EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 July 2021
EMA/552844/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ultomiris

International non-proprietary name: ravulizumab

Procedure No. EMEA/H/C/004954/II/0010

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
ADR	adverse drug reaction
AE	adverse event
aHUS	atypical haemolytic uremic syndrome
BTH	breakthrough haemolysis
C5	complement component 5
CHMP	Committee for Medicinal Products for Human Use
Cmax	maximum observed serum ravulizumab concentration
cRBC	chicken red blood cell
CSR	clinical study report
Ctrough	serum ravulizumab concentration at the end of the dosing interval
DBL	database lock
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IV	intravenous(ly)
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MAVE	major adverse vascular event
NAb	neutralizing antibody
PD	pharmacodynamic(s)
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
Pop-PK	population PK
q2w/q3w/q4w/q8w	every 2/3/4/8 weeks
QoL	quality of life
REMS	risk evaluation and mitigation strategy
RMP	risk management plan
SAE	serious adverse events
SD	standard deviation
TA	transfusion avoidance
ULN	upper limit of normal

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 17 December 2020 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 treatment of paediatric patients with paroxysmal nocturnal haemoglobinuria (PNH) for Ultomiris; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, Annex II is updated to reflect the addition of a PNH Parent guide. Version 2.1 of the RMP has also been submitted, in order to include the new indication.

The requested variation proposed 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 an EMA Decision P/0399/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0399/2020 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 MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Blanca Garcia-Ochoa Co-Rapporteur: Agnes Gyurasics

Timetable	Actual dates
Submission date	17 December 2020
Start of procedure:	23 January 2021
CHMP Co-Rapporteur Assessment Report	19 March 2021
CHMP Rapporteur Assessment Report	30 March 2021
PRAC Rapporteur Assessment Report	25 March 2021
PRAC members comments	29 March 2021
PRAC Outcome	9 March 2021
CHMP members comments	12 March 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 April 2021
Request for supplementary information (RSI)	22 April 2021
CHMP Rapporteur Assessment Report	25 June 2021
CHMP members comments	12 July 2021
Updated CHMP Rapporteur Assessment Report	15 July 2021
Opinion	22 July 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The purpose of the current submission is to extend the indication for ravulizumab to paediatric patients with paroxysmal nocturnal haemoglobinuria (PNH). The proposed updated indication is as follows:

ULTOMIRIS *is indicated in the treatment of adult and paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH):*

- *in patients with haemolysis with clinical symptom(s) indicative of high disease activity.*
- *in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months.*

Epidemiology

The overall prevalence of PNH is estimated at 15.9 cases per million individuals worldwide and occurs more frequently in Asia than in western countries (Hill, 2017; Hill, 2006). Paroxysmal nocturnal haemoglobinuria has an estimated worldwide incidence of 1.3 per million population (Hill, 2006).

The epidemiological data for paediatric patients is sparse and given the low incidence of PNH in paediatric patients, studies of children with PNH have been limited to case reports and case series. The extreme rarity of PNH in paediatric patients poses a challenge for recruitment in a clinical study. The onset of PNH is typically in adulthood, with paediatric cases accounting for 5% to 10% of reported cases (Ware, 1991; van den Heuvel-Eibrink, 2007; Urbano-Ispizua, 2015).

The median survival for paediatric patients with PNH is estimated to be 13.5 years (Ware, 1991), aligning with the median survival rate of 10 years seen in adults (Hillmen,1995). While it is well established that mortality risk in adults with PNH is most often attributed to thrombotic events, this is less clear in paediatric patients. Mortality rates in paediatric patients are often difficult to establish due to the challenges in identifying the thrombosis leading to death as a consequence of PNH.

Clinical presentation, diagnosis

Paroxysmal nocturnal haemoglobinuria (ICD-10 classification: D59.5) is an ultra-rare, progressive, destructive, and life-threatening disease in which uncontrolled complement activation leads to systemic complications, principally through intravascular haemolysis and thrombophilia (Brodsky, 2014; Brodsky, 2015).

In adults, the clinical manifestations of PNH include haemoglobinuria, chronic renal insufficiency, erectile dysfunction, thrombosis, abdominal pain, dyspnoea, and dysphagia (Parker, 2005).

In contrast, children with PNH usually present with nonspecific symptoms related to the underlying bone marrow disorder, such as pallor, fatigue, or jaundice, and less commonly haemoglobinuria (Ware, 1991). Clinical evaluation in paediatric patients also reveals more frequent bone marrow failure syndromes, such as aplastic anaemia and refractory cytopenia (Van den Heuvel-Eibrink, 2007). Once the bone marrow disorder is resolved in paediatric patients or the PNH clone expands (the cause of which is still unknown), the disease eventually evolves into one more typically seen in adults at presentation. Thus, paediatric patients can be expected to suffer substantial morbidity related to haemolysis, as seen in adult PNH patients (Parker, 2005).

Management

Prior to the investigation of eculizumab in paediatric patients with PNH, treatments were mainly supportive, including blood transfusions, anticoagulant therapies, thrombolytic therapies corticosteroids, and iron supplementation. However, these therapies generally provide transient benefit, rather than substantive disease improvement. Additionally, anti-coagulant therapy increases the risk of bleeding and haemorrhage. Overall, there is inadequate evidence supporting a positive benefit-risk profile due to the lack of controlled studies with these therapies.

Since PNH in the paediatric population frequently presents with bone marrow failure, patients are commonly referred to bone marrow transplantation (Urbano-Ispizua, 2017). However, this procedure is restricted to a limited number of patients due to the availability of matched donors and carries a high risk of morbidity and mortality (Parker 2005).

Eculizumab was the first C5 inhibitor to be evaluated as treatment option in paediatric patients with PNH. Patients achieved important clinical benefits as demonstrated by the impact of eculizumab treatment to effectively inhibit terminal complement activation in all treated patients and reduce haemolysis as measured by lactate dehydrogenase (LDH). The safety profile of eculizumab in paediatric patients with PNH was generally favourable.

An analysis of PNH Registry data (from 2007 to Jun 2020 data cut-off) showed that of a total of 2,409 PNH registry participants, only 49 (2.0%) were aged < 18 years, with 10 (20.4%) of these paediatric participants < 12 years old. The youngest enrolled participant was age 3.7 years at enrolment. This analysis included patients who were enrolled at an active PNH Registry site and were not discontinued from the registry. Only 15 of 49 (30.6%) patients with PNH aged < 18 years were treated with a C5 inhibitor, of whom only 1 was aged < 12 years.

2.1.2. About the product

Ravulizumab (ALXN1210) is a long-acting monoclonal antibody (mAb) with high affinity for complement component 5 (C5).

Ravulizumab is administered every 8 weeks (q8w) in patients weighing ≥ 20 kg or every 4 weeks (q4w) for patients weighing < 20 kg.

Ravulizumab was approved by the European Commission on 02 Jul 2019 for the treatment of adult patients with PNH, and on 25 Jun 2020 for the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS).

Ravulizumab is marketed in 2 different strengths, ravulizumab 10 mg/mL and 100 mg/mL.

2.1.3. The development programme/compliance with CHMP guidance

This submission presents interim analysis results from the Primary Evaluation Period (through Day 183 [Week 26]) of the paediatric Study ALXN1210-PNH-304.

In addition, supplementary ravulizumab PK, PD, efficacy, and safety data from 4 studies in adult patients with PNH (ALXN1210-PNH-103, ALXN1210-PNH-201, ALXN1210-PNH-301 and ALXN1210-PNH-302) and 2 studies in paediatric and adult patients with aHUS (ALXN1210-aHUS-311 and ALXN1210-aHUS-312) have been submitted. These data are presented to support the assumption that the outcome of treatment is likely to be similar in paediatric subsets by weight compared to adults. Further, data from 7 eculizumab studies in paediatric (children and adolescents) and adult patients with PNH or aHUS are also included as both ravulizumab and eculizumab have the same mechanism of action.

2.1.4. General comments on compliance with GCP

The MAH confirmed that the CSR submitted is in compliance with the guidance ICH Topic E3 Structure and Content of Clinical Study Reports as well as the Note for guidance on the inclusion of appendices to CSR. Study ALXN1210-PNH-304 was conducted in compliance with GCP. No Regulatory Agency GCP inspections have taken place to date, and no inspections are planned at this time

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 guidelines "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/S/4447/00).

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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 **Ravulizumab Clinical Trials in Paediatric Patients With Paroxysmal Nocturnal Haemoglobinuria**

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-PNH-304	M5.3.5.2	Assess PK, PD, safety, and efficacy in pediatric patients (< 18 years) with PNH	Phase 3, open-label, uncontrolled, multicenter, single treatment arm study in pediatric patients with PNH who are complement inhibitor treatment-naïve or eculizumab-experienced	Ravulizumab IV Weight-based loading[a] dose on Day 1 and maintenance[b] dose on Day 15 and q8w (q4w for patients < 20 kg)	13/13[c] (enrollment ongoing)	26-week Primary Evaluation Period followed by Extension Period of up to 4 years	Primary Evaluation Period (Primary Endpoint) complete, Extension Period ongoing; interim report

[a] ALXN1210 loading dose: 600 mg for patients weighing ≥ 5 to < 10 kg, 600 mg for patients weighing ≥ 10 to < 20 kg, 900 mg for patients weighing ≥ 20 to < 30 kg, 1200 mg for patients weighing ≥ 30 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.
[b] 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 to < 30 kg, 2700 mg for patients weighing ≥ 30 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.
[c] The interim CSR for this study includes results from the first 12 patients treated in the study, 8 patients in the eculizumab-experienced cohort and 4 patients in the complement inhibitor treatment-naïve cohort.
Abbreviations: CSR = clinical study report; IV = intravenous; PD = pharmacodynamics; PK = pharmacokinetics; q4w = every 4 weeks; q8w = every 8 weeks; PNH = paroxysmal nocturnal hemoglobinuria.

2.3.2. Pharmacokinetics

Analytical Methods

All PK, PD, and ADA assay methods used in support of Study ALXN1210-PNH-304 in paediatric patients with PNH are the same as the assay methods used in support of the previous Phase 3 studies in adult patients with PNH and paediatric patients with atypical haemolytic uremic syndrome.

The established LTS does cover the maximum study sample storage period for all PK and PD samples.

For PK and PD samples analysis, the individual and global calibration standards and QCs of the in-study validation were acceptable. The reasons for PK and PD samples re-analysis are acceptable.

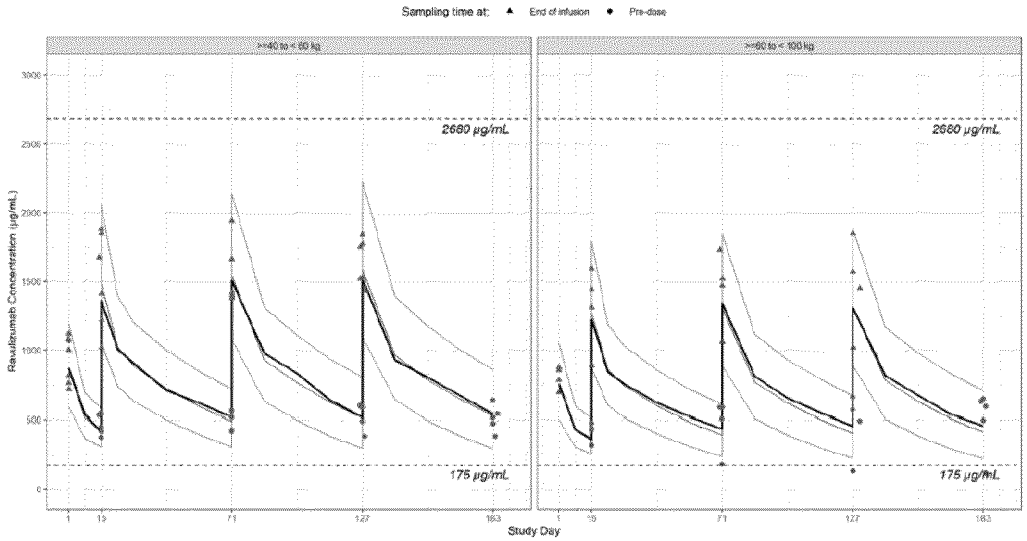
The ISR was performed for ravulizumab and the results show an acceptable reproducibility. No ISR ws performed for Total C5 and Haemolysis and the ISR is ongoing for Free C5. This is considered acceptable as the ISR has only to be performed in the first clinical trial in subjects.

Pharmacokinetics in the target population

Comparison of Adolescent (12 to <18 years) and adult patients with PNH

On the simulated concentration-time profile for adult patients with PNH from Phase 3 studies using the final PNH Pop-PK model (Table 2) in Figure 2. Because ravulizumab dosing regimens are body weight-based, the adult simulations are shown for the ≥ 40 kg to < 60 kg and the ≥ 60 kg to < 100 kg body weight groups.

Figure 2: Observed PK Data From Adolescent Patients With PNH Overlaid on VPC Simulations of Median Serum Ravulizumab Concentration-Time Profile (95% PI) for Adult Patients With PNH From Phase 3 Studies Based on Using the Final PNH Population PK Model



Note: Data for adolescent patients from Study ALXN1210-PNH-304 Primary Evaluation Period are overlaid on PK simulations (N = 500) of Phase 3 data from adult patients with PNH using the final PNH population PK model (PNH Adult Module 2.7.2 Section 3.2.1.2). The lower dashed horizontal line indicates serum concentration of 175 µg/mL, the therapeutic PK threshold for ravulizumab, and the upper dashed horizontal line indicates the maximum serum concentration observed in the ravulizumab clinical development program. Observed adolescent ravulizumab serum concentration data from End of Infusion and Predose are displayed using triangles and circles, respectively. Black lines represent mean observed data from adult patients with PNH and grey lines represent the simulated data (median and 95% PI) for adult patients with PNH. Ravulizumab serum concentrations for adolescent Patient [redacted] who received multiple packed red blood cell transfusions during the 26-week Primary Evaluation Period of Study ALXN1210-PNH-304 are highlighted in blue.

Abbreviations: PI = prediction interval; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; VPC = virtual predictive check

Source: vpc_overlay_pnh_20200806.R (PNH model)

Table 2: Mean ± SD (%CV) PK Parameters of Ravulizumab Following the First IV Loading Dose and the Last IV Maintenance Dose During the Primary Evaluation Period for Adolescent and Adult Patients With PNH

PK Parameter	Dosing Period	Adolescent Patients With PNH[a]		Adult Patients With PNH[b]	
		Complement Inhibitor Treatment-naïve (N = 3[c])	Eculizumab-experienced (N = 7)	Complement Inhibitor Treatment-naïve (N = 125)	Eculizumab-experienced (N = 97[d])
C_{max} (µg/mL)	LD	764.5 ± NA (NA)	923.7 ± 140.68 (15.2)	771.4 ± 165.89 (21.5)	842.9 ± 203.47 (24.1)
	Last MD	1475.0 ± NA (NA)	1680.0 ± 160.73 (9.6)	1378.5 ± 275.94 (20.0)[e]	1386.3 ± 268.42 (19.4)[f]
C_{trough} (µg/mL)	LD	397.0 ± NA (NA)	469.7 ± 50.97 (10.9)	391.2 ± 136.77 (35.0)	405.4 ± 121.24 (29.9)
	Last MD	448.5 ± NA (NA)	573.1 ± 70.88 (12.4)	472.7 ± 157.94 (33.4)[e]	500.8 ± 143.17 (28.6)[g]

[a] Data for adolescent patients with PNH are from Study ALXN1210-PNH-304 Primary Evaluation Period.

[b] Data for complement inhibitor treatment-naïve adult patients with PNH are from Study ALXN1210-PNH-301 and data for eculizumab-experienced adult patients with PNH are from Study ALXN1210-PNH-302, Primary Evaluation Periods.

[c] Serum ravulizumab concentrations from adolescent Patient (complement inhibitor treatment-naïve) were excluded due to administration of packed red blood cell transfusions during the study. Because n = 2, SD and %CV are not applicable.

[d] Data for Patient were not included due to missing concentration records; thus, n = 96.

[e] Data for Patient were excluded from the summary statistics for the last MD dosing period due to missing Day 127 dosing information; thus, n = 124.

[f] In addition to data for Patient not included (footnote [d] above), data for Patient are not included because the Day 127 end of infusion sample was missing; thus, n = 95.

[g] In addition to data for Patient not included (footnote [d] above), data for Patient are not included because the Day 183 predose sample was missing; thus, n = 95.

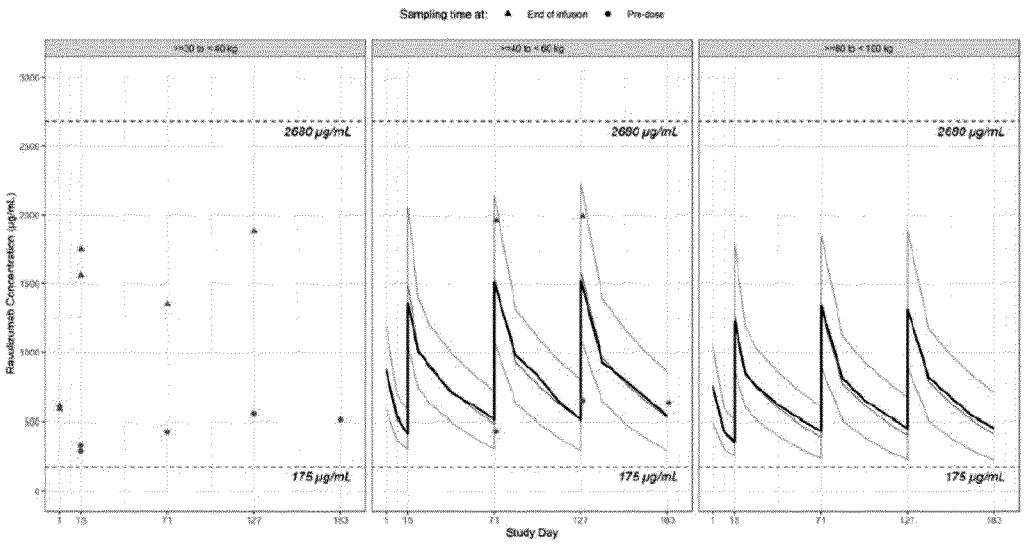
Abbreviations: C_{max} = maximum observed serum concentration; C_{trough} = serum concentration at the end of the dosing interval; CV = coefficient of variation; IV = intravenous; LD = loading dose; MD = maintenance dose; NA = not applicable; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; SD = standard deviation

Source: Module 5.3.5.3 Extrapolation Report Table 14.2.1.1.4.3.s; ALXN1210-PNH-301 CSR Table 14.2.5.1.1 and Table 14.2.5.2.1; ALXN1210-PNH-302 CSR Table 14.2.6.1.1 and Table 14.2.6.2.1

Comparison of Children (Birth to <12 years) and adult patients with PNH

Observed serum ravulizumab concentrations for the children with PNH are overlaid on simulations of the PK for adult patients with PNH from Phase 3 studies using the final PNH Pop-PK model – as below.

Figure 3: **Observed PK Data From Children With PNH Overlaid on VPC Simulations of Median Serum Ravulizumab Concentration-Time Profile (95% PI) for Adult Patients With PNH From Phase 3 Studies Using the Final PNH Population PK Model**



Note: Data for children with PNH from Study ALXN1210-PNH-304 Primary Evaluation Period (Patients [redacted] and [redacted]) are overlaid on PK simulations of Phase 3 data from adult patients with PNH using the final PNH population PK model (PNH Adult Module 2.7.2 Section 3.2.1.2). The lower dashed horizontal line indicates serum concentration of 175 µg/mL, the therapeutic PK threshold for ravulizumab, and the upper dashed horizontal line indicates the maximum serum concentration observed in the ravulizumab clinical development program. Black lines represent median observed data from adult patients with PNH and grey lines represent the simulated data (median and 95% PI) for adult patients with PNH. Observed ravulizumab serum concentration data for children from End of Infusion and Predose are displayed using triangles and circles, respectively.

