30 April 2020
EMA/280465/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ultomiris

International non-proprietary name: ravulizumab

Procedure No. EMEA/H/C/004954/II/0002

Note

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

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List of abbreviations

Abbreviation	Definition
ADA	antidrug antibody
ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
BLA	biologics license application
C5	complement component 5
CAC	Complement-amplifying condition
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CKD	chronic kidney disease
CSR	clinical study report
C_{trough}	concentration at the end of the dosage interval
DSUR	Development Safety Update Report
eGFR	estimated glomerular filtration rate
EOP2	End of Phase 2
ESKD	end-stage kidney disease
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FcRn	neonatal Fc receptor
gMG	generalized myasthenia gravis
HUS	hemolytic uremic syndrome
IgG	immunoglobulin G
IV	intravenous
LDH	lactate dehydrogenase
MAA	marketing authorization application
mAb	monoclonal antibody
NAb	neutralizing antibody
ODD	Orphan Drug Designation
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)

Abbreviation	Definition
PMDA	Pharmaceuticals and Medical Devices Agency
PNH	paroxysmal nocturnal hemoglobinuria
Pop-PK	population-pharmacokinetics
PSP	Pediatric Study Plan
PSUR	Periodic Safety Update Report
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
q8w	every 8 weeks
RMP	Risk Management Plan
SC	subcutaneous
SmPC	Summary of Product Characteristics
STEC	Shiga toxin-producing *Escherichia coli*
TEAEs	treatment-emergent adverse events
TMA	thrombotic microangiopathy
TTP	thrombotic thrombocytopenic purpura

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Alexion Europe SAS submitted to the European Medicines Agency on 25 July 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include the treatment of patients with atypical hemolytic uremic syndrome (aHUS) for Ultomiris; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, Annex II.D is proposed to be updated to include the new indication in the educational materials. The RMP version 1.6 has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0034/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0034/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with an authorised orphan medicinal product for the same therapeutic indication.

Derogation of market exclusivity

Pursuant to Article 8 of Regulation (EC) No 141/2000, the application submitted a letter addressing the following derogation laid down in Article 8(3)(a) of the same Regulation; the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the MAH.

Scientific advice

The MAH received Scientific Advice from the CHMP on 15 September 2016 (EMEA/H/SA/3331/2/2016/II).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jorge Camarero Jiménez Co-Rapporteur: Agnes Gyurasics

Timetable	Actual dates
Rapporteur's preliminary assessment report circulated on	23 October 2019
Co-Rapporteur's preliminary assessment report circulated on	16 October 2019
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	18 October 2019
Updated Rapporteur's preliminary assessment report on the MAH's responses circulated on	24 October 2019
PRAC RMP advice and assessment overview adopted by PRAC	31 October 2019
Joint Rapporteur's updated assessment report circulated on	10 November 2019
Request for supplementary information and extension of timetable adopted by the CHMP on	14 November 2019
MAH's responses submitted to the CHMP on	23 January 2020
Rapporteur's preliminary assessment report on the MAH's responses circulated on	6 March 2020
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on	28 February 2020
Updated Rapporteur's preliminary assessment report on the MAH's responses circulated on	5 March 2020
PRAC RMP advice and assessment overview adopted by PRAC	12 March 2020
Joint Rapporteur's updated assessment report on the MAH's responses circulated on	21 March 2020
Request for supplementary information and extension of timetable adopted by the CHMP on	26 March 2020
PRAC Rapporteur Assessment Report	02 April 2020
CHMP Rapporteur Assessment Report	17 April 2020
PRAC outcome	17 April 2020
CHMP members comments	20 April 2020
Updated CHMP Rapporteur Assessment Report	27 April 2020
Opinion	30 April 2020

Timetable	Actual dates
The CHMP adopted a report on similarity of Ultomiris with Soliris (Appendix 1)	30 April 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Atypical hemolytic uremic syndrome (aHUS; ICD-10 classification: D58.8) is a rare, progressive, and life-threatening disorder characterized by hemolytic anemia, thrombocytopenia, acute renal injury, and extra-renal complications (Muus, 2013; Noris, 2009; Sellier-Leclerc, 2007). The predominant underlying cause of aHUS is dysregulation of the alternative pathway of complement, resulting in uncontrolled complement activation (Campistol, 2015; Noris, 2009; Zuber, 2012; George 2014). This uncontrolled complement activation causes inflammation, endothelial activation and damage, and a prothrombotic/procoagulant state resulting in systemic thrombotic microangiopathy (TMA; Noris, 2009; Stahl, 2008; Karpman, 2006; Licht, 2009). Approximately 20% to 48% of patients are reported to have signs and symptoms of damage to extra-renal organs at presentation, including elevated liver or pancreatic enzymes, pericarditis, intra-alveolar hemorrhage, seizures, altered consciousness, and focal neurologic deficits (Loirat, 2011; Brodsky, 2015; Fidan, 2018; Fremeaux-Bacchi, 2013). In many cases, multiorgan dysfunction is associated with poor prognosis and necessitates critical care. This underscores the importance of early recognition and treatment. Complement gene mutations are identified in 50% to 60% of patients with aHUS (Noris, 2010; Fremeaux-Bacchi, 2013; Maga, 2010), although evidence of a genetic abnormality is not required for diagnosis (Noris, 2010).

The prognosis of aHUS in the absence of complement inhibitor therapy is poor. In a nationwide study of French pediatric and adult patients with aHUS, 17% of children and 46% of adults progressed to end-stage kidney disease (ESKD) or death by 1 month after clinical manifestation, and 56% of adults and 29% of children progressed to ESKD or death by 1 year (Fremeaux-Bacchi, 2013). More recent data from a large aHUS registry demonstrated that without eculizumab therapy, 31% of adult patients with aHUS developed ESKD within 1 year of aHUS diagnosis and required dialysis or kidney transplant (Schaefer, 2018). Within 6 months of aHUS diagnosis in non-eculizumab-treated patients, 25% of patients were on chronic dialysis, 19% had received a kidney transplant, and approximately 67% had incurred further manifestations of aHUS, despite the use of plasma exchange/plasma infusion in 57% of patients. Furthermore, extra-renal manifestations persist for some patients even 6 months after aHUS diagnosis, including gastrointestinal (24%), cardiovascular (17%), pulmonary (12%), and central nervous system (22%). In summary, without complement inhibitor therapy, aHUS can lead to early mortality and significant morbidities such as ESKD.

Management

Currently, the only approved treatment for aHUS is eculizumab, a humanized monoclonal antibody that specifically binds to the complement protein complement component 5 (C5) with high affinity. When eculizumab was approved for aHUS in 2011, it was the first treatment for life-threatening complement-mediated TMA events. Because the administration regimen requires every 2 week (q2w) intravenous (IV) infusions (every 3 weeks for patients weighing 5 kg to < 10 kg), this frequency is relatively burdensome for patients. Repeated IV administrations are also associated with more frequent infusion-related morbidities such as infusion site reactions, infection risk, and pain at the infusion site.

Prior to eculizumab, treatment of aHUS was limited to plasma therapy, though its clinical benefit had not been established. Since the approval of eculizumab, patients with aHUS are probably no longer treated with long-term plasma therapy, which can transiently maintain normal levels of hematologic measures while the underlying complement dysregulation and thrombotic microangiopathic processes likely persist (Loirat, 2010).

2.1.2. About the product

Ravulizumab is a humanized monoclonal antibody that binds to C5 and blocks its activation by complement pathway convertases, thereby preventing the release of the proinflammatory anaphylatoxin C5a and the formation of the membrane attack complex via C5b. Ravulizumab specifically target the identical C5 epitope motif.

The mechanism of action of ravulizumab is entirely through binding to C5, independent of any secondary pathways being induced or antagonized. Ravulizumab was constructed by introducing four unique mutations into the heavy chain of eculizumab resulting in increased antibody half-life allowing administration (in the maintenance phase) once every 8 weeks (see EPAR Ultomiris).

Ravulizumab is currently approved for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) in the US and EU.

The recommended dosing regimen for ravulizumab consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. The doses to be administered are based on the patient's body weight.

The dose and schedule of the administration of Ultomiris is provided in section 4.2 of the SmPC.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The active substance, ravulizumab is a protein and therefore no environmental risk assessment studies have been submitted, in line with the Guideline on the Environmental Risk Assessment of Medicinal Product for Human Use.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the dMAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1. Listing of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design, Type of Control, and Subject Type	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (Planned/ Treated)	Duration of Treatment	Study Status; Type of Report
Uncontrolled Clinical Studies								
Efficacy and Safety	ALXN1210-aHUS-311	M5.3.5.2	Efficacy, safety, tolerability, immunogenicity, PK, PD, and long-term safety of multiple IV doses of ALXN1210 administered to complement inhibitor treatment-naïve adolescent and adult patients with aHUS	Phase 3, open-label, uncontrolled, multicenter, single treatment arm study in adolescent and adult patients with evidence of TMA who are naïve to complement inhibitor treatment	Ravulizumab IV Weight-based loading[a] dose on Day 1 and maintenance[b] dose on Day 15 and q8w	55/58 enrollment closed	26-week Initial Evaluation Period followed by Extension Period of up to 2 years	Initial Evaluation Period (Primary Endpoint) complete; Extension Period ongoing; Interim report
Efficacy and Safety	ALXN1210-aHUS-312	M5.3.5.2	Efficacy, safety, tolerability, immunogenicity, PK, PD, and long-term safety and efficacy of multiple IV doses of ALXN1210 administered to pediatric patients with aHUS	Phase 3, open-label, uncontrolled, multicenter, single treatment arm study in pediatric patients with evidence of TMA who are naïve to complement inhibitor treatment (Cohort 1) or were clinically stable after having been treated with eculizumab according to the labeled dosing recommendation for aHUS for at least 90 days (Cohort 2)	Ravulizumab IV Weight-based loading[c] dose on Day 1 and maintenance[d] dose on Day 15 and q8w (q4w for patients < 20 kg)	28/16[e] enrollment ongoing	26-week Initial Evaluation Period followed by Extension Period of up to 2 years	Ongoing; Interim report

[a] ALXN1210 loading dose: 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 mg for patients weighing ≥ 100 kg
[b] ALXN1210 maintenance dose: 3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg
[c] ALXN1210 loading dose: 600 mg (originally 300 mg prior to ALXN1210-aHUS-312 Protocol Amendment 5) for patients weighing ≥ 5 to < 10 kg, 600 mg for patients weighing ≥ 10 to < 20 kg, 900 mg for patients weighing ≥ 20 kg to < 30 kg; 1200 mg for patients weighing ≥ 30 kg to < 40 kg; 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg; 3000 mg for patients weighing ≥ 100 kg
[d] ALXN1210 maintenance dose: 300 mg for patients weighing ≥ 5 to < 10 kg, 600 mg for patients weighing ≥ 10 to < 20 kg, 2100 mg for patients weighing ≥ 20 kg to < 30 kg; 2700 mg for patients weighing ≥ 30 kg to < 40 kg; 3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg
[e] As of 22 Feb 2019, 28 patients have received at least 1 dose of ravulizumab in Study ALXN1210-aHUS-312 (18 in Cohort 1 and 10 in Cohort 2). The interim CSR for this study includes results from the first 16 patients treated in the study, all of whom are in the treatment-naïve cohort (Cohort 1).
Abbreviations: aHUS = atypical hemolytic uremic syndrome; IV = intravenous; PD = pharmacodynamics; PK = pharmacokinetics; q4w = every 4 weeks; q8w = every 8 weeks; TMA = thrombotic microangiopathy.

2.3.2. Pharmacokinetics

Absorption

Because the route of administration is an IV infusion and the dosage form is a solution, absorption is not applicable as 100% of the administered dose is considered bioavailable. The time to maximum observed concentration (tmax) is expected at the end of infusion (EOI); however, because of the long terminal elimination half-life of ravulizumab and variability, the observed tmax in clinical trials occurred either at or soon after EOI.

Distribution

The mean (standard deviation [SD]) volume of distribution at steady state for patients with aHUS on the studied weight-based dose regimen was 5.22 (1.85) L.

Elimination

As an immunoglobulin G (IgG) monoclonal antibody, ravulizumab is expected to be metabolized in the same manner as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways) and is subject to similar elimination.

The mean (SD) values for terminal elimination half-life and clearance of ravulizumab in patients with aHUS are 51.8 (16.2) days and 0.08 (0.04) L/day, respectively.

Dose proportionality and time dependencies

Ravulizumab exhibited dose-proportional increases in the maximum observed serum concentration (Cmax), concentration at the end of the dosing interval (Ctrough), and area under the serum concentration versus time curve over the dosing interval (AUC_T) as assessed using a power model.

Special populations

Impact of Hepatic or Renal Insufficiency

No impact of hepatic or renal function on ravulizumab PK was identified in the studied patients with aHUS; hepatic: ALT range, 7.00 to 266 U/L; AST range, 12.0 to 645 U/L; renal: eGFR range, 4.00 to 107 mL/min/1.73 m2.

Impact of Dialysis

No effect of dialysis on ravulizumab PK was identified.

Impact of sex

The mean body weight in adult female patients was 14% lower than that those observed in adult male patients. The mean Cave,ss values of ravulizumab in adult female patients was 17% higher than that observed in adult male patients.

Impact of race

Despite the 19% lower body weight in adult Japanese versus non-Japanese patients (56.1 and 69.4 kg, respectively), mean Cave,ss values of ravulizumab in adult Japanese patients were within 2% of those observed in non-Japanese patients.

Impact of PNH vs aHUS

The mean Cave,ss in patients with aHUS > 100 kg (756 µg/mL, N = 3) was 19% higher than that observed in patients PNH > 100 kg (634 µg/mL, N = 13).

The mean Cave,ss in patients with aHUS ≥60 to < 100 kg (722 μg/mL, N = 30) was within 2% of that observed in patients PNH ≥60 to < 100 kg (735 μg/mL, N = 141).

The mean Cave,ss in patients with aHUS ≥40 to < 60 kg (763 μg/mL, N = 22) was 13% lower than that observed in patients PNH ≥40 to < 60 kg (873 μg/mL, N=68).

The typical CL and Vc of ravulizumab in patients with PNH were 0.00369 L/h and 3.45 L, respectively. The mean (SD) terminal elimination half-life of ravulizumab in 222 patients with PNH enrolled in Phase 3 trials was 49.7 (8.94) days.

Pharmacokinetic interaction studies

The base Pop-PK model was used to evaluate the effects of concomitantly administered drugs on ravulizumab PK. The impact of concomitant medications from assorted drug classes (ie, anabolic agents for systemic use, antithrombotic agents, antianemic preparations, antihypertensives, corticosteroids for systemic use, antibacterials for systemic use, antimycolitics for systemic use, and immunosuppressants on subject-level variability parameters of ravulizumab were assessed. The assessment showed that the studied concomitant drugs do not impact ravulizumab PK in patients with aHUS or with PNH.

2.3.3. Pharmacodynamics

Mechanism of action

No new data on the mechanism of action has been presented in this application.

Ravulizumab is a terminal complement inhibitor that specifically binds to complement component 5 (C5) with high affinity, inhibiting the enzymatic cleavage of C5 into C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement membrane attack complex [C5b-9]). By binding specifically to C5, ravulizumab antagonizes terminal complement-mediated inflammation, cell activation, and cell lysis.

Primary and secondary pharmacology

Immunogenicity

Across both studies in patients with aHUS in the ravulizumab development program (Studies ALXN1210-aHUS-311 and ALXN1210-aHUS-312), ravulizumab exhibited a low incidence of immunogenicity, with 1 treatment-emergent ADA observed with a low titer (< 1), no evidence of in vitro neutralization, and no apparent impact of ADA on PK, PD, safety, or efficacy. This is consistent with the low immunogenicity seen following previously reported ravulizumab treatment.

With only 1 transient treatment-emergent ADA positive sample observed in the aHUS Phase 3 studies, formal covariate testing of ADA in the Final Pop-PK model was not conducted. A preliminary visual assessment of the impact of ADA at baseline was completed. No trend was noted, suggesting no impact of ADA at baseline on ravulizumab PK.

2.3.4. PK/PD modelling

Exposure-efficacy analysis

Longitudinal concentrations of free C5 (semi-log scale) by study (ALXN1210-aHUS-311 and ALXN1210-aHUS-312) and frequency of dosing (q4w and q8w) were presented.

In adult patients, the loading dose resulted in an immediate, complete, and sustained terminal complement inhibition, with all free C5 concentrations below 0.5 µg/mL. Concentrations of free C5 remained suppressed for the MDs (q8w) of ravulizumab in adult patients with aHUS.

For pediatric patients with body weight ≥ 20 kg (q8w dosing, middle panel), the loading dose resulted in an immediate, complete, and sustained terminal complement inhibition, with all free C5 concentrations below 0.5 µg/mL. Concentrations of free C5 remained suppressed for the MDs in pediatric patients with body weight ≥ 20 kg.

For paediatric patients with body weight ≥ 5 to < 10 kg and ≥ 10 to < 20 kg (q4w dosing), the loading dose resulted in an immediate, complete, and sustained terminal complement inhibition, with all free C5 concentrations below 0.5 µg/mL with the exception of one patient in the ≥ 5 to < 10 kg group (patient with a free C5 of 0.999 µg/mL on Day 15). The free C5 on Day 15 in the second patient in the ≥ 5 to < 10 kg group was 0.263 µg/mL.

Concentrations of free C5 remained completely suppressed for the maintenance dose (q4w) in paediatric patients with body weight ≥ 5 to < 10 kg.

The serum free C5 versus time profiles were characterized by immediate and complete terminal complement inhibition, as defined by serum free C5 < 0.5 µg/mL, that was sustained throughout the 26-week treatment period.

Exposure-safety analysis

No exposure-response relationships were observed for TEAEs reported in greater than 5% of adult patients in Study ALXN1210-aHUS-311 or in 2 or more paediatric patients in Study ALXN1210-aHUS-312 due to the small sample size (N = 14).

2.3.5. Discussion on clinical pharmacology

The MAH has conducted two Phase 3 clinical trials (ALXN1210-aHUS-311 and ALXN1210-aHUS-312) to evaluate the pharmacokinetic and pharmacodynamic properties of ravulizumab for atypical hemolytic uremic syndrome. 55 adult patients and 14 paediatric patients were recruited. The PK and PD modelling building, covariate assessment, model qualification and exposure-response analyses are considered adequate for purpose.

A two-compartment model with a combined residual error model and inter-individual variability on CL and Vc succesfully described the observed data. Covariate analysis identified the effect of body weight (as time-varying covariate) on CL, Q, Vc and VP, the effect of transfusion on CL and the effect of BMI (as time-varying covariate) on Vc and Vp as statistically significant covariates. Standard model assessment of the base model and covariate analysis revealed the adequacy of the PK structure to capture the observed data. Parameter precision was assessed through the bootstrap analysis, which showed the concordance between parameter estimates from the final population PK model and bootstrap analysis. A prediction-corrected visual predictive check showed the ability of the model to capture the mean and the dispersion of the data during 26 weeks of treatment in the adult population. Pc-VPC from pediatric population were provided stratified by each dosing regimen, showing that the model is slightly biased for the q4w schedule (for pediatric patients with less than 20kg). Other covariates might be affecting the estimation of CL, but due to the low number of pediatric patients, their effect is difficult to estimate. No renal nor hepatic effect were identified on ravulizumab PK. The vast majority of patients showed severe and ESRD renal impairment and normal/mild hepatic impairment, which may impede its inclusion as significant covariates on CL. Differences due to sex, race, type of disease were less than ±20% and therefore, no clinically relevant.

No dosing adjustments are required for patients presenting with hepatic or renal insufficiency.

Immunogenicity was low and it did not impact the PK or PD properties of ravulizumab.

Because ravulizumab is a monoclonal antibody, clinically meaningful drug-drug PK interactions with small molecule drugs or other biologics are generally not expected. The clearance pathways of therapeutic proteins differ from those of small molecules. The latter are usually metabolized by oxidation via cytochrome P450s and/or conjugation. In addition, ravulizumab does not bind to a cytokine and the available safety data (> 450 patient-years) have not shown a drug-induced cytokine modulation, indicating that the potential of drug-related cytokine-based drug interaction is negligible. This is consistent with clinical and post-marketing eculizumab experience.

The exposure-efficacy relationship was assessed through longitudinal concentrations of free C5. All schedules (q8w and q4w) achieved an immediate, complete and sustained terminal complement inhibition with free C5 concentrations below 0.5 µg/mL. The PK/PD relationship of ravulizumab was very steep, suggesting that the trough ravulizumab concentration greater than 175µg/mL would lead to free C5 concentrations below 0.5 µg/mL.

No exposure-safety relationship was established. A probability >20% of headache, diarrhoea, vomiting, hypertension and nausea was reported, but it was irrespective of the Cmax,ss, Ctrough,ss, Cave,ss and AUCss levels in adults and pediatrics.

With regard to the PK/PD model, as the model underpredicts the exposure in paediatric patients with body weight less than 20kg, the proposed change to increase the loading dose (i.e. from 300 mg to 600 mg) to reach the target concentration based on population PK model is not justified since observed concentrations are already higher than those predicted by the population PK model.

The dose regimen for the Phase 3 studies in patients with aHUS was based on pharmacokinetic (PK)/pharmacodynamic (PD) modelling and the adult dosing is the same as used in the PNH studies. The weight-based dose regimen for ravulizumab was designed to maintain serum drug concentrations above a threshold that provides complete terminal complement inhibition sustained throughout the entire dosing interval.

The body weight-based ravulizumab treatment regimen for adult patients with aHUS is identical to the one approved for adult patients with PNH and includes a loading dose on Day 1, followed by maintenance doses on Day 15 and every 8 weeks (q8w) thereafter, administered by IV infusion.

The body weight-based dosing in paediatric patients with aHUS consists of a loading dose on Day 1, followed by maintenance doses on Day 15 and q8w, for patients weighing ≥20 kg, or every 4 weeks (q4w), for patients weighing < 20 kg, thereafter, administered by IV infusion.

In Study ALXN1210-aHUS-312, a planned PK/PD initial analysis of ravulizumab PK and serum free C5 levels was conducted after 4 complement inhibitor treatment-naïve (i.e., Cohort 1) patients weighing ≥ 5 kg to <40 kg completed dosing through Day 71. Based on the results of this analysis, the loading dose for patients weighing between ≥5 to < 10 kg was changed from 300 mg to 600 mg.

Dosages were based on the patient's body weight.

Table 2: Ravulizumab weight-based dosing regimen for paediatric patient below 40 kg

Body weight range (kg)	Loading dose (mg)	Maintenance dose (mg)*	Dosing interval
≥ 10 to < 20	600	600	Every 4 weeks

≥ 20 to < 30	900	2,100	Every 8 weeks
≥ 30 to < 40	1200	2,700	Every 8 weeks

2.3.6. Conclusions on clinical pharmacology

The Pharmacokinetic and Pharmacodynamic properties of ravulizumab for atypical haemolytic uremic syndrome were adequately characterized in 55 adults and 14 paediatric patients through two Phase 3 clinical trials. In general, the modelling strategy is considered acceptable and the population PK model was considered able to account for the ravulizumab longitudinal observations in both populations. Overall, the population PK and PD parameter estimates of aHUS patients were no different from that of PNH patients. Currently available data are described in section 4.8 of the SmPC but no recommendation for treatment can be made for patients below 10 kg body weight, as reflected in section 4.1 and 4.2 of the SmPC.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose response studies were submitted.

2.4.2. Main studies

Table 3: Clinical Studies Supporting the Efficacy of Ravulizumab in Patients With aHUS

Descriptor	ALXN1210-aHUS-311	ALXN1210-aHUS-312
Study design	Phase 3 open-label, single-arm efficacy and safety study	Phase 3 open-label, single-arm efficacy and safety study
Patient population	Complement inhibitor treatment-naïve adolescents[a] and adult patients weighing ≥ 40 kg with evidence of TMA	Cohort 1: Complement inhibitor treatment-naïve patients (age < 18 years) weighing ≥ 5 kg with evidence of TMA Cohort 2: Eculizumab-experienced pediatric patients (12 to < 18 years)[b] with documented aHUS
Study duration	Initial Evaluation Period: 26 weeks (183 days) Extension Period: up to 2 years	Initial Evaluation Period: 26 weeks (183 days) Extension Period: up to 2 years
Ravulizumab treatment regimens during Initial Evaluation Period	On Day 1: ≥ *40 to < 60 kg*: 2400 mg ≥ *60 to < 100 kg*: 2700 mg ≥ *100 kg*: 3000 mg On Day 15 and q8w thereafter: ≥ *40 to < 60 kg*: 3000 mg ≥ *60 to < 100 kg*: 3300 mg ≥ *100 kg*: 3600 mg	On Day 1: ≥ *5 to < 10 kg*: 600 mg[c] ≥ *10 to < 20 kg*: 600 mg ≥ *20 to < 30 kg*: 900 mg ≥ *30 to < 40 kg*: 1200 mg ≥ *40 to < 60 kg*: 2400 mg ≥ *60 to < 100 kg*: 2700 mg ≥ *100 kg*: 3000 mg On Day 15 and q8w thereafter: ≥ *5 to < 10 kg*: 300 mg ≥ *10 to < 20 kg*: 600 mg ≥ *20 to < 30 kg*: 2100 mg ≥ *30 to < 40 kg*: 2700 mg ≥ *40 to < 60 kg*: 3000 mg ≥ *60 to < 100 kg*: 3300 mg ≥ *100 kg*: 3600 mg (q4w for patients < 20 kg)
Ravulizumab treatment regimens during Extension Period	Weight-based maintenance dose q8w	Weight-based maintenance dose q4w (< 20 kg) and q8w (≥ 20 kg)
Study status	Initial Evaluation Period completed Extension Period ongoing	Initial Evaluation Period completed for the first 16 treated patients (Interim Analysis Population) Extension Period ongoing
Initial evaluation time point	Day 183	Day 183
Countries	Australia, Austria, Belgium, Canada, France, Germany, Italy, Japan, Korea, Russia, Spain, Taiwan, the United Kingdom, and the US	Belgium, Germany, Japan, Korea, Spain, and the US
Link to clinical study report	ALXN1210-aHUS-311	ALXN1210-aHUS-312

[a] Although enrollment of both adult and adolescent patients was planned, enrollment completed with only adult patient participation; enrollment of eligible adolescent patients was deferred to a pediatric protocol (Study ALXN1210-aHUS-312).
[b] Data from Cohort 2 are not included in this submission.
[c] The loading dose for patients 5 to < 10 kg was increased from 300 mg to 600 mg in Protocol Amendment 5. The 2 patients in this weight group were enrolled prior to implementation of Protocol Amendment 5 and received the 300 mg loading dose.
Abbreviations: aHUS = atypical hemolytic uremic syndrome; q4w = every 4 weeks; q8w = every 8 weeks; TMA = thrombotic microangiopathy.

Study ALXN1210-aHUS-311:

This is an ongoing Phase 3, open-label, single-arm, multicenter study to evaluate the safety and efficacy of ravulizumab administered by IV infusion to adult patients with complement-mediated TMA including aHUS who are naïve to complement inhibitor treatment.

Methods

Study participants

Main inclusion criteria

1. Male or female patients ≥12 years of age and weighing ≥40 kg at the time of consent.
2. Evidence of TMA, including thrombocytopenia, evidence of hemolysis, and kidney injury, based on the following laboratory findings:

a. Platelet count < 150,000/μL during the Screening Period or within 28 days prior to the start of the Screening Period, and

b. Lactate dehydrogenase ≥ 1.5 × ULN during the Screening Period or within 28 days prior to the start of the Screening Period, and hemoglobin ≤ LLN for age and gender during the Screening Period or within 28 days prior to the start of the Screening Period, and

c. Serum creatinine level ≥ ULN during the Screening Period in adults (≥ 18 years of age), or ≥ 97.5th percentile for age at Screening in adolescents (12 to < 18 years of age) (patients who require dialysis for acute kidney injury were also eligible).

3. Among patients with a kidney transplant:

a. Known history of aHUS prior to current kidney transplant, or

b. No known history of aHUS, and 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 patients with onset of TMA postpartum, persistent evidence of TMA for > 3 days after the day of childbirth.
5. Vaccination against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who received meningococcal vaccine less than 2 weeks before initiating ALXN1210 treatment must have received treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients who had not been vaccinated prior to initiating ALXN1210 treatment should have received prophylactic antibiotics prior to and for at least 2 weeks after meningococcal vaccination.
6. Patients < 18 years of age must have been vaccinated against Haemophilus influenza type b (Hib) and Streptococcus pneumoniae according to national and local vaccination schedule guidelines.

Main exclusion criteria

1. Known familial or acquired ADAMTS13 ("a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13") deficiency (activity < 5%).

2. Known Shiga toxin-related hemolytic uremic syndrome (HUS) as demonstrated by a positive test result for Shiga toxin or culture of Shiga toxin-producing bacteria.
3. Positive direct Coombs test
4. Known human immunodeficiency virus 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 bacterial infection that, in the opinion of the Investigator, confounded an accurate diagnosis of aHUS or impeded the ability to manage the aHUS disease.
8. Pregnancy or breastfeeding.
9. Heart, lung, small bowel, pancreas, or liver transplant.
10. Among patients with a kidney transplant, acute kidney dysfunction within 4 weeks of transplant consistent with the diagnosis of acute antibody-mediated rejection (AMR) according to Banff 2013 criteria.
11. Among patients 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, or

b. Known kidney ultrasound finding consistent with an alternative diagnosis to aHUS (eg, small kidneys for age), or

c. Known family history and/or genetic diagnosis of non-complement-mediated genetic renal disease (eg, focal segmental glomerulosclerosis).

12. Identified drug exposure-related HUS.
13. Received plasma exchange/plasma infusion, for 28 days or longer, prior to the start of screening for the current TMA.
14. History of malignancy within 5 years of screening with the exception of a non-melanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
15. Bone marrow transplant/hematopoietic stem cell transplant within the last 6 months prior to the start of screening.
16. Hemolytic uremic syndrome related to known genetic defects of cobalamin C metabolism.
17. Known systemic sclerosis (scleroderma), systemic lupus erythematosus, or antiphospholipid antibody positivity or syndrome.
18. Chronic dialysis (defined as dialysis on a regular basis as renal replacement therapy for ESKD).
19. Received chronic intravenous immunoglobulin (IVIg) within 8 weeks prior the start of screening, unless for unrelated medical condition (eg, hypogammaglobinemia); or chronic rituximab therapy within 12 weeks prior to the start of screening.
20. Patients that received other immunosuppressive therapies such as steroids, mTORi (eg, sirolimus, everolimus), CNI (eg, cyclosporine or tacrolimus) were excluded unless:

a. Part of an established post-transplant antirejection regimen, or

21. Patient had confirmed anti-complement factor antibodies requiring immunosuppressive therapy, or
22. Steroids were being used for a condition other than aHUS (eg, asthma).
23. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever was greater.
24. Prior use of eculizumab or other complement inhibitors.
25. Hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins.
26. Any medical or psychological condition that, in the opinion of the Investigator or Sponsor, could have increased the risk to the patient by participating in the study or confound the outcome of the study.
27. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of screening.
28. Use of tranexamic acid within 7 days prior to screening was prohibited.

Treatments

During the 26-week Initial Evaluation Period, patients received a weight-based loading dose of ALXN1210 IV on Day 1, followed by maintenance treatment with ALXN1210 on Day 15 and q8w thereafter for patients weighing ≥ 20 kg, or q4w for patients weighing < 20 kg.

The loading and maintenance doses were based on the patient's body weight recorded on Dose Regimen Decision Days.

Objectives

The primary objective of the study was to assess the efficacy of ALXN1210 in complement inhibitor treatment-naïve adolescent and adult patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA) as characterized by thrombocytopenia, hemolysis, and renal impairment.

The secondary objectives of the study were as follows:

- To characterize the safety and tolerability of ALXN1210 in this patient population
- To evaluate the efficacy of ALXN1210 by additional efficacy measures
- To characterize the pharmacokinetics (PK)/pharmacodynamics (PD) of ALXN1210
- To evaluate the long-term safety and efficacy of ALXN1210

Outcomes/endpoints

Primary endpoint

Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline.

Patients must have met all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. To be considered a responder during the 26-week Initial Evaluation Period, the latest time point a patient could first meet the response criteria was 28 days before the Day 183 assessment.

Baseline value was defined as the average of the values from the assessments performed prior to the first dose of study drug (ie, results from screening and the Day 1 visit). When a patient was on dialysis at baseline, then the first valid creatinine value used as the baseline value was the first assessment ≥ 6 days post dialysis. If a patient was on dialysis during the entire 26-week Initial Evaluation Period, then the baseline creatinine was not calculated.

Key secondary endpoints

- Time to Complete TMA Response
- Complete TMA Response status over time
- Dialysis requirement status (for patients requiring dialysis within 5 days prior to ravulizumab treatment initiation)
- Observed value and change from baseline in eGFR
- CKD stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline
- Observed value and change from baseline in hematologic parameters
- Increase in hemoglobin of ≥ 20 g/L from baseline
- Change from baseline in QoL

Sample size

The planned sample size of 55 patients, in order to yield at least 50 evaluable patients by Day 183, for Study ALXN1210-aHUS-311 required more than 150 sites to be opened for enrolment to complete within an acceptable time frame. The sample size was increased to 55 patients to account for a potential 10% dropout rate.

Randomisation

This was an open-label study. Patients who satisfied all criteria for enrolment were assigned to study treatment with ravulizumab at the Baseline Visit (Day 1). The Interactive Voice/Web Response System (IWRS) was used to assign vials containing ravulizumab to each patient.

Blinding (masking)

This was a single-arm, open-label study; therefore, blinding was not necessary.

Statistical methods

Efficacy Analyses

Efficacy analyses were performed using the Full Analysis Set (FAS), the primary efficacy population.

The primary analysis and selected secondary efficacy analyses were repeated on the PP Set as sensitivity analyses.

The primary analysis consisted of estimating the proportion of complete TMA responders among ravulizumab-treated patients. This was performed by calculating the point estimate and a 95% confidence interval (CI) for the proportion of complete TMA responders in ravulizumab-treated patients. The 95% CI was based on the asymptotic Gaussian approximation method with a continuity correction.

To be considered a responder during the 26-week Initial Evaluation Period, the latest time point a patient could first meet the response criteria was 28 days before the Day 183 assessment.

Formal statistical comparison analyses were not planned for this estimation study.

Sensitivity Analysis

A sensitivity analysis was prespecified in the SAP to evaluate a slightly modified version of Complete TMA Response. This modification applied only to the patients who were on dialysis at baseline (ie, patients requiring dialysis within 5 days prior to first dose of ravulizumab). For these patients, the criterion requiring an improvement from baseline of 25% or more in serum creatinine was replaced by a post-baseline change in dialysis status (from requiring dialysis at baseline to no longer requiring dialysis) that was maintained for at least 4 weeks. The definition of Complete TMA Response remained the same for all other patients.

