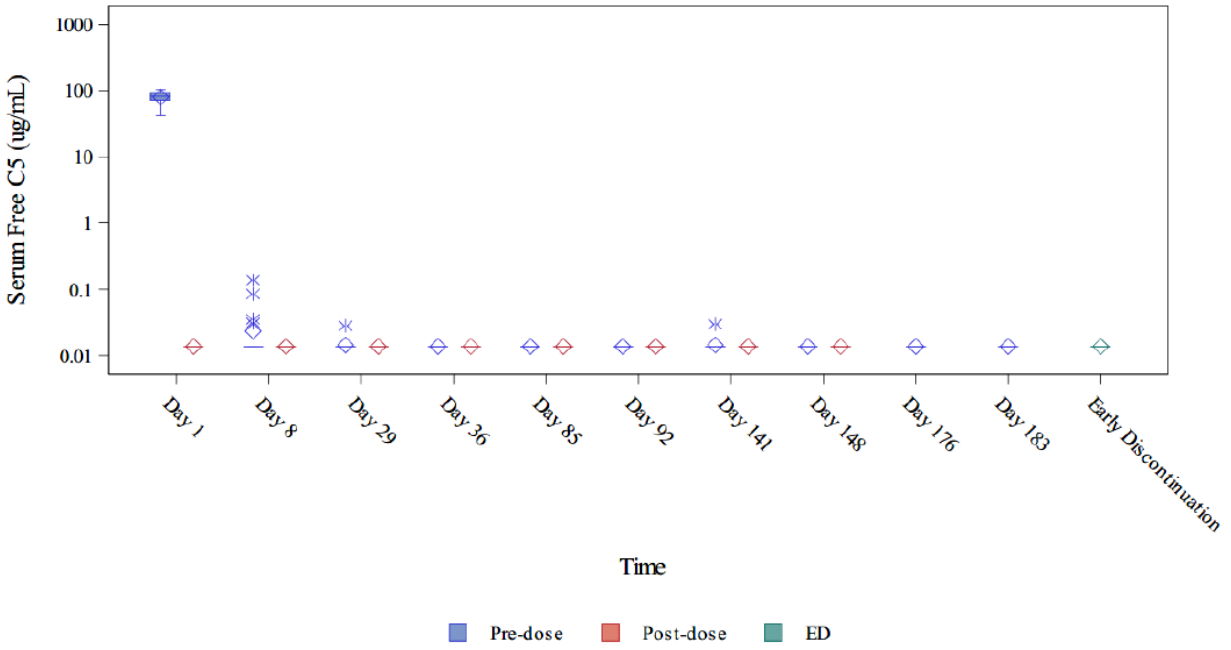
Note: The box limits represented the 25th and 75th percentile, the horizontal line was the median, diamond was the mean and whiskers showed range of observations up to 1.5 times the interquartile range. Outliers were represented by asterisk beyond the whiskers.

PD Results

Free Complement C5

The mean (SD) baseline of serum free C5 concentration is 79.8979 (17.5197) µg/mL. After the first dose on Day 1, the serum free C5 concentrations for all 25 participants were immediately inhibited to levels below LLOQ (0.0274 µg/mL). All individual free C5 concentrations in all participants after administering eculizumab were < 0.5 µg/mL.

Figure 3. Box-plot of Free C5 (µg/mL) Actual Values Over Time (Semi-log Scale) (PD Analysis Set)



Note: The box limits represented the 25th and 75th percentile, the horizontal line was the median, diamond was the mean, and whiskers showed range of observations up to 1.5 times the interquartile range. Outliers were represented by asterisk beyond the whiskers.

Total Complement C5

The mean (SD) serum total C5 concentration at Baseline is 69.9436 (14.3013) µg/mL, which decreased to 57.9169 (10.6342) µg/mL after the first dose. After initial dosing, the mean total C5 concentration increased over time.

Immunogenicity Results

No positive ADA response to eculizumab was observed in all the 25 participants in the Safety Set.