Abbreviations: PI = prediction interval; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; VPC = virtual predictive check

Source: vpc_overlay_pnh_20200806.R (PNH model)

Table 3: PK Parameters of Ravulizumab Following the First IV Loading Dose and the Last IV Maintenance Dose During the Primary Evaluation Period for Children and Adult Patients With PNH

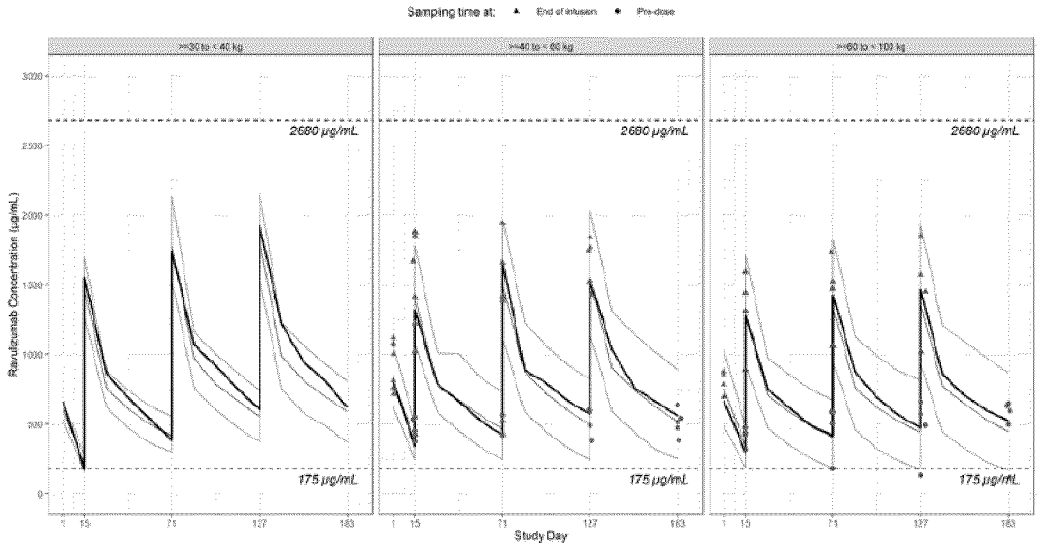
PK Parameter	Dosing Period	Statistic	Children With PNH[a]		Adult Patients With PNH[b]	
			Complement Inhibitor Treatment-naïve (N = 1)	Eculizumab-experienced (N = 1)	Complement Inhibitor Treatment-naïve (N = 125)	Eculizumab-experienced (N = 97[c])
C_{max} (µg/mL)	LD	Mean ± SD (%CV) Min, max	589	611	771.4 ± 165.89 (21.5) 403, 1310	842.9 ± 203.47 (24.1) 511, 1750
	Last MD	Mean ± SD (%CV) Min, max	1990	1880	1378.5 ± 275.94 (20.0)[d] 780, 2100	1386.3 ± 268.42 (19.4)[e] 902, 2320
C_{trough} (µg/mL)	LD	Mean ± SD (%CV) Min, max	292	330	391.2 ± 136.77 (35.0) 199, 1500	405.4 ± 121.24 (29.9) 197, 1040
	Last MD	Mean ± SD (%CV) Min, max	630	513	472.7 ± 157.94 (33.4)[d] 135, 1000	500.8 ± 143.17 (28.6)[f] 232, 854

[a] Data for children with PNH are from Study ALXN1210-PNH-304
[b] Data for complement inhibitor treatment-naïve adult patients with PNH are from Study ALXN1210-PNH-301 and data for eculizumab-experienced adult patients with PNH are from Study ALXN1210-PNH-302.
[c] Data for Patient were not included due to missing concentration records; thus, n = 96.
[d] Data for Patient were excluded from the summary statistics for the last MD dosing period due to missing Day 127 dosing information; thus, n = 124.
[e] In addition to data for Patient not included (footnote [c] above), data for Patient are not included because the Day 127 end of infusion sample was missing; thus, n = 95.
[f] In addition to data for Patient not included (footnote [c] above), data for Patient are not included because the Day 183 predose sample was missing; thus, n = 95.
Abbreviations: C_{max} = maximum observed serum concentration; C_{trough} = serum concentration at the end of the dosing interval; CV = coefficient of variation; IV = intravenous; LD = loading dose; max = maximum; MD = maintenance dose; Min = minimum; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; SD = standard deviation
Source: ALXN1210-PNH-304 CSR Listing 16.2.5.2.3; ALXN1210-PNH-301 CSR Table 14.2.5.1.1 and Table 14.2.5.2.1; ALXN1210-PNH-302 CSR Table 14.2.6.1.1 and Table 14.2.6.2.1

Comparison of Adolescent with PNH (12 to <18 years) and patients with aHUS treated with ravulizumab

Observed serum ravulizumab concentrations for the adolescent patients with PNH are overlaid on simulations of the PK for patients with aHUS from Phase 3 studies using the final aHUS Pop-PK model.

Figure 4: Observed PK Data From Adolescent Patients With PNH Overlaid on VPC Simulations of Median Serum Ravulizumab Concentration-Time Profile (95% PI) for Patients With aHUS From Phase 3 Studies Using the Final aHUS Population PK Model



Note: Data for adolescent patients with PNH from Study ALXN1210-PNH-304 Primary Evaluation Period are overlaid on PK simulations of Phase 3 data from patients with aHUS using the final aHUS population PK model (aHUS Module 2.7.2 Section 3.3.2). The lower dashed horizontal line indicates serum concentration of 175 µg/mL, the therapeutic PK threshold for ravulizumab, and the upper dashed horizontal line indicates the maximum serum concentration observed in the ravulizumab clinical development program. Black lines represent median observed data from adult patients with PNH and grey lines represent the simulated data (median and 95% PI) for adult patients with PNH. Observed adolescent ravulizumab serum concentration data from End of Infusion and Predose are displayed using triangles and circles, respectively. Ravulizumab serum concentrations for adolescent Patient [redacted] who received multiple packed red blood cell transfusions during the 26-week Primary Evaluation Period of Study ALXN1210-PNH-304 are highlighted in blue.
Abbreviations: aHUS = atypical hemolytic uremic syndrome; PI =prediction interval; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; VPC = virtual predictive check
Source: vpc_overlay_ahus_20200807.R (aHUS model)

Table 4: PK Parameters of Ravulizumab Following the First IV Loading Dose and the Last IV Maintenance Dose During the Primary Evaluation Period for Adolescent Patients With PNH and Patients With aHUS

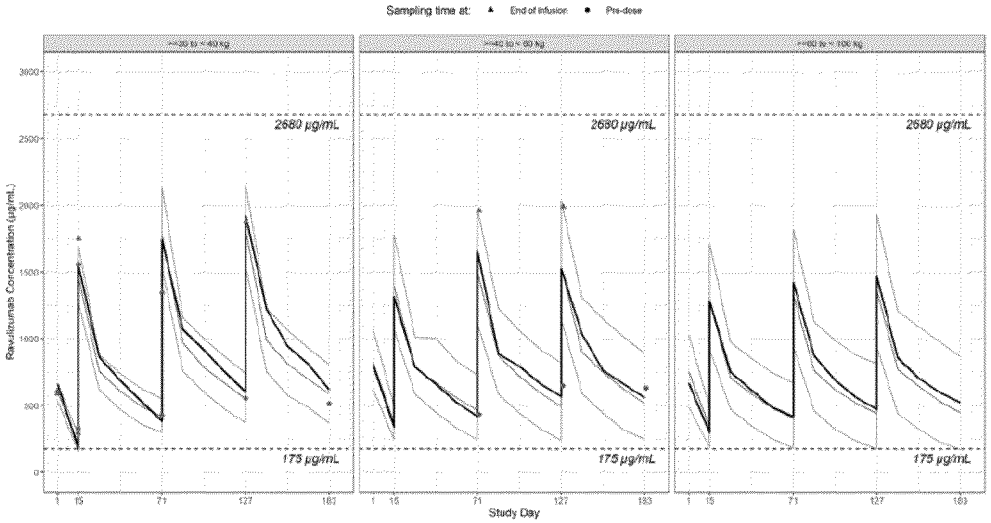
PK Parameter	Dosing Period	Statistic	Adolescent Patients With PNH[a]		Patients With aHUS				
			Study ALXN1210-PNH-304		Study ALXN1210-aHUS-311	Study ALXN1210-aHUS-312			
					Adults	Children[a]		Adolescent Patients	
			Complement Inhibitor Treatment-naïve	Eculizumab-experienced	Complement Inhibitor Treatment-naïve	Complement Inhibitor Treatment-naïve	Eculizumab-experienced	Complement Inhibitor Treatment-naïve	Eculizumab-experienced
C_{max} (µg/mL)	LD	Mean ± SD (%CV); n	764.5 ± NA (NA); 2[b]	923.7 ± 140.68 (15.2); 7	754.3 ± 265.31 (35.2); 52	584.0 ± 72.66 (12.4); 4	550[c]	987.0 ± NA (NA); 2[b]	929.3 ± 136.58 (14.7); 7
	Last MD	Mean ± SD (%CV); n	1475.0 ± NA (NA); 2[b]	1680.0 ± 160.73 (9.6); 7	1458.4 ± 256.19 (17.6); 46	1856.7 ± 280.62 (15.1); 6	2060[c]	2020[b]	1655.7 ± 296.02 (17.9); 7
C_{trough} (µg/mL)	LD	Mean ± SD (%CV); n	397.0 ± NA (NA); 2[b]	469.7 ± 50.97 (10.9); 7	313.2 ± 106.16 (33.9); 55	202.8 ± 23.39 (11.5); 5	315[c]	288.5 ± NA (NA); 2[b]	458.7 ± 83.32 (18.2); 7
	Last MD	Mean ± SD (%CV); n	448.5 ± NA (NA); 2[b]	573.1 ± 70.88 (12.4); 7	506.9 ± 215.51 (42.5); 46	532.3 ± 184.42 (34.6); 6	639[c]	531.5 ± NA (NA); 2[b]	456.7 ± 77.98 (17.1); 7

[a] Data for children who received ravulizumab once every 4 weeks are not included.
[b] Because n = 2, SD and %CV are not applicable.
[c] Observed value only presented as n = 1.
Abbreviations: aHUS = atypical haemolytic uremic syndrome; C_{max} = maximum observed serum concentration; C_{trough} = serum concentration at the end of the dosing interval; CV = coefficient of variation; IV = intravenous; LD = loading dose; MD = maintenance dose; NA = not applicable; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; SD = standard deviation
Source: Module 5.3.5.3 Extrapolation ReportTable 14.2.1.1.4.3.s; ALXN1210-aHUS-311 CSR Table 14.2.5.1.1 and Table 14.2.5.2.1; and Module 5.3.5.3 Extrapolation ReportTables 14.2.5.1.1.4.AGE.312.c1 and 14.2.5.1.1.4.AGE.312.c2

Comparison of Children with PNH (Birth to <12 years) and patients with aHUS treated with ravulizumab

Observed serum ravulizumab concentrations for the children with PNH are overlaid on simulations of the PK for patients with aHUS from Phase 3 studies using the final aHUS Pop-PK model.

Figure 5: **Observed PK Data From Children With PNH Overlaid on VPC Simulations of Median Serum Ravulizumab Concentration-Time Profile (95% PI) for Patients With aHUS From Phase 3 Studies Using the Final aHUS Population PK Model**



Note: Data for children with PNH from Study ALXN1210-PNH-304 Primary Evaluation Period (Patients [redacted] and [redacted]) are overlaid on PK simulations of Phase 3 data from patients with aHUS using the final aHUS population PK model (aHUS Module 2.7.2 Section 3.3.2). The lower dashed horizontal line indicates serum concentration of 175 µg/mL, the therapeutic PK threshold for ravulizumab, and the upper dashed horizontal line indicates the maximum serum concentration observed in the ravulizumab clinical development program. Black lines represent median observed data from adult patients with PNH and grey lines represent the simulated data (median and 95% PI) for adult patients with PNH. Observed ravulizumab serum concentration data for children from End of Infusion and Predose are displayed using triangles and circles, respectively.

Abbreviations: aHUS = atypical hemolytic uremic syndrome; PI = prediction interval; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; VPC = virtual predictive check

Source: vpc_overlay_ahus_20200807.R (aHUS model)

Table 5: PK Parameters of Ravulizumab Following the First IV Loading Dose and the Last IV Maintenance Dose During the Primary Evaluation Period for Children With PNH and Patients With aHUS

PK Parameter	Dosing Period	Statistic	Children With PNH		Patients With aHUS				
			Study ALXN1210-PNH-304		Study ALXN1210-aHUS-311	Study ALXN1210-aHUS-312			
					Adults	Children[a]		Adolescent Patients	
			Complement Inhibitor Treatment-naïve	Eculizumab-experienced	Complement Inhibitor Treatment-naïve	Complement Inhibitor Treatment-naïve	Eculizumab-experienced	Complement Inhibitor Treatment-naïve	Eculizumab-experienced
C_{max} (µg/mL)	LD	Mean ± SD (%CV); n	589[b]	611[b]	754.3 ± 265.31 (35.2); 52	584.0 ± 72.66 (12.4); 4	550[b]	987.0 ± NA (NA); 2[c]	929.3 ± 136.58 (14.7); 7
	Last MD	Mean ± SD (%CV); n	1990[b]	1880[b]	1458.4 ± 256.19 (17.6); 46	1856.7 ± 280.62 (15.1); 6	2060[b]	2020b	1655.7 ± 296.02 (17.9); 7
C_{trough} (µg/mL)	LD	Mean ± SD (%CV); n	292[b]	330[b]	313.2 ± 106.16 (33.9); 55	202.8 ± 23.39 (11.5); 5	315[b]	288.5 ± NA (NA); 2[c]	458.7 ± 83.32 (18.2); 7

	Last MD	Mean ± SD (%CV); n	630[b]	513[b]	506.9 ± 215.51 (42.5); 46	532.3 ± 184.42 (34.6); 6	639[b]	531.5 ± NA (NA); 2[c]	456.7 ± 77.98 (17.1); 7

[a] Data for children who received ravulizumab once every 4 weeks are not included.
[b] Observed value only presented as n = 1.
[c] Because n = 2, SD and %CV are not applicable.
Abbreviations: aHUS = atypical haemolytic uremic syndrome; C_{max} = maximum observed serum concentration; C_{trough} = serum concentration at the end of the dosing interval; CV = coefficient of variation; IV = intravenous; LD = loading dose; MD = maintenance dose; NA = not applicable; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; SD = standard deviation

Immunogenicity

In Study ALXN1210-PNH-304, no paediatric patients had ADAs to ravulizumab at baseline (pretreatment) or developed ADAs at any time during the Primary Evaluation Period.

Ravulizumab exhibited a low incidence of immunogenicity (< 0.5%) in adult patients with PNH (both complement inhibitor-naïve and eculizumab-experienced) in Phase 3 studies, with only 1 treatment-emergent ADA positive result (complement inhibitor-naïve patient with PNH in Study ALXN1210-PNH-301) observed with a low titer, no evidence of neutralization, and no apparent impact of immunogenicity on PK, PD, safety, or efficacy.

Similarly, ravulizumab exhibited a low incidence of immunogenicity in adult patients with aHUS in the Phase 3 studies (Study ALXN1210-aHUS-311 and Study ALXN1210-aHUS-312), with only 1 treatment-emergent ADA positive result (complement inhibitor-naïve adult patient with aHUS in Study ALXN1210-aHUS-311) observed with a low titer, only transiently positive no evidence of neutralization, and no apparent impact of immunogenicity on PK, PD, safety, or efficacy.

No immunogenicity was observed in the paediatric Study ALXN1210-PNH-304 and, overall, ravulizumab exhibited a low incidence of immunogenicity in patients with PNH or aHUS in the Phase 3 studies. Thus, there is a low likelihood of ADAs occurring in paediatric patients with PNH weighing < 30 kg.

2.3.3. Pharmacodynamics

Primary and secondary pharmacology

Pharmacodynamic parameters include serum free C5 concentration, cRBC haemolytic activity, and serum total C5 concentration.

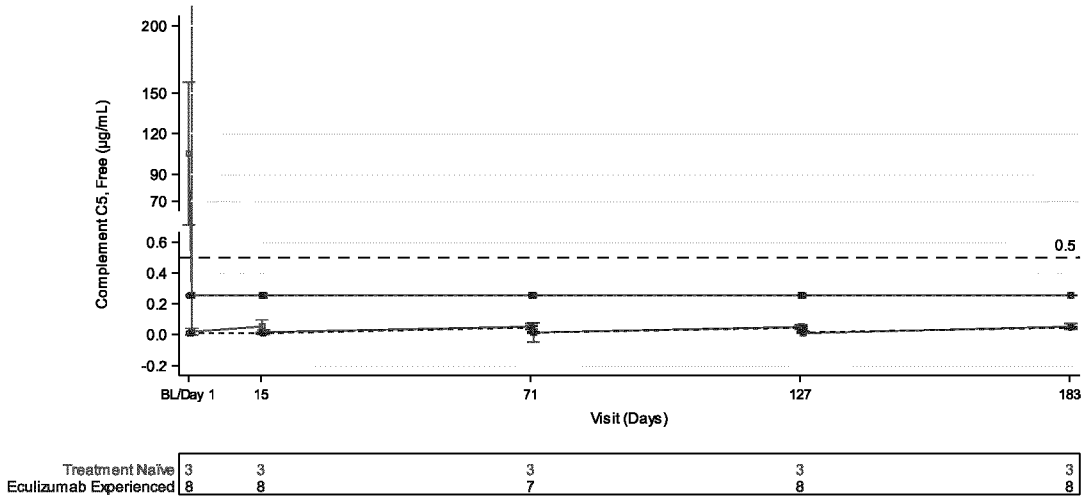
Free C5

Mean (95% confidence interval [CI]) serum free C5 concentration is presented over time in Figure 1 for complement inhibitor treatment-naïve and eculizumab-experienced patients. Figure 2 presents box plots of serum free C5 concentrations versus time profiles following treatment with ravulizumab for complement inhibitor treatment-naïve and eculizumab-experienced patients. For these figures, the data for Patient were excluded due to pRBC transfusions during the study. The exclusions were corroborated with paired PK data.

As expected, the eculizumab-experienced patients had complete terminal complement inhibition at baseline, which was maintained throughout treatment with ravulizumab. Following initiation of treatment with ravulizumab, complement inhibitor treatment-naïve patients had immediate (after the

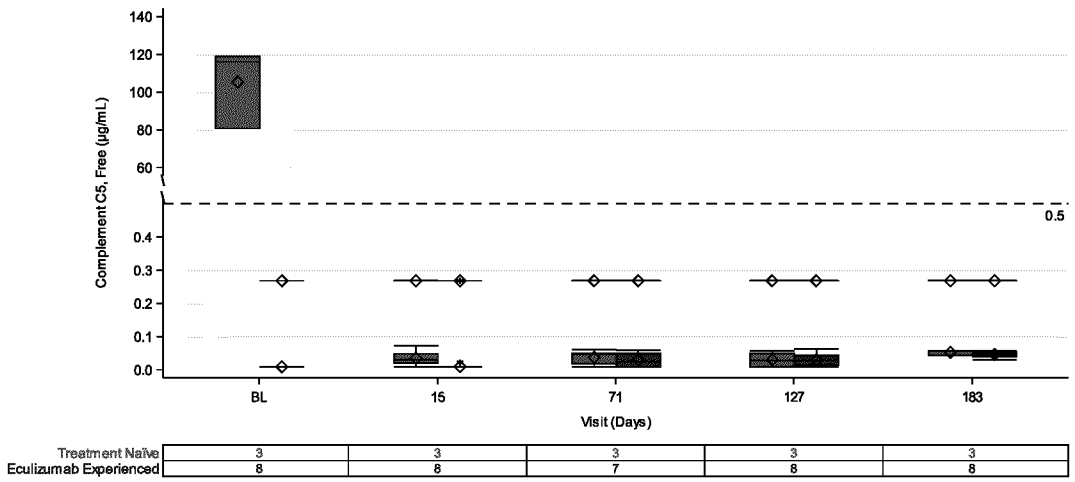
end of infusion of the first dose on Day 1) and complete terminal complement inhibition that was maintained throughout the treatment period.

Figure 1: Mean (95% CI) Serum Free C5 Concentration Over Time (Study ALXN1210-PNH-304 Pharmacodynamic Set)



Note: Baseline was defined as the last nonmissing value prior to first dose of ravulizumab. For the free C5 BLOQ values, LLOQ/2 = 0.00915 µg/mL was utilized. The dashed horizontal line indicates serum free C5 concentration of 0.5 µg/mL, the level at which complete terminal complement inhibition occurs. The Day 71 sample from Patient in the eculizumab-experienced cohort was processed incorrectly (predose and postdose samples were combined in the same cryovial) and, therefore, it was not shipped to the central laboratory. Serum free C5 values from Patient (complement inhibitor treatment-naïve) were excluded due to administration of packed red blood cell transfusions during the study
Abbreviations: BL = baseline; BLOQ = below the limit of quantification; C5 = complement component 5; LLOQ = lower limit of quantification

Figure 2: Box Plots of Serum Free C5 Concentration Over Time (Study ALXN1210-PNH-304 Pharmacodynamic Set)



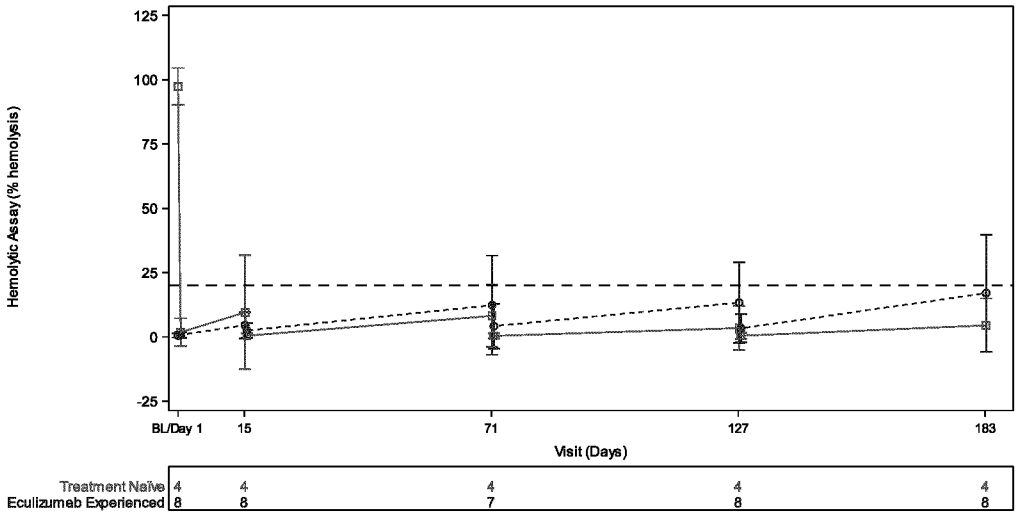
Note: Baseline is defined as the last value prior to the first dose of ravulizumab. The horizontal line in the middle of each box indicates the median, a diamond indicates the mean and the top and the bottom borders of the box mark the 75th and 25th percentiles, respectively. The whiskers represent the minimum and maximum within 1.5 IQR, and outliers are represented by asterisk beyond the 1.5 IQR, where IQR is the difference between the lower quartile and upper quartile. The dashed horizontal line indicates serum free C5 concentration of 0.5 µg/mL, the level at which complete terminal complement inhibition occurs. The Day 71 sample from Patient in the eculizumab-experienced cohort was processed incorrectly (predose and postdose samples were combined in the same cryovial) (ALXN1210-PNH-304 CSR Listing 16.2.2.1.2); therefore, it was not shipped to the central laboratory. Serum free C5 values from Patient (complement inhibitor treatment-naïve) were excluded due to administration of packed red blood cell transfusions during the study.
Abbreviations: BL= baseline; C5 = complement component 5; IQR = interquartile range

None of the eculizumab-experienced patients had a serum free C5 concentration ≥ 0.5 µg/mL at baseline or any visit during the study (ALXN1210-PNH-304 CSR Table 14.2.1.3.1.4). All complement inhibitor treatment-naïve patients had serum free C5 concentrations ≥ 0.5 µg/mL at baseline and none had such a concentration once treatment with ravulizumab was initiated. Thus, ravulizumab provided complete and sustained complement inhibition, which occurred immediately in complement inhibitor treatment-naïve patients.