Secondary Efficacy Analyses

- Time to Complete TMA Response: For the secondary efficacy endpoint of time to Complete TMA Response, Kaplan-Meier cumulative distribution curves were generated along with 2-sided 95% CIs. The corresponding summary table presented the cumulative distribution function estimate, the number of patients at risk, the number of patients responding, and the number of patients censored at each post-baseline time point. The table also presented first quartile, median, and third quartile, along with corresponding 2-sided 95% CI, of time to complete response.
- Complete TMA Response Status Over Time: Complete TMA Response was summarized over time by presenting the number and proportion of responders along with a 2-sided 95% CI for each post-baseline time point.
- Hematologic Normalization: The number and proportion of patients who achieved hematologic normalization, defined as the normalization of both platelet count and LDH, was summarized over time with a 2-sided 95% CI for each post-baseline time point.
- Hematologic TMA Parameters: Hematologic TMA parameters (platelets, LDH, hemoglobin) were summarized at baseline and each post-baseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline. A mixed model for repeated measures (MMRM) with the fixed, categorical effect of visit and fixed, continuous effect of the specific test's baseline value as covariates may have been performed to test whether changes differ from zero at each time point. For analysis purposes, priority was always given to results from the central laboratory, but if at a specific analysis visit no

central lab results were available, the local lab result could be used in the analysis for the specific analysis visit.

- Hemoglobin Response: The number and proportion of patients with an increase from baseline in hemoglobin ≥ 20g/L, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between, was summarized over time by presenting the number and proportion of responders along with a 2-sided 95% CI for each post-baseline time point.
- Dialysis Requirement Status: For patients requiring dialysis within 5 days prior to ravulizumab treatment initiation, the proportion of patients no longer requiring dialysis was summarized over time. A 2-sided 95% CI for the proportion receiving dialysis was provided.
- eGFR Value and Change From Baseline: Kidney function evaluated by eGFR was summarized at baseline and each post-baseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline. A value of 10 mL/min/1.73 m2 for eGFR was imputed for patients requiring dialysis for acute kidney injury. This summary was repeated by kidney transplant status at enrolment, and on the PP Set.
- An MMRM with the fixed, categorical effect of visit and fixed, continuous effect of the baseline value as covariates may have been performed to test whether changes differ from zero at each time point.
- CKD Stage: Chronic kidney disease stage was summarized over time by presenting the number and proportion of patients that improved (excluding those with Stage 1 at baseline as they cannot improve), worsened (excluding those with Stage 5 at baseline as they cannot worsen), and stayed the same compared to CKD stage at baseline. Stage 5 was considered the worst category, while Stage 1 was considered the best category. A 2-sided 95% CI for the proportion was provided for each category.

Table 4: Glomerular Filtration Rate Category/Chronic Kidney Disease Stage

GFR Category/Stage	GFR (mL/min/1.73 m^2)	Terms
1	≥ 90	Normal or high
2	60 to 89	Mildly decreased[a]
3a	45 to 59	Mildly to moderately decreased
3b	30 to 44	Moderately to severely decreased
4	15 to 29	Severely decreased
5	< 15	Kidney failure

Note: In the absence of evidence of kidney damage, neither GFR category/stage G1 nor G2 fulfill the criteria for CKD.
[a] Relative to young adult level.
Abbreviations: CKD = chronic kidney disease; GFR = glomerular filtration rate.
Source: KDIGO 2012

- Quality of Life: Quality of life was evaluated using the EQ-5D-3L and the FACIT-Fatigue version 4 Questionnaire. The EQ-5D-3L and FACIT-Fatigue data were summarized at baseline and each post-baseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline. An MMRM with the fixed, categorical effect of visit and fixed, continuous effect of the specific test's baseline value as covariates may have been performed to test whether changes differ from zero at each time point.
- Handling of Dropouts or Missing Data: For evaluation of Complete TMA Response during the 26-week Initial Evaluation Period (primary endpoint), patients missing an efficacy assessment that was part of the definition of Complete TMA Response while still on study, had their last observation carried forward. For patients who withdrew from the study prior to Week 26, their data up to the time of withdrawal was used to assess Complete TMA Response. A confirmatory

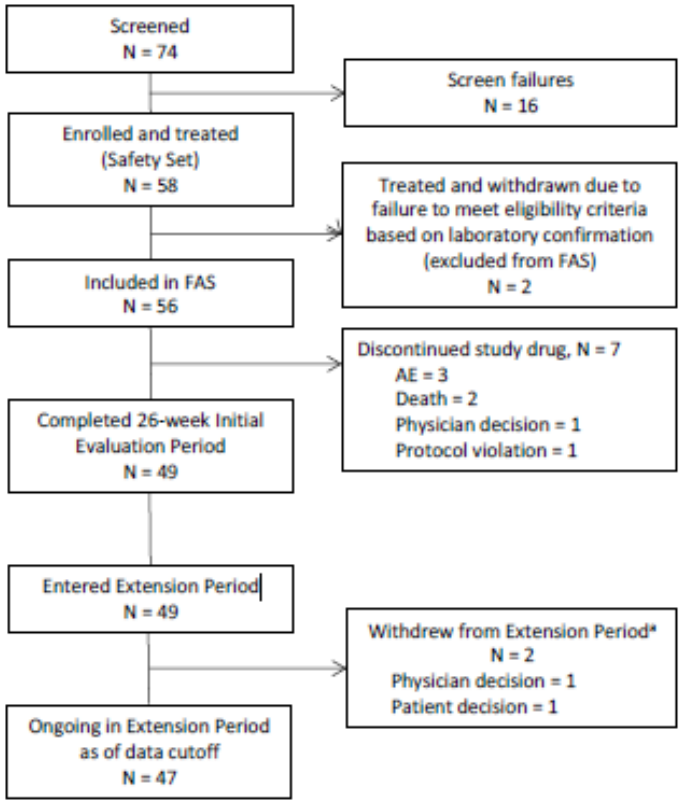
result could not be from an assessment that was carried forward from the initial assessment when all Complete TMA Response criteria were met.

For laboratory data, in the event of duplicate samples from local and central laboratories (for any time point), central laboratory results were used for analysis.

Results

Participant flow

Figure 1: Disposition of Patients – Initial Evaluation Period (All Screened Patients)



* These 2 patients completed the Initial Evaluation Period and entered the Extension Period; however, both patients withdrew from the study prior to receiving a dose during the Extension Period.
Abbreviations: AE = adverse event; FAS = full analysis set.

Recruitment

This study was initiated at 178 sites globally (16 countries). Patients were enrolled in 41 sites across 14 countries (Australia, Austria, Belgium, Canada, France, Germany, Italy, Japan, Korea, Russia, Spain, Taiwan, the United Kingdom, and the United States).

- Date first patient treated: 18 Mar 2017
- Date of last visit in Initial Evaluation Period: 16 Nov 2018

- Date of Extension Period data cut-off: 15 Oct 2018
- Release date of report: 09 Apr 2019

Conduct of the study

Protocol amendments

From the original protocol (dated 09 Aug 2016, which was submitted to regulatory authorities), 11 country-specific and 3 global protocol amendments were made during the Initial Evaluation Period of the study.

Table 5: Summary of protocol changes

Amendment Number	Summary of Significant Changes to the Study Protocol
Amendment 1 (Global) Dated: 28 Sep 2016	• ALXN1210 loading and maintenance doses were lowered for all body weight groups.
Amendment 1.1 (Japan) Dated: 01 Nov 2016	The following additional changes were made to Amendment 1 (Global) for sites in Japan: • Revised Exclusion Criterion 23 to exclude hypersensitivity to any ingredient contained in the study drug. • Clarified that ALXN1210 is a humanized protein derived from Chinese hamster cells. • Removed specification for method of body temperature measurement (ie, oral or tympanic).
Amendment 1.2 (UK) Dated: 04 Nov 2016	The following additional changes were made to Amendment 1 (Global) for sites in the UK: • Added more specific withdrawal criteria to specify serious infusion reaction, severe uncontrolled infection, and pregnancy.
Amendment 1.3 (Japan) Dated: 29 Nov 2016	The following additional change was made to Amendment 1.1 for sites in Japan: • Revised genetic test result reporting language
Amendment 1.4 (Germany) Dated: 30 Nov 2016	The following additional change was made to Amendment 1 (Global) for sites in Germany: • Contraception language aligned with Clinical Trials Facilitation Group definition of highly effective contraceptive methods.
Amendment 1.5 (France) Dated: 06 Dec 2016	The following additional changes were made to Amendment 1 (Global) for sites in the France: • Added more specific withdrawal criteria. • Revised vaccine language to align with Inclusion Criterion 6.
Amendment 1.6 (Japan) Dated: 15 Dec 2016	The following additional change was made to Amendment 1.3 for sites in Japan: • Exploratory genetics endpoint and all information related to this endpoint were removed for Japanese patients.
Amendment 1.7 (Germany) Dated: 05 Jan 2017	The following changes were made to Amendment 1.4 for sites in Germany: • Targeted adverse events were broadened to also include sepsis, serious infections, *Aspergillus* infection, and infusion reactions. • Additional events of interest were defined as serious cutaneous adverse reactions, cardiac disorders (including ventricular fibrillation), and angioedema.

Amendment Number	Summary of Significant Changes to the Study Protocol
Amendment 2 (Global) Dated: 23 Jan 2017	• Added clarification to primary endpoint description that patients must meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. • Added clarification to secondary objectives (CKD stage as evaluated by eGFR; hemoglobin increase observed at 2 separate assessments obtained at least 4 weeks [28 days] apart, and any measurement in between). • Revised Exclusion Criteria 2 to allow administration of the first dose of study drug while awaiting the results of stool Shiga toxin test results. • Removed the requirement of systolic blood pressure ≤ 140 mm Hg for at least 4 days (Exclusion 11a). • Incorporated minor revisions to inclusion and exclusion criteria for clarity and alignment with clinical practice. • Added benefit/risk assessment text. • Clarified withdrawal criteria to specify serious infusion reaction, severe uncontrolled infection, and pregnancy. • Minor corrections and clarifications were made to the schedule of assessments and language describing drug packaging, storage, and preparation; prior/concomitant medications/procedures; prohibited medications; vaccination; contraception; medical history; vital signs; immunogenicity; SUSAR reporting, adverse events; PK/PD assessment; genetics; statistical analysis; DMC; regulatory considerations; references; appendices.
Amendment 2.1 (Germany) Dated: 24 Jan 2017	• Amendment 2 (Global) changes were applied to the protocol for Germany, which had been modified previously by Amendment 1.4 and Amendment 1.7.
Amendment 2.2 (Japan) Dated: 24 Jan 2017	• Amendment 2 (Global) changes were applied to the protocol for Japan, which had been modified previously by Amendments 1.1, 1.3, and 1.6.
Amendment 3 (Global) Dated: 19 Jul 2017	• Revised Inclusion Criteria 2a and 2b to include platelet count, LDH, and hemoglobin laboratory results during the Screening Period or within 28 days prior to the start of the Screening Period from a local laboratory; these changes allow patients with recent plasma exchange/plasma infusion (which alters laboratory results) to enter the study based on laboratory results prior to plasma exchange/plasma infusion. • Continued to require that serum creatinine results for Inclusion Criterion 2c must be based on central laboratory results from a specimen collected during the Screening Period. Since the primary endpoint is a change from baseline in creatinine, it is important to have both baseline and on-treatment serum samples from the same laboratory. • Provided clarification that eligibility may be determined using results from tests carried out as standard of care for the treatment of the current TMA prior to a patient giving informed consent, including tests noted in Exclusion Criteria 1, 2 and 3. • Removed the requirement for culture/antigen test (Exclusion 3). • Clarified patients with genetic defects in vitamin B12 metabolism (a rare cause of HUS not related to complement), rather than a deficit in vitamin B12, were excluded (Exclusion 16). • Provided Sponsor opportunity to exclude patients on basis of risk to patient or impact the interpretation of the efficacy or safety results for the study (Exclusion 24). • Added a requirement to have at least 30 patients enrolled who met all 4 TMA requirements at Day 1 (platelet count of < 150,000/μL, LDH ≥ 1.5 × ULN, hemoglobin ≤ LLN, and serum creatinine level ≥ ULN) to ensure that a majority of patients enrolled had abnormal baseline lab values. • Provided the option for serum pregnancy tests to be used at any time points. • Removed the option for "a designee" to perform the physical examination. • Added pregnancy test assessment prior to first dose in Extension Period; removed requirement for pregnancy test to use urine (serum may now be used at all indicated timepoints). • Clarified terminology on "meeting" vs "satisfying" inclusion and exclusion criteria and added option for the patient's legally authorized representative to provide informed consent. • Corrected use of "assent" vs "consent". • Clarified that there were separate tests for urine chemistry and urinalysis
Amendment 3.1 (Germany) Dated: 04 Aug 2017	• Amendment 3 (Global) changes were applied to the protocol for Germany, which had been modified previously by Amendment 2.1.
Amendment 3.2 (Japan) Dated: 04 Aug 2017	• Amendment 3 (Global) changes were applied to the protocol for Japan, which had been modified previously by Amendment 2.2.

Abbreviations: CKD = chronic kidney disease; DMC = Data Monitoring Committee; eGFR = estimated glomerular filtration rate; HUS = hemolytic uremic syndrome; LDH = lactate dehydrogenase; LLN = lower limit of normal; PD = pharmacodynamics; PK = pharmacokinetics; SUSAR = suspected unexpected serious adverse reactions; TMA = thrombotic microangiopathy; ULN = upper limit of normal.

Protocol deviations

A total of 40 (69%) patients had major protocol deviations. Patients with major protocol deviations that could potentially impact interpretability of study data were excluded from the PP Set. Eleven (19.0%) patients were excluded from the PP Set due to major protocol deviations (eight patients with major protocol deviations related to eligibility and entry criteria and three patients due to administration of prohibited concomitant medication/therapies).

Baseline data

Table 6: Demographics and Baseline Characteristics (Full Analysis Set)

Variable	**Ravulizumab (N = 56)**
Age at time of first infusion (years)	
Mean (SD)	42.2 (14.98)
Median (min, max)	40.1 (19.5, 76.6)
Age at time of first infusion (years) category, n (%)	
18 to < 30 years	11 (19.6)
30 to < 40 years	17 (30.4)
40 to < 50 years	15 (26.8)
50 to < 60 years	5 (8.9)
≥ 60 years	8 (14.3)
Sex, n (%)	
Male	19 (33.9)
Female	37 (66.1)
Ethnicity, n (%)	
Hispanic or Latino	3 (5.4)
Not Hispanic or Latino	41 (73.2)
Unknown	12 (21.4)
Race, n (%)[a]	
American Indian or Alaskan Native	1 (1.8)
Asian	15 (26.8)
Black or African American	2 (3.6)
Native Hawaiian or other Pacific Islander	0
White	29 (51.8)
Unknown	8 (14.3)
Other	1 (1.8)
Japanese descent, n (%)	
Yes	3 (5.4)
No	53 (94.6)
Weight at time of first infusion (kg)	
n	55
Mean (SD)	72.9 (17.61)
Median	67.7
Min, max	46.1, 111.6
Height at baseline (cm)	
n	56
Mean (SD)	166.1 (9.21)
Median	164.5
Min, max	151.5, 189
Met TMA criteria[b] at Day 1 (based on central laboratory results)	30 (53.6)

Note: Percentages are based on the total number of patients.
[a] Patients can have multiple races selected.
[b] Platelet count < 150,000 per µL, LDH ≥ 1.5 × ULN, hemoglobin ≤ LLN, serum creatinine level ≥ ULN.
Abbreviations: LDH = lactate dehydrogenase; LLN = lower limit of normal; max = maximum; min = minimum; TMA = thrombotic microangiopathy; ULN = upper limit of normal.

Table 7: Disease Characteristics (Full Analysis Set)

Variable	**Ravulizumab (N = 56)**
Age (years) at time of first aHUS symptoms Mean (SD) Median (min, max)	 41.49 (15.798) 40.05 (9.3, 76.6)
Dialysis at baseline[a], n (%)	29 (51.8)
Any kidney transplant prior to entering the study[b], n (%) Related to aHUS	8 (14.3) 0
Baseline platelets (10^9/L) blood Mean (SD) Median (min, max)	 118.52 (86.440) 95.25 (18, 473)
Baseline LDH (U/L) serum Mean (SD) Median (min, max)	 702.38 (557.959) 508.00 (229.5, 3249)
Baseline hemoglobin (g/L) blood Mean (SD) Median (min, max)	 86.26 (14.866) 85.00 (60.5, 140)
Baseline eGFR (mL/min/1.73 m^2) Mean (SD) Median (min, max)	 15.86 (14.815) 10.00 (4, 80)
Baseline CKD stage, n (%)[c] 1 2 3A 3B 4 5	 0 3 (5.6) 1 (1.9) 2 (3.7) 9 (16.7) 39 (72.2)

Table 8: Pretreatment Extra-renal Signs or Symptoms of aHUS (Full Analysis Set)

Organ System Sign or Symptom	ALXN1210 (N = 56) n (%)
Any pretreatment extra-renal signs or symptoms of aHUS	52 (92.9)
Cardiovascular	39 (69.6)
Hypertension	34 (60.7)
Palpitations	2 (3.6)
Shortness of breath	4 (7.1)
Sinus tachycardia	3 (5.4)
Pericardial effusion	2 (3.6)
Cardiac insufficiency/failure	1 (1.8)
Other	23 (41.1)
Pulmonary	25 (44.6)
Shortness of breath	13 (23.2)
Tachypnea	3 (5.4)
Pulmonary edema	7 (12.5)
Pulmonary hemorrhage	1 (1.8)
Pleural effusion	9 (16.1)
Other	10 (17.9)
Central Nervous System	29 (51.8)
Lethargy	8 (14.3)
Irritability	1 (1.8)
Confusion	3 (5.4)
Headache	17 (30.4)
Visual deficit	9 (16.1)
Seizures	1 (1.8)
Other	12 (21.4)
Gastrointestinal	35 (62.5)
Nausea	21 (37.5)
Vomiting	19 (33.9)
Diarrhea	10 (17.9)
Abdominal pain	8 (14.3)
Colitis	1 (1.8)
Elevated transaminases (ALT/AST)	7 (12.5)
Pancreatitis	2 (3.6)
Poor glucose control	2 (3.6)
Other	13 (23.2)
Skin	17 (30.4)
Petechiae	8 (14.3)
Maculopapular rash	2 (3.6)
Other	11 (19.6)
Skeletal muscle	13 (23.2)
Myalgias	4 (7.1)
Other	9 (16.1)

Note: In summarizing n (%), if a patient had multiple reports for a particular organ system/sign or symptom, he/she was counted only once for that organ system/sign or symptom. Patients may have been counted in more than 1 organ system/sign or symptom category.
Abbreviations: aHUS = atypical hemolytic uremic syndrome; ALT = alanine aminotransferase; AST = aspartate aminotransferase; max = maximum; min = minimum.

Numbers analysed

58 complement inhibitor treatment-naïve adult patients were enrolled at 41 study sites in 14 countries. Efficacy analyses were performed on the FAS, which was based on a modified intent-to-treat (mITT) approach. With this approach, confirmation of eligibility in patients may have occurred after receiving study drug. The FAS included all patients who received at least 1 dose of ravulizumab, had at least 1 postbaseline efficacy assessment, met serum creatinine eligibility criteria, and did not have ADAMTS13 deficiency or Shiga toxin-related HUS. Of the 58 adult patients enrolled and treated with ravulizumab in Study ALXN1210-aHUS-311, 56 were included in the FAS for the Initial Evaluation Period

Table 9: Efficacy Analysis Data Sets (All Enrolled Patients)

	ALXN1210 n (%)
Number of enrolled patients	58 (100.0)
Number of patients in the FAS Number of patients excluded from the FAS	56 (96.6) 2 (3.4)
Number of patients in the PP Set Number of patients excluded from the PP Set	44 (75.9) 14 (24.1)

Abbreviations: FAS = Full Analysis Set; PK = pharmacokinetics; PP = Per Protocol.

Outcomes and estimation

Primary endpoint

Complete TMA Response was observed in 30 of the 56 patients in the FAS (53.6%; 95% CI: 39.6%, 67.5%) during the 26-week Initial Evaluation Period.

Table 10: Complete TMA Response and Complete TMA Response Components Analysis During the 26-Week Initial Evaluation Period (Full Analysis Set)

	Total	Responder	
		n	Proportion (95% CI)[a]
Complete TMA Response	56	30	0.536 (0.396, 0.675)
Components of Complete TMA Response			
Platelet normalization	56	47	0.839 (0.734, 0.944)
LDH normalization	56	43	0.768 (0.648, 0.887)
≥ 25% improvement in serum creatinine from baseline	56	33	0.589 (0.452, 0.727)
Hematologic normalization[b]	56	41	0.732 (0.607, 0.857)

Note: Patients must have met all Complete TMA Response criteria concurrently, and each criterion must have been 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 patients. The numerator was the number of patients achieving Complete TMA Response during the 26-week Initial Evaluation Period and the denominator was the number of patients in the FAS. Platelet values obtained from the day of a blood transfusion of platelets through 3 days after the transfusion were excluded from all analyses. All serum creatinine values obtained while a patient was on dialysis were excluded from all analyses. If a patient was on dialysis at baseline, then the first valid creatinine value used as the baseline value was the first assessment ≥ 6 days post dialysis. If a patient was on dialysis during the entire 26-week Initial Evaluation Period, then the baseline creatinine was not calculated.
[a]95% CIs for the proportion were based on the asymptotic Gaussian approximation method with a continuity correction.
[b]Hematologic normalization includes normalization of platelet count and LDH.

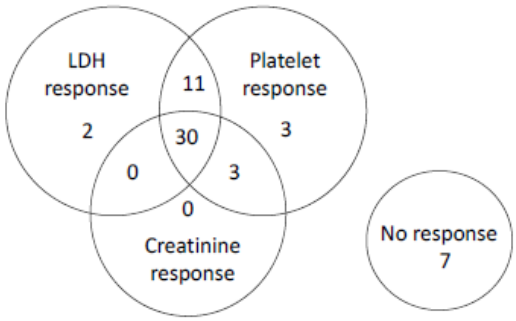
In the PP Set, Complete TMA Response during the 26-week Initial Evaluation Period was observed in 22 of the 44 patients (50% [95% CI: 34.1%, 65.9%]).

Complete TMA Response Components

During the Initial Evaluation Period, 47 (83.9%) patients achieved platelet count normalization, 43 (76.8%) patients achieved LDH normalization, and 33 (58.9%) patients achieved renal function improvement (defined as ≥ 25% reduction in serum creatinine from baseline).

In addition to the 30 patients who achieved a Complete TMA Response, 19 other patients achieved 1 or 2 of the Complete TMA Response components, including 11 patients who had both platelet and LDH normalization and 3 patients who had both platelet count normalization and serum creatinine improvement.

Table 11: Number of Patients Who Achieved 1 or More Components of Complete TMA Response (Full Analysis Set)



Abbreviations: LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Seven patients (12.5%) in the FAS did not respond on any of the 3 components of the Complete TMA Response during the Initial Evaluation Period.

In the PP Set, 39 (88.6%) patients had achieved platelet count normalization, 34 (77.3%) patients had achieved LDH normalization, and 25 (56.8%) patients had achieved renal function improvement.

Complete TMA Response and Complete TMA Response Components

Complete TMA Response was observed in 31 of the 56 patients in the FAS (55.4%; 95% CI: 41.4%, 69.3%). In addition to the 30 patients who achieved Complete TMA Response during the Initial Evaluation Period, 1 additional patient had confirmation of the Complete TMA Response criteria during the Extension Period.

A total of 48 (85.7%) patients had achieved platelet count normalization, 44 (78.6%) patients had achieved LDH normalization, and 33 (58.9%) patients had achieved renal function improvement.

Updated efficacy data

As of the 02 Jul 2019 data cut-off for the second interim analysis of Study ALXN1210-aHUS-311, 4 additional patients had a Complete TMA Response that was confirmed after the 26-week Initial Evaluation Period (with Complete TMA Response occurring at Days 169, 302, 401, and 407), resulting in an overall Complete TMA Response in 34 of 56 patients (60.7%; 95% CI: 47.0%, 74.4%). Platelet count normalization increased from 47 to 48 patients (85.7%; 95% CI: 75.7%, 95.8%), LDH normalization remained at 47 patients (83.9%; 95% CI: 73.4%, 94.4%), and renal function improvement increased from 33 to 35 patients (62.5%; 95% CI: 48.9%, 76.1%).

Table 12: Complete TMA Response and Components Analysis Through Data-cut or End of Study Full Analysis Set

		Responder	
	Total	n	Proportion (95% CI)[a]
Complete TMA Response	56	34	0.607 (0.470, 0.744)
Components of Complete TMA Response			
Platelet Count Normalization	56	48	0.857 (0.757, 0.958)
LDH Normalization	56	47	0.839 (0.734, 0.944)
25% Improvement in Serum Creatinine From Baseline	56	35	0.625 (0.489, 0.761)
Hematologic Normalization	56	45	0.804 (0.691, 0.917)

The criteria for Complete TMA Response are,
1. Normalization of platelet count.
2. Normalization of LDH.
3. >= 25% improvement in serum creatinine from baseline.
Patients must meet all Complete TMA Response criteria concurrently, and each criterion must 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 is based on the responders among treated patients. The numerator is the number of patients achieving complete TMA response through data-cut or end of study, and the denominator is the number of patients in the FAS.
(a) 95% confidence intervals (95% CIs) for the proportion are based on the asymptotic Gaussian approximation method with a continuity correction.
Hematologic normalization includes 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 are excluded from all analyses.
All serum creatinine values obtained while a patient is on dialysis are excluded from all analyses. When a patient is on dialysis at baseline, then the first valid creatinine value to be used as the baseline value is the first assessment >= 6 days post-dialysis. If a patient is on dialysis during the entire 26 week Initial Evaluation Period, then the baseline creatinine is not calculated.

Sensitivity Analyses

- Patients Who Met All Laboratory Criteria for TMA at Day 1

A sensitivity analysis was performed for patients in the FAS who met all laboratory criteria for TMA as determined by the central laboratory at Day 1. Of the 30 patients who met this criteria, Complete TMA Response was observed in 14 patients (46.7% [95% CI: 28.3%, 65.7%]).

- Modified Complete TMA Response – Initial Evaluation Period

A separate analysis was performed using a modified version of Complete TMA Response. The modification applied strictly to the patients on dialysis at baseline. For the Initial Evaluation Period, modified Complete TMA was observed in 32 of the 56 patients in the FAS (57.1%; 95% CI: 43.3%, 71.0). A total of 47 (83.9%) patients had achieved platelet count normalization, 43 (76.8%) patients had achieved LDH normalization, and 35 (62.5%) patients had achieved renal function improvement.

In the PP Set, modified Complete TMA Response was observed in 24 of the 44 patients during the Initial Evaluation Period (54.5%; 95% CI: 38.7%, 70.4%). A total of 39 (88.6%) patients had achieved platelet count normalization, 34 (77.3%) patients had achieved LDH normalization, and 27 (61.4%) patients had achieved renal function improvement.

- Modified Complete TMA Response

Modified Complete TMA Response was observed in 33 of the 56 patients (58.9%; 95% CI: 45.2%, 72.7%) in the FAS. A total of 48 (85.7%) patients had achieved platelet count normalization, 44 (78.6%) patients had achieved LDH normalization, and 35 (62.5%) patients had achieved renal function improvement.

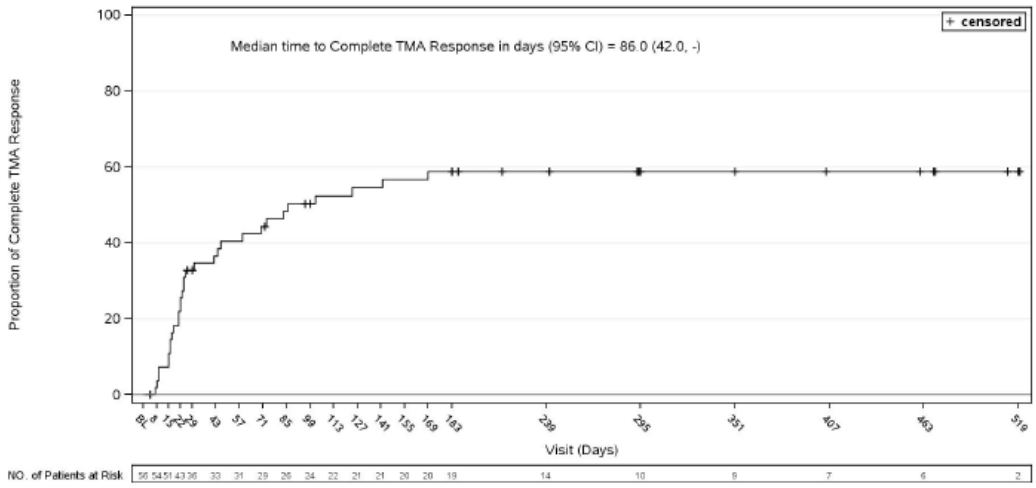
In the PP Set, modified Complete TMA Response was observed in 25 of the 44 patients as of the data cutoff date (56.8%; 95% CI: 41.0%, 72.6%). A total of 40 (90.9%) patients had achieved platelet count normalization, 35 (79.5%) patients had achieved LDH normalization, and 27 (61.4%) patients had achieved renal function improvement.

Secondary Endpoints

- Time to Complete TMA Response

Complete TMA Response was achieved at a median time of 86 days and occurred as early as 7 days following the first dose of ravulizumab. The latest response was observed at 169 days, which was not counted in the primary analysis for the Initial Evaluation Period because it was confirmed (components of the response maintained for at least 28 days) after the Initial Evaluation Period.

Figure 2: Time to Complete TMA Response – Kaplan Meier Cumulative Distribution Curves (Full Analysis Set)



Note: The criteria for Complete TMA Response are normalization of platelet count; normalization of LDH; and ≥ 25% improvement in serum creatinine from baseline. Patients must have met all Complete TMA Response criteria concurrently, and each criterion at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. The time of the event of a confirmed Complete TMA Response was considered as the first time point at which all the criteria for Complete TMA Response were met. Patients who did not have a response were censored at the date of last visit or study discontinuation at the time when the analysis was performed.
Abbreviations: BL = baseline; CI = confidence interval; LDH = lactate dehydrogenase; NO. = number; TMA = thrombotic microangiopathy.

- Complete TMA response status over time

The 30 patients who achieved Complete TMA Response status during the Initial Evaluation Period had all done so by the Day 141 visit and as early as the Day 8 visit. From the median time to Complete TMA Response (86 days), the proportion of responders was stable. After achieving Complete TMA Response, some patients had transient periods during which not all components of response continued to be met.

Table 13: Complete TMA Response Status Over Time With a Confirmatory Result During the Initial Evaluation Period (Full Analysis Set)

Visit	ALXN1210 (N = 56)	
	n/m	Proportion (95% CI)[a]
Day 8	4/53	0.075 (0.021, 0.182)
Day 15	10/53	0.189 (0.094, 0.320)
Day 22	18/53	0.340 (0.215, 0.483)
Day 29	19/53	0.358 (0.231, 0.502)
Day 43	22/53	0.415 (0.281, 0.559)
Day 57	22/53	0.415 (0.281, 0.559)
Day 71	23/53	0.434 (0.298, 0.577)
Day 85	27/52	0.519 (0.376, 0.660)
Day 99	28/51	0.549 (0.403, 0.689)
Day 113	27/50	0.540 (0.393, 0.682)
Day 127	24/50	0.480 (0.337, 0.626)
Day 141	26/50	0.520 (0.374, 0.663)
Day 155	25/50	0.500 (0.355, 0.645)
Day 169	28/50	0.560 (0.413, 0.700)
Day 183	26/49	0.531 (0.383, 0.675)

Note: The criteria for Complete TMA Response are 1) normalization of platelet count; 2) normalization of LDH; and 3) ≥ 25% improvement in serum creatinine from baseline. A patient was in the analysis for a specific post-baseline time point if it was possible for the result at that time point to be confirmed.

Hematologic normalization includes 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 are excluded from all analyses. All serum creatinine values obtained while a patient is on dialysis were excluded from all analyses. When a patient was on dialysis at Baseline, then the first valid creatinine value to be used as the baseline value is the first assessment ≥ 6 days post dialysis. If a patient was on dialysis during the entire 26-week Initial Evaluation Period, then the baseline creatinine was not calculated.

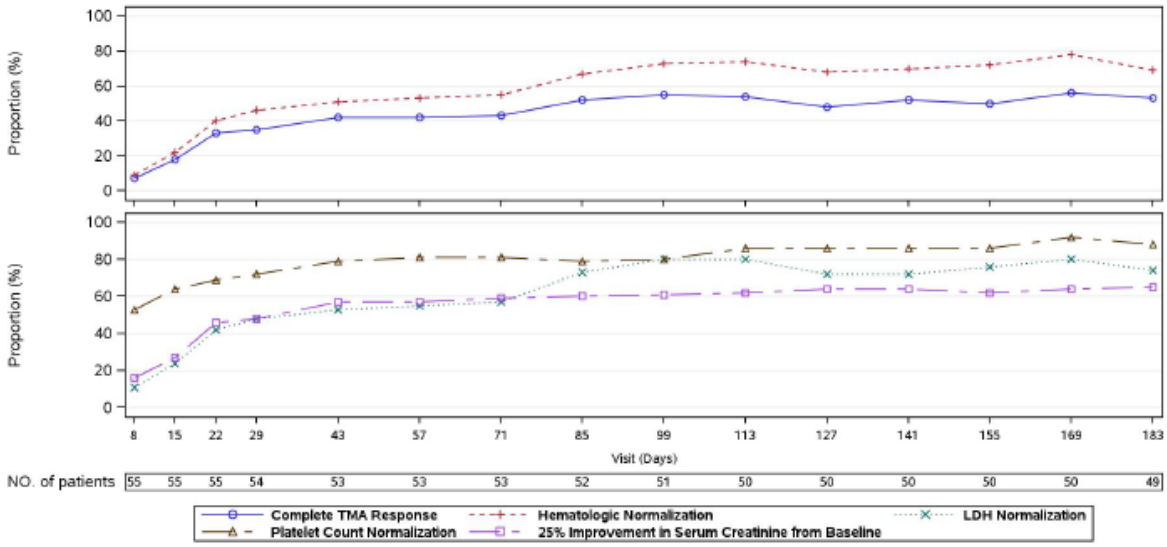
[a] 95% CIs for the proportion are based on exact confidence limits using the Clopper-Pearson method.

Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase; m = number of patients with a possible confirmatory result available at each visit; TMA = thrombotic microangiopathy.

- Complete TMA response components status over time

Of the 3 Complete TMA Response components, platelets showed the earliest response, with more than half of patients achieving platelet count normalization by the Day 15 visit. In general, normalization of LDH and renal function required a longer duration of treatment to show the same extent of improvement.