Table 11. Anti-drug antibody responses to eculizumab (Safety set)

	Statistic	Eculizumab N=25	
ADA negative at baseline and post-baseline	n/Nobs [a] (%)	25/25	(100)
ADA positive at baseline and/or post-baseline	n/Nobs [a] (%)	0/25	
ADA positive at baseline	n/Nobs [c] (%)	0/25	
Treatment-emergent ADA responses	n/Nobs [b] (%)	0/24	
Persistent treatment-emergent responses	n/Nobs [b] (%)	0/24	
Indeterminant treatment-emergent responses	n/Nobs [b] (%)	0/24	
Transient treatment-emergent responses	n/Nobs [b] (%)	0/24	
Treatment-boosted ADA responses	n/Nobs [b] (%)	0/24	
nAb negative: NAb-negative at all time points	n/Nobs [a] (%)	0/25	
nAb positive: NAb-positive at any time during the study	n/Nobs [a] (%)	0/25	

[a] Nobs is the number of subjects with an ADA result at baseline and/or post-baseline.
[b] Nobs is the number of subjects with an ADA result at baseline and at least one post-baseline assessment.

[c] Nobs is the number of subjects with an ADA result at baseline.

Efficacy results

All efficacy analyses were performed using the FAS (N = 25), and the sensitivity analyses of efficacy data were performed using PP Set (N = 23).

Primary Endpoint

The primary efficacy endpoint was **Complete TMA Response** during the 26-week treatment period, defined as:

1. Platelet count ≥ 150000/µL
2. lactate dehydrogenase (LDH) normalization (LDH ≤ upper limit of normal)
3. ≥ 25% improvement in serum creatinine from baseline

Participants had to meet all Complete TMA Response criteria concurrently, and each criterion had to be met at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

Table 12. Proportion of Complete TMA Responders during the 26-week Treatment Period: Composite Strategy (FAS)

	Responder	
	n/N	Proportion (95% CI)[a]
Complete TMA Response	16/25	0.640 (0.425, 0.820)
Components of Complete TMA Response		
Platelet count normalization	20/25	0.800 (0.593, 0.932)
LDH normalization	23/25	0.920 (0.740, 0.990)
≥ 25% improvement in serum creatinine from Baseline	16/25	0.640 (0.425, 0.820)
Hematologic normalization	20/25	0.800 (0.593, 0.932)

Note: The criteria for Complete TMA Response were: 1. normalization of platelet count 2. normalization of LDH 3. ≥ 25% improvement in serum creatinine from Baseline
Participants had to meet all Complete TMA Response criteria concurrently, and each criterion had to be met at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.
The proportion of Complete TMA Response was based on the responders among treated participants. The numerator was the number of participants achieving Complete TMA Response during the 26-week treatment period and the denominator was the number of participants in the FAS.

Hematologic normalization included normalization of platelet count and normalization of LDH.
Platelet values obtained from the day of a blood transfusion of platelets through 3 days after the transfusion were excluded from all analyses.
[a] 95% CIs for the proportion were based on exact confidence limits using the Clopper Pearson method.
Source: Table 14.2.1.1.1

The proportion of participants who achieved Complete TMA Response in the Per Protocol Set (sensitivity analysis) during the 26-week treatment period (65.2%; 95% CI: 42.7%, 83.6%) was similar to that observed in the FAS [16/25 (64.0%); 95% CI: 42.5%, 82.0%)].

A modified Complete TMA Response (which applied to the participants on dialysis at Baseline) was observed in 17 out of 25 participants (68%; 95% CI: 46.5%, 85.1%) in the FAS during the 26-week treatment period.

Table 13. Proportion of Modified Complete TMA Responders during the 26-week Treatment Period: Composite Strategy – Supplementary Analyses (FAS)

	Responder	
	n/N	Proportion (95% CI)[a]
Modified Complete TMA Response	17/25	0.680 (0.465, 0.851)
Components of modified Complete TMA Response		
Platelet count normalization	20/25	0.800 (0.593, 0.932)
LDH normalization	23/25	0.920 (0.740, 0.990)
≥ 25% improvement in serum creatinine from Baseline or post-baseline change in dialysis status	17/25	0.680 (0.465, 0.851)
Hematologic normalization	20/25	0.800 (0.593, 0.932)