Chicken Red Blood Cell Haemolytic Activity

Mean (95% CI) %cRBC haemolysis is presented for complement inhibitor treatment-naïve and eculizumab-experienced patients in Figure 3. During treatment with ravulizumab, mean haemolytic activity for both the complement inhibitor treatment-naïve and the eculizumab-experienced patients was < 20%, indicating mean complete inhibition of terminal complement that was indistinguishable between the 2 cohorts of patients.

Figure 3: Mean (95%CI) %cRBC Haemolysis Over Time (Study ALXN1210-PNH-304 Pharmacodynamic Set)



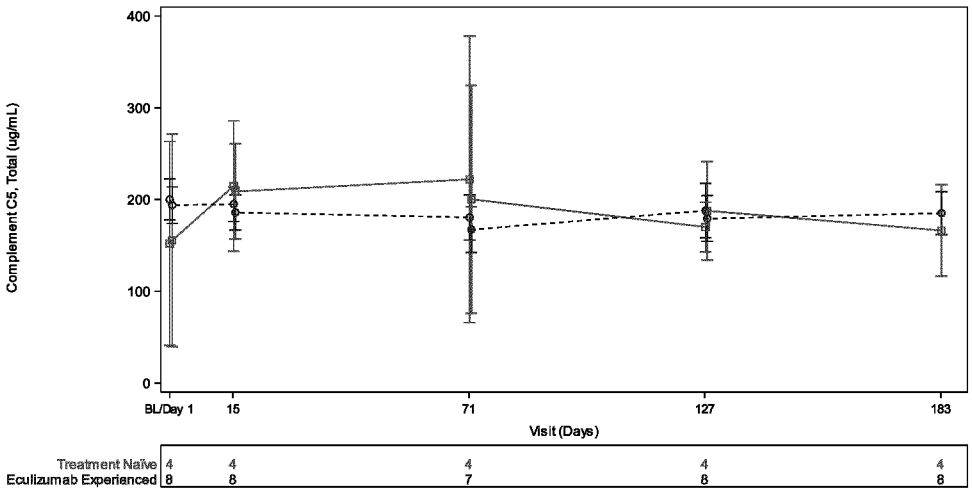
Note: Baseline was defined as the last non missing value prior to first dose of ravulizumab. The cRBC assay was validated as a semiquantitative assay. The assay yields a continuous quantitative result (% haemolysis) with a discrete (qualitative) category of < 20% representing complete complement inhibition, represented by the horizontal dashed line. The Day 71 sample from Patient in the eculizumab-experienced cohort was processed incorrectly (predose and postdose samples were combined in the same cryovial) and, therefore, it was not shipped to the central laboratory.
Abbreviation: BL = baseline; CI = confidence interval; cRBC = chicken red blood cell
Source: ALXN1210-PNH-304 CSR Figure 14.2.4.2.1.4

Total C5

Total C5 level was not considered a primary endpoint for this study.

Mean (95% CI) serum total C5 concentration is presented over time in Figure 4 for complement inhibitor treatment-naïve and eculizumab-experienced patients. The serum total C5 values were slightly elevated in the eculizumab-experienced cohort at baseline but were similar between the 2 cohorts by the end of the Primary Evaluation Period.

Figure 4: Mean (95% CI) Total C5 Over Time (Study ALXN1210-PNH-304 Pharmacodynamic Set)

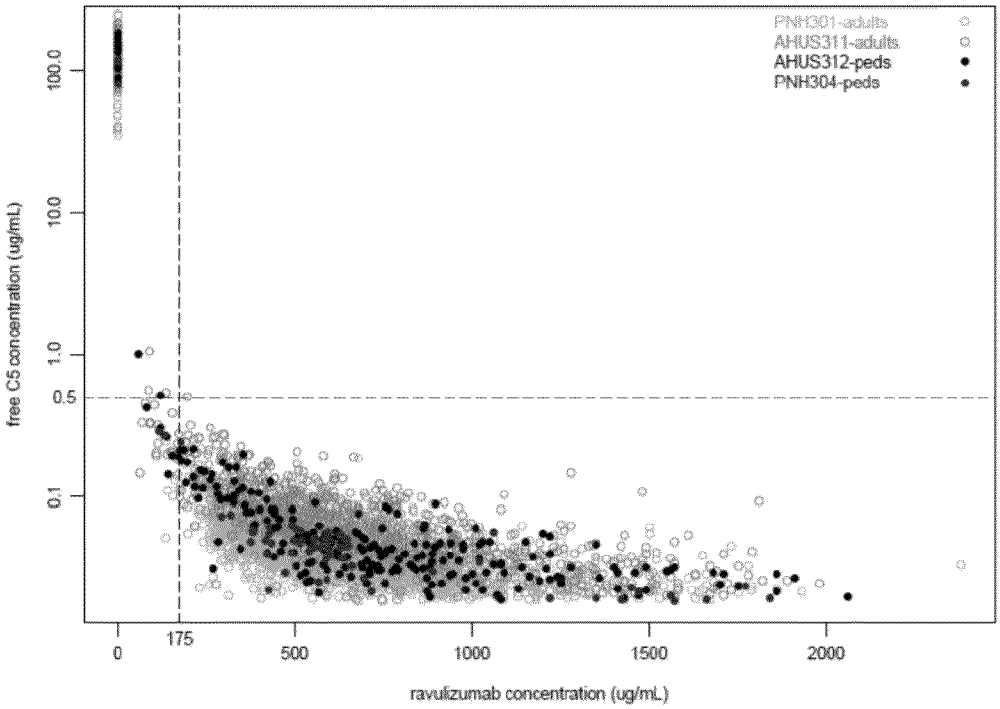


Note: Baseline was defined as the last non missing value prior to first dose of ravulizumab. The Day 71 sample from Patient in the eculizumab-experienced cohort was processed incorrectly (predose and postdose samples were combined in the same cryovial) and, therefore, it was not shipped to the central laboratory.

2.3.3. PK/PD modelling

A plot visualizing the relationship between serum free C5 concentration versus serum ravulizumab concentrations with serum free C5 concentrations stratified by age and disease was created to reveal similarities and differences among the stratification factors (Figure 6). All postbaseline individual serum free C5 concentrations were < 0.5 µg/mL, the threshold defined as achieving complete terminal complement inhibition, in both the complement inhibitor treatment-naïve and the eculizumab-experienced adolescent patients and children with PNH treated with ravulizumab (Study ALXN1210-PNH-304), adult patients with PNH treated with ravulizumab (Study ALXN1210-PNH-301), and nearly all (> 99.5% of analyzed samples) adult and paediatric patients with aHUS treated with ravulizumab (Studies ALXN1210-aHUS-311 and ALXN1210-aHUS-312). Generally, a consistent and nearly identical correlation is seen between serum ravulizumab concentration and serum free C5 concentration among the various patient populations treated with ravulizumab: paediatric and adult patients with PNH as well as paediatric and adult patients with aHUS.

Figure 6: Serum Ravulizumab Concentration Versus Time Matched Serum Free C5 Concentration for Pediatric Patients With PNH, Adult Patients With PNH, Pediatric Patients With aHUS, and Adult Patients With aHUS



Note: The dashed horizontal line indicates serum free C5 concentration of 0.5 µg/mL, the level at which complete terminal complement inhibition occurs. The dashed vertical line indicates serum ravulizumab concentration of 175 µg/mL, the therapeutic PK threshold for ravulizumab.
Abbreviations: aHUS = atypical hemolytic uremic syndrome; C5 = complement component 5; peds = pediatric patients; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria
Source: _001_PKfC5_PedsAdult_PNHaHUS_24AUG2020 (Splus script)

2.3.4. Discussion on clinical pharmacology

All PK, PD, and ADA assay methods used in support of Study ALXN1210-PNH-304 in paediatric patients with PNH are the same as the assays used in support of the Phase 3 studies and were previously assessed.

For PK and PD samples analysis, the individual and global calibration standards and QCs of the in-study validation were acceptable. The reasons for PK and PD samples re-analysis are considered acceptable. The ISR was performed for ravulizumab and the results show an acceptable reproducibility.

The clinical pharmacology properties of ravulizumab in paediatric patients (children and adolescent) have been characterized using experimental data from 12 paediatric patients with PNH (Study ALXN1210-PNH-304) together with supplementary data from studies of ravulizumab in adult patients with PNH and in paediatric and adult patients with atypical haemolytic uremic syndrome (aHUS). Additional characterization of the exposure-response relationship has been conducted on several pharmacodynamic endpoints.

The major limitation of the current approach is the limited experimental evidence of paediatric patients enrolled (n=12) due to the low incidence of the disease in paediatric patients. Data from only 10 adolescents (3 treatment naïve and 7 eculizumab-experienced) and 2 children <12 years (1 treatment naïve and 1 eculizumab-experienced) were considered as external validation for model predictions. The adequacy of a body weight-based ravulizumab dosing regimen for paediatric patients has been checked/conducted by comparing the experimental exposures reported in study ALXN1210-PNH-304 in

12 paediatric patients with the model-predicted exposure in adults derived from a previously developed population PK model in adults. The concordance between the exposure achieved in paediatric patients and the model-predicted exposure in paediatric patients from the population PK model revealed the prediction ability of the population PK model to capture the observed data. It is important to highlight that the low incidence of PNH disease in paediatric patients may support the use of a model-based approach to evaluate exposure in such patients. However, in principle, additional efforts would be expected to support the use of ravulizumab in paediatric patients below 2 years of age since PK differences in absorption, distribution and metabolism occur, which may reduce the prediction ability of the population PK model predictions to be used as the reference PK range. On the other hand, the experimental comparison and model-based predictions between PNH and aHUS indications showed similar exposure ranges across the different subgroups of patients and schedules (naïve and eculizumab-treated), which indicates that PK characteristics in paediatric patients with PNH treated with ravulizumab were comparable to that observed in adults with PNH and adults and paediatric patients with aHUS (see SmPC section 5.2).

The pharmacodynamic evaluation of free-C5, Chicken Red Blood Cell Haemolytic Activity, and total C5 showed that the current dosing regimen of ravulizumab in paediatric patients with PNH allowed to achieve (i) complete terminal complement inhibition by the end of the first ravulizumab infusion and sustained throughout the evaluation period, (ii) complete haemolysis inhibition, and (iii) a slight increase but comparable total C5 values among both cohorts of patients. Moreover, the exposure-free C5 concentration relationship confirmed the observed trend in adult patients, since paediatric observations laid over the observed values in the adult population and similar trend was observed between both populations, suggesting no major differences across the treated groups.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology properties of ravulizumab in paediatric patients (naïve and eculizumab-treated) have been characterized using scarce and limited experimental evidence (n=12) with model predictions from a population PK model of ravulizumab in adults. The modelling strategy is endorsed and shows the adequacy of the body weight-based dosing regimen of ravulizumab in adolescents.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dose response studies were submitted.

The weight-based dosages of ravulizumab in this study were premised on PK/PD data from early development studies in healthy adult volunteers as well as the available data from patients with PNH in an ongoing Phase 1b dose-finding study (ALXN1210-PNH-103) and an ongoing Phase 2 proof-of-concept study (ALXN1210-PNH-201). Ravulizumab paediatric dosing was predicted to not exceed maximum ravulizumab exposures achieved in adult patients with PNH in Phase 2. Based on an interim analysis of data from paediatric patients in Study ALXN1210-aHUS-312 (aHUS-312 Initial PK/PD Analysis) it was decided to amend the protocol (Protocol Amendment 2 dated 23 Aug 2018) to increase the loading dose for patients in the weight range ≥ 5 to < 10 kg from 300 mg to 600 mg (or 300 mg divided in 2 infusions administered within a 24-hour window).

2.4.2. Main study(ies)

Study ALXN1210-PNH-304

This is an ongoing Phase 3, open-label, single-arm multicentre study to evaluate the PK, PD, safety, and efficacy of ravulizumab in complement inhibitor treatment-naïve and eculizumab-experienced paediatric patients (< 18 years of age) with a documented PNH diagnosis.

The study consists of a 4-week Screening Period, a 26-week Primary Evaluation Period, and an Extension Period until the product is registered or approved (in accordance with country-specific regulations) or for of up to 4 years (with the exception of any country specific mandates), whichever occurs first. After completion of all assessments on Day 183, patients entered into an Extension Period and continued to receive ravulizumab according to the appropriate weight-based dose regimen until the product is registered or approved (in accordance with country-specific regulations) or for up to 4 years (with the exception of any country specific mandates), whichever occurs first.

Methods

Study participants

Inclusion criteria

Patients were eligible for enrolment in the study only if they met all of the following criteria:

1. Male and female patients < 18 years of age and weighing ≥ 5 kg at the time of consent.
2. Documented diagnosis of PNH, confirmed by high-sensitivity flow cytometry evaluation (Borowitz, 2010) of RBCs and white blood cells (WBCs), with granulocyte or monocyte clone size of ≥ 5%.
3. For patients not currently treated with eculizumab, presence of 1 or more of the following PNH-related signs or symptoms within 3 months of Screening: fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnoea), anaemia, history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of packed red blood cell (pRBC) transfusion due to PNH.
4. Lactate dehydrogenase values at Screening as follows:

    a. For patients not currently treated with eculizumab, LDH level ≥ 1.5 × ULN

    b. For patients who are currently taking eculizumab, LDH ≤ 1.5× ULN (sample must be obtained on a scheduled eculizumab-dosing day prior to dose administration [ie, at trough eculizumab level] and analysed by the central laboratory)
5. To reduce the risk of meningococcal infection (Neisseria meningitidis [N meningitidis]), all patients must have been vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiate study drug treatment less than 2 weeks after receiving a meningococcal vaccine must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients who cannot be vaccinated must receive antibiotic prophylaxis for the entire treatment period and for 8 months following last dose.
6. Patients must have been vaccinated against *Haemophilus influenzae type b* (*Hib*) and *Streptococcus pneumoniae* (*S pneumoniae*) according to national and local vaccination schedule guidelines, as appropriate.

7. Female patients of childbearing potential (i.e. had achieved menarche) 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.
8. Patient's legal guardian must have been willing and able to give written informed consent and the patient must have been willing to give written informed assent (if applicable as determined by the central or local IRB/IEC and comply with the study visit schedule.

Exclusion criteria

Patients were excluded from study enrolment if they met any of the following criteria:

1. Platelet count < 30,000/mm3 (30 × 109 /L) at Screening
2. Absolute neutrophil count < 500/μL (0.5 × 109 /L) at Screening
3. History of bone marrow transplantation
4. History of N meningitidis infection
5. History of unexplained, recurrent infection
6. Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1
7. History of malignancy within 5 years of Screening with the exception of adequately treated nonmelanoma skin cancer or carcinoma in situ of the cervix
8. History of or ongoing major cardiac, pulmonary, renal, endocrine, or hepatic disease (eg, active hepatitis) that, in the opinion of the Investigator or Alexion, precludes the patient's participation in an investigational clinical study
9. Unstable medical conditions (eg, myocardial ischemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of Screening, coexisting chronic anaemia unrelated to PNH) that would have made them unlikely to tolerate the requirements of the protocol
10. Concomitant use of anticoagulants was prohibited if not on a stable regimen for at least 2 weeks prior to Day 1
11. History of hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins
12. Females who planned to become pregnant or were currently pregnant or breastfeeding
13. Females of childbearing potential who had a positive pregnancy test result at Screening or on Day 1
14. 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
15. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening
16. Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator or Alexion, might have interfered with the patient's full participation in the study, posed any

additional risk for the patient, or confounded the assessment of the patient or outcome of the study

Treatments

Patients received a weight-based loading dose on Day 1 followed by a weight-based maintenance treatment on Day 15 and then once every 4 weeks (q4w) for patients weighing < 20 kg and once every 8 weeks (q8w) for patients weighing ≥ 20 kg. For patients entering the study on eculizumab therapy, Day 1 of study treatment was to be 2 weeks after the patient's last dose of eculizumab.

Table 6: *Loading and Maintenance Treatment Regimens*

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

[a] Dose regimen was based on body weight obtained at the study visit. If the study drug needed to be prepared the day prior to the visit, the weight from the previous visit would be used.
[b] With the agreement of the Alexion Medical Monitor, the 600 mg loading dose could have been given to patients weighing ≥ 5 to < 10 kg as 2 separate infusions administered no more than 24 hours apart.
Abbreviations: q4w = once every 4 weeks; q8w = once every 8 weeks.

Objectives

The objectives of this study were to assess the pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy of ravulizumab in paediatric patients with paroxysmal nocturnal haemoglobinuria (PNH).

Outcomes/endpoints

Primary endpoints

PK/PD parameters (trough and peak) at baseline and Weeks 2, 10, 18, and 26

- PK: maximum serum concentration (Cmax), trough serum concentration (measured at end of dosing interval at steady state; Ctrough), accumulation ratio.
- PD: change in free C5 concentrations and in chicken red blood cell (cRBC) haemolytic activity over time 8.2.

Secondary endpoints

- Percentage change in LDH from baseline to Day 183 (Week 26)
- Transfusion avoidance (TA), defined as the proportion of patients who remained transfusion-free and do not require a transfusion through Day 183 (Week 26)
- Change in QoL, as measured by Paediatric Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue questionnaire (patients ≥ 5 years of age), from baseline to Day 183 (Week 26)

- Proportion of patients with stabilized haemoglobin, defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26)
- Percentage change in free haemoglobin from baseline to Day 183 (Week 26)
- Proportion of patients with breakthrough haemolysis (BTH), defined as at least one new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnoea], anaemia, major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH as follows:
  - For patients who entered the study naïve to complement inhibitor treatment, elevated LDH ≥ 2 × the upper limit of normal (ULN) after prior LDH reduction to < 1.5 × ULN on therapy.
  - For patients who entered the study stabilized on eculizumab treatment, elevated LDH ≥ 2 × ULN

Sample size

This study is descriptive in nature and not statistically powered for hypothesis testing due to the rarity of disease in paediatric patients. Approximately 13 patients were planned to be enrolled in this study to ensure at least 10 evaluable patients would complete the Primary Evaluation Period. A sample size of 10 was expected to be sufficient to adequately describe PK/PD in paediatric patients with PNH.

Randomisation

As this was an open-label, single-arm study, all enrolled patients were assigned to receive ravulizumab. The Interactive Voice/Web Response System was used to assign vials containing ravulizumab to each patient.

Blinding (masking)

This was an open label study.

Statistical methods

Analysis population

- Pharmacokinetic Analysis Set: The PK Analysis Set included all patients who received at least 1 dose of ravulizumab and who had evaluable PK data. The PK Analysis Set was used for all PK analyses.
- Pharmacodynamic Analysis Set: The PD Analysis Set included all patients who received at least 1 dose of ravulizumab and who had evaluable PD data. The PD Analysis Set was used for all PD analyses.
- Full Analysis Set (FAS): The FAS included all patients who received at least 1 dose of ravulizumab and had at least 1 efficacy assessment after the first infusion of ravulizumab. The FAS was the population used for all efficacy analyses.

- Safety Set: The Safety Set included all patients who received at least 1 dose of ravulizumab. The Safety Set was used for all safety and immunogenicity analyses.

Efficacy analyses

All analyses were performed through the end of the Primary Evaluation Period (Day 183 [Week 26]).

The efficacy analyses were performed on the Full Analysis Set (FAS), which included all patients who received at least 1 dose of ravulizumab and had at least 1 postbaseline assessment. Continuous variables were summarized using descriptive statistics, including number of observations and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables were summarized by frequency counts and percentage of patients. Analyses were conducted separately for complement inhibitor treatment-naïve and eculizumab-experienced patients.

- *Percentage change in lactate dehydrogenase from baseline to Day 183 (Week 26)*

Absolute LDH levels, and the change and percent change from baseline, were summarized at all study visits up to Day 183 (Week 26) by both observed case (OC) and last observation carried forward (LOCF). Baseline was defined as the average of all assessments analysed by the central laboratory prior to first study drug administration.

The number (%) of patients achieving LDH levels at or below 1.0 × ULN and levels at or below 1.5 × ULN were displayed. Mean (±95% confidence interval [CI]) of absolute LDH levels, and the change and percent change from baseline were plotted over time, by complement inhibitor treatment-naïve and eculizumab-experienced patients.

- *Transfusion avoidance*

Point estimates and 2-sided 95% exact CIs were computed. Patients who withdrew from the study due to lack of efficacy during the Primary Evaluation Period were to be considered as non-responders and were to be counted in the group needing transfusion. For patients who withdrew from the study for any other reason during the Primary Evaluation Period, their data up to the time of withdrawal will be used to assess TA.

A summary of the number of pRBC transfusion requirements up to Day 183 study were presented including number of transfusion episodes and units transfused.

- *Quality of life*

Change in QoL, as measured by Paediatric Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue questionnaire from baseline to Day 183 (Week 26):

  - The scoring guideline for the Paediatric FACIT-Fatigue instrument was used to calculate a FACIT-Fatigue score.
  - Absolute scores, change from baseline, and percent change from baseline in FACIT-Fatigue scores were summarized by both OC and LOCF at baseline and at the study visits where this assessment was collected up to Day 183 (Week 26).
  - At each study visit, the proportion of patients who showed an improvement of at least 3 points for the Paediatric FACIT-Fatigue scores were summarized by point estimates and 2-sided 95% exact CIs.

- *Stabilized haemoglobin*

Stabilized haemoglobin was defined as avoidance of ≥ 20 g/L decrease in haemoglobin from baseline in the absence of transfusion through Day 183. Point estimates and 2-sided 95% exact CIs were

computed. Patients who withdrew from the study due to lack of efficacy during the Primary Evaluation Period were to be considered as non-responders and were to be counted in the group who did not meet the stabilized haemoglobin definition. For patients who withdrew from the study for any other reason during the Primary Evaluation Period, their data up to the time of withdrawal were to be used to assess stabilized haemoglobin.