Figure 3: Complete TMA Response Components and Hematologic Normalization Status Over Time During the Initial Evaluation Period (Full Analysis Set)



Note: The criteria for Complete TMA Response are 1) normalization of platelet count; 2) normalization of LDH; and 3) ≥ 25% improvement in serum creatinine from Baseline. A patient was in the analysis for a specific post-baseline time point if it was possible for the result at that time point to be confirmed. Hematologic normalization includes normalization of platelets and LDH. Platelet values obtained from the day of a blood transfusion of platelets through 3 days after the transfusion were excluded from all analyses. All serum creatinine values obtained while a patient was on dialysis were excluded from all analyses. When a patient was on dialysis at baseline, then the first valid creatinine value to be used as the baseline value was the first assessment ≥ 6 days post dialysis. If a patient is on dialysis during the entire 26-week Initial Evaluation Period, then the baseline creatinine was not calculated.
Abbreviations: LDH = lactate dehydrogenase; NO. = number; TMA = thrombotic microangiopathy.

- Hematologic Normalization

Hematologic normalization included normalization of platelets and LDH. During the Initial Evaluation Period, hematologic normalization was observed in 41 of 56 patients in the FAS (73.2% [95% CI: 60.7%, 85.7%]). In the PP Set, hematologic normalization during the Initial Evaluation Period was observed in 33 of the 44 patients (75% [95% CI: 61.1%, 88.9%]).

As of the data cut-off date, hematologic normalization was observed in 43 of the 56 patients in the FAS (76.8% [95% CI: 64.8%, 88.7%]).

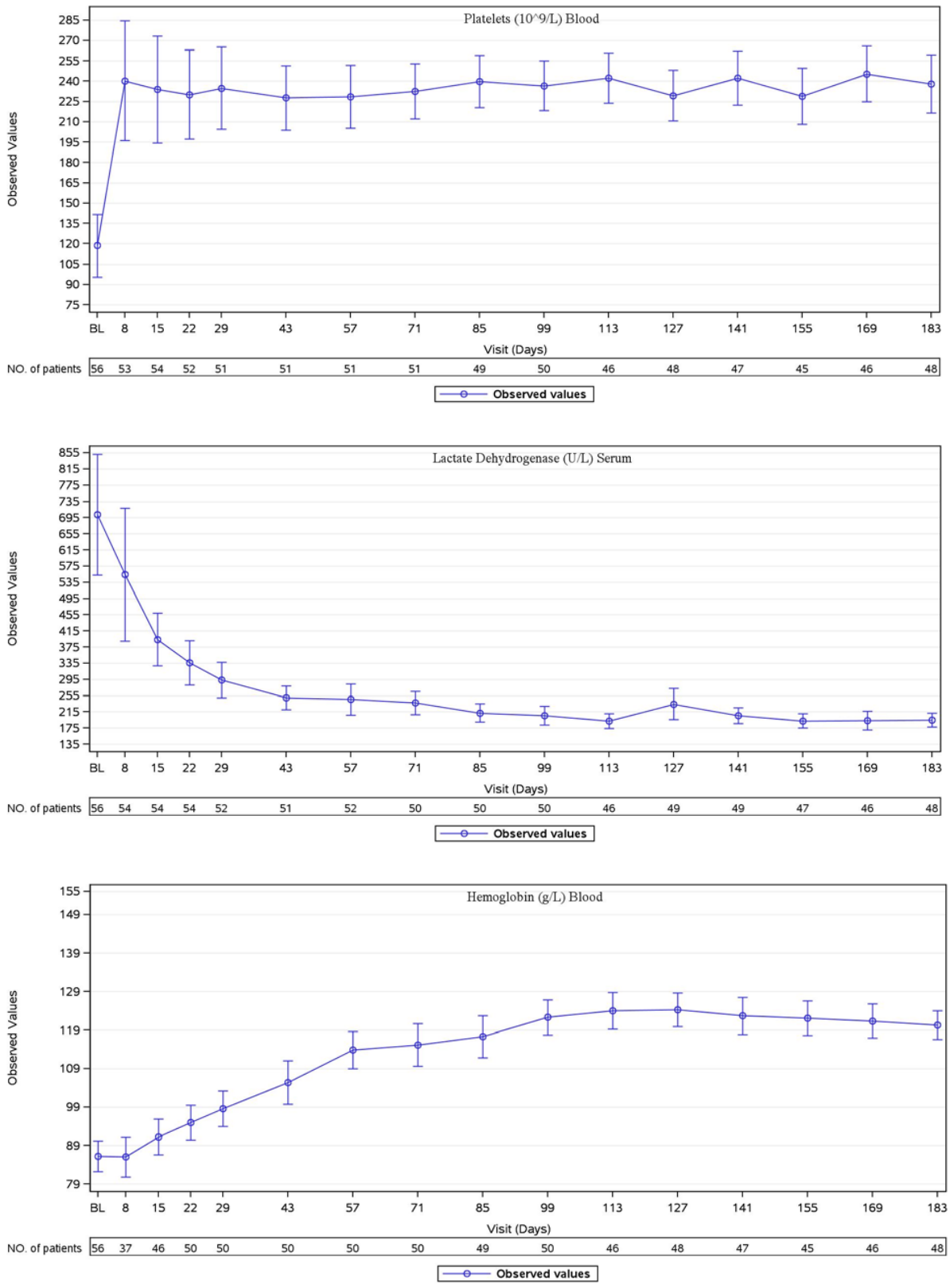
- Hematologic TMA Parameters

Mean platelet count increased from baseline early in treatment, and this mean improvement was sustained over the duration of the Initial Evaluation Period. Mean (SD) platelet count improved rapidly after initiation of ravulizumab treatment, increasing from 118.52 (86.440) × 10^9/L at baseline to 240.34 (160.646) × 109/L at Day 8. The mean platelet count remained above 227 × 10^9/L at all subsequent visits in the Initial Evaluation Period.

Similarly, mean LDH value decreased from baseline rapidly, with the majority of the decrease occurring during the first month of ravulizumab treatment; this mean reduction in LDH was sustained over the duration of the Initial Evaluation Period. Mean (SD) LDH value decreased from 702.38 (557.959) U/L at baseline to 554.31 (603.954) U/L at Day 8 and further to 293.27 (156.999) U/L at Day 29. Mean LDH value remained below 250 U/L at all subsequent visits in the Initial Evaluation Period.

In contrast, mean hemoglobin value increased more gradually over time during the Initial Evaluation Period. Mean (SD) hemoglobin value increased from 86.26 (14.866) g/L at baseline to 91.24 (15.397) g/L at Day 15 and 113.82 (17.086) g/L at Day 57, with mean values remaining above this level at subsequent visits in the Initial Evaluation Period.

Figure 4: Platelets, LDH, and Hemoglobin Over Time During the Initial Evaluation Period (Full Analysis Set)



- Hemoglobin Response

During the Initial Evaluation Period, 40 of the 56 patients (71.4% [95% CI: 58.7%, 84.2%]) in the FAS achieved a hemoglobin response (ie, increase in hemoglobin of ≥20 g/L compared to baseline with a confirmatory result).

Table 14: Hemoglobin Response With a Confirmatory Result During the Initial Evaluation Period (Full Analysis Set)

Parameter	Visit	ALXN1210 (N = 56)	
		n/m	Proportion (95% CI)[a]
Hemoglobin ≥ 20 g/L increase from baseline	Day 8	0/53	0.000 (0.000, 0.067)
	Day 15	3/53	0.057 (0.012, 0.157)
	Day 22	12/53	0.226 (0.123, 0.362)
	Day 29	15/53	0.283 (0.168, 0.423)
	Day 43	23/53	0.434 (0.298, 0.577)
	Day 57	27/53	0.509 (0.368, 0.649)
	Day 71	31/53	0.585 (0.441, 0.719)
	Day 85	32/52	0.615 (0.470, 0.747)
	Day 99	36/51	0.706 (0.562, 0.825)
	Day 113	37/50	0.740 (0.597, 0.854)
	Day 127	40/50	0.800 (0.663, 0.900)
	Day 141	39/50	0.780 (0.640, 0.885)
	Day 155	38/50	0.760 (0.618, 0.869)
	Day 169	38/50	0.760 (0.618, 0.869)
	Day 183	37/49	0.755 (0.611, 0.867)

Note: Baseline value was defined as the average of the values from the assessments performed prior to the first study drug infusion (these could have included results from screening and the Day 1 visit). A patient was included in the analysis for a specific post-baseline time point if it was possible for the result at that time point to be confirmed. 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 were based on exact confidence limits using the Clopper-Pearson method.

Abbreviations: CI = confidence interval; m = number of patients with a possible confirmatory result available at each visit.

- Dialysis Requirement Status

At baseline or within 5 days prior to the first dose of study drug, 29 (51.8%) patients in the FAS had received renal dialysis. As of the data cut-off date, 17 (58.6%) of these 29 patients discontinued dialysis during the study. Of the 27 patients who did not receive dialysis within 5 days prior to their first dose of study drug, 20 (35.7%) patients remained off dialysis and 7 patients initiated dialysis after start of treatment; 6 of these 7 patients required dialysis as of the last available follow-up visit.

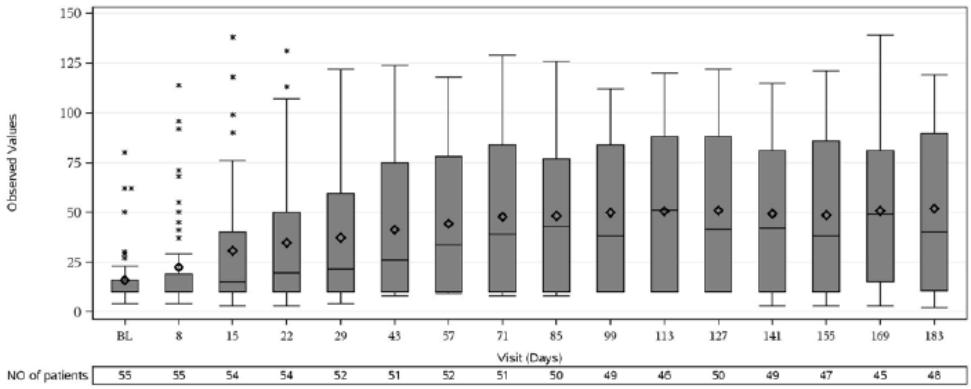
- Observed Value and Change From Baseline in eGFR

Renal function was assessed by eGFR. Mean eGFR gradually improved during the Initial Evaluation Period. For patients on dialysis a value of 10 mL/min/1.73 m2 was imputed.

Overall, the mean eGFR value at baseline was 15.86 mL/min/1.73 m2 (Table 14.2.2.9.1.1). Improvement was seen by Day 15 (mean: 30.63 mL/min/1.73 m2). The mean eGFR was 48.2 mL/min/1.73 m2 by Day 85 and was 51.83 mL/min/1.73 m2 at the end of the Initial Evaluation Period (Day 183).

The mean eGFR value at baseline among the 8 patients with kidney transplant was 14.81 mL/min/1.73 m2. Similar to the overall population, improvement was seen by Day 15 (mean: 23.29 mL/min/1.73 m2). The mean eGFR was 28.29 mL/min/1.73 m2 by Day 85 and was 29.00 mL/min/1.73 m2 at the end of the Initial Evaluation Period (Day 183).

Figure 5: Observed Values of eGFR Over Time (Full Analysis Set)



Note: Baseline value was defined as the average of the values from the assessments performed prior to the first study drug infusion (these could have included results from screening and the Day 1 visit). For eGFR, 10 mL/min/1.73 m^2 was imputed for patients requiring dialysis for acute kidney injury. Time points with fewer than 5 patients were not displayed. The horizontal line in the middle of each box indicates the median, a diamond indicates the mean and the top and the bottom borders of the box mark the 75th and 25th percentiles, respectively. The whiskers represent the highest and lowest values within 1.5 times the interquartile range (IQR) from the lower quartile and upper quartile. Outliers are represented by asterisk beyond the whiskers.
Abbreviations: BL = baseline; eGFR = estimated glomerular filtration rate; NO. = number.

- Chronic Kidney Disease Stage

In Study ALXN1210aHUS311 most patients had CKD Stage 4 or 5 at baseline. For the 47 patients with available baseline and Day 183 data, 32 (68.1%) of 47 patients in the FAS had improvement in CKD stage compared to baseline: 6 patients improved by 5 stages (ie, from ESKD to normal renal function), 7 patients improved by 4 stages, 5 patients improved by 3 stages, 4 patients improved by 2 stages, and 10 patients improved by 1 stage. Two patients experienced worsening CKD stage. One of these patients worsened from Stage 4 at baseline to Stage 5 at Day 8, received dialysis on Day 16, and remained at Stage 5 for the duration of the Initial Evaluation Period. The other patient worsened from Stage 4 at baseline to Stage 5 at Day 8 and remained at Stage 5 for the duration of the Initial Evaluation Period (except for 1 assessment of Stage 4 at Day 15).

Nineteen of the 30 patients who had a Complete TMA Response continued to have improved renal function during the Initial Evaluation Period after achieving Complete TMA Response, as assessed by an improvement in CKD stage from the time of Complete TMA Response to Day 183.

Table 15: CKD Stage Shift From Baseline to End of Initial Evaluation Period (26 Weeks [Day 183]) (Full Analysis Set)

Baseline CKD Stage	Post-Baseline CKD Stage at Day 183 (N = 47)					
	1 n (%)	2 n (%)	3A n (%)	3B n (%)	4 n (%)	5 n (%)
1 (n = 0)	0	0	0	0	0	0
2 (n = 3)	2 (4.3)	1 (2.1)	0	0	0	0
3A (n = 1)	1 (2.1)	0	0	0	0	0
3B (n = 2)	2 (4.3)	0	0	0	0	0
4 (n = 7)	1 (2.1)	0	0	3 (6.4)	1 (2.1)	2 (4.3)
5 (n = 34)	6 (12.8)	6 (12.8)	3 (6.4)	3 (6.4)	5 (10.6)	11 (23.4)
Total	12 (25.5)	7 (14.9)	3 (6.4)	6 (12.8)	6 (12.8)	13 (27.7)

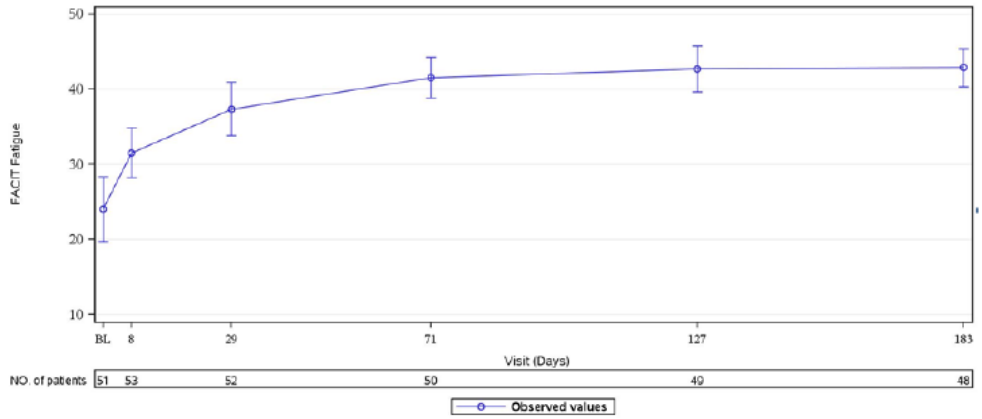
Note: Dark shading indicates improvement compared to baseline and light shading indicates worsening compared to baseline. Baseline was derived based on the last available eGFR before starting treatment. Patients with both baseline and at least 1 value at post-baseline visits were included in the summary. Percentages were based on the total number of patients with non-missing data at both the baseline visit and the post-baseline visit. The CKD stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stages of CKD:
Stage 1 = eGFR ≥ 90 (normal); Stage 2 = eGFR 60 to 89; Stage 3A = eGFR 45 to 59; Stage 3B = eGFR 30 to 44; Stage 4 = eGFR15 to 29; Stage 5: eGFR < 15 (including dialysis: end stage).
Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

- Change from baseline in QoL

FACIT-Fatigue

At baseline, the mean (SD) FACIT-Fatigue score for the 51 patients in the FAS with available data was 24.03 (15.279). Overall, the patients in the FAS showed improvement in FACIT-Fatigue score over time during the Initial Evaluation Period. At Day 183, the 44 patients with available data had a mean improvement from baseline in FACIT-Fatigue score of 19.15 (16.212).

Figure 6: Observed Values of FACIT-Fatigue Score Over time (Full Analysis Set)



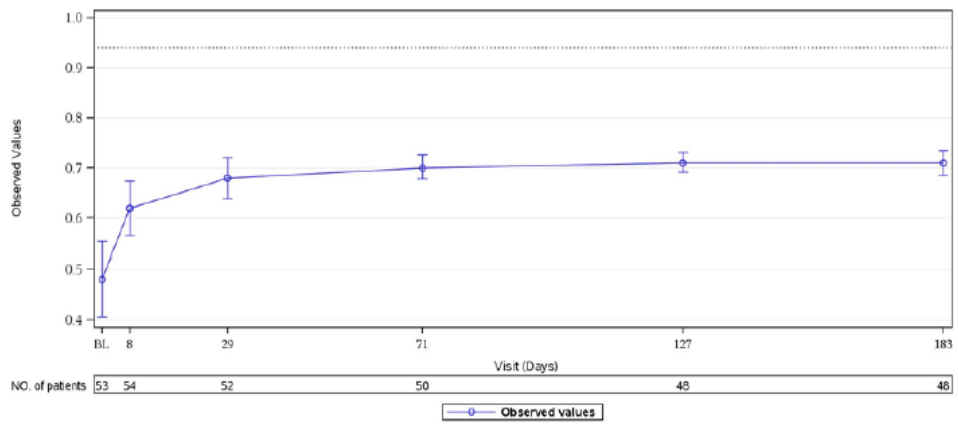
Notes: Baseline was from the Day 1 value. The FACIT-Fatigue questionnaire version 4 was used. The FACIT-Fatigue questionnaire at baseline and each post-infusion time point was scored using standard scoring algorithms. The FACIT-Fatigue score ranges from 0 to 52, with a higher score indicating less fatigue. Mean ± 95% CIs are displayed in the figure. Time points with fewer than 5 patients are not displayed on the figure.
Abbreviations: BL = baseline; CI = confidence interval; NO. = number; FACIT = Functional Assessment of Chronic Illness Therapy.

An improvement of ≥3 points in FACIT-Fatigue score, considered to be a clinically meaningful improvement (Cella, 2002; Webster, 2003), was observed in 37 (84.1%) of the 44 patients with available data. All of these patients had a 3-point improvement from baseline by Day 29.

EQ-5D-3L

At baseline, the mean (SD) EQ-5D-3L score was 0.48 (0.271) for the 53 patients in the FAS with available data. Overall, patients in the FAS showed improvement in EQ-5D-3L score over time during the Initial Evaluation Period. At Day 183, the 46 patients with available data had a mean change from baseline of 0.22.

Figure 7: Observed Values of EQ-5D-3L Score Over Time (Full Analysis Set)



Notes: Baseline was from the Day 1 value. The EQ-5D-3L score was assessed using the index scored according to the US TTO as well as the response on the VAS question. The standard US TTO value set was used to assign a baseline index value as well as a value at each post-infusion time point, based on the health state indicated on the questionnaire. The US TTO > 0.94 indicates full health. Mean ± 95% CIs are displayed in the figure. Time points with fewer than 5 patients are not displayed on the figure.
Abbreviations: EQ-5D-3L = EuroQol 5-Dimension 3-Level; US TTO = time trade-off value set for the United States; VAS = visual analogue scale.

Ancillary analyses

Subgroup analysis

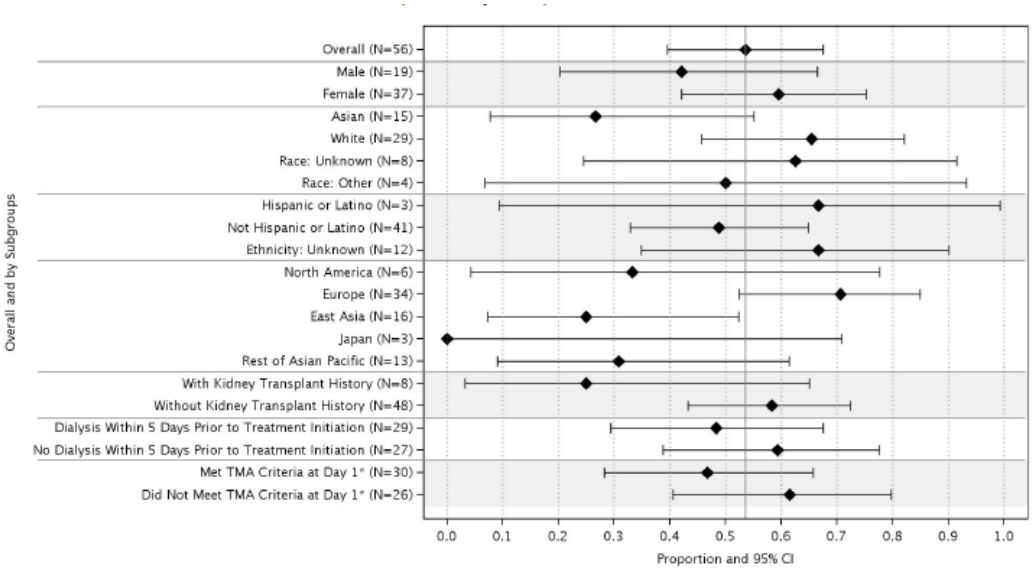
The Complete TMA Response rate was generally consistent across subgroups compared with the overall population (53.6%), with the exception of the following subgroups:

• The percentage of Asian patients (4/15, 26.7%) and patients treated at sites in East Asia (4/16, 25.0%) who achieved Complete TMA Response was lower compared to the overall population; 2/3 patients in Australia and 2/13 patients in the rest of East Asia.

• Patients with a history of kidney transplant had a lower percentage of patients who achieved Complete TMA Response (2/8, 25.0%) compared to non-transplant patients (28/48, 58.3%).

Although not a prespecified subgroup in the protocol, it was noted that 7 of the 8 patients who entered the study with persistent evidence of TMA for > 3 days after childbirth achieved Complete TMA Response by Day 43.

Figure 8: Forest Plot of Proportion and 95% CI of Complete TMA Response (Overall and by Subgroups) During the 26-Week Initial Evaluation Period (Full Analysis Set)



* Based on central laboratory results. TMA criteria at Day 1 included platelet count < 150,000/μL, LDH ≥ 1.5 × ULN, hemoglobin ≤ LLN, and serum creatinine level ≥ ULN (or required dialysis for acute kidney injury).
Abbreviations: CI = confidence interval; LLN = lower limit of normal; TMA = thrombotic microangiopathy; ULN = upper limit of normal.
Source: Figure 14.2.1.1.2.1

Study ALXN1210-aHUS-312:

This is a phase 3, single-treatment arm, multicenter study to evaluate the safety, efficacy, PK, and PD of ravulizumab administered by intravenous (IV) infusion to pediatric patients, from birth to < 18 years of age, with confirmed diagnosis of aHUS (ongoing).

The study has 2 cohorts: Cohort 1 includes complement inhibitor treatment-naïve patients; Cohort 2 includes eculizumab-experienced adolescent patients. In the initial submission results of 16 patients of Cohort 1 (complement inhibitor naive <18 y old patients) were presented.

Updated data through at least Week 26 (16 Oct 2019 database cut-off) have been provided during the procedure. The additional data provided consisted of Primary Evaluation Period (Week 26) efficacy results for 4 additional treatment-naive patients in Cohort 1 (total n = 18) and 10 eculizumab-experienced patients switched to ravulizumab in Cohort 2, and data through at least Week 52 for all Cohort 1 patients and 4 of the 10 Cohort 2 patients.

Methods

Study participants

Inclusion criteria (Cohort 1)

1. Patients from birth up to < 18 years of age and weighed ≥ 5 kg at the time of consent who had not been previously treated with complement inhibitors.
1. Evidence of TMA, including thrombocytopenia, evidence of hemolysis, and kidney injury, based on the following laboratory findings:

   a. Platelet count < 150,000/μL during the Screening Period or within 28 days prior to the start of the Screening Period, and

   b. Lactate dehydrogenase ≥ 1.5 × 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. eGFR > 30 mL/min/1.73m2 using the Schwartz formula.
2. Among patients with a kidney transplant:

   a. Known history of aHUS prior to current kidney transplant, or

   b. No known history of aHUS, and 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).
3. Among patients with onset of TMA postpartum, persistent evidence of TMA for > 3 days after the day of childbirth.
4. Vaccination against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who received the meningococcal vaccine less than 2 weeks before initiating ravulizumab treatment must have received treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients who had not been vaccinated prior to initiating ravulizumab treatment should have received prophylactic antibiotics prior to and for at least 2 weeks after meningococcal vaccination. Patients who could not be vaccinated must have received antibiotic prophylaxis for the entire treatment period and for 8 months following last dose.
5. Vaccination against Haemophilus influenzae type b (Hib) and Streptococcus pneumoniae according to national and local vaccination schedule guidelines.
6. Female patients of childbearing potential and male patients with female partners of childbearing potential must have been willing to follow protocol-specified guidance for avoiding pregnancy while on treatment and for 8 months after last dose of study drug.

Exclusion criteria (Cohort 1)

1. Known familial or acquired ADAMTS13 ("a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13") deficiency (activity < 5%).
2. Known Shiga toxin-related hemolytic uremic syndrome (HUS) as demonstrated by a positive test result for Shiga toxin or culture of Shiga toxin-producing bacteria.
3. Positive direct Coombs test.
4. Known human immunodeficiency virus infection.
5. Unresolved meningococcal disease.
6. Patients with a 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 bacterial infection that, in the opinion of the Investigator, confounded an accurate diagnosis of aHUS or impeded the ability to manage the aHUS disease.
8. Females who planned to become pregnant during the study or were currently pregnant or breastfeeding.
9. Heart, lung, small bowel, pancreas, or liver transplant.
10. Among patients with a kidney transplant, acute kidney dysfunction within 4 weeks of transplant consistent with the diagnosis of acute antibody-mediated rejection (AMR) according to Banff 2013 criteria.
11. Among patients 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)
12. Identified drug exposure-related HUS.
13. Patients received plasma exchange/plasma infusion, for 28 days or longer, prior to the start of screening for the current TMA.
14. History of malignancy within 5 years of screening with the exception of a non-melanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence.
15. Bone marrow transplant/hematopoietic stem cell transplant within the last 6 months prior to the start of screening.
16. Hemolytic uremic syndrome related to known genetic defects of cobalamin C metabolism.
17. Known systemic sclerosis (scleroderma), systemic lupus erythematosus or antiphospholipid antibody positivity or syndrome.
18. Chronic dialysis (defined as dialysis on a regular basis as renal replacement therapy for ESKD).
19. Received 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.

20. Received other immunosuppressive therapies such as steroids, mTORi (eg, sirolimus, everolimus), CNI (eg, cyclosporine or tacrolimus) were excluded unless:

    a. part of an established post-transplant antirejection regimen, or

    b. patient had confirmed anti-complement factor antibodies requiring immunosuppressive therapy, or

    c. steroids were being used for a condition other than aHUS (eg, asthma).

21. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever was greater.

22. Prior use of any complement inhibitors.

23. Use of tranexamic acid within 7 days prior to screening was prohibited.

Table 16: Population Comparison Across Ravulizumab Studies in Patients With aHUS

Main Criteria for Eligibility at Screening	ALXN1210-aHUS-311	ALXN1210-aHUS-312 (Cohort 1)
Age		
Adult (≥ 18 years of age)	X	
Adolescent (12 to < 18 years of age)	X[a]	X
Pediatric (< 12 years of age)		X
Complement inhibitor treatment-naïve	X	X
Prior plasma exchange/plasma infusion for < 28 days	X	X
Baseline platelet count < 150,000/μL	X	X
Baseline LDH ≥ 1.5 × ULN	X	X
Baseline hemoglobin ≤ LLN for age and gender	X	X
Baseline serum creatinine		
≥ ULN	X	
≥ 97.5th percentile for age		X
Body weight		
≥ 5 kg		X
≥ 40 kg	X	

[a] The original protocol planned to enroll adolescent patients. During the approximately 18 months that the study was enrolling patients, no adolescent patients were enrolled at any of the study sites.

Abbreviations: aHUS = atypical hemolytic uremic syndrome; LDH = lactate dehydrogenase; LLN = lower limit of normal; ULN = upper limit of normal.

Treatments

During the 26-week Initial Evaluation Period, patients received a weight-based loading dose of ravulizumab IV on Day 1, followed by maintenance treatment with ravulizumab on Day 15 and q8w thereafter for patients weighing ≥ 20 kg, or q4w for patients weighing < 20 kg.

The loading and maintenance doses were based on the patient's body weight recorded on Dose Regimen Decision Days.

Table 17: Ravulizumab Weight-based Dosing Regimen

Body Weight	Loading Dose (mg)	Maintenance Dose (mg)	Dosing Interval
≥ 5 to < 10 kg	600	300	q4w
≥ 10 to < 20 kg	600	600	q4w
≥ 20 to < 30 kg	900	2100	q8w
≥ 30 to < 40 kg	1200	2700	q8w
≥ 40 to < 60 kg	2400	3000	q8w
≥ 60 to < 100 kg	2700	3300	q8w
≥ 100 kg	3000	3600	q8w

Abbreviations: q4w = every 4 weeks; q8w = every 8 weeks.

Objectives

Primary Objective

The primary objective of the study was to assess the efficacy of ravulizumab in complement inhibitor treatment-naïve pediatric patients (ie, Cohort 1) with aHUS to inhibit complement-mediated TMA as characterized by thrombocytopenia, hemolysis, and renal impairment.

Secondary objectives

The secondary objectives for Cohort 1 were as follows:

- To characterize the safety and tolerability of ravulizumab
- To evaluate the efficacy of ravulizumab by additional efficacy measures
- To characterize the pharmacokinetics (PK)/pharmacodynamics (PD) of ravulizumab
- To evaluate the long-term safety and efficacy of ravulizumab

The secondary objectives for Cohort 2 were the following:

- To characterize the safety and tolerability of ravulizumab
- To evaluate the efficacy of ravulizumab by the following measures:

  a. Dialysis requirement status

  b. Observed value and change from baseline in eGFR

  c. CKD stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline

  d. Observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin)

  e. Change from baseline in QoL, as measured by Pediatrisamc FACIT Fatigue questionnaire

- To characterize the PK/PD of ravulizumab

Outcomes/endpoints

Primary endpoint

Complete TMA Response (Cohort 1 only) during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in

serum creatinine from baseline. Patients must meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.

Key secondary endpoints

- Time to Complete TMA Response (Cohort 1 only)
- Complete TMA Response status over time (Cohort 1 only)
- Dialysis requirement status
- Observed value and change from baseline in estimated glomerular filtration rate (eGFR)
- Chronic kidney disease (CKD) stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline
- Observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin)
- Increase in hemoglobin of ≥ 20 g/L from baseline, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between (Cohort 1 only)
- Change from baseline in quality of life (QoL), as measured by Pediatric Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Questionnaire (patients ≥ 5 years of age)

Sample size

The original protocol had a planned sample size of 16 patients. The total planned sample size was increased to include approximately 23 to 28 patients in Amendment 5 to account for addition of Cohort 2 (complement-inhibitor experienced adolescent patients). The minimum number of patients for each age category is as follows:

- Birth to < 2 years: 4 patients
- 2 to < 6 years: 4 patients
- 6 to < 12 years: 4 patients
- 12 to < 18 years: 8 patients

Data will continue to be collected for a minimum of 2 additional years in order to evaluate safety, durability of response, and long-term benefit/risk of ravulizumab treatment.

Randomisation.

As the study was a single-arm study does not apply randomization.

Blinding.

This was a single-arm, open-label study.

Statistical methods

The efficacy analyses were performed using the FAS, the primary efficacy population, for Cohort 1 only. The primary analysis and selected secondary efficacy analyses were repeated on the PP Set as sensitivity analyses. The FAS included all patients who received at least 1 dose of ravulizumab, had at

least 1 postbaseline efficacy assessment, met all eligibility criteria at baseline, and did not have ADAMTS13 deficiency or Shiga toxin-related HUS. The PP Set included all patients in the FAS who met prespecified criteria

The primary analysis consisted of estimating the proportion of complete TMA responders among ravulizumab-treated patients. This was performed by calculating the point estimate and a 95% confidence interval (CI) for the proportion of complete TMA responders in ravulizumab-treated patients. The CI was based on exact confidence limits using the Clopper-Pearson method.

A sensitivity analysis was prespecified in the SAP to evaluate a slightly modified version of Complete TMA Response. This modification applied only to the patients who were on dialysis at baseline (ie, patients requiring dialysis within 5 days prior to first dose of ravulizumab). For these patients, the criterion requiring an improvement from baseline of 25% or more in serum creatinine was replaced by a post-baseline change in dialysis status (from requiring dialysis at baseline to no longer requiring dialysis) that was maintained for at least 4 weeks. The definition of Complete TMA Response remained the same for all other patients.

Secondary Efficacy Analyses

Time to Complete TMA Response: For the secondary efficacy endpoint of time to Complete TMA Response, Kaplan-Meier cumulative distribution curves were generated along with 2-sided 95% CIs. The corresponding summary table presented the cumulative distribution function estimate, the number of patients at risk, the number of patients responding, and the number of patients censored at each post-baseline time point. The table also presented first quartile, median, and third quartile, along with corresponding 2-sided 95% CI, of time to complete response.

Complete TMA Response Status Over Time: Complete TMA Response was summarized over time by presenting the number and proportion of responders along with a 2-sided 95% CI for each post-baseline time point.

Hematologic Normalization: The number and proportion of patients who achieved hematologic normalization, defined as the normalization of both platelet count and LDH, was summarized over time with a 2-sided 95% CI for each post-baseline time point.

Hematologic TMA Parameters: Hematologic parameters (platelets, LDH, hemoglobin) were summarized at baseline and each post-baseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline. A mixed model for repeated measures (MMRM) with the fixed, categorical effect of visit and fixed, continuous effect of the specific test's baseline value as covariates may have been performed to test whether changes differ from zero at each time point.

For analysis purposes, priority was always given to results from the central laboratory, but if at a specific analysis visit no central lab results were available, the local lab result could be used in the analysis for the specific analysis visit.

Hemoglobin Response: The number and proportion of patients with an increase from baseline in hemoglobin $\geq$ 20 g/L, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between, were summarized over time by presenting the number and proportion of responders along with a 2-sided 95% CI for each post-baseline time point.