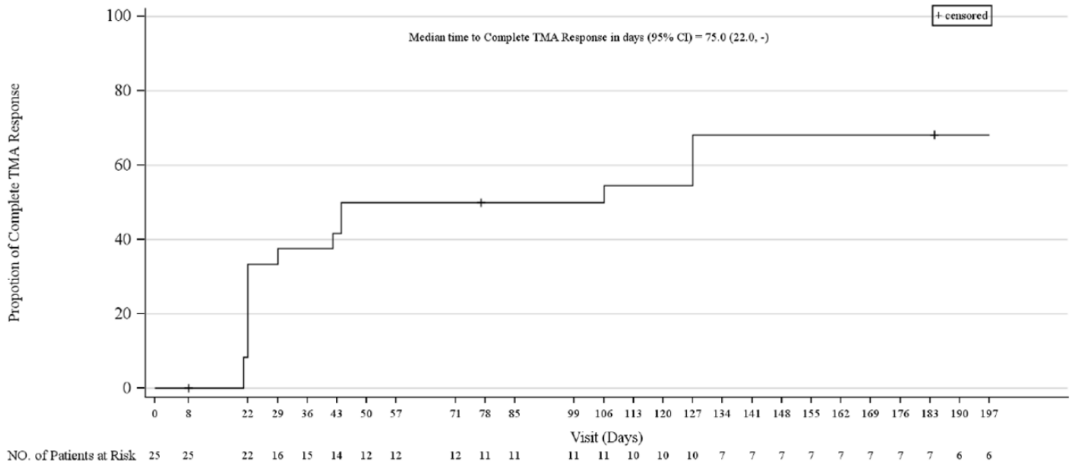
The modification to Complete TMA Response applied strictly to the participants on dialysis at Baseline (ie, participants requiring dialysis within 5 days prior to eculizumab treatment initiation). The definition of Complete TMA Response remained the same for all other participants.
Participant had to meet all modified Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. Hematologic normalization included normalization of platelet count and normalization of LDH.
Platelet values obtained from the day of a blood transfusion of platelets through 3 days after the transfusion were excluded from all analyses.

Secondary Endpoints

Time to Complete TMA Response

The median time to Complete TMA Response was 75 days and occurred in Day 22 visit following the first dose of eculizumab. The latest response was observed on Day 127 visit following the first dose of eculizumab.

Figure 4. Kaplan-Meier Cumulative Distribution Curve for Time to Complete TMA Response (FAS)

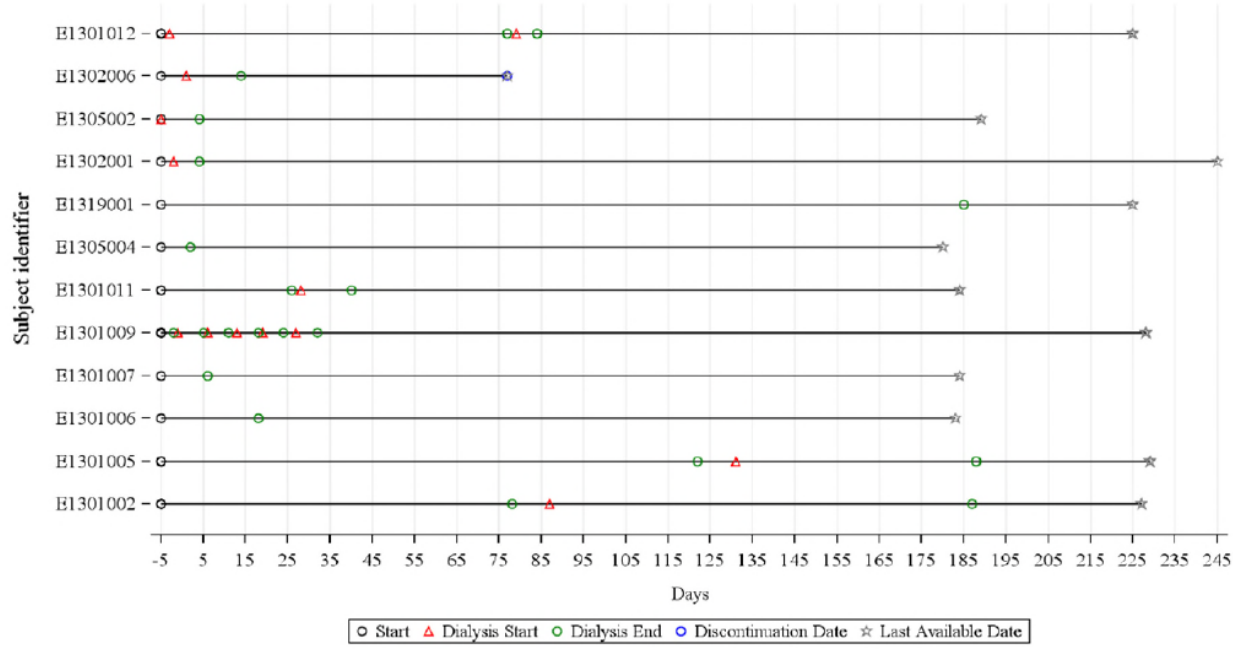


A Kaplan-Meier cumulative distribution curve is presented for time to Complete TMA Response in the FAS. Participants had to meet all Complete TMA Response criteria concurrently, and each criterion had to be met at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. Participants that did not have a response were censored at the date of last visit or study discontinuation at the time when the analysis was performed.