- *Percentage change in free haemoglobin from baseline to Day 183 (Week 26)*
  - Absolute free haemoglobin values, and the change and percent change from baseline, were summarized by both OC and LOCF at all study visits up to Day 183 (Week 26). Baseline was defined as the last non-missing assessment value prior to the first study drug infusion.
  - Mean (±95% CI) of free haemoglobin, and the change and percent change from baseline was plotted over time, by complement inhibitor treatment-naïve and eculizumab-experienced patients.
- *Breakthrough haemolysis*

Point estimates and 2-sided 95% exact CIs were computed. Patients who withdrew from the study due to lack of efficacy during the Primary Evaluation Period were to be considered as non-responders and were to be counted in the group with BTH. For patients who withdrew from the study for any other reason during the Primary Evaluation Period, their data up to the time of withdrawal were to be used to assess BTH.

The number of any treatment-emergent MAVEs (n) and number of patients with events (n, %) were displayed. Each of the MAVE categories was similarly summarized. Patients having multiple MAVEs within a category was be counted once in that category.

Results

Participant flow

Twelve patients, 4 of whom were naïve to complement inhibitor treatment and 8 of whom were eculizumab-experienced, were screened, enrolled, and treated with study drug. There were no screen failures). All 12 patients completed the Primary Evaluation Period and entered the Extension Period of the study.

Recruitment

Patients were enrolled at 9 sites in 6 countries (United States, United Kingdom, France, Netherlands, Russia, and Norway). The first patient was treated on 22 Feb 2018. The date last analysed patient completed Primary Evaluation Period was 25 Mar 2020 (12th patient's Day 183 Visit).

Conduct of the study

Protocol amendments

Since the original protocol (dated 05 Sep 2017), 2 global and 3 country-specific protocol amendments were made. These amendments are summarized in the table below.

Table 7: *Summary of Protocol Changes*

Amendment Number	Summary of Significant Changes to the Study Protocol
Amendment 1 (France) Dated: 19 Dec 2017	• Additional pregnancy assessments have been added during the Extension Period to ensure testing prior to each q8w dose, per request by the French Ethics Committee.
Amendment 2 (Global) Dated: 23 Aug 2018	• Increased loading dose for patients who are ≥5 to <10 kg in body weight based on analysis of interim PK/PD data from an ongoing aHUS pediatric study. • Allowed loading dose to be administered as 2 infusions (no more than approximately 24 hours apart) for patients who are ≥5 to <10 kg in body weight at study entry; predose PK/PD sample collected before the first infusion and EOI sample collected after the second infusion. • Allowed supplemental dose of ravulizumab upon agreement of the Alexion Medical Monitor. • Follow-up phone call 8 weeks after patient's last dose of study drug was added for monitoring of concomitant medications, procedures, and adverse events.
Amendment 2.1 (France) Dated: 13 Sep 2018	• Increased loading dose for patients who are ≥ 5 to < 10 kg in body weight based on analysis of interim PK/PD data from ongoing pediatric studies. • Allowed loading dose to be administered as 2 infusions (no more than approximately 24 hours apart) for patients who are ≥ 5 to < 10 kg in body weight at study entry; predose PK/PD sample collected before the first infusion and EOI sample collected after the second infusion. • Allowed supplemental dose of ravulizumab upon agreement of the Alexion Medical Monitor. • Follow-up phone call 8 weeks after patient's last dose was added for monitoring of concomitant medications, procedures, and adverse events.
Amendment 2.2 (Norway) Dated: 06 Jun 2019	• The term 'primary' was deleted from the overall statement on study objectives in the synopsis to maintain consistency with Section 6.1 of the Protocol. • The statement on the duration of the Extension Period was modified to specify a fixed duration of 2 years. • The SUSAR reporting procedures were clarified in Section 11.7.5.
Amendment 3 (Global) Dated: 22 Apr 2020	• Extension Period was prolonged from 2 years to 4 years and the Schedules of Assessments were revised accordingly. • Number of patients to be enrolled was increased to allow for the enrollment of patients currently identified and to comply with EMA PIP requisites. • Urine pregnancy tests were to be performed prior to each q8w study drug administration for patients who have reached menarche. • Transfusions were to be recorded at every visit. • To ensure patient safety and treatment continuity during the COVID-19 pandemic, the option for patients to receive ravulizumab administration remotely at a medical facility that was located near the patient's home or at the patient's home was added. • Timepoints for interim analyses and CSRs were clarified.

Abbreviations: aHUS = atypical hemolytic uremic syndrome; COVID-19 = coronavirus disease 2019; EMA =European Medicines Agency; EOI = end of infusion; PD = pharmacodynamics; PIP = pediatric investigation plan; PK = pharmacokinetics; q8w = every 8 weeks; SUSAR = suspected unexpected serious adverse reaction.

Changes in planned analyses

The SAP (version 2.0) was finalized on 08 May 2020, prior to database lock for the Primary Evaluation Period.

An interim analysis of data, including ravulizumab PK, free C5 levels, and safety, was planned to be conducted after 4 patients weighing ≥ 5 kg to < 40 kg had completed dosing through Day 71. The purpose of the interim analysis was to ensure that ravulizumab treatment was well tolerated and was providing adequate complement inhibition. Since only 2 patients, corresponding to the required weight range, were enrolled in the AXLN1210-PNH-304 study, the interim analysis results were taken from the interim analysis conducted and reported in Study ALXN1210-aHUS-312. Based on the interim analysis results in the ALXN1210-aHUS-312 Study, the protocol was amended (Protocol Amendment 2 dated 23 Aug 2018) to adjust the loading dose for patients in the weight range ≥ 5 to < 10 kg from 300 mg to

600 mg (or 300 mg divided in 2 infusions administered within a 24-hour window), followed by a maintenance dose of 300 mg on Day 15 and q4w thereafter

Samples from the central laboratory were considered to have undergone table-top haemolysis (TTH) if the serum potassium value was ≥ 6 mmol/L and the LDH value was ≥ 2 × ULN. Central laboratory samples that met these TTH criteria were identified, and all potassium, alanine aminotransferase (ALT), aspartate aminotransferase (AST), magnesium, phosphorous, and LDH samples affected by TTH were excluded from analysis of all efficacy and safety endpoints, with the exception that the LDH values were used for the qualification of BTH. However, the determination of TTH based on potassium level, was not available for some patients at the time of the interim CSR, and no samples were excluded for TTH from the analyses included in the CSR. Instead, a haemolytic index (HI) value is provided for LDH values that were haemolysed. According to the central laboratory, an HI value > 15 causes test interference and may result in falsely elevated LDH levels.

Protocol deviations

Any departure from the approved protocol was considered a protocol deviation. Important deviations were those that could potentially impact the rights, welfare, or safety of the patient and/or the integrity of the study data; all others were considered not important. A total of 8 patients had important protocol deviations in the Primary Evaluation Period.

Table 8: *Important Protocol Deviations (Full Analysis Set)*

Categories of Deviation	Complement Inhibitor Treatment-naïve Patients (N=4)	Eculizumab-experienced Patients (N=8)	All Patients (N=12)
Patients with important deviations, n (%)	3 (75.0)	5 (62.5)	8 (66.7)
Type of important deviations, n (%)			
Laboratory assessment	1 (25.0)	4 (50.0)	5 (41.7)
Source document	0	2 (25.0)	2 (16.7)
Visit schedule	2 (50.0)	0	2 (16.7)
Informed consent	0	1 (12.5)	1 (8.3)
Safety reporting	0	1 (12.5)	1 (8.3)
Study procedures/test	0	1 (12.5)	1 (8.3)

Note: Some patients had more than 1 important protocol deviation. Percentages were based on the total number of patients in each cohort or overall.

Five patients had important deviations related to laboratory assessments: 1 patient had the Day 1 predose PD sample mislabelled and the Day 71 PK/PD and ADA samples processed incorrectly; 1 patient had the Day 71 PD samples for free C5 and cRBC lost due to shipping issues; 1 patient did not have Day 127 PD samples for free C5 and cRBC collected; 1 patient did not have Day 183 haematology results due to clotted samples; and 1 patient did not have ADA serum samples collected at Day 183 due to insufficient amount of blood.

Two patients had important deviations related to source document due to the site failing to remind the patients at each site visit to carry their safety card with them at all times.

Important deviations to the visit schedule were reported for 2 patients due to cancellation of the Day 99 Visit as per Investigator's decision and patient's personal reasons.

One patient had 2 important deviations related to informed consent procedures where the wrong versions of the ICF, as well as the assent form, were signed.

Important protocol deviations relating to safety reporting procedures were noted for 1 patient who had delayed reporting of a single SAE.

One patient had 1 important deviation related to study procedures/tests: screening LDH was not collected within 24 hours of last eculizumab dose.

Baseline data

Demographic characteristics

Eight of the 12 patients were female, and the mean age at the time of first study drug infusion was 14.4 years. Two patients were under 12 years of age at the time of first study drug infusion: Patient in the complement inhibitor treatment-naïve cohort was 11 years old and Patient in the eculizumab-experienced cohort was 9 years old; all others were 12 to 17 years of age at the time of first study drug infusion.

Table 9: *Demographics and Baseline Characteristics (Full Analysis Set)*

Variable	Treatment Naïve (N = 5) n (%)	Eculizumab Experienced (N = 8) n (%)	Total (N = 13) n (%)
Sex, n (%)			
Male	4 (80.0)	1 (12.5)	5 (38.5)
Female	1 (20.0)	7 (87.5)	8 (61.5)
Ethnicity, n (%)			
Not Hispanic or Latino	5 (100)	6 (75.0)	11 (84.6)
Not Reported	0 (0.0)	2 (25.0)	2 (15.4)
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)
Missing/Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Race, n (%)			
White	5 (100)	3 (37.5)	8 (61.5)
Black or African American	0 (0.0)	2 (25.0)	2 (15.4)
Not Reported	0 (0.0)	2 (25.0)	2 (15.4)
Other	0 (0.0)	1 (12.5)	1 (7.7)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Age at First Infusion (years)			
Mean (SD)	14.4 (2.19)	14.4 (3.07)	14.4 (2.66)
Median	15.0	15.0	15.0
Min, Max	11, 17	9, 17	9, 17
Age at First Infusion (years) Category, n (%)			
< 12 years	1 (20.0)	1 (12.5)	2 (15.4)
≥ 12 years	4 (80.0)	7 (87.5)	11 (84.6)
Baseline Weight (kg)			
Mean (SD)	56.26 (11.594)	56.25 (12.247)	56.25 (11.502)
Median	55.60	55.50	55.60
Min, Max	39.5, 72.0	36.7, 69.0	36.7, 72.0
Baseline Weight (kg) Category, n (%)			
≥ 5 to < 10 kg	0 (0.0)	0 (0.0)	0 (0.0)
≥ 10 to < 20 kg	0 (0.0)	0 (0.0)	0 (0.0)
≥ 20 to < 30 kg	0 (0.0)	0 (0.0)	0 (0.0)
≥ 30 to < 40 kg	1 (20.0)	1 (12.5)	2 (15.4)
≥ 40 to < 60 kg	3 (60.0)	4 (50.0)	7 (53.8)
≥ 60 to < 100 kg	1 (20.0)	3 (37.5)	4 (30.8)
≥ 100 kg	0 (0.0)	0 (0.0)	0 (0.0)
Baseline Height (cm)			
Mean (SD)	163.40 (11.760)	160.99 (9.369)	161.92 (9.940)
Median	168.00	158.95	164.00
Min, Max	143.0, 171.0	146.0, 176.2	143.0, 176.2
Baseline Body Mass Index (BMI) (kg/m^2)			

Variable	Treatment Naïve (N = 5) n (%)	Eculizumab Experienced (N = 8) n (%)	Total (N = 13) n (%)
Sex, n (%)			
Male	4 (80.0)	1 (12.5)	5 (38.5)
Female	1 (20.0)	7 (87.5)	8 (61.5)
Ethnicity, n (%)			
Not Hispanic or Latino	5 (100)	6 (75.0)	11 (84.6)
Not Reported	0 (0.0)	2 (25.0)	2 (15.4)
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)
Missing/Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Race, n (%)			
White	5 (100)	3 (37.5)	8 (61.5)
Black or African American	0 (0.0)	2 (25.0)	2 (15.4)
Not Reported	0 (0.0)	2 (25.0)	2 (15.4)
Other	0 (0.0)	1 (12.5)	1 (7.7)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Age at First Infusion (years)			
Mean (SD)	14.4 (2.19)	14.4 (3.07)	14.4 (2.66)
Median	15.0	15.0	15.0
Min, Max	11, 17	9, 17	9, 17
Age at First Infusion (years) Category, n (%)			
< 12 years	1 (20.0)	1 (12.5)	2 (15.4)
≥ 12 years	4 (80.0)	7 (87.5)	11 (84.6)
Baseline Weight (kg)			
Mean (SD)	56.26 (11.594)	56.25 (12.247)	56.25 (11.502)
Median	55.60	55.50	55.60
Min, Max	39.5, 72.0	36.7, 69.0	36.7, 72.0
Baseline Weight (kg) Category, n (%)			
≥ 5 to < 10 kg	0 (0.0)	0 (0.0)	0 (0.0)
≥ 10 to < 20 kg	0 (0.0)	0 (0.0)	0 (0.0)
≥ 20 to < 30 kg	0 (0.0)	0 (0.0)	0 (0.0)
≥ 30 to < 40 kg	1 (20.0)	1 (12.5)	2 (15.4)
≥ 40 to < 60 kg	3 (60.0)	4 (50.0)	7 (53.8)
≥ 60 to < 100 kg	1 (20.0)	3 (37.5)	4 (30.8)
≥ 100 kg	0 (0.0)	0 (0.0)	0 (0.0)
Mean (SD)	20.92 (2.657)	21.45 (2.756)	21.25 (2.618)
Median	20.20	21.60	20.70
Min, Max	18.9, 25.5	17.2, 24.8	17.2, 25.5

Note: Percentages are based on the total number of patients in each group, or overall.
Abbreviation: SD = standard deviation

Disease history and characteristics

Mean age at PNH diagnosis was 13.8 years for the complement inhibitor treatment-naïve cohort and 12.3 years for the eculizumab-experienced cohort. All patients had PNH diagnosis confirmed by flow cytometry at Screening to quantify the percentage of PNH cells (clone size) in the peripheral blood. The mean total PNH granulocyte clone size was 68.10% in the complement inhibitor treatment-naïve cohort and 82.91% in the eculizumab-experienced cohort.

Table 10: *Disease Characteristics (Full Analysis Set)*

Variable Category	**Treatment Naïve (N = 5) n (%)**	**Eculizumab Experienced (N = 8) n (%)**
Age (years) at PNH Diagnosis		
Mean (SD)	13.8 (2.39)	12.3 (3.11)
Median	14.0	12.5
Min, Max	11, 17	7, 16
Method of Initial PNH Diagnosis, n (%)		
Flow Cytometry	5 (100)	7 (87.5)
Ham's Test	0 (0.0)	0 (0.0)
Sucrose Hemolysis Test	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (12.5)
Years from Diagnosis to Informed Consent		
Mean (SD)	0.74 (1.433)	2.01 (0.999)
Median	0.10	1.65
Min, Max	0.0, 3.3	1.1, 3.8
PNH Clone Size at Baseline PNH RBC Type II Clone Size (%)		
n	4	6
Mean (SD)	18.65 (19.467)	10.57 (16.408)
Median	16.25	3.05
Min, Max	0.7, 41.4	0.6, 42.6
PNH RBC Type III Clone Size (%)		
Mean (SD)	19.18 (12.922)	54.51 (22.192)
Median	15.40	62.40
Min, Max	6.2, 39.9	20.6, 80.8
Total PNH RBC Clone Size (%)		
n	4	6
Mean (SD)	38.78 (31.512)	65.65 (22.714)
Median	40.05	71.15
Min, Max	6.9, 68.1	21.2, 85.4
Total PNH Granulocyte Clone Size (%)		
Mean (SD)	68.10 (26.391)	82.91 (26.043)
Median	78.30	91.60
Min, Max	36.8, 99.0	20.3, 97.6
Total PNH Monocyte Clone Size (%)		
Mean (SD)	75.18 (24.012)	91.94 (5.457)
Median	79.90	93.60
Min, Max	34.9, 98.9	81.3, 97.7

Notes: Percentages are based on the total number of patients in each group.

Total RBC, Granulocyte, Monocyte Clone Size = Sum Type II and Type III RBC, Granulocyte, Monocyte clone size, respectively.
Baseline is defined as the last non-missing value prior to first dose of ALXN1210.
Abbreviations: PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; SD = standard deviation

During the 12 months prior to first dose of ravulizumab, 2 patients in the complement inhibitor treatment-naïve cohort and 2 patients in the eculizumab-experienced cohort had received at least 1 pRBC transfusion with a total of 10 and 2 transfusions, respectively.

Table 11: *Packed Red Blood Cell/Whole Blood Transfusions Within 12 Months Prior to First Dose (Full Analysis Set)*

Variable Category	**Treatment Naïve (N = 5) n (%)**	**Eculizumab Experienced (N = 8) n (%)**
Number of Patients with pRBC/Whole Blood Transfusions Within 12 Months Prior to First Dose, n (%)	2 (40.0)	2 (25.0)
pRBC/Whole Blood Transfusions Within 12 Months Prior to First Dose		
Total	10	2
Mean (SD)	5.0 (1.41)	1.0 (0.00)
Median	5.0	1.0
Min, Max	4, 6	1, 1
Units of pRBC/Whole Blood Transfused Within 12 Months Prior to First Dose		
Total	14	2
Mean (SD)	7.0 (5.66)	2.0
Median	7.0	2.0
Min, Max	3, 11	2, 2

Notes: Percentages are based on the total number of patients in each group.
Abbreviations: pRBC = packed red blood cell; SD = standard deviation

Twelve of the 13 patients had at least 1 PNH-associated sign or symptom at any time prior to informed consent. PNH-associated signs or symptoms reported by more than 1 patient included fatigue or asthenia (generalized weakness); abdominal pain; red or dark urine; CNS-related symptoms such as headache, dizziness, or difficulty concentrating; jaundice (yellowing of skin or eyes); back or flank pain; and chest pain.

All 13 patients had at least 1 PNH-associated condition diagnosed at any time prior to informed consent.

Table 12: *PNH Medical History: PNH-Associated Conditions Diagnosed at Any Time Prior to Informed Consent (Full Analysis Set)*

PNH-associated Conditions, n (%)	**Treatment Naïve (N = 5) n (%)**	**Eculizumab Experienced (N = 8) n (%)**	**Total (N = 13) n (%)**
Patients with any PNH Conditions Prior to Informed Consent	5 (100)	8 (100)	13 (100)
Anemia	2 (40.0)	5 (62.5)	7 (53.8)
Hematuria or Hemoglobinuria	2 (40.0)	5 (62.5)	7 (53.8)

PNH-associated Conditions, n (%)	Treatment Naïve (N = 5) n (%)	Eculizumab Experienced (N = 8) n (%)	Total (N = 13) n (%)
Aplastic Anemia	3 (60.0)	1 (12.5)	4 (30.8)
Renal Failure	2 (40.0)	2 (25.0)	4 (30.8)
Other	0 (0.0)	1 (12.5)	1 (7.7)

Notes: Percentages are based on the total number of patients in each group, or overall.
Patients can be counted in more than one category.
Coded using MedDRA Version 24.0.
Abbreviation: PNH = paroxysmal nocturnal hemoglobinuria

Prior medications and treatments

All 13 patients had a history of prior medication use. The most commonly reported (≥ 2 patients) groups of prior medications included bacterial vaccines (13/13); immunosuppressants (11/13); vitamin B12 and folic acid (7/13); bacterial and viral vaccines, combined (6/13); beta-lactam antibacterials, penicillins (5/13); other analgesics and antipyretics; and other vitamin products, combinations (3/13, each); and corticosteroids for systemic use, plain; other vitamin products, combinations; antiseptics and disinfectants; antithrombotic agents; bile therapy; opioids; quinolone antibacterials; and vitamin K and other haemostatics (2/13 each).

Concomitant medications and treatments

All 13 patients took at least 1 concomitant medication. The most commonly reported (≥ 3 patients) groups of concomitant medications were other analgesics and antipyretics; vitamin B12 and folic acid (9/13); beta-lactam antibacterials, penicillins (8/13);other beta-lactam antibacterials(7/13 each); anaesthetics, local; anti-inflammatory and antirheumatic products, non-sterioids; immunosuppressants; opioids; quinolone antibacterials; antipruritics (4/13); anaesthetics, general; antihistamines for systemic use; drugs for peptic ulcer and gastro-oesophageal reflux disease; opioids (3/13 each).

Numbers analysed

All 12 patients initially treated with ravulizumab were included in all of the analysis sets: FAS, Safety Set, PK Analysis Set, and PD Analysis Set. Data from a 13th patient (ongoing in the Primary Evaluation Period as of the cut-off date) was provided during the procedure and was not included in the initial analysis.