Dialysis Requirement Status: For patients requiring dialysis within 5 days prior to ravulizumab treatment initiation, the proportion of patients no longer requiring dialysis was summarized over time. A 2-sided 95% CI for the proportion receiving dialysis was provided.

eGFR Value and Change From Baseline: Kidney function evaluated by eGFR was summarized at baseline and each post-baseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline. A value of 10 mL/min/1.73 m2 for eGFR was imputed for patients requiring dialysis for acute kidney injury. An MMRM with the fixed, categorical effect of visit and fixed, continuous effect of the baseline value as covariates may have been performed to test whether changes differ from zero at each time point.

CKD Stage: Chronic kidney disease stage (Table 7) was summarized over time by presenting the number and proportion of patients that improved (excluding those with Stage 1 at baseline as they cannot improve), worsened (excluding those with Stage 5 at baseline as they cannot worsen), and stayed the same compared to CKD stage at baseline. Stage 5 was considered the worst category, while Stage 1 was considered the best category. A 2-sided 95% CI for the proportion was provided for each category.

Table 18: Glomerular Filtration Rate Category/Chronic Kidney Disease Stage

GFR Category/Stage	GFR (mL/min/1.73 m^2)	Terms
1	≥ 90	Normal or high
2	60 to 89	Mildly decreased[a]
3a	45 to 59	Mildly to moderately decreased
3b	30 to 44	Moderately to severely decreased
4	15 to 29	Severely decreased
5	< 15	Kidney failure

Note: In the absence of evidence of kidney damage, neither GFR category/stage G1 nor G2 fulfill the criteria for CKD.
[a] Relative to young adult level.
Abbreviations: CKD = chronic kidney disease; GFR = glomerular filtration rate.
Source: KDIGO 2012

Quality of Life: Quality of life was assessed in patients > 5 years of age by the Pediatric FACIT-Fatigue Questionnaire (patient-reported for patients who were ≥ 8 years of age at the time of enrolment; caregiver-reported or caregiver assistance for patients who were 5 to < 8 years of age at the time of enrolment; see Appendix F of the study protocol in Appendix 16.1.1). The FACIT-Fatigue data was summarized at baseline and each post-baseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline. An MMRM with the fixed, categorical effect of visit and fixed, continuous effect of the specific test's baseline value as covariates may have been performed to test whether changes differ from zero at each time point. Analyses were performed separately for patients who were 5 to < 8 years of age at the time of enrolment (ie, caregiver-reported or caregiver assistance) and patients who were ≥ 8 years of age at the time of enrolment (ie, patient-reported).

Handling of Dropouts or Missing Data

For evaluation of Complete TMA Response during the 26-week Initial Evaluation Period (primary endpoint), patients missing an efficacy assessment that was part of the definition of Complete TMA Response while still on study, had their last observation carried forward (LOCF). For patients who withdrew from the study prior to Week 26, their data up to the time of withdrawal was used to assess Complete TMA Response. A confirmatory result could not be from an assessment that was carried forward from the initial assessment when all Complete TMA Response criteria were met.

For laboratory data, in the event of duplicate samples from local and central laboratories (for any time point), central laboratory results were used for analysis.

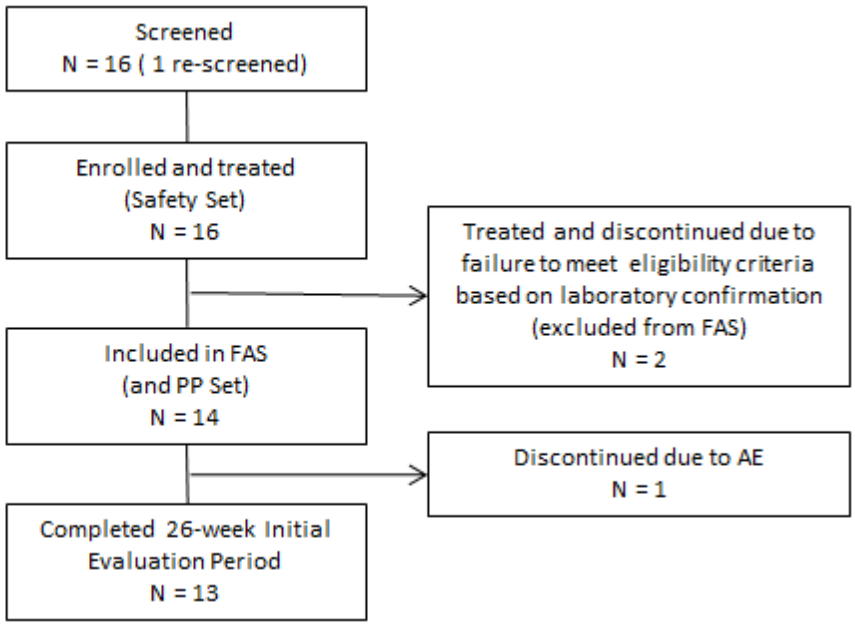
Hypothesis Testing and Significance Level: This was an estimation study and no formal statistical tests were planned.

Results

Participant flow

The presented results are those through the end of the 26-week Initial Evaluation Period for the first 16 patients enrolled in the study, all of whom are in Cohort 1 (complement inhibitor treatment-naïve patients).

Figure 9: Disposition of Patients – Initial Evaluation Period (All Screened Patients)



Abbreviations: AE = adverse event; FAS = full analysis set; PP Set = per protocol set.

In total, 13 patients completed the Initial Evaluation Period. One treated patient discontinued study drug and did not complete the Initial Evaluation Period due to treatment-emergent AEs (hypertensive crisis and anemia).

Recruitment

As of the data cutoff date, this study was initiated at 69 sites globally. Patients were screened and enrolled for the study in 12 sites across 6 countries (Belgium, Germany, Japan, Korea, Spain, and the United States).

- Date first patient treated: 01 Sep 2017
- Date last analyzed patient completed Initial Evaluation Period: 08 Oct 2018
- Date of report: 02 Apr 2019

Conduct of the study

Protocol amendments

From the original protocol (dated 23 Jan 2017, which was submitted to regulatory authorities), 4 country-specific and 1 global protocol amendment were made during the Initial Evaluation Period of the study.

Table 19: Summary of Protocol Changes

Amendment Number	Summary of Significant Changes to the Study Protocol
Amendment 1 (Japan) Dated: 16 Mar 2017	The following change was made for sites in Japan: • Exploratory genetics endpoint was removed for Japanese patients.
Amendment 2 (Germany) Dated: 21 Mar 2017	The following change was made for sites in Germany: • Targeted adverse events were broadened to also include sepsis, serious infections, *Aspergillus* infection, and infusion reactions. • Additional events of interest were defined as serious cutaneous adverse reactions, cardiac disorders (including ventricular fibrillation), and angioedema.
Amendment 3 (Japan) Dated: 19 Oct 2017	The following change was made to Amendment 1 for sites in Japan: • Entry criteria were revised to enroll patients previously treated with eculizumab for at least the past 3 months. • A new objective was added to evaluate the safety and efficacy of patients previously treated with eculizumab. • The statistical language was updated to clarify that patients previously treated with eculizumab will be excluded from the main analyses and summarized separately, as appropriate.
Amendment 4 (Japan) Dated: 02 Feb 2018	The following change was made to Amendment 3 for sites in Japan: • Entry criteria were revised to enroll patients into Cohort 2 who were previously treated with eculizumab for at least the past 90 days. • New Cohort 2 objectives and endpoints were added to evaluate the safety and efficacy of ALXN1210 in Cohort 2. • Updates were made to the statistical language to clarify that data from Cohort 2 patients will be excluded from the main analyses and presented separately, as appropriate.
Amendment 5 (Global) Dated: 23 Aug 2018	• The loading dose for patients 5 to < 10 kg was increased from 300 mg to 600 mg. • The entry criteria were revised to allow enrollment into Cohort 2 of adolescent patients previously treated with eculizumab for at least the past 90 days. • Revised the entry criterion to allow LDH and hemoglobin results obtained during the Screening Period or within 28 days prior to the start of the Screening Period. • New objectives and endpoints were added to evaluate the safety and efficacy of ALXN1210 in Cohort 2. • Added 2 interim analyses: 1) when 12 to 14 complement inhibitor treatment-naïve patients (ie, Cohort 1) have completed or withdrawn from the end of the 26-week Initial Evaluation Period; and 2) when all study patients have completed or withdrawn from the 26-week Initial Evaluation Period. • The Screening Period was clarified as 28 days for Cohort 2. • Added a provision to allow a supplemental dose of ALXN1210 to be administered to a patient if the Investigator and Sponsor mutually agree that a patient will potentially benefit. • Added a provision to allow for a dose to be administered as 2 separate infusion no more than approximately 24 hours apart if the Investigator and Sponsor mutually agree that the infusion volume (120 mL) of the loading dose for patients ≥ 5 to < 10 kg (600 mg) is too high for an individual patient. • The study sample size was increased to align with the planned sample size for each age category. • Statistical language was clarified to indicate that the analyses for Cohort 1 and Cohort 2 would be conducted and reported separately. • To reduce the patient data collection burden, removed the exploratory endpoints of Additional Signs or Symptoms of aHUS and Healthcare Resource Utilization.
Amendment 5.1 (Japan) Dated: 27 Aug 2018	• Amendment 5 (Global) changes were applied to the protocol for Japan, which had been modified previously by Amendment 4. Since the global protocol was amended to allow enrollment of complement-inhibitor experienced adolescent patients (12 to < 18 years of age) into Cohort 2, the Japanese version of the protocol was also amended to align with the global amendment. Complement-inhibitor experienced adolescent patients (birth to < 12 years of age and weighing ≥ 5 kg at the time of consent) are still allowed to enroll only in Japan. • A new PK/PD objective and endpoint was added for Cohort 2.
Amendment 5.2 (Germany) Dated: 14 Sep 2018	• Amendment 5 (Global) changes were applied to the protocol for Germany, which had been modified previously by Amendment 2.

Abbreviations: aHUS = typical hemolytic uremic syndrome; LDH = lactate dehydrogenase; PD = pharmacodynamics; PK = pharmacokinetic.

Protocol Deviations

Table 20: Major Protocol Deviations (Full Analysis Set)

Categories of Deviation	ALXN1210 (N = 16) n (%)
Patients with major deviations	11 (68.8)
Type of major deviations	
Eligibility and entry criteria	7 (43.8)
Serious adverse event reporting criteria	5 (31.3)
Informed consent procedures	3 (18.8)
Study drug compliance	1 (6.3)
Source document criteria	1 (6.3)

Note: Percentages were based on the total number of patients. Patients could have been counted in more than 1 category

Baseline data

Table 21: Demographics and Baseline Characteristics in Cohort 1 of Study ALXN1210-aHUS-312 (Full Analysis Set)

Parameter	Statistics	Ravulizumab (N = 18)
Age at time of first infusion (years) category	n (%)	
Birth to < 2 years		2 (11.1)
2 to < 6 years		9 (50.0)
6 to < 12 years		5 (27.8)
12 to < 18 years		2 (11.1)
Sex	n (%)	
Male		8 (44.4)
Female		10 (55.6)
Race[a]	n (%)	
American Indian or Alaskan Native		1 (5.6)
Asian		5 (27.8)
Black or African American		3 (16.7)
White		9 (50.0)
Unknown		1 (5.6)
History of transplant	n (%)	1 (5.6)
Platelets (10^9/L) blood	Median (min, max)	51.25 (14, 125)
Haemoglobin (g/L)	Median (min, max)	74.25 (32, 106)
LDH (U/L)	Median (min, max)	1963.0 (772, 4985)
eGFR (mL/min/1.73 m^2)	Median (min, max)	22.0 (10, 84)
Required dialysis at baseline	n (%)	6 (33.3)

Note: Data as of 16 Oct 2019. Percentages are based on the total number of patients.
[a] Patients can have multiple races selected.

Numbers analysed

Sixteen complement inhibitor treatment-naïve patients with evidence of TMA were enrolled and treated with ravulizumab; 14 of these patients were included in the FAS at the time of the initial interim analysis for Cohort 1. All 14 patients in the FAS were included in the PP Set.

Outcomes and estimation

Primary endpoint

In Study ALXN1210-aHUS-312, Complete TMA Response was achieved by 10 of 14 patients (71.4%; 95% CI: 41.9%, 91.6%) during the 26-week Initial Evaluation Period.

Table 22: Complete TMA Response and Complete TMA Response Components Analysis During the 26-Week Initial Evaluation Period (Full Analysis Set)

	Total	Responder	
		n	Proportion (95% CI)[a]
Complete TMA Response	14	10	0.714 (0.419, 0.916)
Components of Complete TMA Response			
Platelet count normalization	14	13	0.929 (0.661, 0.998)
LDH normalization	14	12	0.857 (0.572, 0.982)
25% improvement in serum creatinine from baseline	14	11	0.786 (0.492, 0.953)
Hematologic normalization[b]	14	12	0.857 (0.572, 0.982)

Note: Patients must have met all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. Platelet values obtained from the day of a blood transfusion of platelets through 3 days after the transfusion were excluded from all analyses. All serum creatinine values obtained while a patient was on dialysis were excluded from all analyses. When a patient was on dialysis at baseline, then the first valid creatinine value used as the baseline value was the first assessment ≥ 6 days post dialysis. If a patient was on dialysis during the entire 26-week Initial Evaluation Period, then the baseline creatinine was not calculated.

[a]95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.

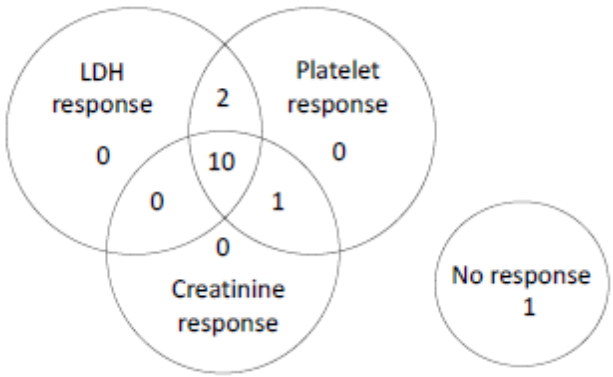
[b]Hematologic normalization includes normalization of platelet count (≥ 150 × 10^9/L) and normalization of LDH (≤ 246 U/L). Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

- Complete TMA Response Components

With the exception of 1 patient who withdrew from the study on Day 21 after 2 doses of ravulizumab, all 13 patients achieved platelet count normalization during the Initial Evaluation Period. Twelve patients achieved LDH normalization and 11 patients achieved renal function improvement (defined as 25% reduction in serum creatinine from baseline) during the Initial Evaluation Period.

Among the 4 patients who did not achieve Complete TMA Response, 2 patients achieved LDH and platelet count normalization and 1 patient achieved platelet count normalization and renal function improvement during the Initial Evaluation Period. The 1 patient who did not have improvement in any of the Complete TMA Response components withdrew from the study due to an AE after receiving 2 doses of study drug.

Figure 10: Number of Patients Who Achieved One or More Components of Complete TMA Response (Full Analysis Set)



Sensitivity Analysis

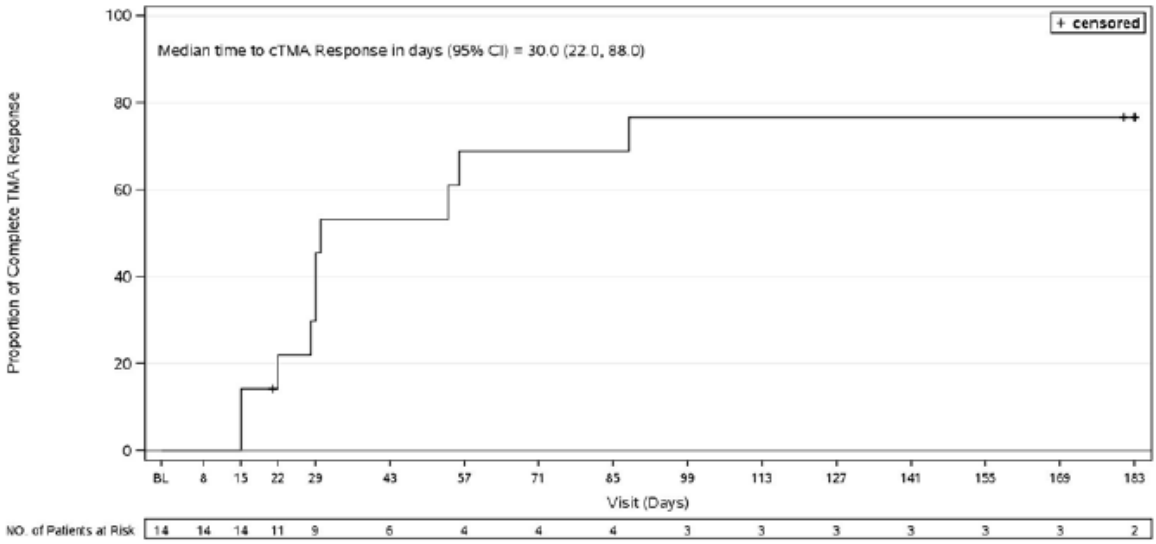
A separate sensitivity analysis was performed using a modified version of Complete TMA Response. The modification applied strictly to the patients on dialysis at baseline. For the modified Complete TMA Response analysis, Complete TMA Response was observed in a majority of these patients (71.4% [95% CI: 41.9%, 91.6%]) in the FAS and PP Set.

Secondary endpoints

- Time to Complete TMA Response

The median time to Complete TMA Response during the Initial Evaluation Period was 30 days and occurred as early as 15 days following the first dose of ravulizumab. The latest response was observed at 88 days.

Figure 11: Time to Complete TMA Response – Kaplan Meier Cumulative Distribution Curves (Full Analysis Set)



Note: Patients must have met all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. The time of the event of a confirmed complete TMA response was considered as the first time point at which all the criteria for Complete TMA Response were met. Patients 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.

Abbreviations: BL = baseline; CI = confidence interval; NO. = number; cTMA = Complete TMA; TMA = thrombotic microangiopathy.

Source: Figure 14.2.2.2.1.1

- Complete TMA Response Status Over Time

The 10 patients who achieved the Complete TMA Response status had all done so by Day 85. Nine of these responders had sustained their response status from the first time point when they achieved Complete TMA Response through the end of the 26-week Initial Evaluation Period. One patient achieved a Complete TMA Response at Day 15 and continued to meet the response criteria through the end of the 26-week Initial Evaluation Period, except at 1 visit time point (Day 71).

Table 23: Complete TMA Response Status Over Time With a Confirmatory Result (Full Analysis Set)

Visit		ALXN1210 (N = 14)
	n/m	Proportion (95% CI)[a]
Day 8	0/13	0.000 (0.000, 0.247)
Day 15	2/13	0.154 (0.019, 0.454)
Day 22	3/13	0.231 (0.050, 0.538)
Day 29	7/13	0.538 (0.251, 0.808)
Day 43	7/13	0.538 (0.251, 0.808)
Day 57	9/13	0.692 (0.386, 0.909)
Day 71	8/13	0.615 (0.316, 0.861)
Day 85	10/13	0.769 (0.462, 0.950)
Day 99	10/13	0.769 (0.462, 0.950)
Day 113	10/13	0.769 (0.462, 0.950)
Day 127	10/13	0.769 (0.462, 0.950)
Day 141	10/13	0.769 (0.462, 0.950)
Day 155	10/13	0.769 (0.462, 0.950)
Day 169	10/13	0.769 (0.462, 0.950)
Day 183	10/13	0.769 (0.462, 0.950)

[a] 95% CIs for the proportion are based on exact confidence limits using the Clopper-Pearson method.
Abbreviations: CI = confidence interval; m = number of patients with a possible confirmatory result available at each visit; TMA = thrombotic microangiopathy.
Source: Table 14.2.2.3.1.1

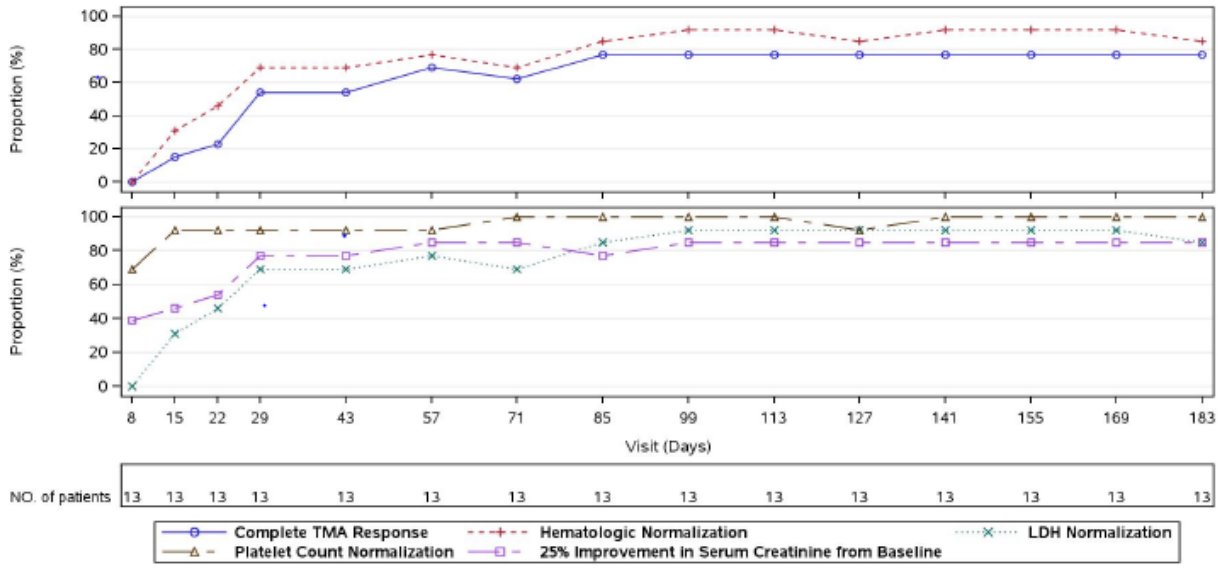
- Complete TMA Response Components Status Over Time

With the exception of 1 patient who withdrew from the study after 2 doses of ravulizumab, all remaining 13 patients in the FAS achieved platelet count normalization. Platelet count normalization was achieved after the first dose of study drug (ie, by Day 15) for 12 patients; 9 patients at Day 8 and 3 patients at Day 15. The latest response was observed at Day 71 (n = 1). When platelet count normalization was achieved, it was sustained by all patients, with the exception of 1 patient who did not meet this criterion at a single time point and then platelet count normalization resumed for the remainder of the Initial Evaluation Period.

Of the 12 patients who achieved LDH normalization, this was achieved by Day 15 for 4 patients. The latest response was observed at Day 99 (n = 1). When LDH normalization was achieved, it was sustained by all patients, with the exception of 2 patients who did not meet this criterion at a single time point (1 patient at Day 183; 1 patient transiently at Day 71 and then LDH normalization resumed for the remainder of the Initial Evaluation Period).

Of the 11 patients in the FAS that achieved renal function improvement, 6 patients achieved this improvement after the first dose of study drug (ie, by Day 15); 5 patients by Day 8 and 1 patient by Day 15. The latest response was observed at Day 57 (n = 1). All of the patients that met the criteria for the renal function improvement component sustained this response during the Initial Evaluation Period.

Figure 12: Complete TMA Response, Hematologic Normalization, and Complete TMA Response Components Status Over Time



Note: The criteria for Complete TMA Response are 1) normalization of platelet count; 2) normalization of LDH; and 3) ≥ 25% improvement in serum creatinine from baseline. A patient was in the analysis for a specific post-baseline time point if it was possible for the result at that time point to be confirmed. Hematologic normalization includes 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. All serum creatinine values obtained while a patient was on dialysis were excluded from all analyses. When a patient was on dialysis at baseline, then the first valid creatinine value to be used as the baseline value was the first assessment ≥ 6 days post dialysis. If a patient is on dialysis during the entire 26-week Initial Evaluation Period, then the baseline creatinine was not calculated.
Abbreviations: LDH = lactate dehydrogenase; NO. = number; TMA = thrombotic microangiopathy.

- Hematologic Normalization

Hematologic normalization included normalization of platelet count and normalization of LDH. During the Initial Evaluation Period, hematologic normalization was observed in 12 of 14 patients (85.7% [95% CI: 57.2%, 98.2%]).

- Hematologic TMA Parameters

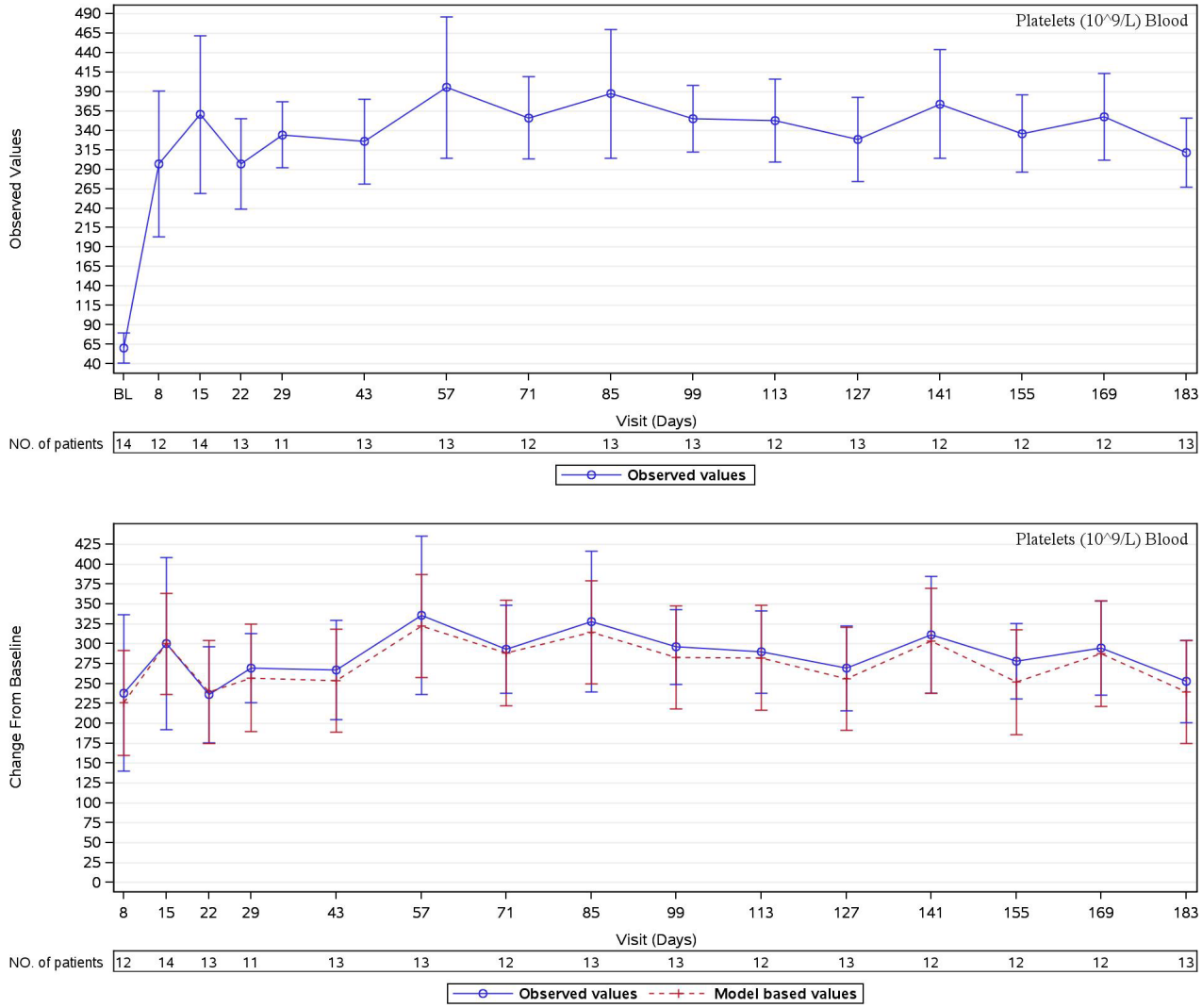
Overall, patients in the FAS showed improvement in all hematologic TMA parameters (platelets, LDH, and hemoglobin) during the Initial Evaluation Period. Improvements in platelet count and LDH level began on Day 8, and improvement in hemoglobin began on Day 22:

The mean (SD) change from baseline in platelet count was 238.08 (154.402) at Day 8 and this mean increase was sustained over the duration of the Initial Evaluation Period.

The mean (SD) change from baseline in LDH was -1330.61 (952.371) at Day 8, and increased to -2111.88 (1350.886) at Day 29, and this mean decrease was sustained over the duration of the Initial Evaluation Period.

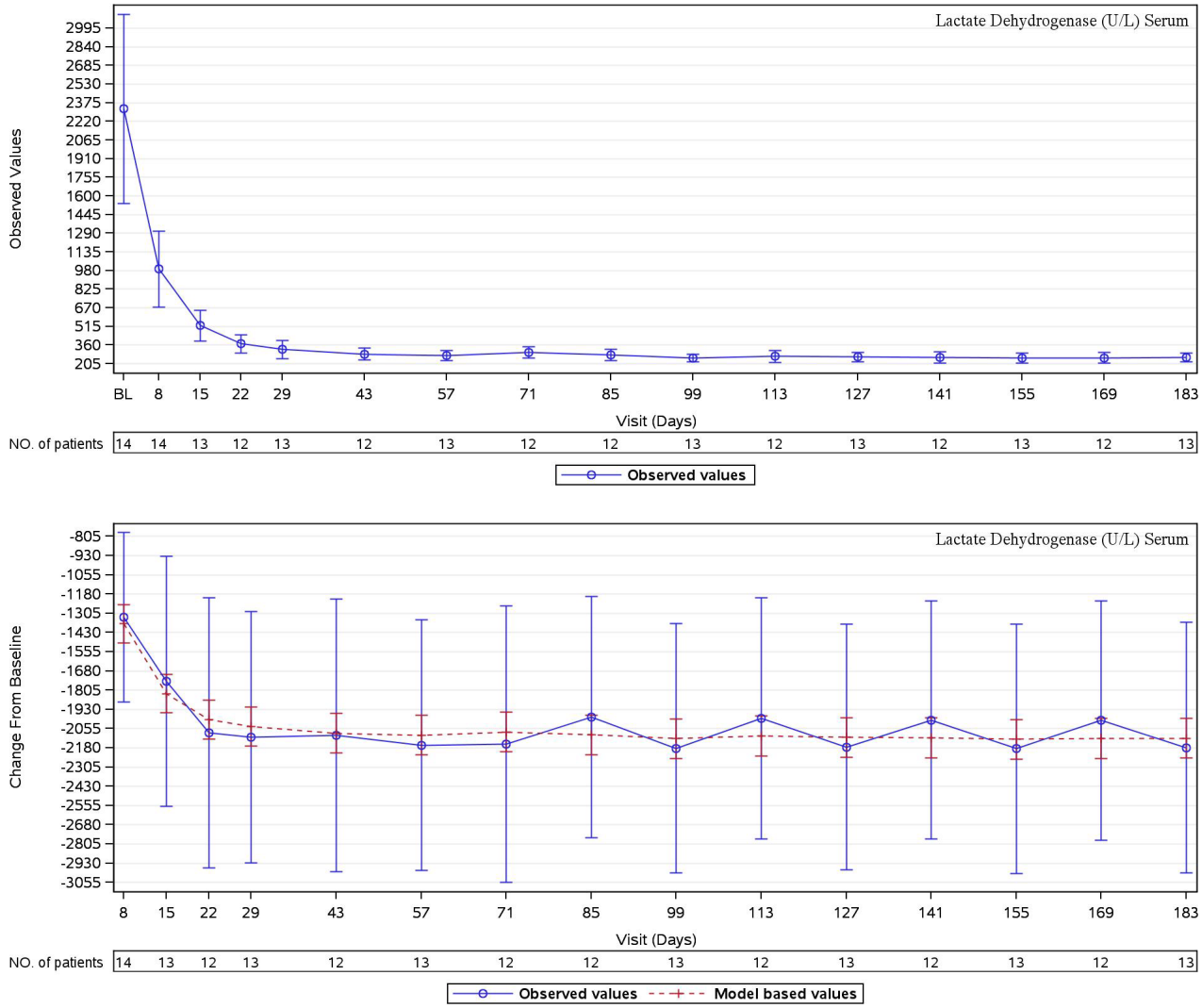
The mean (SD) change from baseline in hemoglobin was 10.79 (16.120) at Day 15, and increased to 36.13 (21.597) at Day 43, and this mean increase was sustained over the duration of the Initial Evaluation Period.

Figure 13: Observed Values and Model-Based Values of Changes in Platelets Over Time During the Initial Evaluation Period (Full Analysis Set)



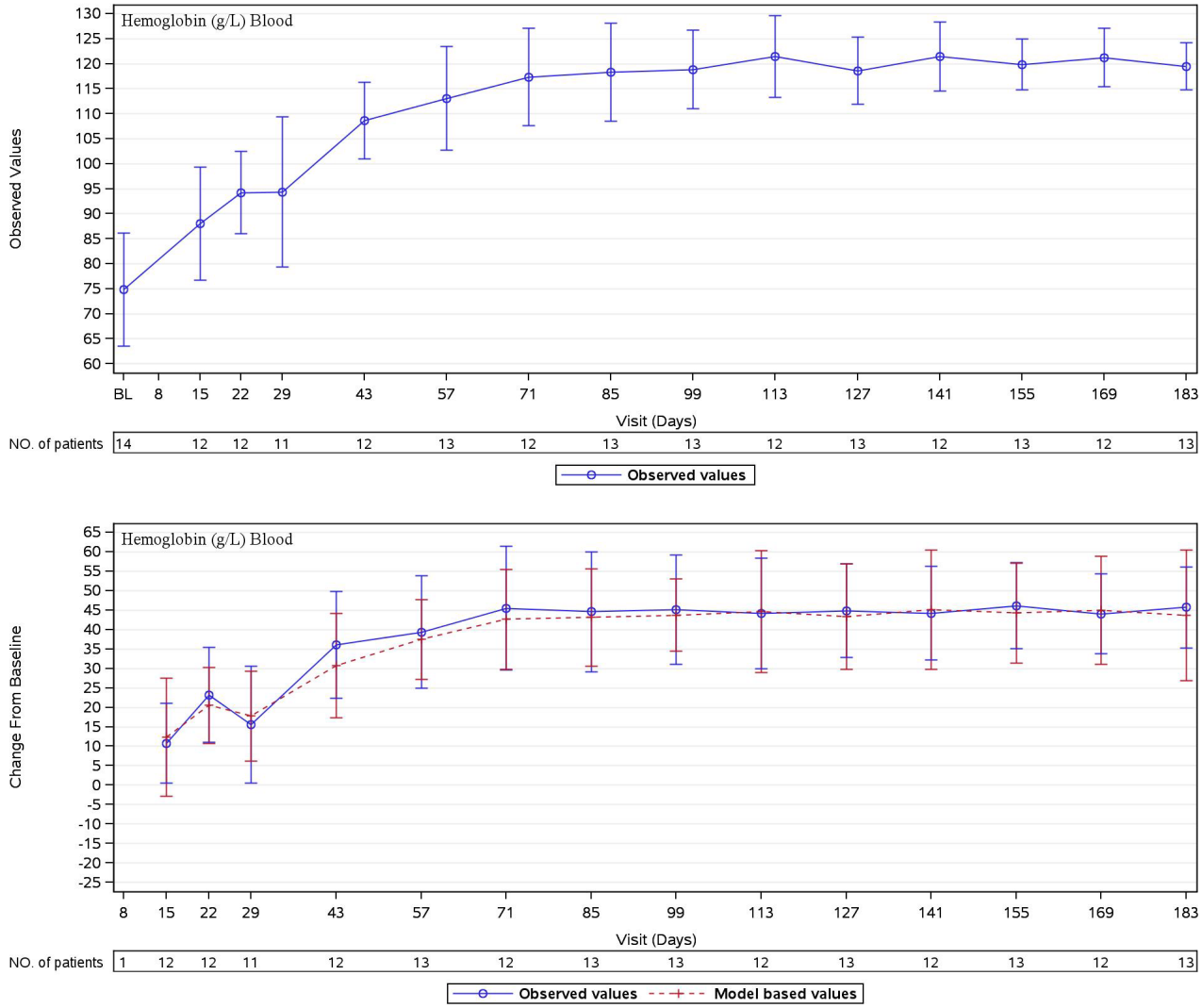
Notes: Baseline value was defined as the average of the values from the assessments performed prior to the first study drug infusion (these could include results from screening and the Day 1 visit). Platelet values obtained from the day of a blood transfusion of platelets through 3 days after the transfusion were excluded from all analyses. A mixed model for repeated measures was used which included the fixed, categorical effect of visit and fixed, continuous effect of the baseline value as covariates. A first-order autoregressive covariance structure was used for platelets to model the within patient errors. Time points with fewer than 5 patients were not displayed in the figure. Observed values: mean ± 95% CI. Model-based values: mean ± 95% CI. Abbreviations: BL = baseline; CI = confidence interval; NO. = number.