Dialysis requirement status

There were 11 participants who received kidney dialysis within 5 days prior to treatment start, and 1 additional participant started dialysis after receiving the first dose of eculizumab. All these 12 participants had discontinued dialysis by the end of the study or upon early withdrawal from the study.

Figure 5. Dialysis Events Over Time (FAS)



The figure represents the plot of dialysis events over time among participants who had dialysis within 5 days of treatment start or after the first dose in the Full Analysis Set (N=25). Day 1 is the Treatment Start Date. 5 days prior to Treatment Start Date is used as the start.

Change from Baseline in eGFR

Overall, the mean eGFR gradually improved from Baseline throughout the study after the participants received eculizumab. However, 3 participants reported eGFR of 10 mL/min/1.73 m^2 at the majority of the visits due to requiring dialysis for acute kidney injury and 1 participant reported lower eGFR values than Baseline at the majority of the visits.

Table 14. Change from Baseline in eGFR (mL/min/1.73 m^2) at Each Scheduled Visit: Treatment Policy (FAS)

Timepoint	Result			Change from Baseline		
	n	Mean	SD	n	Mean	SD
Baseline	24	21.02	17.93			
Day 8	1	76.10	-	1	22.40	-
Day 22	23	62.54	55.59	22	39.82	50.83
Day 29	1	153.10	-	1	138.35	-
Day 36	1	132.90	-	1	122.90	-
Day 43	17	59.31	61.06	16	32.72	44.75
Day 50	5	146.94	54.20	5	126.68	55.14
Day 57	1	10.80	-	1	-13.47	-
Day 71	19	67.71	65.13	18	40.33	47.38
Day 78	3	160.87	25.95	3	140.18	40.41
Day 85	1	19.50	-	1	-4.77	-
Day 99	17	64.97	62.76	16	37.53	47.17
Day 106	3	127.13	88.59	3	108.03	87.64
Day 113	18	63.42	61.52	17	35.88	45.38
Day 120	3	123.57	88.04	3	113.28	88.50
Day 127	18	63.63	65.07	17	35.85	48.01
Day 134	4	150.68	58.75	4	133.23	59.90
Day 141	1	15.20	-	1	-9.07	-
Day 148	1	141.40	-	1	131.40	-
Day 155	17	70.10	63.78	16	43.33	49.32
Day 162	1	223.00	-	1	213.00	-
Day 169	1	15.00	-	1	-9.27	-
Day 176	1	135.10	-	1	125.10	-
Day 183	18	61.93	53.71	17	36.29	44.21
Day 190	2	202.60	21.21	2	178.95	1.91
Day 197	2	71.10	78.49	2	53.97	88.58

Chronic kidney disease (CKD) stage

After treatment with eculizumab, there was a notable improvement in the participants' CKD stages, shifting from more severe stages (Stage 4 or 5) at Baseline to less severe stages over time. On Day 183 compared to Baseline: 12 out of 17 (70.6%) evaluable participants were classified as CKD Stage 5 at Baseline, and only 3 (17.6%) participants remained in Stage 5 on Day 183.

Hematologic parameters

The observed value and change from the Baseline in platelet, LDH, and haemoglobin at each schedule visit in the FAS are presented below.

The platelet counts at Baseline were less than 150 x 10^9 /L for all the participants, and the platelet levels were generally increased relative to Baseline and improved to be within normal limits after treatment.

Table 15. Observed Value and Change from Baseline in Platelet (10^9/L) at Each Scheduled Visit: Treatment Policy (FAS)