Outcomes and estimation

Secondary endpoints

- **Percent change in lactate dehydrogenase**

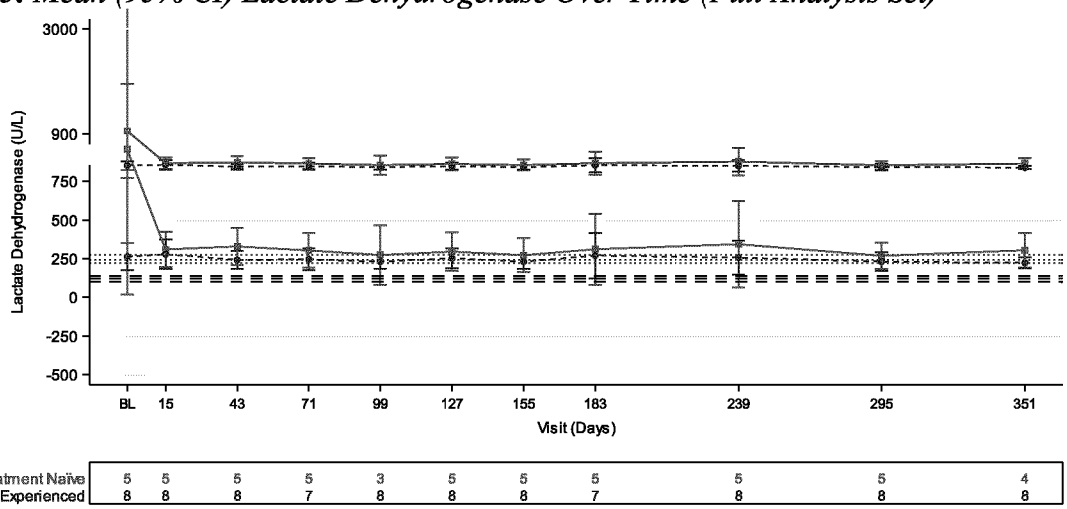
In the complement inhibitor treatment-naïve cohort, the mean LDH at baseline was 957.00 U/L, and all 5 patients had LDH > 1.5 × ULN. By Day 15, the mean LDH had lowered by 55.52% to 309.60 U/L, which was generally sustained throughout the Primary Evaluation Period.

On Day 183, the mean (SD) percent reduction from baseline in LDH was -47.91 % (52.716 %). Two patients had LDH ≤ 1 × ULN and a third had ≤ 1.5 × ULN. The fourth patient had an LDH value of 637 U/L on Day 183, which may be attributable to TTH of the sample, as the laboratory reported an HI of

195. No AE, SAE, or signs or symptoms of PNH were associated with the increase in LDH. Note that on Day 99, data from 2 of the 4 patients were missing.

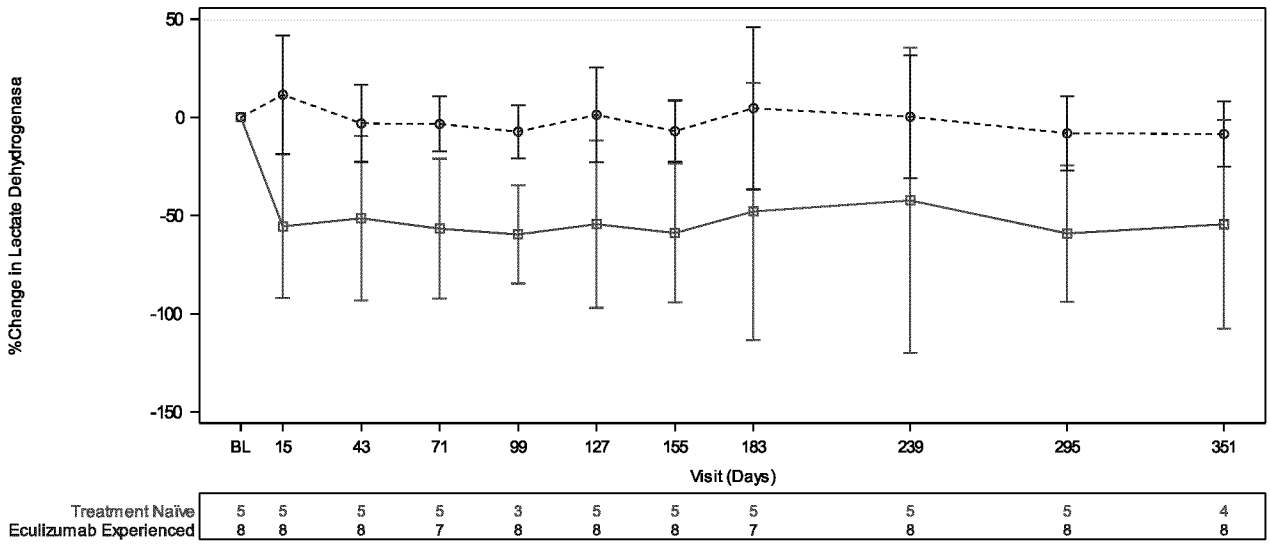
In the eculizumab-experienced cohort, the mean LDH at baseline was 262.75 U/L. Mean LDH values were generally stable throughout the Primary Evaluation Period, with percent change from baseline ranging between -7.27% and +11.5%. At Day 183, the mean (SD) percent change from baseline in LDH was +4.65% (44.702%), and 4 patients had LDH ≤ 1 × ULN; 2 patients had LDH ≤ 1.5 × ULN; 1 patient had the Day 183 sample missing but had LDH ≤ 1.5 × ULN at all other timepoints; 1 patient had LDH of 611 U/L [HI = 236] on Day 183, that may have been attributed to TTH, but had at least ≤ 1.5 × ULN on all other timepoints. No AE, SAE, or signs or symptoms of PNH were reported in connection with the increase of LDH in this patient.

Figure 5: *Mean (95% CI) Lactate Dehydrogenase Over Time (Full Analysis Set)*



Notes: Baseline for LDH is defined as the average of all available values prior to first ALXN1210 infusion.
Multiple LDH normal ranges are present depending on pediatric age and gender group: 100-220, 100-242, 100-275, 120-290, and 140-280 U/L.
Dashed horizontal lines indicate lower normal value. Dotted horizontal lines indicate upper normal value.
Abbreviations: BL = baseline; CI = confidence interval; LDH = lactate dehydrogenase

Figure 6: *Mean (95% CI) Percentage Change From Baseline in Lactate Dehydrogenase Over Time (Full Analysis Set)*

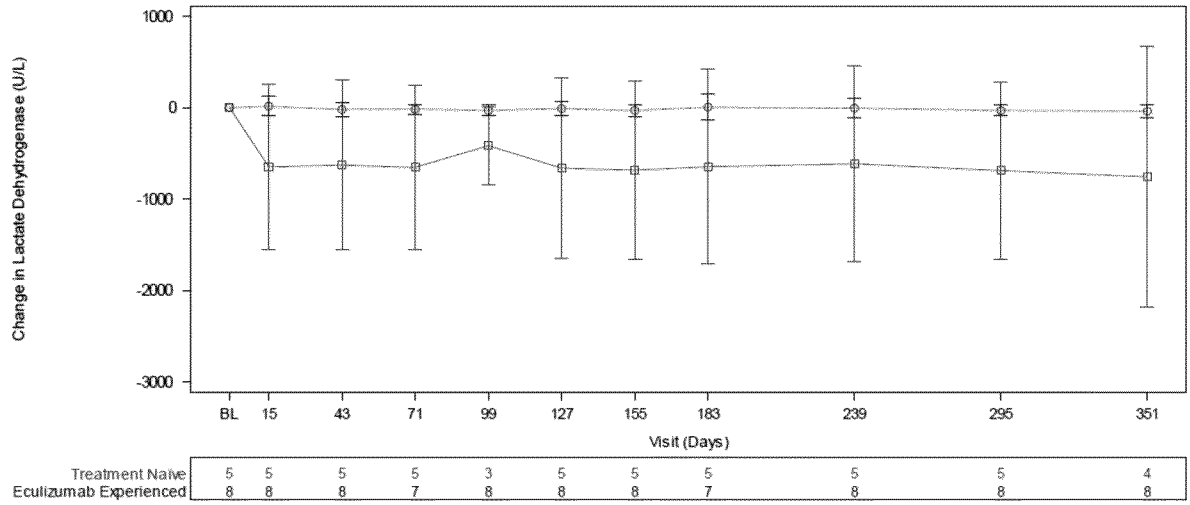


Notes: Baseline for LDH is defined as the average of all available values prior to first ALXN1210 infusion.
Abbreviations: BL = baseline; CI = confidence interval; LDH = lactate dehydrogenase

On Day 351, the mean (SD) percent reduction from baseline in LDH was -54.46% (33.456%) in the complement inhibitor treatment-naïve cohort and -8.48% (19.834%) in the eculizumab-experienced cohort.

In 4 out of 5 complement inhibitor treatment-naïve patients who had LDH > 1.5 × ULN at baseline, LDH improved by 52-weeks of treatment and remained ≤ 1.5 × ULN. Day 351 LDH value was not available for 1 patient because of insufficient sample. However, all other LDH values up to Day 295 for this patient were within normal range. All 8 patients in the eculizumab-experienced cohort maintained LDH ≤ 1.5 × ULN after 52 weeks of ravulizumab treatment.

Figure 7. *Mean (95% CI) change from baseline in LDH over time-Full Analysis Set*



Notes: Baseline for LDH is defined as the average of all available values prior to first ALXN1210 infusion.
Abbreviations: BL = baseline; CI = confidence interval; LDH = lactate dehydrogenase

- **Transfusion avoidance**

During the Primary Evaluation Period, 3 of the 5 complement inhibitor treatment-naïve patients and all 8 eculizumab-experienced patients remained transfusion free.

Patient received 3 blood transfusions, each 1 unit of pRBCs, on Days 44, 46, and 58; these transfusions were given during treatment for multiple SAEs including device-related thrombosis and septic shock. Patient had a transfusion of 2 units of pRBCs on Day 1.

Table 13: *Number (%) of Patients Achieving Transfusion Avoidance Through Day 183 (Week 26), (Full Analysis Set)*

Variable	**Treatment Naïve (N = 5) n (%)**	**Eculizumab Experienced (N = 8) n (%)**
Achieving pRBC/Whole Blood Transfusion Avoidance After First Dose of ALXN1210 Through Day 183		
Number of Patients (n)	3	8
Percentage (%)	60.0	100.0
95% Exact CI	(14.66, 94.73)	(63.06, 100.00)

Notes: Transfusion avoidance is defined as patients who remain transfusion free and do not require a transfusion through Day 183 (Week 26).
Patients who withdraw from the study during primary evaluation period due to lack of efficacy will be considered as non-responders and will be counted in the group requiring transfusions.
Percentages are based on the total number of patients in each group.
Exact unconditional approach was used for calculating the CIs.
Abbreviations: CI = confidence interval; pRBC = packed red blood cells

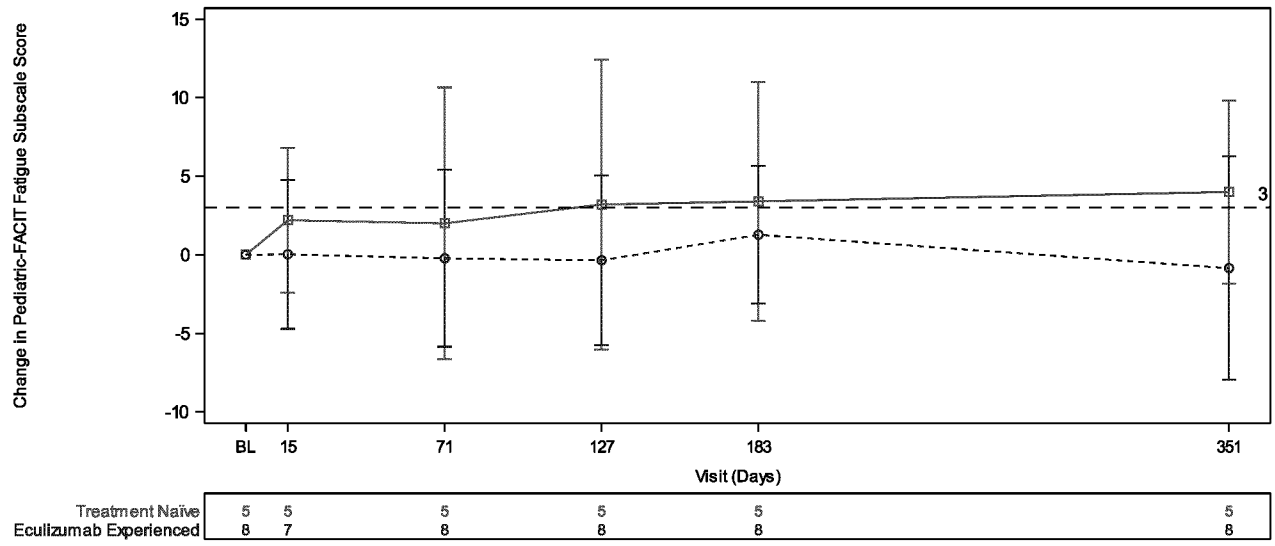
All 5 complement inhibitor treatment-naïve patients and 7 of the 8 eculizumab-experienced patients remained transfusion free during the Extension Period through the data cut-off date; the only eculizumab-experienced patient considered as non-responder withdrew from the study on D341 to receive a bone marrow transplant. Nevertheless the patient remained transfusion free until withdrawal.

- **Quality of life**

Quality of life was assessed using the Paediatric FACIT-Fatigue Questionnaire. The Paediatric FACIT-Fatigue Scale is a 13-item questionnaire that assesses fatigue and its impact upon daily activities and function over the preceding 7 days. Each item is scored on a 5-point scale, and total scores range from 0 to 52, with higher score indicating better QoL. The questionnaire was self-reported by patients who were ≥ 8 years of age at the time of enrollment and reported by caregivers for patients who were > 5 to < 8 years of age at the time of enrollment. Patients < 5 years of age were not to be assessed.

On Day 183, the complement inhibitor treatment-naïve cohort had a mean (SD) improvement in Paediatric FACIT-fatigue score of 3.00 (6.976) compared to baseline, and the eculizumab-experienced cohort had a mean (SD) improvement of 1.28 (5.235) compared to baseline.

Figure 8: *Mean (95% CI) Change from Baseline in Paediatric FACIT-Fatigue Over Time (Full Analysis Set)*



Notes: FACIT score ranges from 0-52, with a higher score indicating less fatigue.
Baseline is defined as the last non-missing assessment value prior to first ALXN1210 infusion.
Dashed horizontal line indicates threshold that delineates clinically meaningful improvement (> 3 points).
Abbreviations: BL = baseline; CI = confidence interval; 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 at Day 15 in 2 (40%) patients in the complement inhibitor treatment-naïve cohort, which was sustained through Day 183.

Through 52-weeks, the complement inhibitor treatment-naïve cohort had a mean (SD) improvement in Paediatric FACIT fatigue score of 4.00 (4.690) compared to baseline, and the eculizumab-experienced cohort had a mean (SD) change of -0.85 (8.509) compared to baseline.

Table 14. *Number (%) of patients who showed an improvement of at least 3 points in Paediatric FACIT-Fatigue Score - Full Analysis Set*

Visit Statistics	**Treatment Naïve (N = 5) n (%)**	**Eculizumab Experienced (N = 8) n (%)**
Day 15		
Number of Patients (n)	2	3
Percentage (%)	40.0	42.9
95% Exact CI	(5.27, 85.34)	(9.90, 81.59)
Day 71		
Number of Patients (n)	3	1
Percentage (%)	60.0	12.5
95% Exact CI	(14.66, 94.73)	(0.32, 52.65)
Day 127		
Number of Patients (n)	3	2
Percentage (%)	60.0	25.0
95% Exact CI	(14.66, 94.73)	(3.19, 65.09)
Day 183		
Number of Patients (n)	3	2
Percentage (%)	60.0	25.0
95% Exact CI	(14.66, 94.73)	(3.19, 65.09)
Day 351		
Number of Patients (n)	4	2
Percentage (%)	80.0	25.0
95% Exact CI	(28.36, 99.49)	(3.19, 65.09)

Notes: Percentages are based on the total number of patients in each group at a visit.
Exact unconditional approach was used for calculating the CIs.
Abbreviations: CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy

- **Stabilized haemoglobin**

Haemoglobin stabilization, defined as avoidance of a 2 g/dL (or greater) decrease in haemoglobin level from baseline in the absence of transfusion through Day 183, was achieved by 3 of 5 complement inhibitor treatment-naïve patients and 6 of 8 eculizumab-experienced patients.

Table 15: *Number (%) of patients with stabilized haemoglobin through Day 183 (Week 26) (Full Analysis Set)*

Variable	**Treatment Naïve (N = 5) n (%)**	**Eculizumab Experienced (N = 8) n (%)**
Achieved Stabilized Hemoglobin Through Day 183 (Week 26)		
Number of Patients (n)	3	6
Percentage (%)	60.0	75.0
95% Exact CI	(14.66, 94.73)	(34.91, 96.81)

Notes: Stabilized hemoglobin is defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26).
Percentages are based on the total number of patients in each group.
Abbreviation: CI = confidence interval

All 5 complement inhibitor treatment-naïve patients and 7 of the 8 eculizumab-experienced patients achieved haemoglobin stabilization during the Extension Period through the data cut-off date. The only eculizumab-experienced patient considered as non-responder during the Extension Period i withdrew from the study on D341 to receive a bone marrow transplant; the patient achieved haemoglobin stabilization until withdrawal.

- **Percent change in free haemoglobin**

In the complement inhibitor treatment-naïve cohort, the mean (SD) free haemoglobin at baseline was 23.75 (15.923) mg/dL. Decreases from baseline in mean free haemoglobin levels were seen at Days 15, 43, 71, 99, 127, and 155, but on Day 183, free haemoglobin increased to 30.23 mg/dL (108.74% change from baseline) due to values above 450 mg/dL for 2 patients. These data are based on the first 12 patients enrolled in the study. No updated data were provided.

In the eculizumab-experienced cohort, the mean (SD) free haemoglobin at baseline was 20.35 (14.775) mg/dL. Mean free haemoglobin levels were generally stable over time, with a value of 14.30 mg/dL at Day 183 (-15.29% change from baseline).

- **Breakthrough haemolysis**

Breakthrough haemolysis is defined as at least 1 new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnoea], anaemia, MAVE, including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH as follows:

- For patients who entered the study naïve to complement inhibitor treatment, elevated LDH ≥ 2 × the ULN after prior LDH reduction to < 1.5 × ULN on therapy.
- For patients who entered the study stabilized on eculizumab treatment, elevated LDH ≥ 2 × ULN.

There were no events of BTH during the Primary Evaluation Period.

During the Extension Period through the data cut-off date, one eculizumab-experienced patient had BTH on Day 666.

LDH normalisation (*post-hoc* analysis)

A post-hoc analysis for LDH normalization (defined as the proportion of patients who achieved LDH levels ≤ 1 × upper limit of normal [ULN]) was performed on the Full Analysis Set. Results are presented below. Multiple LDH normal ranges were used in the analysis based on patient's paediatric age and gender group, as detailed in Table ***16*** below.

On Day 1, none of the patients in the complement inhibitor treatment-naïve cohort and 3 of 8 patients in the eculizumab-experienced cohort had LDH levels ≤ 1 × ULN. At the end of the Primary Evaluation Period (Day 183), LDH normalization was achieved by 3 of 5 complement inhibitor treatment-naïve patients. In the eculizumab-experienced cohort, 4 of 8 eculizumab-experienced patients had normalized LDH; 1 patient achieved LDH normalization in addition to the 3 patients with LDH levels ≤ 1 × ULN on Day 1.

Table 16: *Normal ranges for LDH in specific patients from Study ALXN1210-PNH-304*

LDH normal range (U/L)	Age range (years)	Sex	Patient ID
180-430	0-2	M/F	N/A
155-345	3-6	M	N/A
135-395	3-6	F	N/A
145-325	7-12	M	N/A
140-280	7-12	F	[redacted]
120-290	13-15	M	
100-275	13-15	F	
100-242	>16	M	
100-220	>16	F	

[a] Patient 0199-502 normal range was 140-280 U/L from screening to D183, and 100-275 U/L from D239 until D351
[b] Patient 1003-502 normal range was 120-290 U/L from screening to D239, and 100-242 U/L from D295 until D351

Table 17: *Number (%) of Patients Achieving LDH Normalization by Visit (Full Analysis Set)*

Visit	Treatment Naïve (N = 5) n (%)	Eculizumab Experienced (N = 8) n (%)
Day 1, n (%)	0 (0.0)	3 (37.5)
Day 15, n (%)	2 (40.0)	3 (37.5)
Day 43, n (%)	2 (40.0)	4 (50.0)
Day 71, n (%)	1 (20.0)	4 (50.0)
Day 99, n (%)	1 (20.0)	5 (62.5)
Day 127, n (%)	2 (40.0)	4 (50.0)
Day 155, n (%)	2 (40.0)	4 (50.0)
Day 183, n (%)	3 (60.0)	4 (50.0)

Notes: Stabilized hemoglobin is defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26).
Percentages are based on the total number of patients in each group.
Abbreviation: CI = confidence interval

Summary of efficacy results

Table 18. *Summary of efficacy results in paediatric patients with PNH in Study ALXN1210-PNH-304 through Primary Evaluation Period (Full Analysis Set)*

Key Efficacy Endpoints	Complement Inhibitor Treatment-naïve Patients (N = 5)	Eculizumab-experienced Patients (N = 8)
LDH% change from baseline to end of Primary Evaluation Period[a], Mean (SD)	-47.91 (52.716)	4.65 (44.702)
Transfusion avoidance[b]		
n	3	8
Percentage of patients (%)	60.0	100.0
FACIT-Fatigue, change from baseline to end of Primary Evaluation Period[a]		
Mean (SD)	3.40 (6.107)	1.28 (5.235)
Achieved haemoglobin stabilization[c]		
n	3	6
Percentage of patients (%)	60.0	75.0

[a] End of Primary Evaluation Period was defined as Day 183 for Study ALXN1210-PNH-304.
[b]Transfusion avoidance was defined as patients who remained transfusion free and did not require a transfusion through Day 183 (Week 26). Percentages were based on the total number of patients in each cohort.
[c] Stabilized haemoglobin was defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26). Percentages were based on the total number of patients in each cohort.
Abbreviations: FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; LDH = lactate dehydrogenase; min = minimum; max = maximum; PNH = paroxysmal nocturnal haemoglobinuria

Table 19: *Efficacy response in adolescents with PNH in study ALXN1210-PNH-304 through Primary Evaluation Period, Full Analysis Set*

	LDH (U/L)		TA	FACIT-Fatigue		Achieved Hemoglobin Stabilization (Y/N)
Patient ID	Baseline	Week 26	(Y/N)	Baseline	Week 26	
Cohort: Complement inhibitor treatment-naïve						
ALXN1210-PNH-304[redacted]	543.3	195[a]	N	40	51	N
ALXN1210-PNH-304[redacted]	588.5	257[a]	Y	47	47	Y
ALXN1210-PNH-304[redacted]	2269.7	195[a]	N	51	46	N
Cohort: Eculizumab-experienced						
ALXN1210-PNH-304[redacted]	250	Missing	Y	36.8	39	Y
ALXN1210-PNH-304[redacted]	230.5	221	Y	50	51	Y
ALXN1210-PNH-304[redacted]	275	235	Y	46	42	Y
ALXN1210-PNH-304[redacted]	487	286	Y	42	40	Y
ALXN1210-PNH-304[redacted]	304.5	611[a]	Y	31	43	N
ALXN1210-PNH-304[redacted]	161.5	154	Y	42	39	Y
ALXN1210-PNH-304[redacted]	140.5	145	Y	28	33	Y

[a] Sample hemolyzed without any associated signs and symptoms.
Abbreviations: FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; ID = Identity; LDH =lactate dehydrogenase; N = no; NA = not applicable, PNH = paroxysmal nocturnal hemoglobinuria; TA = transfusion avoidance; Y = yes

Table 20: *Efficacy response in children with PNH in study ALXN1210-PNH-304 through Primary Evaluation Period, Full Analysis Set*

Patient ID	LDH (U/L)		TA (Y/N)	FACIT-Fatigue		Achieved Hemoglobin Stabilization (Y/N)
	Baseline	Week 26		Baseline	Week 26	
Cohort: Complement inhibitor treatment-naïve						
ALXN1210-PNH-[redacted]	444	637[a]	Y	38	44	Y
Cohort: Eculizumab-experienced						
ALXN1210-PNH[redacted]	253	236	Y	50	49	N

[a] Sample hemolyzed without any associated signs and symptoms.