Figure 14: Observed Values and Model Based Values of Changes in LDH Over Time During the Initial Evaluation Period (Full Analysis Set)



Notes: Baseline value was defined as the average of the values from the assessments performed prior to the first study drug infusion (these could include results from screening and the Day 1 visit). A mixed model for repeated measures was used which included the fixed, categorical effect of visit and fixed, continuous effect of the baseline value as covariates. A compound symmetry structure was used to model the within patient errors. Time points with fewer than 5 patients were not displayed in the figure. Observed values: mean ± 95% CI. Model-based values: mean ± 95% CI. Abbreviations: BL = baseline; CI = confidence interval; LDH = lactate dehydrogenase; NO. = number.

Figure 15: Observed Values and Model Based Values of Changes in Hemoglobin Over Time During the Initial Evaluation Period (Full Analysis Set)



Notes: Baseline value was defined as the average of the values from the assessments performed prior to the first study drug infusion (these could include results from screening and the Day 1 visit). 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 mixed model for repeated measures was used which included the fixed, categorical effect of visit and fixed, continuous effect of the baseline value as covariates. A Toeplitz covariance structure was used to model the within patient errors. Time points with fewer than 5 patients were not displayed in the figure. Observed values: mean ± 95% CI. Model-based values: mean ± 95% CI. Abbreviations: BL = baseline; CI = confidence interval; NO. = number.

- Hemoglobin Response

During the Initial Evaluation Period, 12 of the 14 patients in the FAS (85.7% [95% CI: 57.2%, 98.2%]) had an increase in hemoglobin of ≥20 g/L compared to baseline with a confirmatory result. Of the 13 patients who completed the 26 weeks of ravulizumab treatment, 12 patients had a hemoglobin response as of Day 99.

Table 24: Hemoglobin Response With a Confirmatory Result (Full Analysis Set)

Parameter	Visit	ALXN1210 (N = 14)	
		n/m	Proportion (95% CI)[a]
Hemoglobin ≥ 20 g/L increase from baseline	Day 8	0/13	0.000 (0.000, 0.247)
	Day 15	2/13	0.154 (0.019, 0.454)
	Day 22	6/13	0.462 (0.192, 0.749)
	Day 29	6/13	0.462 (0.192, 0.749)
	Day 43	9/13	0.692 (0.386, 0.909)
	Day 57	11/13	0.846 (0.546, 0.981)
	Day 71	11/13	0.846 (0.546, 0.981)
	Day 85	11/13	0.846 (0.546, 0.981)
	Day 99	12/13	0.923 (0.640, 0.998)
	Day 113	12/13	0.923 (0.640, 0.998)
	Day 127	12/13	0.923 (0.640, 0.998)
	Day 141	12/13	0.923 (0.640, 0.998)
	Day 155	12/13	0.923 (0.640, 0.998)
	Day 169	12/13	0.923 (0.640, 0.998)
	Day 183	12/13	0.923 (0.640, 0.998)

Note: Baseline value was defined as the average of the values from the assessments performed prior to the first study drug infusion (these could have included results from screening and the Day 1 visit). A patient was included in the analysis for a specific post-baseline time point if it was possible for the result at that time point to be confirmed. 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 were based on exact confidence limits using the Clopper-Pearson method.

Abbreviations: CI = confidence interval; m = number of patients with a possible confirmatory result available at each visit.

- Dialysis Requirement Status

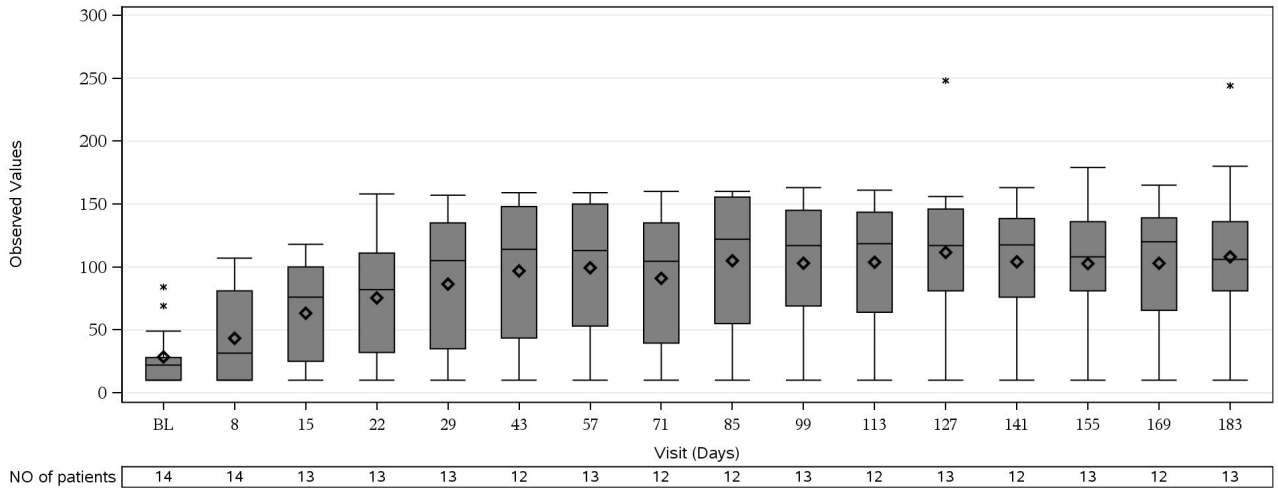
Of the 5 patients who were receiving kidney dialysis at baseline (within 5 days of the first dose of study drug), 4 patients discontinued dialysis after 29 days or less of exposure to ravulizumab. No new patients initiated dialysis after starting treatment with study drug.

- e-GFR Value and Change From Baseline

Renal function, as assessed by mean (SD) eGFR, improved from 28.4 (23.11) mL/min/1.73 m2 at baseline to 108 (63.21) mL/min/1.73 m2 at the end of the Initial Evaluation Period. Results from the MMRM statistical analysis of the change in e-GFR from baseline demonstrated improvements within 29 days of the start of ravulizumab treatment.

One patient had a history of kidney transplant; this patient also had an improvement in e-GFR during the Initial Evaluation Period compared to baseline (22 to 29 mL/min/1.73 m2).

Figure 16: Observed Values of eGFR Over Time (Full Analysis Set)



Note: Baseline value was defined as the average of the values from the assessments performed prior to the first study drug infusion (these could include results from screening and the Day 1 visit). For eGFR, 10 mL/min/1.73 m2 was imputed for patients requiring dialysis for acute kidney injury. The horizontal line in the middle of each box indicates the median, a diamond indicates the mean, and the top and bottom borders of the box mark the 75th and 25th percentiles, respectively. The whiskers represent the highest and lowest values within 1.5 times the interquartile range from the lower quartile and upper quartile. Outliers are represented by asterisk beyond the whiskers. Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; NO. = number.

- Chronic Kidney Disease Stage

Per the CKD stage definitions, Stage 5 (kidney failure) was considered the worst category, while Stage 1 (normal renal function) was considered the best category (note: 3A and 3B are counted as separate CKD stages). The majority of patients (11 of 14 patients) evaluated at baseline were CKD Stage 4 or 5; 5 (35.7%) patients were CKD Stage 5. With the exception of 2 patients, all of these patients improved their CKD stage (ie, shifted to a lower CKD stage from baseline through the end of the Initial Evaluation Period (Day 183); the shift was substantial as 9 patients improved by 2 or more stages.

Table 25: CKD Stage Shift From Baseline to End of Initial Evaluation Period (26 Weeks [Day 183]) (Full Analysis Set)

		Postbaseline CKD Stage at Day 183 (N = 13)[a]					
Baseline CKD Stage	**Baseline n (%)**	**1 n (%)**	**2 n (%)**	**3A n (%)**	**3B n (%)**	**4 n (%)**	**5 n (%)**
1	0	0	0	0	0	0	0
2	2 (14.3)	1 (7.7)	0	0	0	0	0
3A	1 (7.1)	1 (7.7)	0	0	0	0	0
3B	0	0	0	0	0	0	0
4	6 (42.9)	3 (23.1)	1 (7.7)	1 (7.7)	0	1 (7.7)	0
5	5 (35.7)	3 (23.1)	1 (7.7)	0	0	0	1 (7.7)
Total	14 (100.0)	8 (61.5)	2 (15.4)	1 (7.7)	0	1 (7.7)	1 (7.7)

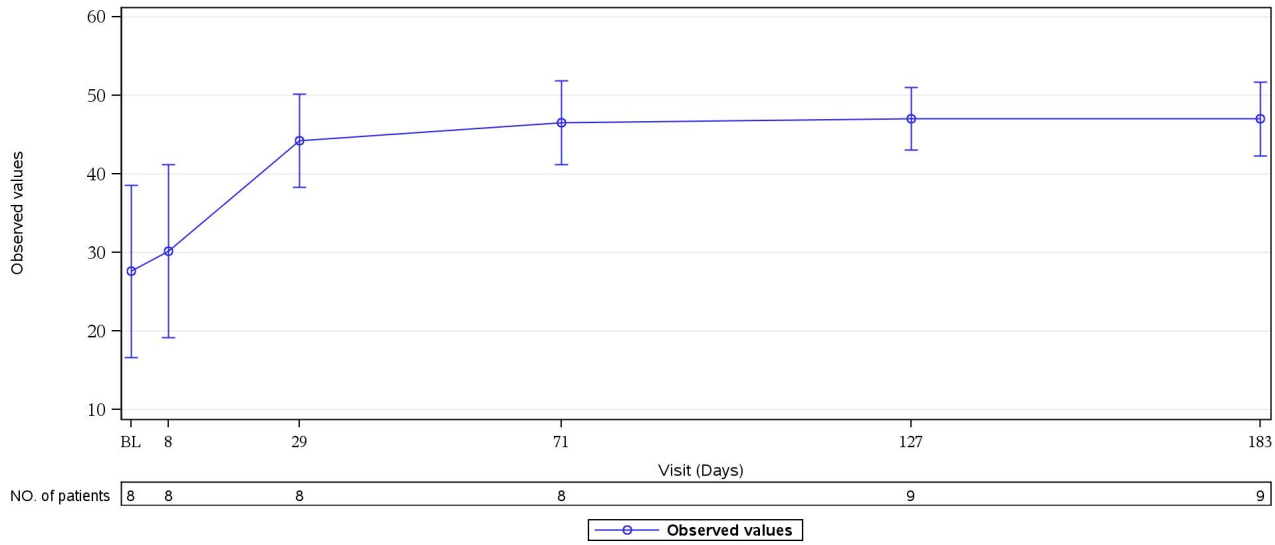
Note: Dark shading indicates improvement compared to baseline and light shading indicates worsening compared to baseline. Baseline was derived based on the last available eGFR before starting treatment. Patients with both baseline and at least 1 value at post-baseline visits were included in the summary. Percentages were based on the total number of patients with non-missing data at both the baseline visit and the post-baseline visit. The CKD stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stages of CKD:Stage 1 = eGFR ≥ 90 (normal); Stage 2 = eGFR 60 to 89; Stage 3A = eGFR 45 to 59; Stage 3B = eGFR 30 to 44; Stage 4 = eGFR 15 to 29; Stage 5: eGFR < 15 (including dialysis: end stage). a The percentages for the post-baseline CKD stage at Day 183 are based on the 13 patients with available data. Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

At the end of the Initial Evaluation Period, 11 (84.6%) of 13 patients had improvement in CKD stage compared to baseline. Three of these patients had improvement by 5 stages, 4 patients had improvement by 4 stages, 3 patients had improvement by 2 stages, and 1 patient improved by 1 stage. Two patients had no improvement in the CKD stage during the Initial Evaluation Period. One of these patients had a history of kidney transplant prior to the study. None of the patients worsened in CKD stage during the Initial Evaluation Period.

- Quality of Life

For the 8 treated patients who were > 5 years of age, QoL was assessed using the Pediatric FACIT-Fatigue Questionnaire. During the Initial Evaluation Period, these 8 patients had a mean (SD) improvement in the Pediatric FACIT-Fatigue score of 18.91 (14.988) compared to baseline. Three (37.5%) of 8 patients had a 3-point improvement in the FACIT-Fatigue total score from baseline at Day 8, 7 (87.5%) patients had a 3-point improvement from baseline at Day 29, and all 8 patients had a 3-point improvement from baseline by Day 71.

Figure 17: Observed Values of Pediatric FACIT-Fatigue Score Over Time (Full Analysis Set)



Notes: Baseline was the Day 1 value. Pediatric FACIT-Fatigue Questionnaire was used. The Pediatric FACIT-Fatigue Questionnaire at baseline and each post-infusion time point was scored using standard scoring algorithms. The FACIT-Fatigue score ranged from 0 to 52, with a higher score indicating less fatigue. Values displayed are mean ± 95% CIs. Abbreviations: CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy; NO. = number.

Updated efficacy analysis (data cut-off 16 Oct 2019)

Cohort 1

Complete TMA Response, the primary endpoint for the trial, was observed in 14 of the 18 naïve patients (77.8%) during the 26-week Initial Evaluation Period. Complete TMA Response during the Initial Evaluation Period was achieved at a median time of 30 days (range 15 to 97 days).

As of the 16 Oct 2019 data cutoff, 3 additional patients had a Complete TMA Response that was confirmed after the 26-week Initial Evaluation Period (with Complete TMA Response occurring at Days 291, 297, and 353); thus, 17 of 18 (94.4%) pediatric patients (95% CI: 72.7%, 99.9%) had a Complete TMA Response in the trial.

Table 26: Complete TMA Response and Complete TMA Response Components Analysis During the 26-Week Initial Evaluation Period in Cohort 1 of Study ALXN1210-aHUS-312 (Full Analysis Set)

	Total	Responder	
		n	Proportion (95% CI)[a]
Complete TMA Response	18	14	0.778 (0.524, 0.936)
Components of Complete TMA Response			
Platelet count normalisation	18	17	0.944 (0.727, 0.999)
LDH normalisation	18	16	0.889 (0.653, 0.986)
≥25% improvement in serum creatinine from baseline	18	15	0.833 (0.586, 0.964)
Haematologic normalisation	18	16	0.889 (0.653, 0.986)

Note: Data as of 16 Oct 2019. One patient withdrew from study after receiving 2 doses of ravulizumab.

[a] 95% CIs for the proportion were based on the asymptotic Gaussian approximation method with a continuity correction.

Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Table 27: Secondary Efficacy Outcome for Study ALXN1210-aHUS-312 (Cohort 1 Full Analysis Set)

Parameters	Study ALXN1210-aHUS-312 (N=18)	
Haematologic TMA parameters, Day 183	Observed value (n=17)	Change from baseline (n=17)
Platelets (10^9/L) blood		
Mean (SD)	304.94 (75.711)	245.59 (91.827)
Median	318.00	247.00
LDH (U/L) serum		
Mean (SD)	262.41 (59.995)	-2044.13 (1328.059)
Median	247.00	-1851.50
Increase in haemoglobin of ≥ 20 g/L from baseline with a confirmatory result through Initial Evaluation Period		
m/N	16/18	
proportion (95% CI)*	0.889 (0.653, 0.986)	
CKD stage shift from baseline, Day 183		
Improved[a]		
m/n	15/17	
Proportion (95% CI)*	0.882 (0.636, 0.985)	
Worsened[b]		
m/n	0/11	
Proportion (95% CI)*	0.000 (0.000, 0.285)	
eGFR (mL/min/1.73 m^2), Day 183	Observed value (n=17)	Change from baseline (n=17)
Mean (SD)	108.5 (56.87)	85.4 (54.33)
Median	108.0	80.0
FACIT-Fatigue score, Day 183	Observed value (n=9)	Change from baseline (n=9)
Mean (SD)	48.22 (5.848)	16.78 (14.704)
Median	52.00	10.0

Note: Data as of 16 Oct 2019.

*95% confidence intervals (95% CIs) are based on exact confidence limits using the Clopper Pearson method.

**95% confidence intervals (95% CIs) for the proportion are based on the asymptotic Gaussian approximation method with a continuity correction.

[a] Improved excludes patients with Stage 1 at baseline, as they cannot improve.

[b] Worsened excludes patients with Stage 5 at baseline as they cannot worsen.

Abbreviations: eGFR = estimated glomerular filtration rate; FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Cohort 2

As of the 16 Oct 2019 data cutoff, 10 eculizumab-experienced patients who switched to ravulizumab have completed the 26-week Initial Evaluation Period and entered the Extension Period, with a cumulative median exposure of 43.6 weeks. This cohort consists primarily of adolescent patients, with a mean age of 11 years. The patients in this cohort had been treated with eculizumab at the approved dosing regimen for at least 90 days prior to screening and had clinical evidence of response indicated by stable TMA parameters, which is reflected in their disease status at baseline. No patients refractory to eculizumab were enrolled.

Table 28: Demographics and Baseline Characteristics in Cohort 2 of Study ALXN1210-aHUS-312 (Full Analysis Set)

Variable	Cohort 2 Patients (N = 10)
Age (years) at first infusion	
Mean (SD)	11.0 (4.97)
Median (min, max)	12.5 (1.2, 15.5)
Age (years) at first infusion category, n (%)	
Birth to < 2 years	1 (10.0)
2 to < 6 years	1 (10.0)
6 to < 12 years	1 (10.0)
12 to < 18 years	7 (70.0)
Sex, n (%)	
Male	9 (90.0)
Female	1 (10.0)
Race, n (%)[a]	
American Indian or Alaskan Native	0 (0.0)
Asian	4 (40.0)
Black or African American	1 (10.0)
White	5 (50.0)
Unknown	0 (0.0)
Weight (kg) at first infusion	
Mean (SD)	41.6 (19.01)
Median (min, max)	47.8 (8.82, 69)

Note: Data as of 16 Oct 2019.
[a] Patients can have multiple races selected.
Abbreviations: max = maximum; min = minimum.

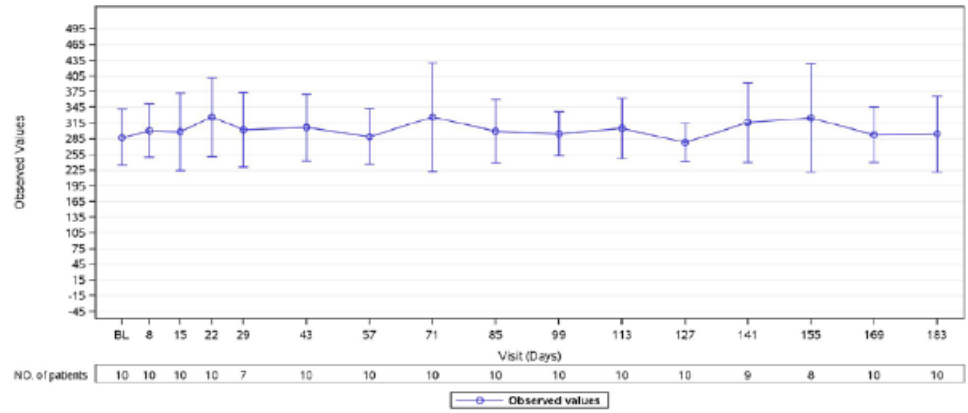
Table 29: Disease Characteristics in Cohort 2 of Study ALXN1210-aHUS-312 (Full Analysis Set)

Parameter	Cohort 2 Patients (N = 10)
Extra-renal signs or symptoms of aHUS, n (%)	
Any	1 (10.0)
Cardiovascular	1 (10.0)
Pulmonary	0 (0.0)
Central nervous system	0 (0.0)
Gastrointestinal	0 (0.0)
Skin	0 (0.0)
Skeletal muscle	0 (0.0)
Dialysis within 5 days of baseline, n (%)	0 (0.0)
History of transplant, n (%)	1 (10.0)
Baseline CKD stage, n (%)	
1	8 (80.0)
2	1 (10.0)
3A	1 (10.0)
3B	0 (0.0)
4	0 (0.0)
5	0 (0.0)
Platelets (10^9/L)	
Mean (SD)	287.90 (74.596)
Median (min, max)	281.75 (207, 415.5)
Hemoglobin (g/L)	
Mean (SD)	131.50 (11.311)
Median (min, max)	132.0 (114.5, 148)
LDH (U/L) serum	
Mean (SD)	219.40 (56.850)
Median (min, max)	206.5 (138.5, 356)
eGFR (mL/min/1.73 m^2)	
Mean (SD)	104.90 (29.545)
Median (min, max)	99.75 (54, 136.5)

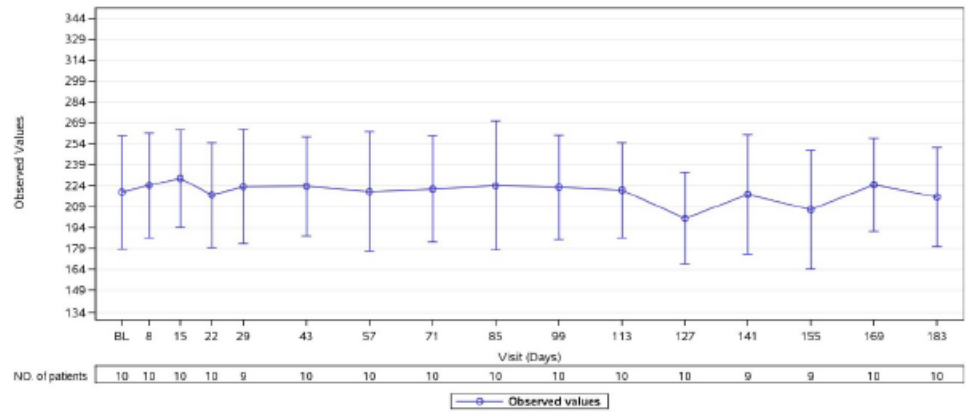
Note: Data as of 16 Oct 2019.

Table 30: Hematologic TMA Parameters Observed Mean (± SD) Values Over Time in Study ALXN1210-aHUS-312 Cohort 2 (Full Analysis Set)

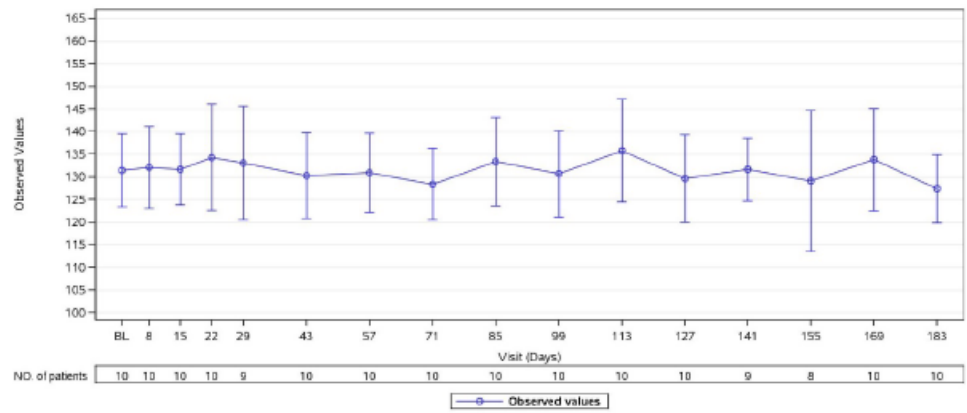
Platelets (10^9/L)



Lactate Dehydrogenase (U/L)

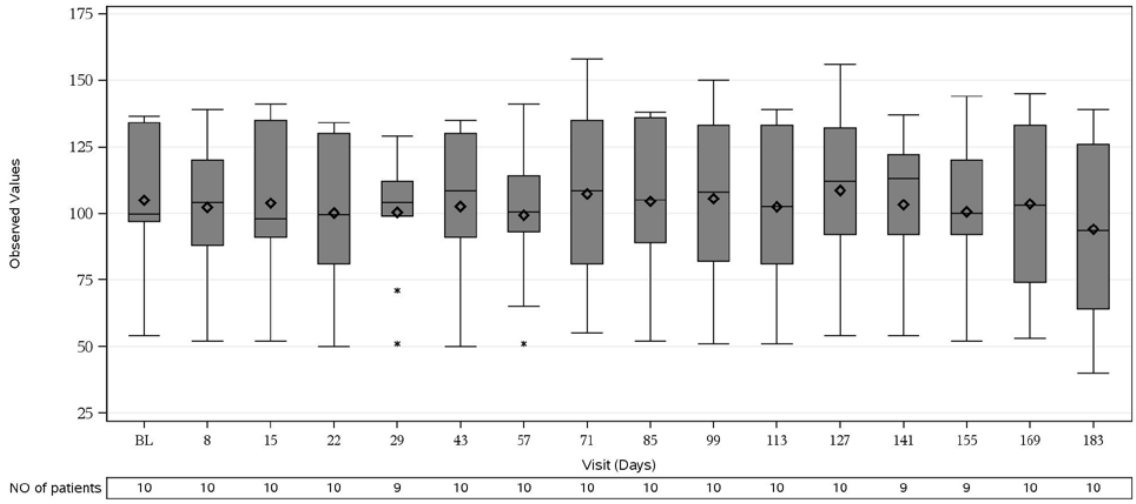


Hemoglobin (g/L)



Note: Data as of 16 Oct 2019.

Table 31: eGFR Observed Values Over Time in Study ALXN1210-aHUS-312 Cohort 2 (Full Analysis Set)



Note: Data as of 16 Oct 2019. Baseline value is defined as the average of the values from the assessments performed prior to the first study drug infusion (these can include results from Screening and the Day 1 visit). 10 mL/min/1.73 m2 for eGFR is imputed for patients requiring dialysis for acute kidney injury. The horizontal line in the middle of each box indicates the median, a diamond indicates the mean and the top and the bottom borders of the box mark the 75th and 25th percentiles, respectively. The whiskers represent the highest and lowest values within 1.5 times the interquartile range (IQR) from the lower quartile and upper quartile. Outliers are represented by asterisk beyond the whiskers.

Ancillary analyses

N/A

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32: Summary of Efficacy for trial ALXN1210-311

Title: Single Arm Study of ALXN1210 in Complement Inhibitor Treatment-Naïve Adult and Adolescent Patients with Atypical Hemolytic Uremic Syndrome (aHUS)		
Study identifier	ALXN1210-aHUS-311	
Design	This is a Phase 3, single arm, multicenter study to evaluate the safety and efficacy of ravulizumab administered by intravenous (IV) infusion to adolescent (12 to < 18 years of age) and adult (≥ 18 years of age) patients with aHUS. All patients must be naïve to complement inhibitor treatment.	
	Duration of main phase:	26 weeks
	Duration of Run-in phase:	<not applicable>
	Duration of Extension phase:	Up to 4.5 years
Hypothesis	Estimation study	

Treatments groups	ravulizumab		Patients will receive a weight-based loading dose of ravulizumab IV (≥ 40 to < 60 kg = 2400 mg; ≥ 60 to < 100 kg = 2700 mg; ≥ 100 kg = 3000 mg) on Day 1, followed by weight-based maintenance doses of ravulizumab IV (≥ 40 to < 60 kg = 3000 mg; ≥ 60 to < 100 kg = 3300 mg; ≥ 100 kg = 3600 mg) on Day 15 and once every 8 weeks (q8w) thereafter. Primary Evaluation Period: 26 weeks (183 days) Number enrolled: - Planned: 55 patients - Observed: 56 patients in the Full Analysis Set (FAS)
Endpoints and definitions	Primary	Complete TMA Response during 26-week Initial Evaluation Period	Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Patients must meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.
	Secondary	Dialysis requirement status	Dialysis requirement status at Day 183 (Week 26). A patient will be considered as not requiring dialysis at a specific postbaseline time point if they have been dialysis free for at least 5 days prior to that time point.
	Secondary	Time to complete TMA response	The time of the event of a confirmed complete TMA response will be considered as the first time point at which all the criteria for complete TMA response were met.
	Secondary	Change in Estimated Glomerular Filtration Rate (eGFR)	Change in in eGFR from baseline through Day 183 (Week 26). eGFR will be imputed with a value of 10 (in mL/min/1.73 m^2) while a patient is on dialysis.
	Secondary	Chronic kidney disease stage (CKD stage)	Evaluated by eGFR categories, shifts from baseline to Day 183 (Week 26).

	Secondary	Change in hematologic parameters (platelets, LDH, hemoglobin)	Change from baseline to Day 183 (Week 26). Platelet values obtained from the day of a blood transfusion of platelets through 3 days after the transfusion will be excluded from all analyses. 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 will be excluded from all analyses.
	Secondary	Hemoglobin response during 26-week Initial Evaluation Period	Increase in hemoglobin of ≥ 20 g/L from baseline, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between
	Secondary	Change in quality of life (QOL)	Change from baseline to Day 183 (Week 26) in QOL. Measured by EuroQol 5 dimensions 3 level (EQ-5D-3L; all patients), and Functional Assessment of Chronic Therapy (FACIT) Fatigue version 4 (patients ≥ 18 years of age), and Pediatric FACIT Fatigue (patients < 18 years of age) questionnaires
Database lock	10 October 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (FAS) during 26-Week Initial Evaluation Period		
Descriptive statistics and estimate variability Primary endpoint	Treatment group	ravulizumab	
	Number of subjects	N = 56	
	Complete TMA Response during 26-week Initial Evaluation Period		
	m Proportion 95% CI**	30 54% (40%, 68%)	

	Secondary Analyses		
	Dialysis requirement status (Off dialysis), Day 183 m/n Proportion 95% CI*	On dialysis at Baseline 16/24 67% (45%, 84%)	Off dialysis at Baseline 21/25 84% (64%, 96%)
	Time to complete TMA response (Days) m (responders) Median 25 and 75 percentiles	 34 86 (22, -)	
	Change in Estimated Glomerular Filtration Rate (eGFR) (mL/min/1.73 m^2), Day 183 n Mean (SD) Median	 47 34.80 (35.45) 29.00	
Analysis description	CKD stage shift from baseline, Day 183 Improved[a] m/n Proportion (95% CI)* Worsened[b] m/n Proportion (95% CI)*	 32/47 68% (53%, 81%) 2/13 15% (2%, 45%)	
	Change in Haematologic TMA parameters, Day 183 Platelets (10^9/L) blood n Mean (SD) Median LDH (U/L) serum n Mean (SD) Median Hemoglobin n Mean (SD) Median	 48 114.79 (105.57) 125.00 48 -519.83 (572.47) -310.75 48 34.64 (18.09) 35.00	

	Hemoglobin response during 26-week Initial Evaluation Period m Proportion 95% CI**	 40 71% (59%, 84%)
	Change in quality of life (QOL), Day 183 EQ-5D-3L, US TTO n Mean (SD) Median FACIT Fatigue n Mean (SD) Median	 46 0.32 (0.32) 0.22 44 19.15 (16.21) 20.00

Note: n: number of patients with available data for specific assessment at Day 183 visit. m: number of patients meeting specific criterion. Chronic kidney disease (CKD) stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stage 5 is considered the worst category, while Stage 1 is considered the best category. Baseline is derived based on the last available eGFR before starting treatment. Improved/Worsened: compared to CKD stage at baseline. *95% confidence intervals (95% CIs) are based on exact confidence limits using the Clopper-Pearson method. ** 95% confidence intervals (95% CIs) are based on the normal approximation method with a continuity correction. [a]Excludes those with CKD Stage 1 at baseline as they cannot improve .[b]Excludes patients with Stage 5 at baseline as they cannot worsen.
Abbreviations: eGFR = estimated glomerular filtration rate; Therapy; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

Table 33: Summary of Efficacy for trial ALXN1210-aHUS-312

Title: A Phase 3, Open-Label, Multicenter Study of ravulizumab **in Children and Adolescents with Atypical Hemolytic Uremic Syndrome (aHUS)**		
Study identifier	ALXN1210-aHUS-312	
Design	This is a Phase 3, single-treatment arm, multicenter study to evaluate the safety, efficacy, PK, and PD of ravulizumab administered by intravenous (IV) infusion in approximately 23 to 28 pediatric patients, from birth to < 18 years of age, with confirmed diagnosis of aHUS. The study has 2 cohorts. Cohort 1 includes complement inhibitor treatment-naïve patients; Cohort 2 includes eculizumab-experienced adolescent patients (12 to < 18 years of age). Data from Cohort 2 is not included in the initial data cut off.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	26 weeks <not applicable> Up to 4.5 years
Hypothesis	Estimation study	

Treatments groups	ravulizumab		Patients will receive a weight-based loading dose of ravulizumab on Day 1, followed by weight-based maintenance treatment with ravulizumab on Day 15 and q8w thereafter for patients weighing ≥ 20 kg, or once every 4 weeks (q4w) for patients weighing < 20 kg. Primary Evaluation Period: 26 weeks (183 days) Number enrolled: - Planned: 23-28 patients - Observed: 18 Cohort 1 patients in the Full Analysis Set (FAS)
Endpoints and definitions	Primary	Complete TMA Response during 26-week Initial Evaluation Period	Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Patients must meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.
	Secondary	Dialysis requirement status	Dialysis requirement status at Day 183 (Week 26). A patient will be considered as not requiring dialysis at a specific postbaseline time point if they have been dialysis free for at least 5 days prior to that time point.
	Secondary	Time to complete TMA response	The time of the event of a confirmed complete TMA response will be considered as the first time point at which all the criteria for complete TMA response were met.