Timepoint	Result			Change from Baseline		
	n	Mean	SD	n	Mean	SD
Baseline	25	134.2	72.3	-	-	-
Day 8	1	390.0	-	1	247.0	-
Day 22	23	213.9	94.3	23	76.5	117.7
Day 29	1	241.0	-	1	187.0	-
Day 36	1	407.0	-	1	317.0	-
Day 43	16	208.9	75.9	16	65.5	90.1
Day 50	5	344.6	79.8	5	243.4	91.7
Day 57	1	109.0	-	1	-110.0	-
Day 71	19	212.4	70.6	19	71.3	97.9
Day 78	2	278.0	25.5	2	241.8	50.6
Day 85	1	144.0	-	1	-75.0	-
Day 99	16	222.4	67.3	16	79.4	68.1
Day 106	3	277.0	88.7	3	151.2	179.1
Day 113	16	209.0	61.4	16	60.1	82.7
Day 120	3	290.7	34.2	3	208.8	122.9
Day 127	17	209.9	51.2	17	61.8	86.1
Day 134	4	299.0	24.0	4	196.9	97.4
Day 141	1	133.0	-	1	-86.0	-
Day 148	1	309.0	-	1	267.0	-
Day 155	18	223.4	69.4	18	76.8	98.2
Day 162	2	356.0	52.3	2	272.3	144.6
Day 169	1	155.0	-	1	-64.0	-
Day 176	1	320.0	-	1	278.0	-
Day 183	18	227.0	74.9	18	80.3	98.0
Day 190	2	280.5	91.2	2	196.8	183.5
Day 197	2	204.5	84.1	2	74.0	209.3

Baseline value is defined as the average of the values from the assessments performed prior to the first study drug infusion. Platelet values obtained from the day of a blood transfusion of platelets through 3 days after the transfusion were excluded from all analyses.

The LDH value, which was above normal level at Baseline, decreased and remained consistently within normal limits throughout the study.

Table 16. Observed Values and Change from Baseline in LDH (µkat/L) at Each Scheduled Visit: Treatment Policy (FAS)

Timepoint	Result			Change from Baseline		
	n	Mean	SD	n	Mean	SD
Baseline	25	14.243	13.461	-	-	-
Day 8	1	6.051	-	1	-8.452	-
Day 22	23	3.901	1.261	23	-9.445	12.459
Day 29	1	4.968	-	1	-29.648	-
Day 36	1	5.885	-	1	-39.408	-
Day 43	17	3.006	0.735	17	-6.147	10.175
Day 50	5	4.424	0.834	5	-22.395	9.353
Day 57	1	3.701	-	1	-2.878	-
Day 71	19	3.068	0.705	19	-7.083	10.099
Day 78	3	4.690	1.630	3	-27.586	6.610
Day 85	1	3.584	-	1	-2.995	-
Day 99	17	3.045	0.734	17	-5.861	8.356
Day 106	3	3.556	1.298	3	-18.601	15.699
Day 113	18	3.078	0.860	18	-5.769	8.041
Day 120	3	3.023	0.359	3	-22.274	19.018
Day 127	18	2.943	0.508	18	-5.444	8.314
Day 134	4	3.709	1.142	4	-23.967	11.831
Day 141	1	3.351	-	1	-3.228	-
Day 148	1	5.118	-	1	-32.106	-
Day 155	17	2.833	0.527	17	-5.848	8.478
Day 162	1	3.017	-	1	-32.673	-
Day 169	1	3.217	-	1	-3.362	-
Day 176	1	3.901	-	1	-33.323	-
Day 183	18	2.967	0.560	18	-5.680	8.172
Day 190	2	3.926	1.332	2	-27.180	7.815
Day 197	2	3.801	0.495	2	-18.101	21.174

Note: Post-baseline assessments include assessments on or after date of first dose.
Baseline value is defined as the average of the values from the assessments performed prior to the first study drug infusion.
Source: Table 14.2.1.12.1

There was a trend of sustained improvement on haemoglobin value from Baseline, with the values generally increased over time.

Table 17. Observed Values and Change from Baseline in Haemoglobin (g/L) at Each Scheduled Visit: Treatment Policy (FAS)

Timepoint	Result			Change from Baseline		
	n	Mean	SD	n	Mean	SD
Baseline	25	87.2	17.3	-	-	-
Day 8	1	81.0	-	1	22.0	-
Day 22	23	105.8	17.0	23	17.0	18.3
Day 29	1	105.0	-	1	25.0	-
Day 36	1	109.0	-	1	9.0	-
Day 43	16	117.1	15.0	16	25.7	20.1
Day 50	5	117.0	20.5	5	41.7	19.8
Day 57	1	101.0	-	1	4.0	-
Day 71	19	120.2	14.3	19	30.5	22.6
Day 78	2	112.0	22.6	2	36.0	17.0
Day 85	1	98.0	-	1	1.0	-
Day 99	17	120.6	14.3	17	30.3	19.3
Day 106	3	120.0	16.5	3	37.5	21.5
Day 113	18	120.2	13.1	18	29.8	17.8
Day 120	3	116.3	21.2	3	34.3	41.5
Day 127	18	117.4	11.1	18	25.2	16.4
Day 134	4	126.0	16.5	4	55.3	15.6
Day 141	1	108.0	-	1	11.0	-
Day 148	1	122.0	-	1	61.0	-
Day 155	18	121.8	12.8	18	30.5	14.9
Day 162	2	108.5	9.2	2	38.0	11.3
Day 169	1	119.0	-	1	22.0	-
Day 176	1	125.0	-	1	64.0	-
Day 183	18	127.4	13.6	18	36.2	15.8
Day 190	2	113.0	19.8	2	42.5	21.9
Day 197	2	130.5	13.4	2	51.5	38.9