Abbreviations: FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; ID = Identity, LDH =lactate dehydrogenase; N = no; NA = not applicable; PNH = paroxysmal nocturnal hemoglobinuria; TA = transfusion avoidance; Y = yes

Ancillary analyses

N/A

Summary of main study

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 1. Summary of Efficacy for trial ALXN1210-PNH-304

Title: A phase 3, open-label study of ALXN1210 in children and adolescents with paroxysmal nocturnal haemoglobinuria (PNH)			
Study identifier	Protocol No: ALXN1210-PNH-304 EudraCT Number: 2017-002820-26r		
Design	Ongoing Phase 3, open-label, single-arm multicentre study to evaluate the PK/PD, safety, and efficacy of ravulizumab administered by intravenous (IV) infusion to paediatric patients (< 18 years of age) with PNH. The study consists of a *4-week Screening Period*, a *26-week Primary Evaluation Period*, and an *Extension Period of up to 4 years*.		
	Duration of main phase:		Date first patient treated: 22 Feb 2018 Date last analysed patient completed Primary Evaluation Period: 25 Mar 2020 (12th patient's Day 183 Visit)* *Updated data including 13th patient were provided based on a data cut-off of 4 May 2021 and are presented below
Hypothesis	N/A		
Treatments groups	Ravulizumab (10mg/mL solution) IV infusion. n=13		Loading dose on Day 1 and maintenance Doses on Day 15 and q8w thereafter for patients weighing ≥ 20 kg, or q4w for patients weighing < 20 kg. Posology based on patient's body weight.
	Complement Inhibitor Treatment-naïve Patients		n = 5
	Eculizumab-experienced Patients		n = 8
Endpoints and definitions	Efficacy endpoint	%LDH change	Percentage change in LDH from baseline to Day 183 (Week 26)
	Efficacy endpoint	Transfusion avoidance	Proportion of patients who remained transfusion-free and do not require a transfusion through Day 183 (Week 26)
	Efficacy endpoint	QoL	Change in quality of life, as measured by Paediatric FACIT-Fatigue questionnaire (patients ≥ 5 years of age), from baseline to Day 183 (Week 26)
	Efficacy endpoint	Hb stabilization	Proportion of patients with stabilized haemoglobin, defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26)
Database lock	27 May 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Complement inhibitor naïve	Eculizumab experienced
	Number of subject	n=5	n=8

	LDH% change (Mean)	-47.91	4.65
	(SD)	(52.716)	(44.702)
	Transf avoidance (n)	3	8
	(%)	60	100
	QoL – FACITT (mean)	3.40	1.28
	(SD)	(6.107)	(5.235)
	Achieved Hb stabiliz (n)	3	6
	(%)	60.0	75.0
Notes	End of Primary Evaluation Period was defined as Day 183 for Study ALXN1210-PNH-304. Transfusion avoidance was defined as patients who remained transfusion free and did not require a transfusion through Day 183 (Week 26). Percentages were based on the total number of patients in each cohort. Stabilized haemoglobin was defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26). Percentages were based on the total number of patients in each cohort. ***Abbreviations:*** FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; LDH = lactate dehydrogenase; min = minimum; max = maximum; PNH = paroxysmal nocturnal haemoglobinuria		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

Not applicable

Supportive studies

To supplement efficacy data generated in Study ALXN1210-PNH-304, the MAH has conducted an extrapolation exercise to bridge data from the Primary Evaluation Period of the Study ALXN1210-PNH-304 compared with the data from adult and/or paediatric patients treated in ongoing studies of ravulizumab (PNH and aHUS) and with data from adults and paediatric patients from eculizumab studies.

Ravulizumab efficacy in adult patients with PNH

A summary of the efficacy results for the Phase 1b, Phase 2 and Phase 3 studies in adult patients with PNH are provided below.

Table 21: *Overview of Population Characteristics and Efficacy Results for Phase 1b/2 and Phase 3 Ravulizumab Studies in Adult Patients With PNH*

	Complement Inhibitor Treatment-naïve Patients			Eculizumab-experienced Patients
Study	**ALXN1210-PNH-103 (N = 13)**	**ALXN1210-PNH-201 (N = 26)**	**ALXN1210-PNH-301 (N = 125)**	**ALXN1210-PNH-302 (N = 97)**
Population Characteristics				
Sex, n (%)				
Male	6 (46.2)	20 (76.9)	65 (52.0)	50 (51.5)
Female	7 (53.8)	6 (23.1)	60 (48.0)	47 (48.5)
Race, n (%)				
Asian	12 (92.3)	7 (26.9)	72 (57.6)	23 (23.7)
White	1 (7.7)	15 (57.7)	43 (34.4)	50 (51.5)
Black or African American	0	0	2 (1.6)	5 (5.2)
American Indian or Alaska Native	0	0	1 (0.8)	0
Other	0	1 (3.8)	4 (3.2)	2 (2.1)
Not reported	0	3 (11.5)	3 (2.4)	13 (13.4)
Unknown	0	0	0	3 (3.1)
Body weight (kg) category, n (%)	NA	NA		
≥ 40 to < 60			41 (32.8)	27 (27.8)
≥ 60 to < 100			79 (63.2)	62 (63.9)
≥ 100			5 (4.0)	8 (8.2)
Body weight (kg) mean (SD)	67.7 (10.51)	77.8 (14.62)	68.2 (15.58)	72.4 (16.84)
Baseline LDH (U/L)				
Mean (SD)	1614.52	1668.90	1633.53 (778.752)	228.01 (48.712)
Median			1513.50	224.00
Min, max			378.0, 3759.5	135.00, 383.5
Number of patients with pRBC/whole blood transfusions within 12 months prior to first dose, n (%)	5 (38.5)	7 (26.9)	103 (82.4)	13 (13.4)
Efficacy results				
LDH % change from baseline to end of Primary Evaluation Period[a],				
n	13	26	124	95
Mean (SD)	–85.297 (3.4289)	–81.23 (9.422)	-77.90 (17.395)	-0.81 (13.845)
Transfusion avoidance[b]				
n (%)	NA	NA	92 (73.6)	85 (87.6)
FACIT-Fatigue, change from baseline to end of Primary Evaluation Period[a]				
n	13	23	125	96
Mean (SD)	10.4 (11.11)	10.6 (11.22)	7.48 (10.709)	1.59 (6.433)
Achieved hemoglobin stabilization				
n (%)	NA	NA	85 (68.0)	74 (76.3)

[a] End of Primary Evaluation Period was defined as Day 169 for Study ALXN1210-PNH-103, Day 253 (Cohorts 1 through 3) or Day 281 (Cohort 4) for Study ALXN1210-PNH-201, and Day 183 for Studies ALXN1210-PNH-301 and ALXN1210-PNH-302.

Efficacy data from eculizumab studies in adult and paediatric patients with PNH

Table 22: *Overview of Population Characteristics and Efficacy Results for Eculizumab Studies in Paediatric and Adult Patients With PNH*

	Pediatric and Adolescent Patients	Adult Patients	
Study	**M07-005 (N = 7)**	**C04-001 (N = 43)**	**C04-002 (N = 97)**
Population characteristics			
Sex, n (%)			
Male	3 (43)	20 (46.5)	48 (49.5)
Female	4 (57)	23 (53.5)	49 (50.5)
Race, n (%)			
Asian	0	1 (2.3)	3 (3.1)
White	5 (71)	37 (86.0)	88 (90.7)
Black or African American	2 (29)	4 (9.3)	3 (3.1)
Other	0	0	3 (3.1)
Not required	0	1 (2.3)[a]	0
Weight (kg)			
Mean (SD)	59.19 (6.874)	74.9 (11.69)	73.59 (14.18)
Baseline LDH (U/L)			
Mean (SE)	1019.6 (967.34)[b]	2199.7 (157.66)	2200.7 (104.90)
Median (min, max)	651.0 (308.0, 3144.0)	2032.0 (499.0, 5962.0)	2051.0 (537.0, 5245.0)
Number of patients with pRBC/whole blood transfusions within 12 months prior to first dose, n (%)	6 (85.7)	43 (100.0)	97 (100.0)
Efficacy results			
Change from baseline in LDH at Week 26			
Mean (SE)	-771.1 (914.19)[c]	-1850 (127.69)	-1869.4 (109.33)
Transfusion avoidance			
n (%)	6[d] (85.7)	22 (51.2)	NA
FACIT-Fatigue, change from baseline to Week 26			
Mean (SE)	NA	6.4 (1.19)	11.8 (1.20)
Achieved hemoglobin stabilization			
n (%)	NA	21 (48.8)	NA

[a] Local law did not allow the collection of race data at sites in France.
[b] Mean (standard deviation).
[c] Mean (standard deviation) change from baseline in LDH at Week 12.
[d] Based on results of number of patients with at least 1transfusion episode post dosing.
Abbreviations: FACIT = Functional Assessment of Chronic Illness Therapy fatigue; LDH = lactate dehydrogenase; NA = not applicable; PNH = paroxysmal nocturnal hemoglobinuria; SE = standard error

2.4.3. Discussion on clinical efficacy

Ravulizumab is currently authorised in the EU for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) and for the treatment of patients with a body weight of 10 kg or above with atypical haemolytic uremic syndrome (aHUS). Through the current variation application, the MAH is seeking an extension of the indication for ravulizumab to paediatric patients with PNH.

In support of this application, results from the study ALXN1210-PNH-304 have been submitted.

Design and conduct of clinical studies

Study ALXN1210-PNH-304 is a Phase 3, open-label, single-arm study in paediatric patients (< 18 years and weighing ≥5 kg) with PNH.

The study was descriptive in nature and not statistically powered for hypothesis testing. This approach was discussed in the context of the agreed ravulizumab PIP in PNH with the EMA (EMEA-002077-PIP01-16).

The study included patients < 18 years of age, weighing ≥ 5 kg with documented diagnosis of PNH, confirmed by high-sensitivity flow cytometry evaluation (Borowitz, 2010) of RBCs and white blood cells (WBCs), with granulocyte or monocyte clone size of ≥ 5%. Both eculizumab-experienced and complement inhibitor treatment-naïve patients were included. Complement inhibitor -naïve patients should present 1 or more PNH signs or symptoms within 3 months of screening (e.g. fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia, history of a major adverse vascular event, dysphagia, or erectile dysfunction) or history of packed red blood cell (pRBC) transfusion due to PNH and LDH level ≥ 1.5 × ULN. For eculizumab-experienced patients LDH levels should be LDH ≤ 1.5× ULN. Overall, inclusion and exclusion criteria seem acceptable.

The study consisted of a 4-week screening period, a 26-week Primary Evaluation Period and an extension period of up to 4 years. Through the initial submission, results from the Primary Evaluation Period of the first 12 patients treated were provided, with a data cut-off of 27 May 2020. Updated efficacy data up to week 26 including an additional patient (13th patient) as well as data during the Extension Period (i.e. 52 weeks) were provided during the procedure and are described below.

The primary objective of the study was to assess PK and PD of ravulizumab in paediatric patients with PNH. Efficacy was a secondary objective in this study. Efficacy endpoints included percent change from baseline in LDH, transfusion avoidance, change in quality of life (using the Paediatric FACIT-Fatigue Questionnaire), stabilised haemoglobin, percent change in free haemoglobin and breakthrough haemolysis. All analyses were performed through the end of the Primary Evaluation Period (i.e. day 183). The efficacy endpoints are overall in line with endpoints assessed in ravulizumab PNH studies in adult patients and are considered acceptable. While normalisation of LDH was not a planned endpoint, a *post-hoc* analysis of LDH normalisation has been provided, which is welcomed, since this was a co-primary endpoint in the ravulizumab study ALXN1210-PNH-301 in complement inhibitor treatment-naïve adult patients.

The proposed posology is the same currently authorised for ravulizumab in adults (PNH and aHUS) and in paediatric patients with aHUS and is mostly based on extrapolation (see discussion on clinical pharmacology). The loading dose in patients weighting ≥5 to <10 kg was modified (Protocol amendment 2, dated 23 Aug 2018) from 300 mg to 600 mg based on the ALXN1210-aHUS-312 study in aHUS paediatric patients. It should be noted that ravulizumab is not currently authorised in patients weighting <10 kg; see additional comments in this respect below.

There were important protocol deviations related to laboratory assessments, related to source document, to the visit schedule related to the study procedure (screening LDH was not collected within 24 hours of last eculizumab dose) and relating to safety reporting (delayed reporting of a single SAE). Protocol deviations assigned as non-important ones occurred at all sites enrolling patient(s). All eculizumab-experienced patients and two of four eculizumab-naive patients had non important protocol deviations. Non important protocol deviations included haemolysed PNH clone and/or haematology samples, clotted blood samples and pre-dose PK/PD sample collection performed more than 30 minutes prior the infusion (30 minutes was the pre-dose sample collection time window pre-specified in the protocol) as most often ones. Further, Day 1 haematology, urinalysis and clinical chemistry haemolysed samples of Patien[redacted](eculizumab-experienced cohort) were not available because the samples were too old for analysis. In other words, a remarkable part of baseline data is missing for this patient.

Efficacy data and additional analyses

The Full Analysis Set (FAS), which included patients who received at least 1 dose of ravulizumab and had at least 1 efficacy assessment after the first infusion of ravulizumab, was the population used for all efficacy analyses.

A total of 13 patients were enrolled in the study. However, only data from the first 12 patients enrolled were initially provided. All these 12 patients completed the Primary Evaluation Period and entered the Extension Period of the study. According to the MAH the 13th patient was ongoing in the Primary Evaluation Period and was not initially included in the analyses. Of the 13 patients, 5 patients were eculizumab-naïve and 8 patients had been treated with eculizumab. In the eculizumab-experienced paediatric patients, treatment duration of prior eculizumab ranged from 89 days to 1324 days. All patients except one received eculizumab for more than 400 days before enrolment in the study.

One of the main limitations of this study is the lack of control arm and the limited sample size, which hinder the appropriate interpretation of the results. However, due to the rarity of the disease in children, this design is acknowledged. Besides, this study was part of the agreed PIP (P/0199/2017; EMEA-002077-PIP01-16). According to the PIP at least 10 patients, of whom at least 5 were eculizumab-naïve should be enrolled. Nevertheless, only data from 4 eculizumab-naïve patients were initially submitted. The MAH was requested to provide further information on the 13thpatient enrolled. The MAH confirmed that this patient was a 14 years old male complement inhibitor treatment-naïve patient. Thus, 5 eculizumab-naïve patients were enrolled in the study, which is in line with the PIP.

Patients included in the study were between 9 and 17 years (median age 15 years), with a median weight of 55.6 kg (range: 36.7, 72.0). Only two patients were under 12 years and no patient with a body weight lower than 30 kg was included in the study. Thus, ravulizumab clinical data in children with PNH, though in line with the agreed PIP, are very limited. Of note, the proposed posology in the SmPC is for patients weighting at least 10 kg (in line with the authorised posology in paediatric patients with aHUS) and is mostly based on extrapolation (see discussion on clinical pharmacology above). Indeed, in order to support the proposed posology in patients with PNH weighting < 30 kg the MAH has performed an extrapolation exercise of PK/PD data from adult patients with PNH and paediatric/adult patients with aHUS to paediatric patients with PNH. As noted, no dose recommendation is given for paediatric patients with PNH below 10 kg. Therefore, the indication was restricted to patients with a body weight of 10 kg or above, in line with the aHUS indication.

All patients had PNH diagnosis confirmed by flow cytometry at screening to quantify the percentage of PNH cells (clone size) in the peripheral blood. The mean total PNH granulocyte clone size was 68.10% in the complement inhibitor treatment-naïve cohort and 82.91% in the eculizumab-experienced cohort.

As per inclusion criteria, LDH (at screening) in patients who were eculizumab-naïve should be ≥1.5 ULN and <1.5 ULN in patients treated with eculizumab. However, median LDH at baseline in eculizumab-experienced patients was 251.50 U/L (range: 140.5, 487), thus, some of the patients had a higher LDH level than the required as per inclusion criteria when assessed at baseline. In the subgroup of eculizumab-naïve patients, median LDH at baseline was 565.90 (range: 444, 2269.7).

Further, according to the MAH, 12 of the 13 patients had at least one PNH-associated sign or symptom at any time prior to informed consent.

Regarding protocol amendments, during the primary evaluation period, 3 country-specific and 2 global protocol amendments were made. No relevant impact on results is expected. With Amendment 2 (dated 23 Aug 2018), administration of a supplemental dose of ravulizumab was allowed. According to the MAH only one patient received a supplemental dose of ravulizumab during the extension period due to BTH.

With regards to efficacy results, a decrease in the LDH levels was observed in eculizumab-naïve patients at day 183 (mean [SD] LDH% change -47.91 [52.716]). However, there was one patient with a LDH value of 637 U/l at day 183 in the complement inhibitor treatment-naïve group and another patient in the eculizumab-experienced group had a LDH of 611 U/L on day 183. According to the MAH in both cases it could be attributable to haemolysis of the sample. In eculizumab-experienced patients, a slightly increase in LDH was observed, with a mean (SD) LDH (%) change of 4.65 (44.70). The MAH states there was one patient with a missing value at day 183. Mean LDH change (LOCF) was 3.57 (41.50).

Three (60%) complement inhibitor treatment-naïve patients and all eculizumab-experienced patients remained transfusions free at day 183. Results appear similar to that observed in studies in adult patients (53.6% eculizumab-naïve and 87.6% eculizumab-experienced).

Mean baseline QoL according to the FACIT-Fatigue scale was 44.00 in eculizumab-naïve patients and 40.73 in eculizumab-experienced patients, with an improvement in the score of 3.40 points and 1.28 points, respectively, at day 183. These data are however difficult to interpret due to the lack of comparator and open-label design of the study.

Three (60%) patients in the eculizumab-naïve group and 6 (75%) patients in the eculizumab-experienced group had stabilised haemoglobin through D183. These results do not appear quite different from the results observed in adult patients (68% and 76%, respectively).

During the Primary Evaluation Period, no events of breakthrough haemolysis were reported.

Results of a post-hoc analysis for LDH normalization (LDH levels ≤ 1 × ULN) have also been provided. At day 183, 60% of patients of eculizumab-naïve patients and 57% of the eculizumab-experienced patients had LDH normalisation. Three of these patients (eculizumab-experienced) had LDH normalisation at day 1.

Supportive data from studies of ravulizumab in PNH adult patients have been provided and discussed. Overall, efficacy results in PNH paediatric patients do not appear dissimilar to those reported in adult patients.

Updated efficacy data including the 13th patient during the Extension Period were provided. On Day 351 the mean (SD) percent reduction from baseline in LDH was -54.46% (33.456%) in the complement inhibitor treatment-naïve cohort and -8.48% (19.834%) in the eculizumab-experienced cohort. All 5 complement inhibitor treatment-naïve patients and 7 of the 8 eculizumab-experienced patients achieved haemoglobin stabilization during the Extension Period. All 5 complement inhibitor treatment-naïve patients and 7 of the 8 eculizumab-experienced patients remained transfusion free during the Extension Period through the data cut-off date; the only eculizumab-experienced patient considered as non-responder withdrew from the study on D341 to receive a bone marrow transplant but nevertheless remained transfusion free until withdrawal.

None of the 13 patients experienced BTH during the 26-Week Primary Evaluation. During the Extension Period through the data cut-off date, one eculizumab-experienced patient had BTH on Day 666.

2.4.4. Conclusions on the clinical efficacy

Ravulizumab has shown efficacy in the treatment of paediatric patients with PNH. Moreover, efficacy results in paediatric patients with PNH do not seem dissimilar to those reported in adult patients.

However, data are limited due to the low number of patients, particularly in patients weighting < 30 kg.

The following measures are considered necessary to address issues related to efficacy: Registry study M07-001 will collect clinical outcomes for PNH patients of any age treated with ravulizumab.

2.5. Clinical safety

Introduction

Available safety data focuses on the 26 week Primary Evaluation Period of the Study ALXN1210-PNH-304, which enrolled children from birth to < 12 years of age and adolescents ≥ 12 to < 18 years of age who were either complement inhibitor treatment-naïve or eculizumab experienced.

In addition, data from 6 ravulizumab studies in adult patients with PNH or atypical haemolytic uremic syndrome (aHUS) and from 7 eculizumab studies in paediatric and adult patients with PNH or aHUS are discussed to complement the overall safety data package. Studies included are displayed on Table 1.