	Secondary	Change in Estimated Glomerular Filtration Rate (eGFR)	Change in in eGFR from baseline through Day 183 (Week 26). eGFR will be imputed with a value of 10 (in mL/min/1.73 m^2) while a patient is on dialysis.
	Secondary	Chronic kidney disease stage (CKD stage)	Evaluated by eGFR categories, shifts from baseline to Day 183 (Week 26).
	Secondary	Change in hematologic parameters (platelets, LDH, hemoglobin)	Change from baseline to Day 183 (Week 26). Platelet values obtained from the day of a blood transfusion of platelets through 3 days after the transfusion will be excluded from all analyses. 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 will be excluded from all analyses.
	Secondary	Hemoglobin response during 26-week Initial Evaluation Period	Increase in hemoglobin of ≥ 20 g/L from baseline, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between
	Secondary	Change in quality of life (QOL)	Change from baseline to Day 183 (Week 26) in QOL. Measured by Functional Assessment of Chronic Therapy (FACIT) Fatigue questionnaire (patients5 years of age)
Database lock	11 December 2019		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Full Analysis Set (FAS) during 26-Week Initial Evaluation Period which include interim results from the Initial Evaluation Period (through Day 183 [Week 26]) for Cohort 1 only.	
Descriptive statistics and estimate variability	Treatment group	ravulizumab
	Number of subjects	N = 18

Primary endpoint	**Complete TMA Response during 26-week Initial Evaluation Period**		
	m Proportion 95% CI*	14 78% (52%, 94%)	
Analysis description	**Secondary Analyses**		
	Dialysis requirement status (Off dialysis), Day 183 m/n Proportion 95% CI*	On dialysis at Baseline 5/6 83% (36%, 100%)	Off dialysis at Baseline 11/11 100% (72%, 100%)
	Time to complete TMA response (Days) m (responders) Median 25 and 75 percentiles	17 30 (25, 88)	
	Change in Estimated Glomerular Filtration Rate (eGFR) (mL/min/1.73 m^2), Day 183 n Mean (SD) Median	17 85.4 (54.33) 80.00	
	CKD stage shift from baseline, Day 183 Improved[a] m/n Proportion (95% CI)* Worsened[b] m/n Proportion (95% CI)*	15/17 88% (64%, 99%) 0/11 0% (0%, 29%)	

	Change in Haematologic TMA parameters, Day 183 Platelets (10^9/L) blood n Mean (SD) Median LDH (U/L) serum n Mean (SD) Median Hemoglobin n Mean (SD) Median	 17 245.59 (91.83) 247.00 16 -2044.13 (1328.06) -1851.50 17 46.50 (16.74) 46.50
	Hemoglobin response during 26-week Initial Evaluation Period m Proportion 95% CI*	 16 89% (65%, 99%)
	Change in quality of life (QOL), Day 183 Pediatric FACIT Fatigue n Mean (SD) Median	 9 16.78 (14.70) 10.00

Note: n: number of patients with available data for specific assessment at Day 183 visit. m: number of patients meeting specific criterion. Chronic kidney disease (CKD) stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. . Stage 1 is considered the best category ,while Stage 5 is considered the worst category. Baseline is derived based on the last available eGFR before starting treatment. Improved/Worsened: Compared to CKD stage at baseline.
*95% confidence intervals (95% CIs) are based on exact confidence limits using the Clopper Pearson method.
[a] Improved excludes patients with Stage 1 at baseline, as they cannot improve; [b]worsened excludes patients with Stage 5 at baseline as they cannot worsen.
Abbreviations: eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.

2.4.3. Discussion on clinical efficacy

This type II variation is to add a new therapeutic indication for ravulizumab in the treatment of patients with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.

Design and conduct of clinical studies

For the support of the current application, the MAH provided results from two studies to evaluate the safety and efficacy of ravulizumab administered by IV infusion in patients with aHUS:

- Study ALXN1210-aHUS-311 is a Phase 3, open-label, single-arm, multicenter study finally carried out in adult patients with complement-mediated TMA including aHUS who are naïve to complement inhibitor treatment.
- Study ALXN1210-aHUS-312 is a Phase 3, single-treatment arm, multicenter study in pediatric patients, from birth to < 18 years of age, with confirmed diagnosis of aHUS.

  The study has 2 cohorts: Cohort 1 includes complement inhibitor treatment-naïve patients; Cohort 2 includes eculizumab-experienced patients.

The primary efficacy endpoint was defined as normalization of platelet count and lactate dehydrogenase (LDH), and ≥ 25% improvement in serum creatinine from baseline (Complete TMA Response) during the 26-week Initial Evaluation Period at 2 separate assessments 4 weeks apart. All serum creatinine values obtained while a patient was on dialysis were excluded from all analyses. If a patient was on dialysis at baseline, then the first valid creatinine value used as the baseline value was the first assessment ≥ 6 days post dialysis. If a patient was on dialysis during the entire 26-week Initial Evaluation Period, then the baseline creatinine was not calculated.

After a 26-week Initial evaluation period, patients were allowed to enter an extension period for up to 2 years

Given that eculizumab is the current standard of care in this setting, a randomised controlled study against eculizumab would have been preferable. However, bearing in mind the low prevalence and the severity of the condition, the lack of a comparator arm can be considered acceptable. According to the MAH the sample size for a randomized, actively controlled non-inferiority study would have been at least twice as large (>100) and would have required twice as many sites (>300). The single-arm design of the Phase 3 studies was considered adequate and acceptable by the CHMP Scientific Advice (EMEA/H/SA/3331/2/2016/II).

Eligibility criteria for the ravulizumab studies required patients to have evidence of TMA (including thrombocytopenia, evidence of haemolysis, and kidney injury) based on platelet count, LDH, and serum creatinine level. However, patients with ADAMTS13 deficiency and Shiga toxin-related haemolytic uremic syndrome, were excluded (see SmPC section 5.1). Likewise, patients with chronic dialysis due to ESKD or those who had received plasma exchange/plasma infusion for 28 days or longer for the current TMA, were also excluded. The latter could mean to exclude a population already studied in the eculizumab studies, defined as patients with longer term aHUS without apparent evidence of TMA manifestations and receiving chronic plasma exchange/plasma infusion. The main population studied in the ravulizumab trials can be defined as complement inhibitor treatment-naïve, even though in the cohort 2 of the study aHUS-312 eculizumab-experienced patients were included. The Applicant provided data from 10 patients with aHUS included in Cohort 2 of Study aHUS-312, who have been previously exposed to eculizumab. In this case patients should have received eculizumab for at least 3 months and have evidence of response to eculizumab prior to switching (i.e. LDH<1.5 x ULN and platelet count ≥150,000 /µL and eGFR>30 mL/min/1.73 m^2).

In the aHUS-311 study 58 complement inhibitor treatment-naïve adult patients were enrolled, however two patients were excluded from the mITT due to positive stool test results for Shiga toxin once all screening test results were available. Mean age at the time of first infusion was 42.2 years, whereas the mean age at the time of first aHUS symptoms was 41.49 years, which is representative of population with a reasonable short history of the disease and naïve to eculizumab treatment. At

baseline (within 5 days of the first dose of study drug), 29 (51.8%) patients received kidney dialysis related to kidney failure caused by aHUS, with 48 patients at CKD Stage 4 or 5. Mean baseline platelets, LDH and haemoglobin were 118.52 (10^9/L), 702.38 (U/L) and 86.26 (g/L) respectively. Eight patients had any kidney transplant prior to entering the study, none of them was related to aHUS, however baseline kidney diseases leading to ESRD in these cases is not described.

In Study aHUS-311, testing for complement gene mutations and anticomplement antibodies was performed in 38 patients (66%) of whom 7 (18%) were positive for a pathogenic mutation and 3 (8%) were positive for an anti-complement antibody. In Study ALXN1210-aHUS-312, genetic analysis was performed in 10 (56%) of the 18 patients in the Full Analysis Set (FAS) from Cohort 1. Of these, 2/10 (20%) patients were positive for a known pathogenic mutation.

Regarding protocol amendments, during the initial evaluation period, 11 country-specific and 3 global protocol amendments were made in Study aHUS-311 and 4 country-specific and 1 global protocol amendment were made in Study aHUS-312. No relevant impact on results are expected.

Efficacy data and additional analyses

Patients included in Study aHUS-311 (and also in Study aHUS-312) were allowed to receive other immunosuppressive therapies if they had confirmed anti-complement factor antibodies requiring immunosuppressive therapy. Four patients in the Study aHUS-311 and 7 patients in Study aHUS-312 were positive for anti-complement-factor antibodies. Anti-FH positive autoimmune aHUS patient may respond to immunosuppressive treatment and achieve TMA remission, therefore, their presence in the study may represent potential bias. Of these 11 subjects, only 2 paediatric patients received immunosuppressive therapy (mycophenolate mofetil). Therefore, it is unlikely immunosuppressive therapy had an effect on the response in this study (study aHUS-312). Nearly all patients with autoimmune disease reached a complete TMA response.

In the study aHUS-311, complete TMA Response was observed in 30 of the 56 patients (53.6%; 95%CI [39.6, 67.5]) during the 26-week Initial Evaluation Period. Platelet normalization, LDH normalization and renal function improvement were achieved in 47 (83.9%), 43 (76.8%) and 33 (58.9%) respectively. Seven patients (12.5%) in the mITT did not respond to any of the 3 components of the Complete TMA. One additional patient had confirmation of the Complete TMA Response criteria during the Extension Period. Sensitivity analyses carried out were consistent with the primary endpoint (PP analysis, patients who met all laboratory criteria for TMA as determined by the central laboratory, patients who were on dialysis at baseline and modified complete TMA response at the date of data cut-off).

According to the SAP, for evaluation of Complete TMA Response during the 26-week Initial Evaluation Period (primary endpoint), patients missing an efficacy assessment that is part of the definition of Complete TMA Response while still on-study, were to have their last observation carried forward (LOCF). In addition, a worst-case scenario with baseline observation carried forward (BOCF) was submitted as sensitivity analysis and results were in line with the primary analysis. On the other hand, for patients discontinuing from the study prior to Week 26, their data up to the time of discontinuation were to be used to assess Complete TMA Response.

The primary population analysis cannot be considered ITT, since the MAH has carried out the analysis through a mITT. In the Study 311 two patients were excluded from the efficacy analysis. According to the Applicant no efficacy data were collected for those patients that were not finally included in the mITT population. Median time to complete TMA response was 86 days. However, the duration of the response was not uniform and some patients had transient periods during which not all components of response continued to be met. Overall, the complete TMA response was deemed reasonably stable

(above 45% approximately) once was achieved. 17 (58.6%) out of 29 patients who were on dialysis at baseline, discontinued dialysis during the conduct of the trial. Regarding the improvement in CKD stage, 6 patients improved by 5 stages (ie, from ESKD to normal renal function), 7 patients improved by 4 stages, 5 patients improved by 3 stages, 4 patients improved by 2 stages, and 10 patients improved by 1 stage. Of the 27 patients who were not on dialysis when they entered the study, 20 patients remained off dialysis and 7 patients initiated dialysis after start of treatment; 6 of these 7 patients required dialysis as of the last available follow-up visit. It can be deduced that 18 patients in study 311 remained dialysis dependent at the time of last follow up (32.1%).

QoL data are not interpretable due to the lack of comparator and open label design.

In the paediatric patients (312 trial) 14 out of 16 patients initially recruited were finally included in the mITT (same criteria as in the Study 311). The two patients were excluded due to failure to establish eligibility criteria based on central laboratory confirmation (aHUS was not confirmed). These 14 patients represent those enrolled and treated in Cohort 1 (complement inhibitor treatment-naïve patients). The mean age at the time of first infusion was 6.1 years, whereas the mean age at the time of first aHUS symptoms was 4.94 years. Mean baseline platelets, LDH and hemoglobin were 60.50 (10^9/L), 2324.11 (U/L) and 74.82 (g/L) respectively.

Complete TMA Response was achieved by 10 of 14 patients (71.4%; 95% CI: 41.9%, 91.6%) during the 26-week Initial Evaluation Period. 13 patients achieved platelet count normalization, 12 patients achieved LDH normalization and 11 patients achieved renal function improvement (defined as 25% reduction in serum creatinine from baseline). Sensitivity analyses were in agreement with the primary endpoint. For the modified Complete TMA Response analysis, Complete TMA Response was observed in a majority of these patients (71.4% [95% CI: 41.9%, 91.6%]) in the FAS and PP Set. Results for modified Complete TMA Response over time with a confirmatory result for the FAS and PP Set were similar to the secondary endpoint Complete TMA Response over time. The median time to complete TMA response was 30 days. The duration of the response was overall sustained since nine of these responders had sustained their response status from the first time point when they achieved Complete TMA Response through the end of the 26-week Initial Evaluation Period. Of the 5 patients who were receiving kidney dialysis at baseline (within 5 days of the first dose of study drug), 4 patients discontinued dialysis after 29 days or less of exposure to ravulizumab. No new patient initiated dialysis after starting treatment with study drug. At the end of the Initial Evaluation Period, 11 (84.6%) of 13 patients had improvement in CKD stage compared to baseline.

Updated efficacy data (data cut-off: 10 Oct 2019 for Study ALXN1210-aHUS-311 and 11 December 2019 for Study ALXN1210-aHUS-312) were also provided. In addition, the applicant provided further data on 10 adolescent patients included in Study 312 up to the data cut-off date for the second interim analysis. Of these, there were 3 patients in Cohort 1 (treatment- naïve patients) and 7 patients in Cohort 2 (eculizumab-experienced patients).

In Study 311, results from the second interim analysis showed a Complete TMA response after week 26 for 4 additional patients. In Study 312, at the data cut-off for the second interim analysis primary endpoint results were available for 4 additional patients from Cohort 1 (n=18). Complete TMA response in Cohort 1 during the initial evaluation period was of 77.8%. Moreover, 3 additional patients had a Complete TMA response after week 26. Overall, responses were maintained up to week 52. With regard to Cohort 2 (i.e. eculizumab-exposed patients), during the 26 weeks of the initial evaluation period TMA parameters remained stable. After week 26 parameters seem to remain stable too, although data are still limited.

The submitted studies are subject to bias due to the absence of a comparator arm. To contextualise the data and bearing in mind the limitations of indirect comparisons, efficacy results with ravulizumab were compared with eculizumab efficacy data. Eculizumab obtained the MA based on the results from

two different clinical studies, study C08-002A/B which enrolled adolescent and adult patients with less severe disease, and study C08-003A/B that enrolled adolescent and adult patients with longer term aHUS without apparent evidence of TMA manifestations and receiving chronic plasma exchange/plasma infusion (plasma sensitive). Results from studies C10-004 (an open-label, multi-center clinical trial of eculizumab in adult patients with aHUS. performed as a post-marketing commitment) and C10-003 (an open-label, multi-center clinical trial of eculizumab in paediatric patients with aHUS) were subsequently submitted (see EPAR for Soliris).

On observing to the complete TMA response from ravulizumab study in adults, and comparing to the eculizumab ones, similar percentage of responders is obtained; 30/56 (53.6%) [95%CI 39.6, 67.5] vs 11/17 (65%) [95% CI: 38%, 86%] and 23/41 (56%) [95% CI: 40%, 72%] ALXN1210-aHUS-311 vs C08-002A/B and C10-004 respectively. This comparability should be carried out assuming that in the study C08-002A/B results could be overestimated due to smaller sample size, whereas in the study C10-004, where both the sample size and patients are more comparable to the ravulizumab trial in adults, the point estimate is closer to that obtained in the 311 study. Of note, confidence intervals are overlapping. Besides, populations even not totally comparable, could be considered of having similar baseline characteristics, such as early aHUS, adult population, thrombocytopenia, elevated LDH and renal impairment. On the contrary, patients in the study C08-003 were considered to be in a later stage, being plasma therapy sensitive as they had normal platelet count and normal LDH levels. The same applies to the paediatric studies, both in baseline characteristics and results in terms of complete TMA response.

Ravulizumab is a terminal complement inhibitor that specifically binds to complement component 5 (C5) with high affinity, inhibiting the enzymatic cleavage of C5 into C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement membrane attack complex [C5b-9]) and ravulizumab has already demonstrated an activity comparable to the one of eculizumab in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH).

Overall, ravulizumab has shown a clinically meaningful response in the adult population.

However, according to EMEA-001943-PIP01-16-M02, in paediatric study ALXN1210-aHUS-312, the minimum patients number required for each age category were: at least 4 patients from birth to < 2 years of age; at least 4 patients from 2 years to < 6 years of age; at least 4 patients from 6 years to < 12 years of age and at least 8 patients from 12 years to < 18 years of age. Overall, the number of patients in each subgroup required in the PIP is fulfilled, except for patients <2 years.

The MAH applied for a reduction of the number of patients < 2 years of age (from 4 to 2 patients). However, the PDCO was of the opinion that recruitment should be kept open for at least the originally planned time. Additionally, PDCO deemed that it is important not to decrease the patients' number in this most fragile subset, and to generate data from at least 4 patients to support a model for dosing confirmation in children below 2 years of age. Seven paediatric patients (6 complement inhibitor-naïve patients and 1 eculizumab-exposed patient) from birth to less than 2 years of age have been enrolled in Study ALXN1210-aHUS-312. Nevertheless, of these patients only 2 were included in the original efficacy analysis. Moreover, the loading dose received by both patients was 300 mg (1 received only two doses and the other completed the initial evaluation period). Four patients (3 complement inhibitor-naïve patients and the eculizumab-exposed patient) were part of the FAS and Safety Set. Among those 4 patients, 2 complement inhibitor-naïve patients received at least one dose of ravulizumab, but later discontinued following a confirmed diagnosis of hemolytic uremic syndrome caused by Shiga toxin-producing Escherichia coli. One additional complement inhibitor-naïve patient was enrolled early 2020 and is undergoing the initial evaluation.

Therefore, due to the limited data on patients below 2 years of age no recommendation on a posology can be made for patients below 10 kg body weight. In addition, safety data profile seems to be slightly worse for patients < 2 years old (see Clinical Safety section).

It is also noted the MAH was seeking a wording of the indication in the treatment of patients with atypical haemolytic uremic syndrome (aHUS), regardless of the previous treatment with eculizumab. Based on the results of the 10 patients included in Cohort 2 of the Study 312 and the Phase 3 study in PNH (Study PNH-302) the latter could be acceptable provided that patients have been treated with eculizumab and are stable (i.e. LDH<1.5 x ULN and platelet count ≥150,000 / μL and eGFR>30 mL/min/1.73 m2). However, the extrapolation of the indication to a population of patients refractory to eculizumab treatment is not supported, since no aHUS patients who were refractory to eculizumab-treatment were included in Cohort 2.

2.4.4. Conclusions on the clinical efficacy

Overall and despite the studies limitations, efficacy of ravulizumab has been shown in patients with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab. Considering the limited efficacy and safety data in patients below 10 kg body weight, these patients are excluded from the indication..

2.5. Clinical safety

Introduction

The safety evaluation supporting the use of ravulizumab (ALXN1210) administered intravenously (IV) for the treatment of patients with aHUS is based on study ALXN1210-aHUS-311 and study ALXN1210-aHUS-312.

The extent of the data consists of the Initial Evaluation Period (26 weeks) or study discontinuation for all patients. In addition, for adult patients in Study ALXN1210-aHUS-311 who had visits in the Extension Period, data up to 15 Oct 2018 were included in the clinical safety database.

Patient exposure

Table 34: Patient Disposition in Ravulizumab Clinical Program in aHUS

	ALXN1210-aHUS-311 (N = 58)	ALXN1210-aHUS-312 (N = 16)	Total (N = 74)
Enrolled, n	58	16	74
Treated, n (%)	58 (100.0)	16 (100.0)	74 (100.0)
Completed Initial Evaluation Period, n (%)	49 (84.5)	13 (81.3)	62 (83.8)
Completed study, n (%)	0	0	0
Initial Evaluation Period (Week 26), n (%)			
Discontinued from study during Initial Evaluation Period	9 (15.5)	3 (18.8)	12 (16.2)
Adverse event	3 (5.2)	1 (6.3)	4 (5.4)
Death	2 (3.4)	0	2 (2.7)
Physician decision	1 (1.7)	0	1 (1.4)
Protocol violation	1 (1.7)	1 (6.3)	2 (2.7)
Deemed ineligible post treatment	2 (3.4)	1 (6.3)	3 (4.1)
Extension Period, n (%)			
Entered into Extension Period	49 (84.5)	13 (81.3)	62 (83.8)
Received treatment during Extension Period	46 (79.3)	13 (81.3)	59 (79.7)
Ongoing in Extension Period at data cutoff	47 (81.0)	13 (81.3)	60 (81.1)
Discontinued from study during Extension Period	2 (3.4)	NA	2 (2.7)
Physician decision	1 (1.7)	NA	1 (1.4)
Withdrawal by subject	1 (1.7)	NA	1 (1.4)

Note: Percentages were based on the number of patients in the Safety Set in each column.
The data cutoff dates were 15 Oct 2018 or the end of Initial Evaluation Period whichever came last for Study ALXN1210-aHUS-311 and the end of Initial Evaluation Period for Study ALXN1210-aHUS-312.
Abbreviations: aHUS = atypical hemolytic uremic syndrome; NA = not applicable.

As of the data cut-off date, 74 patients (52.9 patient-years [PY] of exposure) received at least 1 dose of ravulizumab in the Initial Evaluation Period (58 patients in Study ALXN1210-aHUS-311 and 16 patients in Study ALXN1210-aHUS-312), of whom 62 patients completed the Initial Evaluation Period (49 patients in Study ALXN1210-aHUS-311 and 13 patients in Study ALXN1210-aHUS-312) and continued into the Extension Period.

Overall, the median treatment duration was 215.0 days (range: 4 to 568 days). The median treatment duration in adult patients in Study ALXN120-aHUS-311 was 262.5 days (range: 4 to 568 days) and that in paediatric patients in Study ALXN1210-aHUS-312 was 183.0 days (range: 7 to 186 days).

Fifty patients received the 4 planned infusions according to the protocol-specified number of infusions for the Initial Evaluation Period, including 1 patient who withdrew from the study on Day 163 and 2 patients who received 5 infusions (which were reported as major protocol deviations (Study 311)

Table 35: Summary of Treatment Exposure up to Data Cut-off in Ravulizumab Clinical Program in aHUS (Safety Set)

Variable	ALXN1210-aHUS-311 (N = 58)	ALXN1210-aHUS-312 (N = 16)	Total (N = 74)
Treatment duration from Day 1 to data cutoff (days)[a]			
n	58	16	74
Mean (SD)	291.4 (158.42)	151.4 (68.25)	261.2 (154.66)
Median	262.5	183.0	215.0
Min, max	4, 568	7, 186	4, 568
Total PY of exposure (years)[a]	46.3	6.6	52.9
Treatment duration category, n (%)[a]			
0 to 6 months (≤ 182 days)	11 (19.0)	7 (43.8)	18 (24.3)
> 6 to 12 months	31 (53.4)	9 (56.3)	40 (54.1)
> 12 to 18 months	12 (20.7)	0	12 (16.2)
> 18 to 24 months	4 (6.9)	0	4 (5.4)
> 24 months	0	0	0
Number of infusions from Day 1 to data cutoff			
n	58	16[b]	74
Mean (SD)	6.4 (2.84)	5.8 (2.57)	6.3 (2.78)
Median	6.0	6.0	6.0
Min, max	1, 11	1, 8	1, 11
Number of patients with an infusion interruption from Day 1 to data cutoff, n (%)	9 (15.5)	2 (12.5)	11 (14.9)
Number of infusions interrupted from Day 1 to data cutoff			
Total	14	2	16
Mean (SD)	1.6 (1.33)	1.0 (0.00)	1.5 (1.21)
Median	1.0	1.0	1.0
Min, max	1, 5	1, 1	1, 5
Number of infusions interrupted due to adverse event from Day 1 to data cutoff			
Total	0	1	1
Mean (SD)	NA	1.0	1.0
Median	NA	1.0	1.0
Min, max	NA	1, 1	1, 1
Drug compliance from Day 1 to data cutoff, n (%)			
≥ 100%	58 (100.0)	16 (100.0)	74 (100.0)

Note: Percentages were based on the number of patients in the Safety Set in each column.
The data cutoff dates were 15 Oct 2018 or the end of Initial Evaluation Period whichever came last for Study ALXN1210-aHUS-311 and the end of Initial Evaluation Period for Study ALXN1210-aHUS-312.
[a] Treatment duration = the earliest of (data cutoff date, study discontinuation date, or [treatment discontinuation date + 56 days]) - date of first ravulizumab infusion + 1.
[b] Patients weighing < 20 kg were dosed q4w and ≥ 20 kg were dosed q8w; therefore, the number of infusions were different.
Abbreviations: aHUS = atypical hemolytic uremic syndrome; max = maximum; Min = minimum; NA = not applicable; PY = patient-years; q4w = once every 4 weeks; q8w = once every 8 weeks; SD = standard deviation.

Adverse events

Table 36: Overview of All Treatment-Emergent Adverse Events and Serious Adverse Events (Safety Set)

Variables	ALXN1210-aHUS-311 (N = 58) (PY = 46.3)		ALXN1210-aHUS-312 (N = 16) (PY = 6.6)		Total (N = 74) (PY = 52.9)	
	n (%)	E (rate)	n (%)	E (rate)	n (%)	E (rate)
Any TEAE	58 (100.0)	818 (1767.5)	15 (93.8)	162 (2442.0)	73 (98.6)	980 (1852.0)
Related TEAE	20 (34.5)	58 (125.3)	8 (50.0)	22 (331.6)	28 (37.8)	80 (151.2)
Unrelated TEAE	58 (100.0)	760 (1642.2)	15 (93.8)	140 (2110.4)	73 (98.6)	900 (1700.9)
Grade 1	54 (93.1)	454 (981.0)	13 (81.3)	120 (1808.9)	67 (90.5)	574 (1084.8)
Grade 2	46 (79.3)	223 (481.8)	11 (68.8)	33 (497.5)	57 (77.0)	256 (483.8)
Grade 3	31 (53.4)	116 (250.6)	3 (18.8)	8 (120.6)	34 (45.9)	124 (234.3)
Grade 4	14 (24.1)	22 (47.5)	1 (6.3)	1 (15.1)	15 (20.3)	23 (43.5)
Grade 5	3 (5.2)	3 (6.5)	0	0	3 (4.1)	3 (5.7)
TEAE leading to study drug interruption	0	0	1 (6.3)	1 (15.1)	1 (1.4)	1 (1.9)
TEAE leading to study drug discontinuation	3 (5.2)	3 (6.5)	1 (6.3)	2 (30.1)	4 (5.4)	5 (9.4)
TEAE leading to study discontinuation	3 (5.2)	3 (6.5)	1 (6.3)	2 (30.1)	4 (5.4)	5 (9.4)
Any serious TEAE (SAE)	30 (51.7)	71 (153.4)	8 (50.0)	13 (196.0)	38 (51.4)	84 (158.7)
Related SAE	2 (3.4)	2 (4.3)	3 (18.8)	4 (60.3)	5 (6.8)	6 (11.3)
Unrelated SAE	29 (50.0)	69 (149.1)	8 (50.0)	9 (135.7)	37 (50.0)	78 (147.4)
SAE leading to study drug interruption	0	0	0	0	0	0
SAE leading to study drug discontinuation	3 (5.2)	3 (6.5)	1 (6.3)	2 (30.1)	4 (5.4)	5 (9.4)
SAE leading to study discontinuation	3 (5.2)	3 (6.5)	1 (6.3)	2 (30.1)	4 (5.4)	5 (9.4)
TEAE leading to death[a]	3 (5.2)	NA	0	NA	3 (4.1)	NA

Note: Percentages were based on the number of patients in the Safety Set in each column, ie, % = n/N*100.
Rate = rate of AE adjusted by PY of exposure, defined as (number of events)/100 PY.
The data cutoff dates were 15 Oct 2018 or the end of Initial Evaluation Period whichever came last for Study ALXN1210-aHUS-311 and the end of Initial Evaluation Period for Study ALXN1210-aHUS-312.
Related AEs were defined as AEs that were possibly, probably, or definitely related to study drug. Not related AEs were defined as AEs that were unlikely or not related to study drug.
Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = fatal.
[a] In addition to TEAEs leading to deaths, 1 patient reported a pretreatment AE that led to death.
Abbreviations: AE = adverse event; aHUS = atypical hemolytic uremic syndrome; E = number of events; NA = not applicable; PY = patient-years; TEAE = treatment-emergent adverse event; SAE = serious adverse event.

Table 37: Overall Treatment-Emergent Adverse Events During the Initial Evaluation Period (Safety Set) – Study ALXN1210-aHUS-312

Adverse Event Categories	Birth to < 6 years (N = 9)		6 to < 18 years (N = 7)		Overall (N = 16)	
	n (%)	E	n (%)	E	n (%)	E
Any AE	8 (88.9)	70	7 (100.0)	92	15 (93.8)	162
Any SAE	3 (33.3)	6	5 (71.4)	7	8 (50.0)	13
Deaths	0	0	0	0	0	0
AEs resulting in study drug discontinuations	1 (11.1)	2	0	0	1 (6.3)	2
SAEs resulting in study drug discontinuations	1 (11.1)	2	0	0	1 (6.3)	2
AEs resulting in study withdrawal	1 (11.1)	2	0	0	1 (6.3)	2
SAEs resulting in study withdrawal	1 (11.1)	2	0	0	1 (6.3)	2
Relationship to study drug[a]						
Related AEs	4 (44.4)	8	4 (57.1)	14	8 (50.0)	22
Not related AEs	8 (88.9)	62	7 (100.0)	78	15 (93.8)	140
Severity						
Grade 1	7 (77.8)	46	6 (85.7)	74	13 (81.3)	120
Grade 2	6 (66.7)	19	5 (71.4)	14	11 (68.8)	33
Grade 3	2 (22.2)	5	1 (14.3)	3	3 (18.8)	8
Grade 4	0	0	1 (14.3)	1	1 (6.3)	1
Grade 5	0	0	0	0	0	0

Note: Adverse events were coded using MedDRA Version 21.0 and the severity of AEs was graded using CTCAE version 4.03.

[a] Related AEs include AEs classified as possibly, probably, or definitely related. Not related AEs include AEs classified as not related or unlikely related.

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; E = total number of events; SAE = serious adverse event.

Common adverse events

Among all patients, the most frequently reported AE was headache (33.8%; 25 patients) with an exposure-adjusted rate of 71.8 events/100 PY. The other AEs reported by at least 20% of all patients were diarrhoea (28.4%; 21 patients), vomiting (25.7%; 19 patients), hypertension (23.0%; 17 patients), and nausea and pyrexia (20.3%; 15 patients, each).

Table 38: Treatment-Emergent Adverse Events Occurring in ≥ 10% of Patients by MedDRA System Organ Class and Preferred Term, by Study (Safety Set)

SOC Preferred Term	ALXN1210-aHUS-311 (N = 58) (PY = 46.3)		ALXN1210-aHUS-312 (N = 16) (PY = 6.6)		Total (N = 74) (PY = 52.9)	
	n (%)	E (rate)	n (%)	E (rate)	n (%)	E (rate)
Patients with TEAEs	48 (82.8)	264 (570.4)	12 (75.0)	76 (1145.6)	60 (81.1)	340 (642.5)
Blood and lymphatic system disorders						
Anaemia	8 (13.8)	8 (17.3)	2 (12.5)	3 (45.2)	10 (13.5)	11 (20.8)
Gastrointestinal disorders						
Diarrhoea	18 (31.0)	24 (51.9)	3 (18.8)	4 (60.3)	21 (28.4)	28 (52.9)
Vomiting	15 (25.9)	18 (38.9)	4 (25.0)	17 (256.3)	19 (25.7)	35 (66.1)
Nausea	13 (22.4)	16 (34.6)	2 (12.5)	3 (45.2)	15 (20.3)	19 (35.9)
Constipation	8 (13.8)	10 (21.6)	4 (25.0)	6 (90.4)	12 (16.2)	16 (30.2)
Abdominal pain	7 (12.1)	10 (21.6)	2 (12.5)	4 (60.3)	9 (12.2)	14 (26.5)
General disorders and administration site conditions						
Pyrexia	10 (17.2)	11 (23.8)	5 (31.3)	15 (226.1)	15 (20.3)	26 (49.1)
Oedema peripheral	9 (15.5)	13 (28.1)	0	0	9 (12.2)	13 (24.6)
Fatigue	7 (12.1)	8 (17.3)	1 (6.3)	1 (15.1)	8 (10.8)	9 (17.0)
Infections and infestations						
Nasopharyngitis	8 (13.8)	12 (25.9)	3 (18.8)	4 (60.3)	11 (14.9)	16 (30.2)
Urinary tract infection	10 (17.2)	21 (45.4)	1 (6.3)	1 (15.1)	11 (14.9)	22 (41.6)
Metabolism and nutrition disorders						
Hypokalaemia	9 (15.5)	18 (38.9)	0	0	9 (12.2)	18 (34.0)
Musculoskeletal and connective tissue disorders						
Arthralgia	10 (17.2)	12 (25.9)	1 (6.3)	1 (15.1)	11 (14.9)	13 (24.6)
Nervous system disorders						
Headache	21 (36.2)	28 (60.5)	4 (25.0)	10 (150.7)	25 (33.8)	38 (71.8)
Psychiatric disorders						
Anxiety	8 (13.8)	12 (25.9)	0	0	8 (10.8)	12 (22.7)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	10 (17.2)	13 (28.1)	2 (12.5)	2 (30.1)	12 (16.2)	15 (28.3)
Cough	10 (17.2)	10 (21.6)	0	0	10 (13.5)	10 (18.9)
Vascular disorders						
Hypertension	13 (22.4)	20 (43.2)	4 (25.0)	5 (75.4)	17 (23.0)	25 (47.2)

Note: Percentages were based on the number of patients in the Safety Set in each column, ie, % = n/N*100.
Rate = rate of AE adjusted by PY of exposure, defined as (number of events)/100 PY.
Treatment-emergent AEs were AEs with a start date and start time on or after the date and time of the first infusion of study drug. Under patient count columns, n (%), if a patient had more than 1 event for a particular SOC, the patient was counted only once for that SOC under n (%). If a patient had more than 1 event for a particular Preferred Term, the patient was counted only once for that Preferred Term.
The data cutoff dates were 15 Oct 2018 or the end of Initial Evaluation Period whichever came last for Study ALXN1210-aHUS-311 and the end of Initial Evaluation Period for Study ALXN1210-aHUS-312.
All AEs were coded using MedDRA Version 21.0.
Abbreviations: AE = adverse event; aHUS = atypical hemolytic uremic syndrome; E = number of events; SOC = System Organ Class; TEAE = treatment-emergent adverse event; PY = patient-years.