Note: Post-baseline assessments included assessments on or after date of first dose.
Baseline is defined as the average of the values from the assessments performed prior to the first study drug infusion.
Hemoglobin values obtained from the day of a blood transfusion of either whole blood or packed red blood cells through 7 days after the transfusion were excluded from all analyses.
Source: Table 14.2.1.12.1

Increase in haemoglobin of ≥ 20 g/L from Baseline through Week 26

An increase in haemoglobin of ≥ 20 g/L from Baseline through Week 26 was observed in 19 out of 25 participants (76%; 95% CI: 54.9%, 90.6%) in the FAS.

Table 18. Haemoglobin Response during the 26-week Treatment Period: Treatment Policy (FAS)

Parameter	Statistic	Eculizumab N = 25
Increase in hemoglobin of ≥ 20 g/L from Baseline through Week 26	n	19
	Proportion (95% CI)[a]	0.760 (0.549, 0.906)

Note: Baseline value is defined as the average of the values from the assessments performed prior to the first study drug infusion. Hemoglobin values obtained from the day of a blood transfusion of either whole blood or packed red blood cells through 7 days after the transfusion were excluded from all analyses. [a] 95% CIs for the proportion are based on exact confidence limits using the Clopper-Pearson method.

Safety results

The safety analysis was conducted on the Safety Set, which comprised all 25 participants who received at least 1 dose of eculizumab.

Treatment Exposure

Among the 25 participants, the median treatment duration was 24.10 weeks (range: 0.1 to 27.0 weeks), the median exposure duration was 26.00 weeks (range: 2.0 to 28.9 weeks), and the median follow-up duration was 27.60 weeks (range: 1.1 to 36.1 weeks).

Adverse Events

Table 19. Adverse Events (Reported in ≥ 5% of Participants) by SOC and PT by Period (Safety Set)

SOC PT (MedDRA Version 27.1)	Eculizumab N = 25 n (%)
Any AE	24 (96.0)
Infections and infestations	**16 (64.0)**
Upper respiratory tract infection	5 (20.0)
Infection	4 (16.0)
Respiratory tract infection	4 (16.0)
Pneumonia	3 (12.0)
Bronchitis	2 (8.0)
Influenza	2 (8.0)
Metabolism and nutrition disorders	**11 (44.0)**
Hyperkalaemia	7 (28.0)
Hyperphosphataemia	3 (12.0)
Electrolyte imbalance	2 (8.0)

SOC PT (MedDRA Version 27.1)	Eculizumab N = 25 n (%)
Hypokalaemia	2 (8.0)
Gastrointestinal disorders	**8 (32.0)**
Vomiting	5 (20.0)
Diarrhoea	2 (8.0)
Blood and lymphatic system disorders	**5 (20.0)**
Anaemia	2 (8.0)
Leukopenia	2 (8.0)
Hepatobiliary disorders	**5 (20.0)**
Hepatic function abnormal	5 (20.0)
Vascular disorders	**4 (16.0)**
Hypertension	2 (8.0)
General disorders and administration site conditions	**3 (12.0)**
Pyrexia	3 (12.0)
Respiratory, thoracic and mediastinal disorders	**3 (12.0)**
Cough	2 (8.0)

Note: The table includes AEs that started during or after the first infusion of study drug.
Participants with multiple occurrences were counted once per SOC and PT regardless of the number of occurrences.
Table was sorted by decreasing frequency for SOC and PT.
Source: Table 14.3.2.2

The most frequently reported AE was hyperkalaemia (28.0%). The other AEs reported by ≥ 20% of participants were hepatic function abnormal, upper respiratory tract infection, and vomiting (20.0% each).