Clinical Studies in Ravulizumab			**Studies in PNH**		**Studies in aHUS**	
Study Number	**ALXN1210-PNH-103 (N = 13)**	**ALXN1210-PNH-201 (N = 26)**	**ALXN1210-PNH-301 (N = 246)**	**ALXN1210-PNH-302 (N = 195)**	**ALXN1210-aHUS-311 (N = 58)**	**ALXN1210-aHUS-312 (N = 31)**
Study design	Phase 1b, open-label, multiple-dose, dose escalation	Phase 2, open-label, uncontrolled, multiple ascending dose	Phase 3, randomized (1:1), open-label, active-controlled	Phase 3, randomized (1:1), open-label, active-controlled	Phase 3, open-label, uncontrolled, single-arm	Phase 3, open-label, uncontrolled, single-a
Population	Complement inhibitor treatment-naïve adult patients	Complement inhibitor treatment-naïve adult patients	Complement inhibitor treatment-naïve adult patients [a] Ravulizumab n = 125 Eculizumab n = 121	Adult patients who have been treated with eculizumab (eculizumab-experienced) for at least the past 6 months[a] Ravulizumab n = 97 Eculizumab n = 98	Adult patients with evidence of TMA naïve to complement inhibitor treatment	Paediatric patients with evidence of TMA either naïve to inhibitor treatment (Cohort 1) or eculizumab-experience 90 days (Cohort 2)

Clinical Studies in Eculizumab			Studies in PNH	Studies in aHUS		
Study Number	**M07-005 (N = 7)**	**C04-001 (N = 87)**	**C04-002 (N = 97)**	**C10-003[b] (N = 22)**	**C08-002A/B (N = 17)**	**C08-003A/B (N = 20)**
Study design	Open-label, single-arm	Phase 3 double-blind, placebo-controlled	Phase 3 open-label, single-arm	Phase 2 open-label, single-arm	Phase 2 open-label, single-arm	Phase 2 open-label, single-arm
Population	Paediatric patients with PNH	Transfusion-dependent adult patients with haemolytic PNH Eculizumab n = 43, Placebo n = 44	Transfusion-dependent adult patients with haemolytic PNH	Paediatric patients with aHUS	Adults (C08-002A) and adolescents (C08-002B) with plasma therapy-resistant aHUS	Adults (C08-003A) and adolescents (C08-003B) with plasma therapy-sensitive aHUS

[a] Patients in Study ALXN1210-PNH-301 and Study ALXN1210-PNH-302 received ravulizumab and eculizumab during the first 26 weeks; all patients in both studies either continued or switched (from eculizumab) to ravulizumab during the Extension Period.
Abbreviations: aHUS = atypical haemolytic uremic syndrome; PNH = paroxysmal nocturnal; TMA = thrombotic microangiopathy
Source: Module 5.3.5.3 Extrapolation Report Table 3, Table 4, Table 5, and Table 6

Abbreviations: aHUS = atypical haemolytic uremic syndrome; PNH = paroxysmal nocturnal; TMA = thrombotic microangiopathy
Source: Module 5.3.5.3 Extrapolation Report Table 3, Table 4, Table 5, and Table 6

Patient exposure

All patients in the paediatric Study ALXN1210-PNH-304 received infusions according to the protocol-specified visit schedule during the Primary Evaluation Period, with no missed doses (4 infusions). The mean treatment duration up to the 52-week evaluation period was 740.8 days for all 13 patients. Extent of exposure is detailed on Table 2.

Table 2. Study Duration, Treatment Duration, Compliance, and Exposure (Safety Set)

Variable	Treatment Naïve (N = 5)	Eculizumab Experienced (N = 8)	Total (N = 13)
Study Duration from Informed Consent to Extension Period at Data Cut-off (days)			
Mean (SD)	529.2 (100.08)	873.1 (238.93)	740.8 (258.79)
Median	546.0	899.0	753.0
Min, Max	359, 618	369, 1121	359, 1121
Treatment Duration (days)			
Mean (SD)	514.6 (95.91)	855.4 (243.30)	724.3 (259.56)
Median	529.0	878.0	737.0
Min, Max	351, 597	341, 1107	341, 1107
Total Patient-Years of Exposure (years)	7.0	18.7	25.8
Number of Infusions			
Mean (SD)	8.0 (0.00)	7.9 (0.35)	7.9 (0.28)

Variable	Treatment Naïve (N = 5)	Eculizumab Experienced (N = 8)	Total (N = 13)
Median	8.0	8.0	8.0
Min, Max	8, 8	7, 8	7, 8
Number of Patients with an Infusion Interruption, n (%)	1 (20.0)	1 (12.5)	2 (15.4)
Number of Infusions Interrupted			
Total	1	1	2
Mean (SD)	1.0	1.0	1.0 (0.00)
Median	1.0	1.0	1.0
Min, Max	1, 1	1, 1	1, 1
Number of Infusions Interrupted due to Adverse Event			
Total	0	0	0
Mean (SD)			
Median			
Min, Max			
Drug Compliance, n (%)			
≥ 100%	5 (100.0)	8 (100.0)	13 (100.0)
≥ 80% to < 100%	0 (0.0)	0 (0.0)	0 (0.0)
≥ 60% to < 80%	0 (0.0)	0 (0.0)	0 (0.0)
≥ 40% to < 60%	0 (0.0)	0 (0.0)	0 (0.0)
≥ 20% to < 40%	0 (0.0)	0 (0.0)	0 (0.0)
≥ 0% to < 20%	0 (0.0)	0 (0.0)	0 (0.0)

A single infusion interruption was reported for 1 complement inhibitor treatment-naïve patient due to technical issue and 1 eculizumab-experienced patient due to a problem with the infusion pump.

The median duration of treatment in the pooled ravulizumab treatment group of Phase 3 studies in adult patients with PNH (Study ALXN1210-PNH-301 and Study ALXN1210-PNH-302) was 182 days. The median treatment duration for adult patients in Study ALXN120 aHUS-311 was 262.5 days, and that in paediatric patients in Study ALXN1210 aHUS-312 was 183.0 days.

Baseline characteristics

Table 3. Key Demographic and Baseline Characteristics for Phase 3 Study ALXN1210-PNH-304 in Paediatric Patients With PNH (Full Analysis Set)

Variable	Treatment Naïve (N = 5) n (%)	Eculizumab Experienced (N = 8) n (%)	Total (N = 13) n (%)
Sex, n (%)			
Male	4 (80.0)	1 (12.5)	5 (38.5)
Female	1 (20.0)	7 (87.5)	8 (61.5)
Ethnicity, n (%)			
Not Hispanic or Latino	5 (100)	6 (75.0)	11 (84.6)
Not Reported	0 (0.0)	2 (25.0)	2 (15.4)
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)
Missing/Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Race, n (%)			
White	5 (100)	3 (37.5)	8 (61.5)
Black or African American	0 (0.0)	2 (25.0)	2 (15.4)
Not Reported	0 (0.0)	2 (25.0)	2 (15.4)
Other	0 (0.0)	1 (12.5)	1 (7.7)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Age at First Infusion (years)			
Mean (SD)	14.4 (2.19)	14.4 (3.07)	14.4 (2.66)
Median	15.0	15.0	15.0
Min, Max	11, 17	9, 17	9, 17
Age at First Infusion (years) Category, n (%)			
< 12 years	1 (20.0)	1 (12.5)	2 (15.4)
≥ 12 years	4 (80.0)	7 (87.5)	11 (84.6)
Baseline Weight (kg)			
Mean (SD)	56.26 (11.594)	56.25 (12.247)	56.25 (11.502)
Median	55.60	55.50	55.60
Min, Max	39.5, 72.0	36.7, 69.0	36.7, 72.0
Baseline Weight (kg) Category, n (%)			
≥ 5 to < 10 kg	0 (0.0)	0 (0.0)	0 (0.0)
≥ 10 to < 20 kg	0 (0.0)	0 (0.0)	0 (0.0)
≥ 20 to < 30 kg	0 (0.0)	0 (0.0)	0 (0.0)
≥ 30 to < 40 kg	1 (20.0)	1 (12.5)	2 (15.4)
≥ 40 to < 60 kg	3 (60.0)	4 (50.0)	7 (53.8)
≥ 60 to < 100 kg	1 (20.0)	3 (37.5)	4 (30.8)
≥ 100 kg	0 (0.0)	0 (0.0)	0 (0.0)
Baseline Height (cm)			
Mean (SD)	163.40 (11.760)	160.99 (9.369)	161.92 (9.940)
Median	168.00	158.95	164.00
Min, Max	143.0, 171.0	146.0, 176.2	143.0, 176.2
Baseline Body Mass Index (BMI) (kg/m^2)			

Variable	Treatment Naïve (N = 5) n (%)	Eculizumab Experienced (N = 8) n (%)	Total (N = 13) n (%)
Sex, n (%)			
Male	4 (80.0)	1 (12.5)	5 (38.5)
Female	1 (20.0)	7 (87.5)	8 (61.5)
Ethnicity, n (%)			
Not Hispanic or Latino	5 (100)	6 (75.0)	11 (84.6)
Not Reported	0 (0.0)	2 (25.0)	2 (15.4)
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)
Missing/Unknown	0 (0.0)	0 (0.0)	0 (0.0)
Race, n (%)			
White	5 (100)	3 (37.5)	8 (61.5)
Black or African American	0 (0.0)	2 (25.0)	2 (15.4)
Not Reported	0 (0.0)	2 (25.0)	2 (15.4)
Other	0 (0.0)	1 (12.5)	1 (7.7)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian	0 (0.0)	0 (0.0)	0 (0.0)
Multiple	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Age at First Infusion (years)			
Mean (SD)	14.4 (2.19)	14.4 (3.07)	14.4 (2.66)
Median	15.0	15.0	15.0
Min, Max	11, 17	9, 17	9, 17
Age at First Infusion (years) Category, n (%)			
< 12 years	1 (20.0)	1 (12.5)	2 (15.4)
≥ 12 years	4 (80.0)	7 (87.5)	11 (84.6)
Baseline Weight (kg)			
Mean (SD)	56.26 (11.594)	56.25 (12.247)	56.25 (11.502)
Median	55.60	55.50	55.60
Min, Max	39.5, 72.0	36.7, 69.0	36.7, 72.0
Baseline Weight (kg) Category, n (%)			
≥ 5 to < 10 kg	0 (0.0)	0 (0.0)	0 (0.0)
≥ 10 to < 20 kg	0 (0.0)	0 (0.0)	0 (0.0)
≥ 20 to < 30 kg	0 (0.0)	0 (0.0)	0 (0.0)
≥ 30 to < 40 kg	1 (20.0)	1 (12.5)	2 (15.4)
≥ 40 to < 60 kg	3 (60.0)	4 (50.0)	7 (53.8)
≥ 60 to < 100 kg	1 (20.0)	3 (37.5)	4 (30.8)
≥ 100 kg	0 (0.0)	0 (0.0)	0 (0.0)
Mean (SD)	20.92 (2.657)	21.45 (2.756)	21.25 (2.618)
Median	20.20	21.60	20.70
Min, Max	18.9, 25.5	17.2, 24.8	17.2, 25.5

Note: Percentages are based on the total number of patients in each group, or overall.
Abbreviation: SD = standard deviation
Source: Table 14.1.1.1.1, Response to D90 RSI

Table 4. Key Population Characteristics of Ravulizumab Studies in Patients with PNH and aHUS

Patients Treated with Ravulizumab						
	Adult Patients with PNH		Adult Patients with PNH		Adolescent and Adult Patients with aHUS	
	Study ALXN1210 - PNH-103 (N = 13)	Study ALXN1210 - PNH-201 (N = 26)	Study ALXN1210-PNH-301 (N = 125)	Study ALXN1210 - PNH-302 (N = 97)	Study ALXN1210 -aHUS-311 (N = 58)	Study ALXN1210 -aHUS-312 (N = 31)
Sex, n (%)						
Male	6 (46.2)	20 (76.9)	65 (52.0)	50 (51.5)	19 (32.8)	19 (61.3)
Female	7 (53.8)	6 (23.1)	60 (48.0)	47 (48.5)	39 (67.2)	12 (38.7)
Race, n (%)						
Asian	12 (92.3)	7 (26.9)	72 (57.6)	23 (23.7)	16 (27.6)	11 (35.5)
White	1 (7.7)	15 (57.7)	43 (34.4)	50 (51.5)	30 (51.7)	15 (48.4)
Black or African American	0	0	2 (1.6)	5 (5.2)	2 (3.4)	4 (12.9)
American Indian or Alaska Native	0	0	1 (0.8)	0	1 (1.7)	1(3.2)
Other	0	1 (3.8)	4 (3.2)	2 (2.1)	1 (1.7)	0
Not reported	0	3 (11.5)	3 (2.4)	13 (13.4)	NA	0
Unknown	0	0	0	3 (3.1)	8 (13.8)	1 (3.2)
Age (years) at first infusion in study						
Mean (SD)	42.4 (11.91)	44.3 (16.33)	44.8 (15.16)	46.6 (14.41)	43.4 (16.04)	8.1 (5.17)
Median	41.5	41.0	43.0	45.0	41.1	8.5
Min, max	24.5, 62.3	18.8, 80.2	18, 83	18, 79	19.5, 77.1	0.5, 17.3
Age categories, n						
Birth to < 12 years	0	0	0	0	0	22
≥ 12 to < 18 years	0	0	0	0	0	9
≥ 18 years	13	26	125	121	58	0
Body weight (kg) category, n (%)						
≥ 5 to < 20 kg	0	0	0	0	0	14 (45.2)
≥ 20 to < 40 kg	0	0	0	0	0	8 (25.8)
≥ 40 to < 60 kg	3 (23.1)	3 (11.5)	41 (32.8)	27 (27.8)	13 (22.4)	7 (22.6)
≥ 60 to < 100 kg	10 (76.9)	21 (80.8)	79 (63.2)	62 (63.9)	39 (67.2)	2 (6.5)
≥ 100 kg	0	2 (7.7)	5 (4.0)	8 (8.2)	6 (10.3)	0
pRBC/whole blood transfusions prior to first dose, n (%)	5 (38.5)	7 (27.0)	103 (82.4)	13 (13.4)	17 (29.3)	12 (57.1)

Abbreviations: aHUS = atypical haemolytic uremic syndrome; LDH = lactate dehydrogenase; max = maximum; min = minimum; PNH = paroxysmal nocturnal hemoglobinuria; pRBC = packed red blood cell; SD = standard deviation

Table 5. Key Population Characteristics From Eculizumab Studies in Patients with PNH and aHUS

Patients Treated With Eculizumab							
	Pediatric Study	Adult PNH Studies		Pediatric and Adult aHUS Studies			
Variable	Study M 07-005 (N = 7)	Study C 04-001 (N = 43)	Study C 04-002 (N = 97)	Study C10 -003 (N = 22)	Study C08-00 2A/B (N = 17)	Study C08-00 3A/B (N = 20)	Study C10 -004 (N = 41)
Sex, n (%)							

Patients Treated With Eculizumab							
	Pediatric Study	Adult PNH Studies		Pediatric and Adult aHUS Studies			
Variable	**Study M 07-005 (N = 7)**	**Study C 04-001 (N = 43)**	**Study C 04-002 (N = 97)**	**Study C10 -003 (N = 22)**	**Study C08-00 2A/B (N = 17)**	**Study C08-00 3A/B (N = 20)**	**Study C10 -004 (N = 41)**
Male	3 (43)	20 (46.5)	48 (49.5)	12 (54.5)	5 (29.4)	8 (40.0)	13 (31.7)
Female	4 (57)	23 (53.5)	49 (50.5)	10 (45.5)	12 (70.6)	12 (60.0)	28 (68.3)
Race, n (%)							
Not available	0	1 (2.3)	0	NA	NA	NA	NA
Caucasian/ White	5 (71.4)	37 (86.0)	88 (90.7)	18 (81.8)	15 (88.2)	17 (85.0)	38 (92.7)
Black or African American	2 (28.6)	4 (9.3)	3 (3.1)	0	1 (5.9)	2 (10.0)	2 (4.9)
Asian	0	1 (2.3)	3 (3.1)	2 (9.1)	1 (5.9)	0	1 (2.4)
Other	0	0	3 (3.1)	2 (9.1)	0	1 (5.0)	0
Age (years)							
Mean (SD)	15.0 (2.28)	42.1 (15.47)	41.05 (14.41)	6.6 (6.06)	31.8 (13.32)	32.3 (14.92)	40.3 (15.33)
Median (min, max)	15.6 (11.0, 17.1)	41.0 (20.0, 85.0)	41.0 (18.0, 78.0)	6.5 (0.0, 17.0)	28 (17, 68)	28 (13, 63)	35.0 (18.0, 80.0)
Age categories, n							
Birth to < 12 years	1	0	0	18	0	0	0
≥ 12 to < 18 years	6	0	0	4	1	5	0
≥ 18 years	0	43	97	0	16	15	41
Weight (kg)							
Mean (SD)	59.19 (6.874)	74.9 (11.69)	73.59 (14.18)	28.6 (24.16)	Not available	Not available	69.2 (16.03)
pRBC/whole blood transfusions n (%) prior to first dose	6 (85.7)	43 (100.0)	97 (100.0)	Not available	Not available	Not available	Not available

Adverse events

In the interim analysis of Study ALXN1210 PNH 304, 10 of 12 patients experienced at least 1 AE during the Primary Evaluation Period (Table 6). Most AEs were Grade 1 or Grade 2 in severity. One patient reported AEs of Grade 4 severity. Four (33.3%) patients had AEs assessed by the Investigator to be related to study drug.

Three patients experienced 1 or more serious adverse events (SAEs) (device related sepsis, staphylococcal infection, multiple organ dysfunction syndrome, septic shock, and device related thrombosis in 1 patient; influenza A virus test positive in 1 patient; and viral upper respiratory tract infection [URTI] in 1 patient). None of the SAEs were assessed to be related to study drug. No patients had meningococcal infections.

No patients died or discontinued from the study due to AEs during the Primary Evaluation Period. No patients experienced AEs leading to permanent discontinuation of study drug.

Table 6. Overview of All Treatment-Emergent Adverse Events and Serious Adverse Events through 52 weeks of Study ALXN1210-PNH-304 (Safety Set)

	Treatment Naïve (N = 5)		Eculizumab Experienced (N = 8)		Total (N = 13)	
	n (%)	E	n (%)	E	n (%)	E
Total Patient-Years of Exposure (years) to ALXN1210		7.0		18.7		25.8
Any Adverse Event (AE)	5 (100)	17	8 (100)	71	13 (100)	88
Any Serious AE (SAE)	1 (20.0)	5	2 (25.0)	3	3 (23.1)	8
Death	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
AEs Leading to Withdrawal of Study Drug	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
SAEs Leading to Withdrawal of Study Drug	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
AEs by Relationship						
Related[a]	1 (20.0)	1	5 (62.5)	10	6 (46.2)	11
Definitely Related	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Probably Related	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Possibly Related	0 (0.0)	0	5 (62.5)	10	5 (38.5)	10
Not Related	5 (100)	16	8 (100)	61	13 (100)	77
Unlikely Related	1 (20.0)	5	5 (62.5)	27	6 (46.2)	32
Not Related	5 (100)	11	8 (100)	34	13 (100)	45
AEs by Toxicity						
Grade 1	4 (80.0)	7	8 (100)	40	12 (92.3)	47
Grade 2	3 (60.0)	5	7 (87.5)	20	10 (76.9)	25
Grade 3	1 (20.0)	2	2 (25.0)	10	3 (23.1)	12
Grade 4	1 (20.0)	3	1 (12.5)	1	2 (15.4)	4
Grade 5	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
SAEs by Relationship						
Related[a]	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Definitely Related	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Probably Related	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Possibly Related	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Not Related	1 (20.0)	5	2 (25.0)	2	3 (23.1)	7
Unlikely Related	1 (20.0)	5	2 (25.0)	2	3 (23.1)	7
Not Related	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
AEs of Special Interest						
Meningococcal Infections	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

Notes: Patients are counted in each relationship and severity category in case of multiple events.
Percentages are based on the number of patients in each column, ie, % = n/N × 100.
Treatment-emergent AEs are AEs with a start date on or after first dose date in the study.
Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = Fatal.

The toxicity of AEs are graded using CTCAE version 4.03 or higher.
AEs are coded using MedDRA 20.1.
[a]Related AEs are defined as AEs that are possibly, probably, or definitely related to study treatment. Not related AEs are defined as AEs that are unlikely or not related to study treatment.
Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event
Source: Table 14.3.1.2.1.2, Response to Rapporteur preliminary assessment report

The analysis of AEs by SOC is presented in Table 7. The most frequently reported AEs belonged to the Infections and infestations SOC (11 patients, 84.6%) and Gastrointestinal disorders (6 patients, 46.2%).

Abdominal pain and nasopharyngitis were each experienced by 3 (23.1%) patients. Most of the rest of AEs were reported by 1 patient each in Study ALXN1210-PNH-304 (Table 7).