Table 39: Treatment-Emergent Adverse Events Experienced by 2 or More Patients Overall During the Initial Evaluation Period, by System Organ Class and Preferred Term (Safety Set) – Study ALXN1210-aHUS-312

System Organ Class Preferred Term	Birth to < 6 years (N = 9)		6 to < 18 years (N = 7)		Overall (N = 16)	
	n (%)	E	n (%)	E	n (%)	E
Any TEAE	8 (88.9)	70	7 (100.0)	92	15 (93.8)	162
Gastrointestinal disorders						
Constipation	3 (33.3)	5	1 (14.3)	1	4 (25.0)	6
Vomiting	2 (22.2)	6	2 (28.6)	11	4 (25.0)	17
Diarrhoea	2 (22.2)	3	1 (14.3)	1	3 (18.8)	4
Abdominal pain	0	0	2 (28.6)	4	2 (12.5)	4
Nausea	0	0	2 (28.6)	3	2 (12.5)	3
Infections and infestations						
Nasopharyngitis	2 (22.2)	3	1 (14.3)	1	3 (18.8)	4
Tonsillitis	2 (22.2)	2	0	0	2 (12.5)	2
Upper respiratory tract infection	1 (11.1)	1	1 (14.3)	1	2 (12.5)	2
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	1 (11.1)	1	1 (14.3)	1	2 (12.5)	2
Vascular disorders						
Hypertension	2 (22.2)	2	2 (28.6)	3	4 (25.0)	5
Hypotension	0	0	2 (28.6)	2	2 (12.5)	2
General disorders and administration site conditions						
Pyrexia	2 (22.2)	8	3 (42.9)	7	5 (31.3)	15
Investigations						
Vitamin D decreased	1 (11.1)	1	1 (14.3)	1	2 (12.5)	2
Blood and lymphatic system disorders						
Anaemia	1 (11.1)	2	1 (14.3)	1	2 (12.5)	3
Lymphadenopathy	1 (11.1)	1	1 (14.3)	1	2 (12.5)	2
Metabolism and nutrition disorders						
Iron deficiency	1 (11.1)	1	1 (14.3)	1	2 (12.5)	2
Musculoskeletal and connective tissue disorders						
Myalgia	1 (11.1)	1	1 (14.3)	2	2 (12.5)	3
Nervous system disorders						
Headache	0	0	4 (57.1)	10	4 (25.0)	10
Injury, poisoning and procedural complications						
Contusion	0	0	2 (28.6)	4	2 (12.5)	4

Abbreviations: E = total number of events; TEAE = treatment-emergent adverse event.

Adverse events of special interest

The most important risk associated with complement component 5 (C5) inhibition is increased susceptibility to infections caused by *Neisseria meningitidis*. As of the data cut-off dates, no events of meningococcal infections were reported in Studies ALXN1210-aHUS-311 and ALXN1210-aHUS-312.

Serious infections

Overall, serious infections were reported in 15 (20.3%) patients across the 2 studies. Pneumonia was reported by 3 (4.1%) patients and *Escherichia* pyelonephritis, septic shock, and urinary tract infection were reported by 2 (2.7%) patients, each. Most SAEs were considered not related to study drug by the Investigator and likely related to the underlying condition in these patients.

Infusion reactions

Infusion-related reaction was reported in 2 (3.4%) patients in Study ALXN1210-aHUS-311 and in none of the patients in Study ALXN1210-aHUS-312. These AEs did not lead to infusion interruption and resolved during the study.

Seven patients experienced nonserious AEs during infusion of study drug. These AEs were hypertension, limb discomfort, muscle spasm, paraesthesia, dysgeusia (2 episodes in 1 patient), and dizziness. Hypertension in 1 patient in Study ALXN1210-aHUS-312 led to interruption of the infusion

for 10 minutes. The infusion was then restarted, and the full dose was completed. As of the data cut-off date for this submission, hypertension was resolving. The other AEs did not lead to interruption of the infusion and resolved.

Adverse reactions

The most common adverse reactions associated with ravulizumab are diarrhoea, nausea, vomiting, nasopharyngitis, and headache. The most serious adverse reactions in patients in clinical trials with ravulizumab are meningococcal infection and meningococcal sepsis, although neither has been reported in the aHUS trials as of the respective database cut-offs.

Adverse reactions observed in clinical trials for PNH and aHUS with ravulizumab are summarized in Table 40. Adverse reactions reported at a very common (≥ 1/10) common (≥ 1/100 to < 1/10) or uncommon (≥ 1/1,000 to < 1/100) frequency with ravulizumab are listed by System Organ Class and Preferred Term. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 40: Adverse Reactions in Ravulizumab Clinical Trials

MedDRA System Organ Class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Gastrointestinal disorders	Diarrhoea, nausea, vomiting	Abdominal pain, dyspepsia	
General disorders and administration site conditions		Pyrexia, fatigue, influenza-like illness, asthenia	Chills
Infections and infestations	Nasopharyngitis	Meningococcal infection*	
Musculoskeletal and connective tissue disorders		Arthralgia, back pain, myalgia, muscle spasms	
Nervous system disorders	Headache	Dizziness	
Respiratory, thoracic and mediastinal disorders			Upper respiratory tract inflammation
Skin and subcutaneous tissue disorders		Rash, pruritus	

* Meningococcal infection includes preferred terms of meningococcal infection and meningococcal sepsis.

Serious adverse event/deaths/other significant events

Deaths

Overall, 4 deaths were reported in Study ALXN1210-aHUS-311 and all deaths were considered not related to study drug by the Investigator; no deaths were reported in Study ALXN1210-aHUS-312.

One patient died due a pre-treatment AE and 3 (5.2%) patients died due to treatment-emergent SAEs (2 due to septic shock and 1 due to intracranial haemorrhage). Of the 3 patients who died due to treatment-emergent SAEs, 2 patients died early in the treatment period, 1 on Day 4 and the other on Day 26.

Serious adverse events

Overall, 38 (51.4%) patients across the 2 studies had at least 1 SAE (exposure-adjusted rate of 158.7 events/100 PY). In both studies, SAEs were reported most frequently in the SOC Infections and

Infestations (11 [19%] adult patients and 4 [25%] paediatric patients). The most frequently reported SAE was hypertension (5.4%; 4 patients) with an exposure-adjusted rate of 11.3 events/100 PY). Hypertension was expected in this population as a consequence of renal disease. No meningococcal infection was reported.

Table 41: Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term, by Study (Safety Set)

SOC Preferred Term	ALXN1210-aHUS-311 (N = 58) (PY = 46.3)		ALXN1210-aHUS-312 (N = 16) (PY = 6.6)		Total (N = 74) (PY =52.9)	
	n (%)	E (rate)	n (%)	E (rate)	n (%)	E (rate)
Patients with at least 1 serious TEAE	30 (51.7)	71 (153.4)	8 (50.0)	13 (196.0)	38 (51.4)	84 (158.7)
Blood and lymphatic system disorders	**6 (10.3)**	**6 (13.0)**	**1 (6.3)**	**1 (15.1)**	**7 (9.5)**	**7 (13.2)**
Atypical haemolytic uraemic syndrome	2 (3.4)	2 (4.3)	0	0	2 (2.7)	2 (3.8)
Anaemia	0	0	1 (6.3)	1 (15.1)	1 (1.4)	1 (1.9)
Autoimmune haemolytic anaemia	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Febrile neutropenia	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Immune thrombocytopenic purpura	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Thrombocytopenia	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Ear and labyrinth disorders	**1 (1.7)**	**1 (2.2)**	**0**	**0**	**1 (1.4)**	**1 (1.9)**
Vertigo positional	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Eye disorders	**1 (1.7)**	**1 (2.2)**	**0**	**0**	**1 (1.4)**	**1 (1.9)**
Vitreous haemorrhage	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Gastrointestinal disorders	**4 (6.9)**	**5 (10.8)**	**3 (18.8)**	**3 (45.2)**	**7 (9.5)**	**8 (15.1)**
Abdominal pain	1 (1.7)	2 (4.3)	2 (12.5)	2 (30.1)	3 (4.1)	4 (7.6)
Diarrhoea	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Lower gastrointestinal haemorrhage	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Pancreatitis	0	0	1 (6.3)	1 (15.1)	1 (1.4)	1 (1.9)
Toothache	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
General disorders and administration site conditions	**0**	**0**	**1 (6.3)**	**1 (15.1)**	**1 (1.4)**	**1 (1.9)**
Pyrexia	0	0	1 (6.3)	1 (15.1)	1 (1.4)	1 (1.9)
Immune system disorders	**2 (3.4)**	**2 (4.3)**	**0**	**0**	**2 (2.7)**	**2 (3.8)**
Hypersensitivity	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Kidney transplant rejection	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Infections and infestations	**11 (19.0)**	**18 (38.9)**	**4 (25.0)**	**5 (75.4)**	**15 (20.3)**	**23 (43.5)**
Pneumonia	3 (5.2)	3 (6.5)	0	0	3 (4.1)	3 (5.7)
Escherichia pyelonephritis	1 (1.7)	1 (2.2)	1 (6.3)	1 (15.1)	2 (2.7)	2 (3.8)
Septic shock	2 (3.4)	2 (4.3)	0	0	2 (2.7)	2 (3.8)
Urinary tract infection	2 (3.4)	4 (8.6)	0	0	2 (2.7)	4 (7.6)
Cytomegalovirus enteritis	0	0	1 (6.3)	1 (15.1)	1 (1.4)	1 (1.9)
Device related infection	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Escherichia bacteraemia	0	0	1 (6.3)	1 (15.1)	1 (1.4)	1 (1.9)
Fungaemia	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Gastroenteritis rotavirus	0	0	1 (6.3)	1 (15.1)	1 (1.4)	1 (1.9)
Gastrointestinal infection	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Infectious colitis	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Peritonitis bacterial	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Pharyngitis	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Sepsis	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Sinusitis	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Viral infection	0	0	1 (6.3)	1 (15.1)	1 (1.4)	1 (1.9)

SOC Preferred Term	ALXN1210-aHUS-311 (N = 58) (PY = 46.3)		ALXN1210-aHUS-312 (N = 16) (PY = 6.6)		Total (N = 74) (PY =52.9)	
	n (%)	E (rate)	n (%)	E (rate)	n (%)	E (rate)
Injury, poisoning and procedural complications	**2 (3.4)**	**2 (4.3)**	**0**	**0**	**2 (2.7)**	**2 (3.8)**
Seroma	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Shunt occlusion	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Investigations	**2 (3.4)**	**2 (4.3)**	**0**	**0**	**2 (2.7)**	**2 (3.8)**
Biopsy kidney	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Troponin increased	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Metabolism and nutrition disorders	**2 (3.4)**	**2 (4.3)**	**0**	**0**	**2 (2.7)**	**2 (3.8)**
Hypervolaemia	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Hypokalaemia	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Nervous system disorders	**4 (6.9)**	**4 (8.6)**	**0**	**0**	**4 (5.4)**	**4 (7.6)**
Haemorrhage intracranial	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Lacunar infarction	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Loss of consciousness	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Seizure	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Product issues	**1 (1.7)**	**1 (2.2)**	**0**	**0**	**1 (1.4)**	**1 (1.9)**
Device leakage	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Renal and urinary disorders	**7 (12.1)**	**9 (19.4)**	**0**	**0**	**7 (9.5)**	**9 (17.0)**
Acute kidney injury	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Chronic kidney disease	1 (1.7)	2 (4.3)	0	0	1 (1.4)	2 (3.8)
Hydronephrosis	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Nephrolithiasis	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Renal failure	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Renal haematoma	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Renal impairment	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Renal pseudoaneurysm	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Respiratory, thoracic and mediastinal disorders	**4 (6.9)**	**7 (15.1)**	**1 (6.3)**	**1 (15.1)**	**5 (6.8)**	**8 (15.1)**
Acute pulmonary oedema	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Dyspnoea	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Hypoxia	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Pulmonary haemorrhage	0	0	1 (6.3)	1 (15.1)	1 (1.4)	1 (1.9)
Pulmonary oedema	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Respiratory disorder	1 (1.7)	2 (4.3)	0	0	1 (1.4)	2 (3.8)
Respiratory failure	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Vascular disorders	**6 (10.3)**	**11 (23.8)**	**2 (12.5)**	**2 (30.1)**	**8 (10.8)**	**13 (24.6)**
Hypertension	3 (5.2)	5 (10.8)	1 (6.3)	1 (15.1)	4 (5.4)	6 (11.3)
Hypertensive crisis	1 (1.7)	1 (2.2)	1 (6.3)	1 (15.1)	2 (2.7)	2 (3.8)
Malignant hypertension	2 (3.4)	5 (10.8)	0	0	2 (2.7)	5 (9.4)

Note: Percentages are based on the number of patients in the Safety Set in each column, ie, % = n/N*100.
Rate = rate of AE adjusted by PY of exposure, defined as (number of events)/100 PY.
Treatment-emergent AEs were AEs with a start date and start time on or after the date and time of the first infusion of study drug. Under patient count columns, n (%), if a patient had more than 1 event for a particular SOC, the patient was counted only once for that SOC under n (%). If a patient had more than 1 event for a particular Preferred Term, the patient was counted only once for that Preferred Term.
The data cutoff dates were 15 Oct 2018 or the end of Initial Evaluation Period whichever came last for Study ALXN1210-aHUS-311 and the end of Initial Evaluation Period for Study ALXN1210-aHUS-312.
All AEs were coded using MedDRA Version 21.0.
Abbreviations: AE = adverse event; aHUS = atypical hemolytic uremic syndrome; E = number of events; PY = patient-years; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

Table 42: Overview of All Treatment-Emergent Serious Adverse Events (Safety Set) – Study ALXN1210-aHUS-312

Serious Adverse Events (Preferred Term)	Onset Day/ Resolution Day	Led to Discontinuation (Yes/No)	Relatedness to ALXN1210
Birth to < 6 years			
Escherichia pyelonephritis	20/24	No	Possibly related
Escherichia bacteraemia	20/24	No	Possibly related
Pancreatitis	129/132	No	Unlikely related
Viral infection	9/10	No	Unlikely related
Anaemia	20/37	Yes	Possibly related
Hypertensive crisis	9/37	Yes	Not related
6 to < 18 years			
Cytomegalovirus enteritis	8/Ongoing	No	Not related
Abdominal pain	29/30	No	Not related
Abdominal pain	35/41	Not applicable	Not related
Pulmonary haemorrhage	38/39	No	Unlikely related
Pyrexia	3/10	No	Possibly related
Hypertension	3/12	No	Unlikely related
Gastroenteritis rotavirus	85/88	No	Unlikely related

Laboratory findings

No pooled analysis of clinical laboratory tests was performed. Consistent with the pathogenesis of the disease, at baseline, most patients had low hemoglobin levels and platelet counts, and elevated LDH, serum creatinine, and urine protein.

Haematology

In both studies, the haematology and coagulation parameters did not show clinically important changes over time that would suggest any safety concern or worsening of disease associated with ravulizumab treatment. The mean changes from baseline in hemoglobin level and platelet count showed improvement over time, consistent with resolution of TMA hematologic parameters. The hematology and coagulation parameters did not show clinically important changes over time.

In Study ALXN1210-aHUS-312, 1 patient had Grade 3 anemia that resulted in discontinuation of study drug and withdrawal of the patient from the study. The SAE of anemia was considered possibly related to study drug by the Investigator, although as a component of TMA this anemia may also have been associated with the underlying condition. The anemia responded to a dose of eculizumab that was greater than usually administered per the label. Another patient had a non-serious Grade 4 AE of neutrophil count decreased.

Chemistry

In both studies, no clinically significant mean changes from baseline over time were observed for liver function test parameters (alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, and gamma glutamyl transferase). Other clinical chemistry parameters did not show clinically important changes over time that would suggest any safety concern or worsening of disease associated with ravulizumab treatment. The mean changes from baseline in serum creatinine level and eGFR were consistent with improvement in renal function.

Vital signs

Blood pressure

In Study ALXN1210-aHUS-311, overall, the mean (SD) systolic blood pressure decreased from 143.74 (16.040) mmHg at baseline to 125.54 (16.567) mmHg at Day 183 and mean (SD) diastolic blood pressure decreased from 82.48 (14.254) mmHg at baseline to 77.71(11.879) mmHg at Day 183.

In Study ALXN1210-aHUS-312, overall, the mean (SD) systolic blood pressure decreased from 112.50 (17.877) mmHg at baseline to 103.08 (8.077) mmHg at Day 183 and mean (SD) diastolic blood pressure decreased from 73.03 (12.990) mmHg at baseline to 61.00 (5.902) mmHg at Day 183.

Changes from baseline in mean temperature, mean heart rate, mean respiratory rate, and mean oxygen saturation did not show clinically important trends over time in adult and pediatric patients treated with ravulizumab in Study ALXN1210-aHUS-311 and Study ALXN1210-aHUS-312, respectively.

Immunogenicity

In both the studies, immunogenicity assessment was performed on Day 1, Day 71, Day 127, and Day 183 or the Early Termination Visit. In Study ALXN1210-aHUS-311, 18 (31.6%) patients were ADA positive at baseline (pre-treatment), while post-treatment, 2 ADA positive samples were seen. One of the two post-treatment ADA positive samples came from a patient with ADA positive sample at baseline. The titer decreased post-treatment so this was not considered a treatment-emergent ADA positive sample. One patient had a transient treatment-emergent ADA positive titer of < 1:1 on Day 68.

In Study ALXN1210-aHUS-312, 12 (75%) patients were ADA positive at baseline (pre-treatment). There was no ADA positive result post- ravulizumab treatment. The ADA titers were low in all confirmed positive baseline samples, and the positive baseline results had no apparent impact on safety or efficacy in these patients.

In the aHUS clinical program (N = 74), only 1 patient in Study ALXN1210-aHUS-311 had treatment-emergent ADA. This ADA was transient in nature, low titer, non-neutralizing, and did not correlate with clinical response or AEs.

In total, considering PNH and aHUS studies, 2 (0.6%) patients had treatment-emergent ADA.

Table 43: Immunogenicity (antidrug antibodies) by visit (Safety set) – Study ALXN1210-aHUS-312

		Overall (N=58)	
Visit	m	Positive n (%)	Negative n (%)
Baseline[a]	57	18 (31.6)	39 (68.4)
Day 71	52	2 (3.8)	50 (96.2)
Day 127	49	0 (0.0)	49 (100.0)
Day 183	47	0 (0.0)	47 (100.0)
Day 351	17	0 (0.0)	17 (100.0)
Up to Day 183[b]	54	2 (3.7)	52 (96.3)
Entire Follow-up[b]	54	2 (3.7)	52 (96.3)

m: The number of patients with available data at visit. For 'Up to Day 183' and 'Entire Follow-up', it is the total number of patients who have at least one post-baseline antidrug antibodies result.
(a) Baseline for this specific table is from the Day 1 predose value.
(b) Patients ever positive and patients always negative are summarized.

Table 44: Immunogenicity (antidrug antibodies) by visit: Negative or Titer Category (Safety Set) – Study ALXN1210-aHUS-312

Visit	m	Overall (N=58) n(%)
Baseline[a]	57	
Negative		39 (68.4)
<1:1		2 (3.5)
1:1		6 (10.5)
1:3		4 (7.0)
1:9		3 (5.3)
1:81		1 (1.8)
1:243		1 (1.8)
Day 71	52	
Negative		50 (96.2)
<1:1		1 (1.9)
1:81		1 (1.9)
Day 127	49	
Negative		49 (100.0)
Day 183	47	
Negative		47 (100.0)

(a) Baseline for this specific table is from the Day 1 predose value.
m: The number of patients with available data at visit.

Table 45: Immunogenicity (antidrug antibodies) by visit (Safety set) – Study ALXN1210-aHUS-312

		Overall (N=16)	
Visit	m	Positive n (%)	Negative n (%)
Baseline[a]	16	12 (75.0)	4 (25.0)
Day 71	13	0 (0.0)	13 (100.0)
Day 127	13	0 (0.0)	13 (100.0)
Day 183	13	0 (0.0)	13 (100.0)
Up to Day 183[b]	16	0 (0.0)	16 (100.0)

m: The number of patients with available data at visit. For 'Up to Day 183', it is the total number of patients who have at least one post-baseline antidrug antibodies result.
(a) Baseline is from the Day 1 predose value.
(b) Patients ever positive and patients always negative are summarized.

Safety in special populations

Subgroup analyses were based on age group, sex, body weight group, geographic region, race, kidney transplant history, and dialysis at baseline.

Age

Table 46: Subgroup Overview of All Treatment-Emergent Adverse Events and Serious Adverse Events by Age Group (Safety Set)

Variables	Birth to < 6 years (N = 9) (PY = 4.1)		6 to < 18 years (N = 7) (PY = 2.6)		18 to < 65 years (N = 49) (PY = 43.0)		≥ 65 years (N = 9) (PY = 3.2)	
	n (%)	E (rate)	n (%)	E (rate)	n (%)	E (rate)	n (%)	E (rate)
Any TEAE	8 (88.9)	70 (1717.1)	7 (100.0)	92 (3597.8)	49 (100.0)	730 (1696.5)	9 (100.0)	88 (2707.8)
Related TEAE	4 (44.4)	8 (196.2)	4 (57.1)	14 (547.5)	18 (36.7)	52 (120.8)	2 (22.2)	6 (184.6)
Unrelated TEAE	8 (88.9)	62 (1520.9)	7 (100.0)	78 (3050.3)	49 (100.0)	678 (1575.6)	9 (100.0)	82 (2523.2)
Grade 1	7 (77.8)	46 (1128.4)	6 (85.7)	74 (2893.8)	46 (93.9)	411 (955.1)	8 (88.9)	43 (1323.1)
Grade 2	6 (66.7)	19 (466.1)	5 (71.4)	14 (547.5)	40 (81.6)	197 (457.8)	6 (66.7)	26 (800.0)
Grade 3	2 (22.2)	5 (122.6)	1 (14.3)	3 (117.3)	27 (55.1)	105 (244.0)	4 (44.4)	11 (338.5)
Grade 4	0	0	1 (14.3)	1 (39.1)	9 (18.4)	16 (37.2)	5 (55.6)	6 (184.6)
Grade 5	0	0	0	0	1 (2.0)	1 (2.3)	2 (22.2)	2 (61.5)
TEAE leading to study drug interruption	1 (11.1)	1 (24.5)	0	0	0	0	0	0
TEAE leading to study drug discontinuation	1 (11.1)	2 (49.1)	0	0	3 (6.1)	3 (7.0)	0	0
TEAE leading to study discontinuation	1 (11.1)	2 (49.1)	0	0	3 (6.1)	3 (7.0)	0	0
Any serious TEAEs	3 (33.3)	6 (147.2)	5 (71.4)	7 (273.7)	24 (49.0)	62 (144.1)	6 (66.7)	9 (276.9)
Related SAE	2 (22.2)	3 (73.6)	1 (14.3)	1 (39.1)	2 (4.1)	2 (4.6)	0	0
Unrelated SAE	3 (33.3)	3 (73.6)	5 (71.4)	6 (234.6)	23 (46.9)	60 (139.4)	6 (66.7)	9 (276.9)
SAE leading to study drug interruption	0	0	0	0	0	0	0	0
SAE leading to study drug discontinuation	1 (11.1)	2 (49.1)	0	0	3 (6.1)	3 (7.0)	0	0
SAE leading to study discontinuation	1 (11.1)	2 (49.1)	0	0	3 (6.1)	3 (7.0)	0	0
Death	0	NA	0	NA	1 (2.0)	NA	2 (22.2)	NA

Note: Percentages are based on the number of patients in the Safety Set in each column. ie, % = n/N*100.
Rate = rate of AE adjusted by PY of exposure, defined as (number of events)/100 PY.
Safety Set = All patients from Study ALXN1210-aHUS-311 or Study ALXN1210-aHUS-312 who received at least 1 dose of study drug.
The data cut-off dates are 15 Oct 2018 or the end of Initial Evaluation Period whichever comes last for Study ALXN1210-aHUS-311 and the end of Initial Evaluation Period for Study ALXN1210-aHUS-312.
Related AEs are defined as AEs that are possibly, probably, or definitely related to study drug. Not related AEs are defined as AEs that are unlikely or not related to study drug. Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = Fatal.
Abbreviations: AE = adverse event; aHUS = atypical hemolytic uremic syndrome; E = Number of events; NA = not applicable; PY = patient-years; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Table 47: Subgroup Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and by Age Group (Safety Set)

SOC	Birth to < 6 years (N = 9) (PY = 4.1)		6 to < 18 years (N = 7) (PY = 2.6)		18 to < 65 years (N = 49) (PY = 43.0)		≥ 65 years (N = 9) (PY = 3.2)	
	n (%)	E (rate)	n (%)	E (rate)	n (%)	E (rate)	n (%)	E (rate)
Patients with TEAEs	8 (88.9)	70 (1717.1)	7 (100.0)	92 (3597.8)	49 (100.0)	730 (1696.5)	9 (100.0)	88 (2707.8)
Blood and lymphatic system disorders	3 (33.3)	4 (98.1)	2 (28.6)	2 (78.2)	18 (36.7)	37 (86.0)	1 (11.1)	3 (92.3)
Cardiac disorders	1 (11.1)	1 (24.5)	1 (14.3)	1 (39.1)	9 (18.4)	12 (27.9)	0	0
Ear and labyrinth disorders	0	0	0	0	4 (8.2)	4 (9.3)	0	0
Endocrine disorders	0	0	0	0	2 (4.1)	2 (4.6)	3 (33.3)	3 (92.3)
Eye disorders	1 (11.1)	1 (24.5)	2 (28.6)	2 (78.2)	10 (20.4)	17 (39.5)	1 (11.1)	1 (30.8)
Gastrointestinal disorders	6 (66.7)	19 (466.1)	4 (57.1)	24 (938.5)	34 (69.4)	102 (237.0)	5 (55.6)	9 (276.9)
General disorders and administration site conditions	2 (22.2)	10 (245.3)	4 (57.1)	9 (352.0)	29 (59.2)	54 (125.5)	2 (22.2)	7 (215.4)
Hepatobiliary disorders	0	0	0	0	2 (4.1)	2 (4.6)	1 (11.1)	1 (30.8)
Immune system disorders	0	0	0	0	6 (12.2)	7 (16.3)	1 (11.1)	1 (30.8)
Infections and infestations	5 (55.6)	13 (318.9)	4 (57.1)	8 (312.8)	28 (57.1)	84 (195.2)	6 (66.7)	14 (430.8)
Injury, poisoning and procedural complications	0	0	3 (42.9)	5 (195.5)	16 (32.7)	25 (58.1)	2 (22.2)	3 (92.3)
Investigations	2 (22.2)	2 (49.1)	4 (57.1)	5 (195.5)	16 (32.7)	38 (88.3)	4 (44.4)	9 (276.9)
Metabolism and nutrition disorders	3 (33.3)	5 (122.6)	1 (14.3)	2 (78.2)	23 (46.9)	55 (127.8)	3 (33.3)	8 (246.2)
Musculoskeletal and connective tissue disorders	1 (11.1)	1 (24.5)	3 (42.9)	5 (195.5)	21 (42.9)	48 (111.5)	1 (11.1)	2 (61.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	1 (2.0)	3 (7.0)	0	0
Nervous system disorders	0	0	4 (57.1)	14 (547.5)	32 (65.3)	62 (144.1)	2 (22.2)	7 (215.4)
Product issues	0	0	0	0	3 (6.1)	3 (7.0)	0	0
Psychiatric disorders	1 (11.1)	1 (24.5)	1 (14.3)	1 (39.1)	13 (26.5)	25 (58.1)	1 (11.1)	2 (61.5)
Renal and urinary disorders	1 (11.1)	1 (24.5)	0	0	20 (40.8)	28 (65.1)	1 (11.1)	1 (30.8)
Reproductive system and breast disorders	0	0	0	0	11 (22.4)	13 (30.2)	1 (11.1)	1 (30.8)
Respiratory, thoracic and mediastinal disorders	4 (44.4)	5 (122.6)	3 (42.9)	4 (156.4)	24 (49.0)	39 (90.6)	5 (55.6)	10 (307.7)
Skin and subcutaneous tissue disorders	4 (44.4)	4 (98.1)	3 (42.9)	5 (195.5)	23 (46.9)	35 (81.3)	2 (22.2)	3 (92.3)
Vascular disorders	3 (33.3)	3 (73.6)	4 (57.1)	5 (195.5)	20 (40.8)	35 (81.3)	3 (33.3)	3 (92.3)

Note: Percentages are based on the number of patients in the Safety Set in each column, ie, % = n/N*100. Rate = rate of AE adjusted by PY of exposure, defined as (number of events)/100 PY.
Safety Set = All patients from Study ALXN1210-aHUS-311 or Study ALXN1210-aHUS-312 who received at least 1 dose of study drug.
Treatment-emergent AEs are AEs with a start date and start time on or after the date and time of the first infusion of study drug. Under patient count columns, n (%), if a patient had more than 1 event for a particular SOC, the patient is counted only once for that SOC under n (%).
The data cut-off dates are 15 Oct 2018 or the end of Initial Evaluation Period whichever comes last for Study ALXN1210-aHUS-311 and the end of Initial Evaluation Period for ALXN1210-aHUS-312. The AEs are coded using MedDRA 21.0.
Abbreviations: AE = adverse event; aHUS = atypical hemolytic uremic syndrome; E = number of events; PY = patient-years; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been conducted with ravulizumab.

Discontinuation due to adverse events

Four (5.4%) patients across the 2 studies had an AE leading to discontinuation of study drug (exposure-adjusted rate of 9.4 events/100 PY).

Table 48: Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by MedDRA System Organ Class and Preferred Term, by Study (Safety Set)

SOC Preferred Term	ALXN1210-aHUS-311 (N = 58) (PY = 46.3)		ALXN1210-aHUS-312 (N = 16) (PY = 6.6)		Total (N = 74) (PY = 52.9)	
	n (%)	E (rate)	n (%)	E (rate)	n (%)	E (rate)
Patients with at least 1 TEAE leading to study drug discontinuation	3 (5.2)	3 (6.5)	1 (6.3)	2 (30.1)	4 (5.4)	5 (9.4)
Blood and lymphatic system disorders	2 (3.4)	2 (4.3)	1 (6.3)	1 (15.1)	3 (4.1)	3 (5.7)
Anaemia	0	0	1 (6.3)	1 (15.1)	1 (1.4)	1 (1.9)
Autoimmune haemolytic anaemia	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Immune thrombocytopenic purpura	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Nervous system disorders	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Haemorrhage intracranial	1 (1.7)	1 (2.2)	0	0	1 (1.4)	1 (1.9)
Vascular disorders	0	0	1 (6.3)	1 (15.1)	1 (1.4)	1 (1.9)
Hypertensive crisis	0	0	1 (6.3)	1 (15.1)	1 (1.4)	1 (1.9)

Note: Percentages are based on the number of patients in the Safety Set in each column, ie, % = n/N*100.
Rate = rate of AE adjusted by PY of exposure, defined as (number of events)/100 PY.
Treatment-emergent AEs were AEs with a start date and start time on or after the date and time of the first infusion of study drug.
Under patient count columns, n (%), if a patient had more than 1 event for a particular SOC, the patient was counted only once for that SOC under n (%). If a patient had more than 1 event for a particular Preferred Term, the patient was counted only once for that Preferred Term. The data cutoff dates were 15 Oct 2018 or the end of Initial Evaluation Period whichever came last for Study ALXN1210-aHUS-311 and the end of Initial Evaluation Period for Study ALXN1210-aHUS-312.
All AEs were coded using MedDRA Version 21.0.
Abbreviations: AE = adverse event; aHUS = atypical hemolytic uremic syndrome; E = number of events; PY = patient-years; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

Adverse events leading to infusion interruption

Overall, AEs leading to infusion interruption was reported in 1 (1.4%) patient. This patient was from Study ALXN1210-aHUS-312 and had non-serious Grade 2 hypertension during the second infusion (Day 15) that resulted in transient interruption of the infusion. The infusion was then restarted after 10 minutes and the full dose was completed. Overall, AEs leading to infusion interruption was reported in 1 (1.4%) patient. There were no interruptions for subsequent infusions. The AE was considered unlikely related to study drug by the Investigator and was resolving as of the data cut-off date for this submission. There were no AEs leading to infusion interruption in Study ALXN1210-aHUS-311.

Updated safety data

In the initial submission, the extent of the data consisted of the Initial Evaluation Period (26 weeks) or study discontinuation for all patients; for adult patients in Study ALXN1210-aHUS-311 who had visits in the Extension Period, data up to 15 Oct 2018 were included in the clinical safety database. With this update, safety data are available for 89 patients, 58 in Study ALXN1210-aHUS-311 with data through 02 Jul 2019, and 31 in ALXN1210-aHUS-312 with data through 16 Oct 2019.

Study ALXN1210-aHUS-311 (Adult Patients)

As of 02 Jul 2019, there were no new treatment-emergent adverse events resulting in death, study discontinuation, or immunogenicity in Study ALXN1210-aHUS-311. There were no patients with meningococcal infection. The exposure-adjusted rate for SAEs decreased from 232.7 events/100 PYs in the first 6-month period of the study to 31.1 events/100 PYs in the second 6-month period of the study and 62.3 events/100 PYs beyond 12 months of treatment with ravulizumab. There were no new or different trends in system organ class treatment-emergent adverse events observed during the Extension Period.

Study ALXN1210-aHUS-312 Cohort 1 (Pediatric Treatment-Naïve Patients)

With the addition of 5 patients to the Cohort 1 Safety Set and additional exposure during the Extension Period for the patients included in the initial submission, no safety concerns were identified (note that 1 of these 5 patients was discontinued per protocol due to being diagnosed with STEC-HUS

following administration of 2 doses of ravulizumab and is included in the Safety Set but not the FAS). There were no new treatment-emergent adverse events resulting in death, study discontinuation, or treatment discontinuation. There were no patients with meningococcal infection, and no patients developed immunogenicity. There were no new or different trends in system organ class treatment-emergent adverse events observed in Cohort 1 during the Extension Period.

Post marketing experience

No postmarketing data in the new indication are available as of the data cut-off date.

2.5.1. Discussion on clinical safety

Ravulizumab is currently authorised for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH). The safety dataset in support of the new proposed indication for ravulizumab (i.e. treatment of patients with aHUS) is based mainly on data from 58 adult patients treated with ravulizumab in study ALXN1210-aHUS-311 (Study aHUS-311) and 16 paediatric patients included in study ALXN1210-aHUS-312 (Study aHUS-312). Therefore, a total of 74 patients have received at least one dose of ravulizumab for the treatment of aHUS. All these patients were complement inhibitor treatment-naïve with evidence of thrombotic microangiopathy (characterised by thrombocytopenia, haemolysis and kidney injury).