Four (16%) participants reported at least 1 eculizumab-related AE. The most frequently reported related AE was leukopenia (2 [8.0%] participants). The other related AEs were each reported by 1 (4.0%) participant, including clostridium difficile infection, gastroenteritis, infection, pneumonia, rotavirus infection, urinary tract infection, and dermatitis atopic.

Table 20. Related Adverse Events by SOC, PT (Safety Set)

SOC PT (MedDRA Version 27.1)	Eculizumab N = 25 n (%)
Any related AE[a]	4 (16.0)
Infections and infestations	**3 (12.0)**
Clostridium difficile infection	1 (4.0)
Gastroenteritis	1 (4.0)
Infection	1 (4.0)
Pneumonia	1 (4.0)
Rotavirus infection	1 (4.0)
Urinary tract infection	1 (4.0)
Blood and lymphatic system disorders	**2 (8.0)**
Leukopenia	2 (8.0)
Skin and subcutaneous tissue disorders	**1 (4.0)**
Dermatitis atopic	1 (4.0)

Note: The table includes AEs that started during or after the first infusion of study drug.
Participants with multiple occurrences in the same category were counted once per category regardless of the number of occurrences.
Table was sorted by international order for SOC and in alphabetical order for PT.
[a] Causality due to IP was assessed by Investigator.
Source: Table 14.3.2.6

Deaths

No deaths were reported in this study.

Serious Adverse Events

The only SAE that occurred in more than 1 participant was pneumonia (2 [8.0%] participants). Other SAEs occurred in 1 (4.0%) participant each, including bacterial infection, clostridium difficile infection, hepatic function abnormal, infection, retching, rotavirus infection, synovial cyst, and upper gastrointestinal haemorrhage.

Table 21. Serious Adverse Events by SOC and PT (Safety Set)

SOC PT (MedDRA Version 27.1)	Eculizumab N = 25 n (%)
Any SAE	8 (32.0)
Infections and infestations	**4 (16.0)**
Pneumonia	2 (8.0)
Bacterial infection	1 (4.0)
Clostridium difficile infection	1 (4.0)
Infection	1 (4.0)
Rotavirus infection	1 (4.0)
Gastrointestinal disorders	**2 (8.0)**
Retching	1 (4.0)
Upper gastrointestinal haemorrhage	1 (4.0)
Hepatobiliary disorders	**1 (4.0)**
Hepatic function abnormal	1 (4.0)
Musculoskeletal and connective tissue disorders	**1 (4.0)**
Synovial cyst	1 (4.0)

Note: Percentages were based on the number of participants in the Safety Set.
The table included adverse events that start during or after the first infusion of study drug.
Participants with multiple occurrences were counted once per SOC and PT regardless of the number of occurrences.
Table was sorted by decreasing frequency for SOC and PT.
Source: Table 14.3.4.1

Two participants reported a total of 4 eculizumab-related SAEs, including clostridium difficile infection, infection, pneumonia, and rotavirus infection, and each event was reported once.

Table 22. Serious Related Adverse Events by SOC, PT (Safety Set)

SOC PT (MedDRA Version 27.1)	Eculizumab N = 25 n (%)
Any SAE related to IP[a]	2 (8.0)
Infections and infestations	**2 (8.0)**
Clostridium difficile infection	1 (4.0)
Infection	1 (4.0)
Pneumonia	1 (4.0)
Rotavirus infection	1 (4.0)

Note: The table includes AEs that started during or after the first infusion of study drug.
Participants with multiple occurrences were counted once per SOC and PT regardless of the number of occurrences.
Table was sorted by international order for SOC and in alphabetical order for PT.
[a] Causality due to IP assessed by Investigator.
Source: Table 14.3.2.7

Discontinuations and/or Dose Modifications due to Adverse Events

No AEs leading to discontinuation of eculizumab or participant withdrawal from the study were reported in all the 25 participants in this study.

Adverse Events of Special Interest

No AEs of special interest were reported in all the 25 participants in the study.

2.3.3. Discussion on clinical aspects

The MAH has submitted the results from Study ECU-aHUS-302, as per Article 46 of Regulation (EC) No 1901/2006. This was a Phase 3b, open-label, single-arm, multicentre study designed to assess the efficacy, safety, PK, PD, and immunogenicity of eculizumab (Soliris) in complement inhibitor treatment-naïve paediatric and adult participants with aHUS in China. This was a post-approval commitment study in China.

The study enrolled participants of any age who weighed ≥5 kg and who had not been previously treated with complement inhibitors. Ultimately, 25 patients were enrolled and treated: 14 (56%) were adults (≥ 18 years) and 11 (44.0%) were paediatric patients (<18 years) at the first infusion. From the 11 paediatric patients, two participants (8.0%) were in the birth to < 2 years old age category, no participants were in the 2 to < 6 years old age category, 7 participants (28.0%) were in the 6 to < 12 years old age category, and 2 participants (8.0%) were in the 12 to < 18 years old age category.

The study included a Treatment period of 26 weeks. During this period, participants received eculizumab by IV administration based on body weight cohorts.

The primary objective was to assess the efficacy of eculizumab in the treatment of aHUS. As secondary objectives, the aim of the study was to characterise the safety and tolerability, pharmacokinetics, pharmacodynamics and immunogenicity of eculizumab.

The study population included all Asian patients with a majority of male (76%) participants. The median age at first infusion was 23.90 and the mean weight was 58.62 kg. A total of 21 (84%) participants had ADAMTS-13 activity ≥ 5%, and 4 (16.0%) participants had missing data for ADAMTS-13 activity. Eleven (44%) participants underwent kidney dialysis within 5 days before the first dose of eculizumab, and 8 (72.7%) participants received regular dialysis.

The primary endpoint of Complete TMA Response was achieved in 64.0% of participants during the 26-week treatment period.

Regarding the secondary endpoints, the results confirmed eculizumab activity. The median time to Complete TMA Response during the 26-week treatment period was 75 days and the latest response was observed on Day 127 visit following the first dose of eculizumab. All the patients who received kidney dialysis within 5 days prior to treatment start or right after the first dose had discontinued dialysis by the end of the study or upon early withdrawal of the study. The mean gradually improved from Baseline throughout the study. An improvement in platelet, LDH, and haemoglobin was observed from Baseline after the participants received eculizumab.

Among the 25 participants, the median treatment duration was 24.10 weeks (range: 0.1 to 27.0 weeks) and the median follow-up duration was 27.60 weeks (range: 1.1 to 36.1 weeks).

Focusing on safety data, 24 (96.0%) participants reported at least 1 AE, and 8 (32.0%) participants reported at least 1 SAE.

Four (16.0%) participants had AEs that were considered related to eculizumab, and none of the related AEs were severe.

The most frequently reported AE was hyperkalaemia (28.0%), and the other AEs reported by ≥ 20% of participants were hepatic function abnormal, upper respiratory tract infection, and vomiting.

The most frequently reported related AE was leukopenia (2 [8.0%] participants). The other related AEs were each reported by 1 (4.0%) participant, including clostridium difficile infection, gastroenteritis, infection, pneumonia, rotavirus infection, urinary tract infection, and dermatitis atopic.

The only SAE that occurred in more than 1 participant was pneumonia (2 [8.0%] participants), and other SAEs occurred in 1 (4%) participant each, including bacterial infection, clostridium difficile infection, hepatic function abnormal, infection, retching, rotavirus infection, synovial cyst, and upper gastrointestinal haemorrhage. Two (8.0%) participants reported a total of 4 eculizumab-related SAEs, including clostridium difficile infection, infection, pneumonia, and rotavirus infection, and each event was reported once.

There were no AEs of special interest, no AEs leading to discontinuation of eculizumab or study withdrawal, and no fatal events/deaths reported in this study.

There were no clinically important changes that would suggest any safety concern in the clinical laboratory test results, vital signs, and ECG assessments, or other observations related to safety in this study.

Overall, the results from this study confirm the positive benefit-risk balance for eculizumab for the treatment of aHUS, including paediatric patients.

3. Rapporteur's overall conclusion and recommendation

Eculizumab is approved in the EU for the treatment of aHUS in adults and children, based on the results from four studies in adults and two studies performed in children with aHUS, whose results are also included in section 5.1 of the PI.

The MAH has submitted the results from Study ECU-aHUS-302, a study performed in China as a commitment to the approval of Soliris in China. A total of 25 participants were treated, being 11 of them paediatric patients (<18 years of age at first infusion). Based on the results from the primary and secondary efficacy endpoints, the activity of eculizumab for the treatment of aHUS has been confirmed in this Chinese population.

Regarding safety, no relevant concerns have been raised, and the toxicity profile seems to be in line with the already known safety profile for eculizumab.

The MAH does not plan to include the results from this study in the Soliris PI. Considering the differences in the population and the fact that results from other paediatric studies performed with European population are already included in the PI, this is agreed.

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

Not applicable.