Median age in the pooled population was 34.8 years (range: 0.9, 77.1), with 12% (n=9) of patients being 65 years or older. With regard to the paediatric population, safety data are rather limited for the subgroup of patients <2 years.

Ravulizumab dosing regimen is weight-based. Median baseline body weight was 67.5 kg in adults and 16.7 kg in paediatric patients. Adult patients with a body weight <40 kg or paediatric weighing < 5 kg were not allowed to enter the studies. Regarding baseline disease characteristics, 57% of patients in Study aHUS-311 and 37.5% in Study aHUS-312, respectively, had dialysis at baseline and 9 patients (8 adult patients and 1 paediatric patient) had a history of kidney transplant. Short-term (≤28 days) use of plasma exchange/plasma infusion was allowed. In total, 48 (82.8%) patients received prior plasma exchange/plasma infusion treatment.

The studies included an initial evaluation period of 26 weeks and an extension period after week 26. The MAH initially provided safety data from the initial evaluation period (both studies) and of those patients who had a visit in the extension period (Study aHUS-311). The median treatment duration was of around 37.5 months in adult patients (Study aHUS-311) and of 26 weeks in paediatric patients (Study aHUS-312), with a median of infusions received of 6 (range: 1, 11). Nearly all patients reported at least one treatment emergent adverse event (TEAE). Overall, the most commonly reported TEAEs (≥20%) were headache (33.8%), diarrhoea (28.4%), vomiting (25.7%), hypertension (23.0%) and pyrexia (20.3%). TEAEs of pyrexia, nasopharyngitis and constipation were more frequent in the paediatric population while gastrointestinal adverse events (i.e., diarrhoea, nausea), headache and arthralgia were more common in adult patients. The majority of TEAEs were of grade 1 or grade 2. TEAEs of grade 3 and grade 4 were reported by 34 (45.9%) and 15 (20.3%) patients, respectively, most of them in adult patients. The most commonly reported TEAEs of Grade 3 in adults were hypertension (7 [12%]) and urinary tract infection (5 [9%]). End stage renal disease was the only TEAE of Grade 4 reported in more than one patient. In Study aHUS-312, none of the TEAEs of Grade 3 was reported in more than two patients.

Hypertension was commonly reported in both studies (23%) and it was also one of the most common SAEs reported (5.4%). However, the design of these studies (i.e., single arm), does not allow to

elucidate to what extent hypertension could be related to ravulizumab treatment as it may be related to the underlying disease. In fact, hypertension is common in patients with active TMA and uncontrolled complement activation. For the time being it is not possible to elucidate to what extent the treatment with ravulizumab could be associated with this AE (majority of adult patients with aHUS patients in Study ALXN1210-aHUS-311 had hypertension reported in their medical history at baseline and prior to treatment with ravulizumab) or on the contrary could improve it as a consequence of decreased vascular endothelial activation and improved kidney function (the median [range] systolic BP at baseline for adult aHUS patients in Study ALXN1210-aHUS-311 was 140.50 mm Hg [100, 179.5]. On Day 183, the median [range] systolic BP declined to 123.00 mm Hg [94, 173]). A similar trend was observed in the Study aHUS-312.

The main risk associated to ravulizumab and C5 inhibitors in general is an increased susceptibility to infections caused by Neisseria sp., especially Neisseria meningitidis. Patients are required to be vaccinated against meningococcal infections (as described in section 4.4 of the SmPC). In studies aHUS-311 and aHUS-312 meningococcal infection was considered an adverse event of special interest (AEOSI). No events of meningococcal infections were reported up to the data cut-off in either study, neither infections caused by other Neisseria sp.

Taking into account that both ravulizumab and eculizumab have the same mode of action, a similar safety profile is expected. Therefore, adverse events already considered of special interest for eculizumab were also considered of special interest for ravulizumab. Having said that, apart from meningococcal infections, which so far is the only important identified risk for ravulizumab, several adverse events have been considered important potential risks for ravulizumab (some of them important identified risks for eculizumab), such as serious infections, immunogenicity and severe TMA complications in aHUS patients after ravulizumab discontinuation.

TMA complications have been observed following discontinuation of eculizumab treatment in patients with aHUS. In this sense, the following warning has been included in section 4.4 of the SmPC of ravulizumab. There are no specific data on ravulizumab discontinuation. In a long-term prospective observational study, discontinuation of complement C5 inhibitor treatment (eculizumab) resulted in a 13.5-fold higher rate of TMA recurrence and showed a trend toward reduced renal function compared to patients who continued treatment. If patients must discontinue treatment with ravulizumab, they should be monitored closely for signs and symptoms of TMA on an on-going basis. However, monitoring may be insufficient to predict or prevent severe TMA complications. If TMA complications occur after ravulizumab discontinuation, reinitiation of ravulizumab treatment beginning with the loading dose and maintenance dose should be considered.

Moreover, Aspergillus infection and infusion reactions are important identified risk for eculizumab. According to the MAH no cases of Aspergillus were reported in aHUS ravulizumab studies. Regarding infusion related reactions, they were reported in 2 patients in study aHUS-311 and none in study aHUS-312. According to the MAH none of these adverse events led to infusion interruption and resolved during the study. With regard to serious infections, 15 (20.3%) patients (11 [19.0%] in study aHUS-311 and 4 [25.0%] in study aHUS-312) reported a serious infection. Serious infections reported in at least two patients were pneumonia (3 [4.1%]), Escherichia pyelonephritis, septic shock and urinary tract infection (2 [2.7%], each). There were two fatal serious adverse events of infection (2 shock septic adverse events in Study aHUS-311).

Analysis of all available Extension Period data through the data cut-off date for Study 311 suggests that, the exposure adjusted rates for SAEs decreased over time. A similar pattern is observed in Study 312 (the exposure-adjusted rate for SAEs decreased from 131.5 events/100 patient-years (PYs) in the first 6-month period of the study to 73.0 events/100 PYs in the second 6-month period of the study and 96.9 events/100 PYs beyond 12 months of treatment with ravulizumab).

With regard to deaths, 4 patients died in study aHUS-311 and none in study aHUS-312. One of them died due to a pre-treatment adverse event (cerebral arterial thrombosis). The other 3 deaths occurred due to a TEAE (2 septic shock and 1 intracranial haemorrhage). All of the patients had severe comorbidities and were in bad general condition at the time of receiving the study drug and none of the events was considered related to study drug by the investigator. No fatal adverse events were reported in PNH patients treated with ravulizumab neither in aHUS patients treated with eculizumab in clinical trials. Although the relationship to ravulizumab cannot be fully ruled out, the underlying disease likely had an important contribution. However, it is known that C5 is also produced by type-II epithelial cells and plays role in the tissue damages caused by infective agents like Pseudomonas strains, which was the case in one of the deaths. However, the direct connection of the severe lung manifestations due to Pseudomonas infection with the ravulizumab administration is uncertain.

Four patients required treatment discontinuation (3 adult patients and 1 paediatric patient). The paediatric patient was a 1-year child who discontinued study treatment on day 21 (after having received 2 doses of ravulizumab) due to serious adverse events of hypertensive crisis and anaemia. The patient had not reached complete response. TEAEs in adult patients that led to treatment discontinuation were autoimmune haemolytic anaemia, immune thrombocytopenic purpura and haemorrhage intracranial.

In the aHUS clinical program (N=74), only 1 patient in Study ALXN1210 aHUS 311 had treatment-emergent ADA. This ADA was transient in nature, low titer, non-neutralizing, and did not correlate with clinical response or AEs.

Regarding subgroup analyses, the limited sample size does not allow to obtain sound conclusions. Nevertheless, safety data profile seems to be slightly worse for patients < 2 years old, although data is very limited, only 4 patients (2 patients received 300 mg as loading dose and another 2 received 600 mg) were included in the safety analysis. Of those 4 patients, 2 received only two doses, one due to SAEs (300 mg as loading dose) and another due to discontinuation by exclusion criteria (600 mg as loading dose). Consequently, data to support safety of ravulizumab for patients with body weight below 10 kg are limited. Currently available data are described in section 4.8 but no recommendation on a posology and treatment can be made for patients below 10 kg body weight and the indication in this population cannot be recommended.

No dedicated drug-drug interaction studies were performed. Because ravulizumab, like eculizumab, is a monoclonal antibody, clinically meaningful drug-drug PK interactions with small molecule drugs or other biologics are generally not expected. In addition, ravulizumab does not bind to a cytokine and the available safety data from patients with PNH and aHUS (> 450 PY) have not shown a drug-induced cytokine modulation, indicating that the potential of drug-related cytokine-based drug interaction is negligible. This is consistent with clinical and postmarketing eculizumab experience.

Updated safety data, with a longer follow-up (i.e. extension study period) from Study 311 and Cohort 1 of Study 312 did not show any safety concern. Overall, the safety profile of ravulizumab remained unchanged.

In addition, safety data from Cohort 2 of Study 312 (i.e. eculizumab-exposed patients) were provided and no worrisome findings were identified.

2.5.2. Conclusions on clinical safety

Overall, the safety profile in paediatric patients appears similar to that of adults, except for a higher incidence of pyrexia, nasopharyngitis and constipation in children. Serious infections were also more

frequent in paediatric patients. The main concern is the limited database, especially in regard to children up to two years.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.8 is acceptable.

The CHMP endorsed the Risk Management Plan version 1.8 with the following content:

Safety concerns

Table 49: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Meningococcal infection
Important potential risks	Serious haemolysis after drug discontinuation in PNH patients Severe TMA complications in aHUS patients after ravulizumab discontinuation Immunogenicity Serious infections Malignancies and haematologic abnormalities in PNH patients
Missing information	Use in pregnant and breast-feeding women

Pharmacovigilance plan

Table 50 Ongoing and planned additional pharmacovigilance activities

Study/status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – required additional pharmacovigilance activities				

Study/status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
PNH extension safety study in treatment naïve patients ALXN1210-PNH-301	To evaluate the safety and efficacy of ravulizumab administered by intravenous infusion to adult patients with PNH who are naïve to complement inhibitor treatment To collect and evaluate safety data specific to the use of ULTOMIRIS and to collect data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in treated PNH patients	Meningococcal infection Serious haemolysis after drug discontinuation in PNH patients Immunogenicity Serious infections Malignancies and haematologic abnormalities in PNH patients Use in pregnant and breast-feeding women	Final CSR	Oct 2023
PNH extension safety study in patients treated with eculizumab ALXN1210-PNH-302	To collect and evaluate efficacy and safety data specific to the use of ULTOMIRIS and to collect data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in treated PNH patients	Meningococcal infection Serious haemolysis after drug discontinuation in PNH patients Immunogenicity Serious infections Malignancies and haematologic abnormalities in PNH patients Use in pregnant and breast-feeding women	Final CSR	Sep 2021
M07-001 "PNH REGISTRY"	To collect and evaluate safety data specific to the use of SOLIRIS / ULTOMIRIS	Meningococcal infection	Interim data analysis	Every 2 years interim data analysis report

Study/status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Ongoing	and to collect data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in SOLIRIS / ULTOMIRIS and non-SOLIRIS / ULTOMIRIS treated patients.	Serious haemolysis after drug discontinuation in PNH patients Immunogenicity Serious infections Malignancies and haematologic abnormalities in PNH patients Use in pregnant and breast-feeding women		
M11-001 "aHUS REGISTRY" Ongoing	To collect and evaluate safety and effectiveness data specific to the use of eculizumab / ravulizumab in aHUS patients To assess the long-term manifestations of TMA complications of aHUS as well as other clinical outcomes, including mortality and morbidity in aHUS patients receiving eculizumab / ravulizumab treatment or other disease management.	Meningococcal infection Severe TMA complications in aHUS patients after ravulizumab discontinuation Immunogenicity Serious infections Use in pregnant and breast-feeding women	Interim data analysis	Every 2 years interim data analysis report
aHUS safety study in adults and adolescents ALXN1210-aHUS-311 Ongoing	To assess the efficacy and long-term safety of ravulizumab in complement inhibitor treatment-naïve adolescent and adult patients with aHUS to inhibit complement-mediated TMA as characterised by thrombocytopenia, haemolysis, and renal impairment	Meningococcal infection Severe TMA complications in aHUS patients after ravulizumab discontinuation Immunogenicity Serious infections Use in pregnant and breast-feeding women	Final CSR	Dec 2023

Risk minimisation measures

Table 51 Summary table of risk minimisation activities by safety concern

Safety concern	Risk minimisation measures
Meningococcal infection	Routine risk minimisation measures – SmPC sections 4.3, 4.4, and 4.8 – PL sections 2 and 4 Recommendations for vaccination/antibiotic prophylaxis in SmPC section 4.4 and PL section 2 Signs and symptoms of meningococcal infections listed in SmPC section 4.4 and PL section 2 Restricted medical prescription Additional risk minimisation measures Educational materials – PNH/aHUS Physician's Guide – PNH/aHUS Patient's Information Brochure – aHUS Parent's Information Brochure – Patient safety card Controlled distribution Revaccination reminder
Serious haemolysis after drug discontinuation in PNH patients	Routine risk minimisation measures – SmPC section 4.4 – PL section 3 Monitoring of patients who discontinued ULTOMIRIS recommended in SmPC section 4.4 and PL section 3 Additional risk minimisation measures Educational materials – PNH Physician's Guide – PNH Patient's Information Brochure
Severe TMA complications in aHUS patients after ravulizumab discontinuation	Routine risk minimisation measures – SmPC section 4.4 Additional risk minimisation measures Educational materials – aHUS Physician's Guide – aHUS Patient's Information Brochure – aHUS Parent's Information Brochure
Immunogenicity	Routine risk minimisation measures – SmPC section 4.4

Safety concern	Risk minimisation measures
	Additional risk minimisation measures Educational materials – PNH/aHUS Physician's Guide – PNH/aHUS Patient's Information Brochure – aHUS Parent's Information Brochure
Serious infections	Routine risk minimisation measures – SmPC sections 4.3, 4.4 and 4.8 – PL sections 2, 3 and 4 Recommendations for vaccination of paediatric patients against *Haemophilus influenzae* and pneumococcal infections in SmPC section 4.4 and PL section 2. Additional risk minimisation measures Educational materials – PNH/aHUS Physician's Guide – PNH/aHUS Patient's Information Brochure – aHUS Parent's Information Brochure
Malignancies and haematologic abnormalities in PNH patients	Additional risk minimisation measures: – PNH Physician's Guide – PNH Patient's Information Brochure
Use in pregnant and breast-feeding women	Routine risk minimisation measures – SmPC sections 4.6 and 5.3 – PL section 2 Recommendations on contraception in SmPC section 4.8 and PL section 2 Additional risk minimisation measures Educational materials – PNH/aHUS Physician's Guide – PNH/aHUS Patient's Information Brochure

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Annex II.D has been updated to include the new indication in the educational materials.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed by QRD and accepted by the CHMP.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Ultomiris. The bridging report submitted by the MAH has been found acceptable.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, ravulizumab is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Atypical hemolytic uremic syndrome (aHUS) is a very rare, serious and life-threatening disorder characterized by the diagnostic triad of thrombotic thrombocytopenia, microangiopathic haemolysis and impaired renal function as well as other ischemic complications. Most cases of aHUS are secondary to mutations in genes which encode components of the alternative pathway of the complement cascade. Similar to observations in PNH, uncontrolled complement activation may contribute to the TMA process in aHUS by causing inflammation and prothrombotic activity. Patients with aHUS currently face a very poor prognosis with high likelihood of kidney failure, dialysis and/or death within one year from the time of diagnosis.

3.1.2. Available therapies and unmet medical need

Corticosteroids and plasma exchange/plasma infusion are often the initial treatment used during the diagnostic workup, but they have limited benefit for aHUS. The only approved therapy for aHUS is the C5 inhibitor eculizumab.

Since the approval of eculizumab, patients with aHUS are probably no longer treated with long-term plasma therapy, which can transiently maintain normal levels of haematologic measures while the underlying complement dysregulation and thrombotic microangiopathic processes likely persist.

3.1.3. Main clinical studies

- Study ALXN1210-aHUS-311 is a Phase 3, open-label, single-arm, multicenter study finally carried out in adult patients with complement-mediated TMA including aHUS who are naïve to complement inhibitor treatment.
- Study ALXN1210-aHUS-312 is a Phase 3, single-treatment arm, multicenter study in pediatric patients, from birth to < 18 years of age, with confirmed diagnosis of aHUS.

  The study has 2 cohorts: Cohort 1 includes complement inhibitor treatment-naïve patients; Cohort 2 includes eculizumab-experienced patients. At the time of the initial application only data from cohort 1 were submitted. During the procedure, data from 10 patients included in Cohort 2 were available and were also submitted.

3.2. Favourable effects

Study ALXN1210-aHUS-311 (adults)

- Complete TMA Response (primary endpoint) was observed in 30 of the 56 patients (53.6%; 95%CI [39.6, 67.5]) during the 26-week Initial Evaluation Period.
- Platelet normalization, LDH normalization and renal function improvement were achieved in 47 (83.9%), 43 (76.8%) and 33 (58.9%) respectively.
- Four additional patients had a Complete TMA Response that was confirmed after the 26-week Initial Evaluation Period, resulting in an overall Complete TMA Response in 34 of 56 patients (60.7%; 95% CI: 47.0%, 74.4)

Overall, the complete TMA response was deemed reasonably stable (above 45% approximately) once was achieved.

Regarding the improvement in CKD stage, 6 patients improved by 5 stages (ie, from ESKD to normal renal function), 7 patients improved by 4 stages, 5 patients improved by 3 stages, 4 patients improved by 2 stages, and 10 patients improved by 1 stage.

Study ALXN1210-aHUS-312 (pediatric cohort 1)

- Complete TMA Response, the primary endpoint for the trial, was observed in 14 of the 18 naïve patients (77.8%) during the 26-week Initial Evaluation Period. Complete TMA Response during the Initial Evaluation Period was achieved at a median time of 30 days (range 15 to 97 days).
- As of the 16 Oct 2019 data cut-off, 3 additional patients had a Complete TMA Response that was confirmed after the 26-week Initial Evaluation Period ; thus, 17 of 18 (94.4%) paediatric patients (95% CI: 72.7%, 99.9%) had a Complete TMA Response in the trial.
- 18 patients achieved platelet count normalization, 18 patients achieved LDH normalization and 18 patients achieved renal function improvement (defined as 25% reduction in serum creatinine from baseline).

The duration of the response was overall sustained since 9 of these responders had sustained their response status from the first time point when they achieved Complete TMA Response through the end of the 26-week Initial Evaluation Period.

No new patients initiated dialysis after starting treatment with study drug. At the end of the Initial Evaluation Period, 15 (88.2%) of 17 patients had improvement in CKD stage compared to baseline.

Study ALXN1210-aHUS-312 (pediatric cohort 2)

As of the 16 Oct 2019 data cut-off, 10 eculizumab-experienced patients who switched to ravulizumab have completed the 26-week Initial Evaluation Period and entered the Extension Period, with a cumulative median exposure of 43.6 weeks. TMA parameters remained stable. After week 26 parameters seem to remain stable too, although data are still limited.

3.3. Uncertainties and limitations about favourable effects

The lack of comparator and limited sample size hinder the appropriate interpretation of the results. See discussion under Importance of favourable and unfavourable effects.

QoL data are not interpretable due to the lack of comparator and open label design.

In regard to the Study ALXN1210-aHUS-312, at least 4 patients <2 years old were required by the PDCO during the assessment of the corresponding PIP. However, data from only 2 patients were submitted which is considered too limited. Therefore, further efficacy data in this target population are deemed necessary.

There are no data in patients previously treated with eculizimab without evidence of response to this drug, therefore an indication cannot be recommended for this population.

3.4. Unfavourable effects

Nearly all patients reported at least one TEAE. The most commonly reported TEAEs (≥20%) in patients with aHUS treated with ravulizumab were headache (33.8%), diarrhoea (28.4%), vomiting (25.7%), hypertension (23.0%) and pyrexia (20.3%). The majority of TEAEs were of grade 1 or grade 2. TEAEs of grade 3 and grade 4 were reported by 34 (45.9%) and 15 (20.3%) patients, respectively.

SAEs were reported by around 50% of patients. SAEs most commonly reported were in the infections and infestations SOC (20.3%). By preferred term, the most commonly reported SAE were hypertension (4 [5.4%]), abdominal pain and pneumonia (3 [4.1%], each). In children, the only SAE reported in at least two patients was abdominal pain (2 [12.5%]).

With regard to deaths, 4 patients died in study aHUS-311 and none in study aHUS-312. The causes of death were a pre-treatment adverse event (cerebral arterial thrombosis) and TEAE (2 septic shock and 1 intracranial haemorrhage). None of the events was considered related to study drug by the investigator.

The main risk associated to ravulizumab is an increased susceptibility to infections caused by Neisseria sp., especially Neisseria meningitidis. No meningococcal infections were reported in studies aHUS-311 and aHUS-312.

There were four patients that required treatment discontinuation (3 adult patients and 1 paediatric patient). TEAEs in adult patients that led to treatment discontinuation were autoimmune haemolytic anaemia, immune thrombocytopenic purpura and haemorrhage intracranial. In the paediatric patient, treatment was discontinued due to serious adverse events of hypertensive crisis and anaemia.

Overall, the safety profile in paediatric patients appears similar to that in adults, except for a higher incidence of pyrexia, nasopharyngitis and constipation in children. Serious infections were also more frequent in paediatric patients.

3.5. Uncertainties and limitations about unfavourable effects

Safety data are rather limited, especially for the subgroups of children up to two years. Moreover the safety profile of ravulizumab in this population seems to be slightly worse than for the overall population, therefore a posology cannot be recommended for patients of less than 10kf of weight.

Hypertension was more commonly reported in aHUS studies compared to PNH studies. However, the lack of a control arm does not allow to elucidate the real contribution of ravulizumab versus the underlying disease.

3.6. Effects Table

Table 52: Effects Table for Ultomiris for the Treatment of aHUS (data cut-off: 10 Oct 2019 for Study ALXN1210-aHUS-311 and 11 December 2019 for Study ALXN1210-aHUS-312)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Study ALXN1210-aHUS-311 (Adult patients)						
Complete TMA response	Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline.	% (95% CI)	53.6 (39.6, 67.5)	N/A		Efficacy section of this AR
Platelet normalisation	Platelet count ≥ 150 x 10^9/L	% (95% CI)	83.9 (73.4, 94.4)	N/A		
LDH normalisation	LDH ≤246 U/L	% (95% CI)	76.8 (64.8, 88.7)	N/A		
Creatinine improvement	≥ 25% improvement in serum creatinine from baseline.	% (95% CI)	58.9 (45.2, 72.7)	N/A		
Study ALXN1210-aHUS-312 (Paediatric patients)						
Complete TMA response	Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline.	% (95% CI)	77.8 (52.4, 93.6)	N/A		Efficacy section of this AR
Platelet	Platelet count ≥	%	94.4	N/A		

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
normalisation	150 x 10^9/L	(95% CI)	(72.7, 99.9)			
LDH normalisation	LDH ≤246 U/L	% (95% CI)	88.9 (65.3, 98.6)	N/A		
Creatinine improvement	≥ 25% improvement in serum creatinine from baseline.	% (95% CI)	83.3 (58.6, 96.4)	N/A		
Unfavourable Effects						
TEAEs	Overall incidence of TEAEs, regardless of causality	n (%)	89 (100.0)	N/A	Safety data are based on a pooled population of 89 patients from two single-arm studies (aHUS-311 in 58 adult patients and aHUS-312 in 31 paediatric patients) that had received at least one dose of ravulizumab, with a median treatment duration of 497 days (518.5 in study 311 and 411.0 in study 312).	Safety section of this AR
Grade 3 TEAEs	Incidence of TEAEs of grade 3	n (%)	44 (49.4)	N/A		
Grade 4 TEAEs	Incidence of TEAEs of grade 4	n (%)	15 (16.9)	N/A		
SAEs	Incidence of serious adverse events	n (%)	48 (53.9)	N/A		
Deaths	Deaths due to TEAEs	n (%)	3 (3.4)	N/A		
Headache	Common TEAE	n (%)	30 (33.7)	N/A		
Diarrhoea	Common TEAE	n (%)	27 (30.3)	N/A		
Vomiting	Common TEAE	n (%)	26 (29.2)	N/A		
Pyrexia	Common TEAE	n (%)	22 (24.7)	N/A		
Hypertension	Common TEAE	n (%)	21 (23.6)	N/A		
Serious infections	Adverse event of special interest	n (%)	21 (24)	N/A		
Nausea	Common TEAE	n (%)	19 (21.3)	N/A		
Nasopharyngitis	Common TEAE	n (%)	18 (20.2)	N/A		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Both studies in adults and patients have shown a clinically meaningful complete TMA response with an overall sustained response along the initial period of 26 weeks. Platelet normalization, LDH normalization and renal function improvement were achieved in the majority of patients treated with ravulizumab. Results are supported by the sensitivity analyses carried out. Moreover, efficacy data with a longer follow-up (i.e. up to week 52) suggest that response is maintained over time.

However, the lack of comparator, even acknowledging that from a feasibility perspective (a non-inferiority trial would need more than 300 centers and more than 100 patients) and bearing in mind

the prevalence of the disease (the annual incidence of aHUS is approximately 0.1 to 0.2 cases per million) it would be prohibitive, hinders to a certain extent the achievement of firm conclusions. Taking into account the limitations of indirect comparisons, eculizumab is the only comparator authorised in the same indication the MAH is applying for. Eculizumab obtained the MA based on the results from two different clinical studies, study C08-002A/B which enrolled adolescent and adult patients with less severe disease, and study C08-003A/B that enrolled adolescent and adult patients with longer term aHUS without apparent evidence of TMA manifestations and receiving chronic plasma exchange/plasma infusion (plasma sensitive). Later on, results from studies C10-004 (adults) and C10-003 (paediatrics) were provided.

On observing to the complete TMA response from ravulizumab study in adults, and comparing to the eculizumab ones, similar percentage of responders is obtained; 30/56 (53.6%) [95%CI 39.6, 67.5] vs 11/17 (65%) [95% CI: 38%, 86%] and 23/41 (56%) [95% CI: 40%, 72%] ALXN1210-aHUS-311 vs C08-002A/B and C10-004 respectively. This comparability exercise should be carried out assuming that in the study C08-002A/B results could be overestimated due to a smaller sample size, whereas in the study C10-004, where both the sample size and patients are more comparable to the ravulizumab trial in adults, the point estimate is closer to that obtained in the 311 study. Of note, confidence intervals are overlapping. Besides, populations, even not totally comparable, could be considered of having similar baseline characteristics, such as early aHUS, adult population, thrombocytopenia, elevated LDH and renal impairment. On the contrary, patients in the study C08-003 were considered to be in a later stage, being plasma therapy sensitive as they had normal platelet count and normal LDH levels. The same judgement can be applied to the paediatric studies, both in baseline characteristics and results in terms of complete TMA response.

Bearing in mind that ravulizumab is a terminal complement inhibitor that specifically binds to complement component 5 (C5) with high affinity, inhibiting the enzymatic cleavage of C5 into C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement membrane attack complex [C5b-9]) and the fact that based on this MoA, has been already demonstrated a comparable activity to eculizumab in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH), it is accepted that efficacy has been substantiate in a certain extent in the adult population.

In the paediatric population, data to support safety and efficacy of ravulizumab for patients with body weight below 10 kg are limited. Currently available data are described in section 4.8 of the SmPC but no recommendation on a posology can be made for patients below 10 kg body weight (see SmPC section 4.2). Further data should be provided to support the use of ravulizumab in this patient population. The indication is restricted to patients with a body weight of 10 kg or above (see SmPC section 4.1).

Overall, the safety profile of ravulizumab in aHUS appears comparable to that observed in adult patients with PNH. The reported incidence of some adverse events (gastrointestinal adverse events, arthralgia, hypertension, anaemia, constipation and urinary tract infections) seems to be higher in aHUS patients, which may be partly explained by the underlying disease. Overall, the safety profile in paediatric patients appears similar to that of adults, apart from a higher incidence of pyrexia, nasopharyngitis and constipation in children. Serious infections were also more frequent in paediatric patients.

The safety profile of ravulizumab seems to be slightly worse for patients < 2 years old, although data is very limited (only 4 patients were included in the safety analysis; of those, 2 patients received a loading dose of 300 mg;1 received only two doses and the other completed the initial evaluation period).

It is also noted the MAH was seeking a wording of the indication in the treatment of patients with atypical haemolytic uremic syndrome (aHUS), regardless of the previous treatment with eculizumab. Based on the results of the 10 patients included in Cohort 2 of the Study 312 and the Phase 3 study in PNH (Study PNH-302) the latter could be acceptable provided that patients have been treated with eculizumab and are stable (i.e. LDH<1.5 x ULN and platelet count ≥150,000 /μL and eGFR>30 mL/min/1.73 m2). However, the extrapolation of the indication to a population of patients refractory to eculizumab treatment is not supported, since no aHUS patients who were refractory to eculizumab-treatment were included in Cohort 2.

3.7.2. Balance of benefits and risks

The observed benefit outweighs the unfavourable effects of ravulizumab in the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Ultomiris (ravulizumab) in the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include the treatment of patients with atypical haemolytic uremic syndrome (aHUS) for Ultomiris; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, Annex II.D is updated to include the new indication in the educational materials. The RMP (version 1.8) has been updated.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

This recommendation is subject to the following amended conditions:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Ultomiris in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational and controlled distribution programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational and controlled distribution programme is aimed at education and instruction of healthcare professionals/patients about the detection, careful monitoring, and/or proper management of selected safety concerns associated with Ultomiris.

The MAH shall ensure that in each Member State where Ultomiris is marketed, all healthcare professionals and patients who are expected to prescribe, dispense and use Ultomiris have access to/are provided with the following educational package to be disseminated through professional bodies:

- Physician educational material
- Patient information pack

The physician educational material should contain:

  - The Summary of Product Characteristics
  - Guide for healthcare professionals
- **The Guide for healthcare professionals** shall contain the following key elements:
  - To address the risks of meningococcal infection, serious haemolysis after drug discontinuation in PNH patients, severe TMA complications in aHUS patients after ravulizumab discontinuation, immunogenicity, serious infections, malignancies and

haematological abnormalities in in PNH patients, use in pregnant and breast-feeding women.

- Treatment with ravulizumab increases the risk of N. meningitidis infections.
- All patients must be monitored for signs of meningitidis.
- The need for patients to be vaccinated against N. meningitidis two weeks prior to receiving ravulizumab and/or to receive antibiotic prophylaxis.
- The risk of immunogenicity and advice on post-infusion monitoring.
- The risk of developing antibodies to ravulizumab.
- No clinical data on exposed pregnancies is available. Ravulizumab should be given to a pregnant woman only if clearly needed. The need for effective contraception in women of childbearing potential during and up to eight months after treatment. Breast-feeding should be discontinued during and up to eight months after treatment.
- Risk of serious haemolysis following ravulizumab discontinuation and postponement of administration, its criteria, the required post-treatment monitoring and its proposed management (PNH only).
- Risk of severe TMA complications following ravulizumab discontinuation and postponement of administration, its signs, symptoms, monitoring and management (aHUS only).
- The need to explain to and ensure understanding of by patients:
    - the risk of treatment with ravulizumab (including potential risks of serious infections)
    - the signs and symptoms of meningococcal infection and what action to take
    - the patient's/parent's guides and their contents
    - the need to carry the patient safety card and to tell any healthcare practitioner that he/she is receiving treatment with ravulizumab
    - the requirement for pre-treatment vaccinations/antibiotic prophylaxis
    - the enrolment in the PNH registry and aHUS registry
- Details of the PNH registry, aHUS registry and how to enter patients

The patient/parent's information pack should contain:

- Package leaflet
- A patient guide
- A parent guide (aHUS only)
- A patient safety card

- **The patient guide** shall contain the following key messages:
    - To address the risks of meningococcal infection, serious haemolysis after drug discontinuation in PNH patients, severe TMA complications in aHUS patients after ravulizumab discontinuation, immunogenicity, serious infections, malignancies and haematological abnormalities in PNH patients, use in pregnant and breast-feeding women.

- Treatment with ravulizumab increases the risk of N. meningitidis infections.
- Signs and symptoms of meningococcal infection and the need to obtain urgent medical care.
- The patient alert card and the need to carry it on their person and tell any treating healthcare professional that they are being treated with ravulizumab.
- The importance of meningococcal vaccination prior to treatment and/or to receive antibiotic prophylaxis.
- The risk of immunogenicity with ravulizumab, including anaphylaxis, and the need for clinical monitoring post-infusion.
- The need for effective contraception in women of childbearing potential during and up to eight months after treatment, and that breast-feeding should be discontinued during and up to eight months after treatment.
- Risk of severe haemolysis following discontinuation/postponement of ravulizumab administrations, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing ravulizumab administrations (PNH only).
- Risk of severe TMA complications following discontinuation/postponement of ravulizumab administration, their signs and symptoms and the recommendation to consult the prescriber before discontinuing/postponing ravulizumab administration (aHUS only)
- Potential risks of severe, non-neisserial infections and malignancies and haematologic abnormalities in PNH patients treated with ravulizumab.
- Enrolment in the PNH registry and aHUS registry.
- The parent guide (provided together with patient guide) shall contain the following key messages:
    - To address the risks of meningococcal infection and serious infections in infants and children.

- **The patient safety card** shall contain the following key messages:
    - Signs and symptoms of meningococcal infection
    - Warning to seek immediate medical care if above are present
    - Statement that the patient is receiving ravulizumab
    - Contact details where a healthcare professional can receive further information

      Patient safety card should be retained for 8 months after last dose of ravulizumab

The MAH shall send annually to prescribers or pharmacists who prescribe/dispense ravulizumab, a reminder in order that prescriber/pharmacist checks if a (re)-vaccination against *Neisseria meningitidis* is needed for his/her patients on ravulizumab.

The MAH shall ensure that in each Member State where Ultomiris is marketed, a system aimed to control distribution of Ultomiris beyond the level of routine risk minimisation measures is in place. The following requirements need to be fulfilled before the product is dispensed:

- Submission of written confirmation of the patient`s vaccination against all available meningococcal infection serotypes *N. meningitidis* and/or prophylactic antibiotic treatment according to national vaccination guideline.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ultomiris is similar to Soliris within the meaning of Article 3 of Commission Regulation (EC) No 847/2000 for the same therapeutic indication. See appendix 1.

Derogation(s) from market exclusivity

The CHMP by consensus is of the opinion that with reference to Article 8 of Regulation (EC) No 141/2000the following derogation laid down in Article 8(3)(a) of the same Regulation applies:

the holder of the marketing authorisation for Soliris has given his consent to the MAH.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion EMEA/H/C/004954/II/0002.