Table 7. Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term through 52 Weeks (Safety Set)

System Organ Class Preferred Term	Treatment Naïve (N = 5)		Eculizumab Experienced (N = 8)		Total (N = 13)	
	n (%)	E	n (%)	E	n (%)	E
Total Patient-Years of Exposure (years) to ALXN1210		7.0		18.7		25.8
Patients with Treatment-Emergent Adverse Events	5 (100)	17	8 (100)	71	13 (100)	88
Blood and lymphatic system disorders	1 (20.0)	1	2 (25.0)	6	3 (23.1)	7
Anaemia	0 (0.0)	0	2 (25.0)	5	2 (15.4)	5
Haemolysis	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Lymphadenitis	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Ear and labyrinth disorders	0 (0.0)	0	1 (12.5)	2	1 (7.7)	2
Ear pain	0 (0.0)	0	1 (12.5)	2	1 (7.7)	2
Endocrine disorders	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Cushing's syndrome	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Gastrointestinal disorders	0 (0.0)	0	6 (75.0)	13	6 (46.2)	13
Abdominal pain	0 (0.0)	0	3 (37.5)	3	3 (23.1)	3
Abdominal pain upper	0 (0.0)	0	2 (25.0)	2	2 (15.4)	2
Constipation	0 (0.0)	0	2 (25.0)	2	2 (15.4)	2
Diarrhoea	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Dysphagia	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Nausea	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Rectal haemorrhage	0 (0.0)	0	1 (12.5)	2	1 (7.7)	2
Vomiting	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
General disorders and administration site conditions	1 (20.0)	3	4 (50.0)	5	5 (38.5)	8
Pyrexia	1 (20.0)	1	1 (12.5)	1	2 (15.4)	2
Administration site pain	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Chest pain	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Device related thrombosis	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Fatigue	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Multiple organ dysfunction syndrome	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Non-cardiac chest pain	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Hepatobiliary disorders	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Hyperbilirubinaemia	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1

System Organ Class Preferred Term	Treatment Naïve (N = 5)		Eculizumab Experienced (N = 8)		Total (N = 13)	
	n (%)	E	n (%)	E	n (%)	E
Immune system disorders	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Serum sickness	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Infections and infestations	4 (80.0)	7	7 (87.5)	17	11 (84.6)	24
Nasopharyngitis	1 (20.0)	1	2 (25.0)	2	3 (23.1)	3
COVID-19	2 (40.0)	2	0 (0.0)	0	2 (15.4)	2
Upper respiratory tract infection	0 (0.0)	0	2 (25.0)	2	2 (15.4)	2
Viral upper respiratory tract infection	0 (0.0)	0	2 (25.0)	2	2 (15.4)	2
Cystitis	0 (0.0)	0	1 (12.5)	4	1 (7.7)	4
Device related sepsis	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Hordeolum	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Infected bite	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Paronychia	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Pharyngitis	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Rhinitis	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Septic shock	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Sinusitis	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Staphylococcal infection	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Urinary tract infection	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Viral infection	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Injury, poisoning and procedural complications	0 (0.0)	0	3 (37.5)	4	3 (23.1)	4
Electric shock	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Sunburn	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Transfusion reaction	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Wound	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Investigations	1 (20.0)	1	1 (12.5)	1	2 (15.4)	2
Blood pressure increased	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Influenza A virus test positive	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Metabolism and nutrition disorders	0 (0.0)	0	2 (25.0)	2	2 (15.4)	2
Decreased appetite	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Iron deficiency	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Musculoskeletal and connective tissue disorders	1 (20.0)	1	3 (37.5)	8	4 (30.8)	9
Arthralgia	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Back pain	0 (0.0)	0	1 (12.5)	2	1 (7.7)	2
Kyphosis	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Musculoskeletal chest pain	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Neck pain	0 (0.0)	0	1 (12.5)	3	1 (7.7)	3
Pain in extremity	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Nervous system disorders	1 (20.0)	1	3 (37.5)	3	4 (30.8)	4
Headache	1 (20.0)	1	2 (25.0)	2	3 (23.1)	3
Dizziness	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Reproductive system and breast disorders	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Dysmenorrhoea	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0	3 (37.5)	5	3 (23.1)	5
Oropharyngeal pain	0 (0.0)	0	2 (25.0)	2	2 (15.4)	2

System Organ Class Preferred Term	Treatment Naïve (N = 5)		Eculizumab Experienced (N = 8)		Total (N = 13)	
	n (%)	E	n (%)	E	n (%)	E
Cough	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Nasal congestion	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Rhinitis allergic	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Skin and subcutaneous tissue disorders	0 (0.0)	0	2 (25.0)	2	2 (15.4)	2
Ingrowing nail	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Pruritus	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Vascular disorders	0 (0.0)	0	2 (25.0)	2	2 (15.4)	2
Haematoma	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Pallor	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1

Notes: % = n/N × 100.
Treatment-emergent AEs are AEs with a start date on or after first dose date in the study.
If a patient had more than one event for a particular SOC, he/she is counted only once for that SOC.
If a patient had more than one event for a particular PT, he/she is counted only once for that PT.
AEs are coded using MedDRA 20.1.
Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = System Organ Class
Source: Table 14.3.1.3.2, Response to Rapporteur preliminary assessment report

The majority of AEs were Grade 1 or Grade 2 in severity. Three (23.1%) patients experienced AEs of Grade 3 and 2 (15.4%) patients reported any AEs of Grade 4 severity.

- Patient (complement inhibitor treatment-naïve) had Grade 3 SAEs of staphylococcal infection on Day 43 and device-related thrombosis on Day 44. This patient also had 3 Grade 4 SAEs; device-related sepsis on Day 43, septic shock on Day 44, and multiple organ dysfunction syndrome on Day 44.
- Patient (eculizumab-experienced) had a Grade 3 nonserious AE of anaemia (worsening anemia) on Day 71.
- Patient (eculizumab-experienced) had a Grade 3 serious AE of influenza A virus test positive on Day 129.

Serious adverse event/deaths/other significant events

Deaths

There were no deaths during the Primary Evaluation Period nor the 52-week evaluation of Study ALXN1210-PNH-304.

Serious adverse events

Three patients (25.0%) experienced 1 or more SAEs (1 complement inhibitor treatment naïve patient; 2 eculizumab experienced patients) (Table 8). None of the SAEs were assessed to be related to study drug. None of the SAEs led to discontinuation of study drug. All SAEs resolved during the Primary Evaluation Period.

- Patient (17 years old at study entry, complement inhibitor treatment-naïve) experienced 5 SAEs (device-related sepsis and staphylococcal infection on Day 43, and multiple organ dysfunction syndrome, septic shock, and device-related thrombosis on Day 44). The event of device-related thrombosis on Day 44 met the criteria of MAVE.

- Patient (17 years old at study entry, eculizumab-experienced) was hospitalized for influenza A virus test positive on Day 129.
- Patient (13 years old at study entry, eculizumab-experienced) was hospitalized for viral URTI on Day 77.

Table 8. Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term through 52 Weeks (Safety Set)

System Organ Class Preferred Term	Treatment Naïve (N = 5)		Eculizumab Experienced (N = 8)		Total (N = 13)	
	n (%)	E	n (%)	E	n (%)	E
Total Patient-Years of Exposure (years) to ALXN1210		1.6		4.3		5.9
Patients with Treatment-Emergent Serious Adverse Events	1 (20.0)	5	2 (25.0)	3	3 (23.1)	8
Blood and lymphatic system disorders	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Haemolysis	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
General disorders and administration site conditions	1 (20.0)	2	0 (0.0)	0	1 (7.7)	2
Device related thrombosis	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Multiple organ dysfunction syndrome	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Infections and infestations	1 (20.0)	3	1 (12.5)	1	2 (15.4)	4
Device related sepsis	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Septic shock	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Staphylococcal infection	1 (20.0)	1	0 (0.0)	0	1 (7.7)	1
Viral upper respiratory tract infection	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Investigations	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1
Influenza A virus test positive	0 (0.0)	0	1 (12.5)	1	1 (7.7)	1

Notes: % = n/N × 100.
Treatment-emergent AEs are AEs with a start date on or after first dose date in the study.
If a patient had more than one event for a particular SOC, he/she is counted only once for that SOC.
If a patient had more than one event for a particular PT, he/she is counted only once for that PT.
AEs are coded using MedDRA 20.1.
Abbreviations: AE = adverse event; E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = System Organ Class
Source: Table 14.3.1.4.2, Response to Rapporteur preliminary assessment report

Adverse events of special interest

The AE of special interest for this study was meningococcal infection. None of the 13 patients experienced a meningococcal infection.

Adverse events in studies providing supplementary safety data

Adverse Events in Ravulizumab Studies in Adult Patients with PNH

In the pooled ravulizumab group of the Phase 3 studies, 87.8% of patients experienced at least 1 TEAE, with most AEs of Grade 1/2 severity and most AEs (83.3%) assessed as unrelated to the study drug by the Investigator (Table 9).

Overall, no patients died or discontinued from the study due to AEs through the 26 week Primary Evaluation Period in all 4 ravulizumab studies in PNH. In Study ALXN1210-PNH-301, 2 patients died during the Extension Period through the 52 week data cutoff date, 1 due to pulmonary sepsis and the other due to lung adenocarcinoma (onset during Primary Evaluation Period). Two patients had TEAEs that led to discontinuation of study drug in Study ALXN1210 PNH-301, 1 due to lung adenocarcinoma and the other due to myelodysplastic syndrome.

A total of 2 patients who had meningococcal infections in Study ALXN1210-PNH-201 during the Primary Evaluation Period recovered completely while remaining on ravulizumab without treatment interruption.

Table 9. Overview of All Treatment-Emergent Adverse Events and Serious Adverse Events in Pooled Ravulizumab Group Across Phase 3 Adult PNH Studies During the Primary Evaluation Period (Phase 3 PNH Population)

Variable	All Ravulizumab (N = 222)	
	n (%)	E
Any TEAE	195 (87.8)	932
Related TEAE	75 (33.8)	179
Unrelated TEAE	185 (83.3)	753
Grade 1	172 (77.5)	651
Grade 2	117 (52.7)	228
Grade 3	28 (12.6)	44
Grade 4	7 (3.2)	9
Grade 5	0	0
TEAE leading to study drug interruption	2 (0.9)	4
TEAE leading to study drug discontinuation	0	0
TEAE considered as a MAVE	2 (0.9)	2
TEAE of special interest	27 (12.2)	33
Any serious TEAE (SAE)	15 (6.8)	22
Related SAE	5 (2.3)	8
Unrelated SAE	10 (4.5)	14
SAE leading to study drug interruption	0	0
SAE leading to study drug discontinuation	0	0
SAE considered as a MAVE	1 (0.5)	1
TEAE leading to death	0	0

Notes: Pooled Phase 3 PNH population includes Studies ALXN1210-PNH-301 and ALXN1210-PNH-302.
Abbreviations: AE = adverse event; E = number of events; MAVE = major adverse vascular event; N = total number of patients; PNH = paroxysmal nocturnal hemoglobinuria; SAE = serious adverse event; TEAE = treatment-emergent adverse event
Source: Module 5.3.5.3 Extrapolation Report Table 30

Adverse Events in Ravulizumab Studies in Patients with aHUS

In total, 98.6% of patients experienced at least 1 TEAE in both Phase 3 aHUS studies, with most AEs of Grade 1/2 severity and most AEs (98.6%) assessed as unrelated to the study drug by the Investigator (table 10).

Overall, 4 patients died in Study ALXN1210 aHUS-311 during the Primary Evaluation Period, all assessed as unrelated to ravulizumab by the Investigator: 3 patients died due to treatment emergent SAEs (2 due to septic shock and 1 due to intracranial hemorrhage); 1 patient died due to a pretreatment AE. Four (5.4%) patients had SAEs that led to discontinuation of study drug and withdrawal of patient from the study: autoimmune haemolytic anemia, immune thrombocytopenic purpura, intracranial haemorrhage in Study ALXN1210 aHUS 311, and anemia and hypertensive crisis in Study ALXN1210 aHUS-312.

There were no further deaths or study drug discontinuations due to AEs in patients with aHUS through 52 weeks of treatment.

No meningococcal infections were reported through the 52-week data cut-off date.

Table 10. Overview of All Treatment-Emergent Adverse Events and Serious Adverse Events Across Phase 3 aHUS Studies During the Primary Evaluation Period (Safety Set)

Variables	Study ALXN1210-aHUS-311 (N = 58)		Study ALXN1210-aHUS-312 (N = 16)				Total (N = 74)	
	n (%)	E	Birth to < 12 years (N = 14)		12 to < 18 years (N = 2)		n (%)	E
			n (%)	E	n (%)	E		
Any TEAE	58 (100.0)	818	13 (92.9)	136	2 (100.0)	26	73 (98.6)	980
Related TEAE	20 (34.5)	58	7 (50.0)	16	1 (50.0)	6	28 (37.8)	80
Unrelated TEAE	58 (100.0)	760	13 (92.9)	120	2 (100.0)	20	73 (98.6)	900
Grade 1	54 (93.1)	454	11 (78.6)	104	2 (100.0)	16	67 (90.5)	574
Grade 2	46 (79.3)	223	9 (64.3)	23	2 (100.0)	10	57 (77.0)	256
Grade 3	31 (53.4)	116	3 (21.4)	8	0 (0.0)	0	34 (45.9)	124
Grade 4	14 (24.1)	22	1 (7.1)	1	0 (0.0)	0	15 (20.3)	23
Grade 5	3 (5.2)	3	0 (0.0)	0	0 (0.0)	0	3 (4.1)	3
TEAE leading to study drug interruption	0	0	1 (7.1)	1	0 (0.0)	0	1 (1.4)	
TEAE leading to study drug discontinuation	3 (5.2)	3	1 (7.1)	2	0 (0.0)	0	4 (5.4)	5
Any serious TEAE (SAE)	30 (51.7)	71	7 (50.0)	12	1 (50.0)	1	38 (51.4)	84
Related SAE	2 (3.4)	2	3 (21.4)	4	0 (0.0)	0	5 (6.8)	6
Unrelated SAE	29 (50.0)	69	7 (50.0)	8	1 (50.0)	1	37 (50.0)	78
SAE leading to study drug interruption	0	0	0 (0.0)	0	0 (0.0)	0	0	0
SAE leading to study drug discontinuation	3 (5.2)	3	1 (7.1)	2	0 (0.0)	0	4 (5.4)	5
TEAE leading to death[a]	3 (5.2)	NA	0 (0.0)		0 (0.0)		3 (4.1)	NA

Adverse Events in Eculizumab Studies in Patients with PNH and aHUS

In Study M07-005 in paediatric patients with PNH, all 7 patients experienced at least 1 TEAE (69 TEAEs) through the 12-week evaluation period. Two patients reported 12 SAEs, with 3 SAEs (anemia, thrombocytopenia, and headache) assessed by the Investigator as possibly related to study drug. No patients died or withdrew from the study due to AEs.

Across the 2 adult studies in patients with PNH through the 26-week Primary Evaluation Period, 1 patient died due to a haemorrhagic cerebrovascular event (cerebral herniation) in Study C04-002 (assessed as unrelated to eculizumab). One patient discontinued study drug due to pregnancy in Study C04-001; there were no other treatment/study discontinuations due to AEs in the 3 studies.

None of the paediatric or adult patients with PNH had meningococcal infections across the studies.

Among patients with aHUS treated with eculizumab in the Primary Evaluation Period across 4 studies, 1 patient died due to complications from gastrointestinal haemorrhage, not related to eculizumab therapy in Study C08-003 A/B. In a total of 3 patients across the 4 aHUS studies, AEs led to permanent discontinuation of study drug: SAE of agitation in 1 patient (age cohort ≥ 23 months to < 5 years in Study C10-003), renal impairment or worsening renal function (Study C08-002A/B) and meningococcal

infection Study C10-004). A total of 2 patients had meningococcal infection/sepsis (Study C10-004), which led to permanent discontinuation of study drug in 1 patient.

Laboratory findings

Changes over time for all chemistry parameters have been provided, including boxplots for LDH, bilirubin, creatinine, AST, ALT and GGT. Same for haematology parameters and boxplots for haemoglobin, hematocrit, reticulocytes and free haemoglobin.

Shifts in laboratory parameters (between low, normal and high) from baseline to each post-baseline time point are summarized for haematology, chemistry and coagulation.

Individual laboratory abnormalities of Grade 3 or higher toxicity/severity were as follows:

- Bilirubin: Two eculizumab-experienced patients had Grade 3 increased bilirubin (on Day 43 and on Day 70). One complement inhibitor treatment-naïve patient had Grade 3 increased bilirubin (on Day 65); this patient had an ongoing Grade 2 AE of hyperbilirubinemia that began on Day 45. Of note, Patient had also experienced a Grade 2 AE of drug-induced liver injury that started 6 days prior to the first infusion of ravulizumab and lasted through Day 1 of the Primary Evaluation Period.
- Anaemia: Three eculizumab-experienced patients had Grade 3 anemia: assessed at Screening and on Days 1, 127, and 183; assessed at Screening and on Day 99; and on Day 71. Of these, only the last event was reported as an AE (worsening anemia) with onset on Day 71.

For the LDH level, there were two exceptions at the Day 183 observation: one eculizumab-naive and one eculizumab-experienced patient had elevated (above 600 U/L) LDH concentrations without any other signs/symptoms of breakthrough haemolysis. These findings seemed to be related to table-top haemolysis.

One new SAE of breakthrough haemolysis (BTH) occurred in an eculizumab-experienced patient on Day 666 during the Extension Period through the data cut-off date. This is a patient with a history of splenic and renal infarcts and transfusion prior to study entry. The patient experienced anaemia (haemoglobin [Hb] 5.7 g/dL) 1 week before the reported episode of BTH (Day 659). On the day of BTH diagnosis, the patient's haemoglobin level was 4.6 g/dL and presented with a 1-day history of shortness of breath, racing heart, pounding in the ears, fatigue, and light-headedness. The patient received blood transfusion on the same day and a supplemental dose of ravulizumab the next day (Day 667). The SAE resolved and the investigator assessed the event as possibly related to the study drug since there was no complement activating condition for the BTH.

Vital signs

Mean values for vital signs (temperature, heart rate, systolic BP, diastolic BP, and respiratory rate) at baseline were similar between the complement inhibitor treatment-naïve cohort and the eculizumab-experienced cohort. There were no clinically meaningful mean changes from baseline in temperature, heart rate, respiratory rate, or systolic and diastolic BP values at each post-baseline visit in either the complement inhibitor treatment-naïve cohort or the eculizumab-experienced cohort.

Electrocardiograms

Electrocardiograms were obtained at baseline, Day 71, and Day 183. No patients had ECG findings that were of clinical significance. No patients had QT or QTcF abnormalities in either the complement inhibitor treatment-naïve cohort or the eculizumab-experienced cohort. No AEs of QT prolongation,

syncope, or torsades de pointes were reported in any patients. Electrocardiograms by visit for each patient have been provided.

Inmunogenicity

No patients had antidrug antibodies (ADA) positive response through Day 911 visit of ravulizumab treatment.

Adverse Drug Reactions

The ADRs identified for ravulizumab are consistent with ADRs observed with eculizumab. Adverse drug reactions by ravulizumab-treated patients in the integrated PNH and aHUS population (N = 576) are summarized in table 10.

Table 11. Adverse Drug Reactions Reported During Ravulizumab Treatment - PNH and aHUS Combined (Safety Set)

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	Abdominal pain, Vomiting, Dyspepsia	NA
General disorders and administration site conditions	Pyrexia, Fatigue	Influenza like illness, Asthenia	Chills
Infections and infestations	Upper respiratory tract infection, Nasopharyngitis	NA	Meningococcal infection, Meningococcal sepsis
Musculoskeletal and connective tissue disorders	NA	Arthralgia, Back pain, Myalgia, Muscle spasms	NA
Nervous system disorders	Headache	Dizziness	NA
Skin and subcutaneous tissue disorders	NA	Rash, Pruritus	NA

Discontinuation due to adverse events

There were no AEs leading to withdrawal of study drug during the Primary Evaluation Period. No AEs led to interruption or permanent discontinuation of study drug during the Primary Evaluation Period.

No AEs led to the interruption of study drug infusion during the Primary Evaluation Period.

Post marketing experience

Overall, the estimated exposure to ravulizumab since the first Marketing Authorization (21 Dec 2018) through 30 Jun 2020 was 1529.4 patient-years (PY) for PNH and aHUS indications (Periodic Benefit-Risk Evaluation Report [PBRER]).

Alexion closely monitored the following risks for ravulizumab in the postmarketing setting:

- Important identified risk: Meningococcal infection
- Important potential risks: Serious haemolysis after drug discontinuation in PNH patients, severe thrombotic microangiopathy (TMA) complications in aHUS patients after ravulizumab discontinuation, immunogenicity, serious infections, and malignancies and hematologic abnormalities in PNH patients
- Missing information: Use in pregnant and breast-feeding women

Meningococcal infection: Two patients reported meningococcal infection in the postmarketing setting (serotype: non typeable). The events were reported within approximately 10 months to 6 years of first dose of ravulizumab for PNH, and within approximately 3.5 to 3.8 years of first meningococcal vaccination. Administration of a meningococcal vaccination at least 2 weeks prior to or at the time of ravulizumab administration was confirmed in both the patients. Both patients were noncompliant with the antibiotic prophylaxis.

- One patient who had meningococcal infection was reported with a history of meningococcal infection prior to 2 years while on eculizumab treatment. The physician reported that the patient was "more likely a carrier of Neisseria." The event was reported as resolved.
- One patient had meningococcal sepsis, which was fatal. The patient experienced rapidly progressive multiorgan failure, which was refractory to vasopressors and broad spectrum antibiotics. Family members of the patient decided to allow for natural death. The cause of death was reported as Neisseria meningitis septic shock, complicated by aplastic anaemia and PNH.

As of 30 Jun 2020, the cumulative postmarketing rate of meningococcal infection was approximately 0.13 per 100 PY (2 patients per 1529.4 PY). This reporting rate was within the postmarketing meningococcal rate observed with eculizumab treatment (0.30 per 100 PY). Long term postmarketing experience with eculizumab showed stable overall reporting rates of meningococcal infections in eculizumab-treated patients over the past 10 years at approximately 0.3 to 0.5 per 100 PY with the reporting rate for fatal outcomes at 0.03 per 100 PY representing 9.2% of patients who experienced meningococcal infections, similar to the proportion of fatal events in the general population (10% to 15%).

The understanding and characterization of this risk remain unchanged based on the cumulative data. Mitigation measures of the risk of meningococcal infections appear appropriate and effective.

2.5.1. Discussion on clinical safety

The safety dataset in support for this new claimed indication for treatment of paediatric patients with PNH with ravulizumab is mainly based on data from the 26-week primary evaluation period of Study ALXN1210-PNH-304 (DBL 27-May-2020) for 12 patients. The study is still ongoing and patients are to be followed for up to 4 years in the long-term extension period, so the MAH later provided updated safety data up to the 52-week evaluation period (DBL 4-Mar-2021), including the 13th enrolled patient for whom safety data was not available at the initial cut-off date.

As supportive data, a summary of safety results from four clinical studies with ravulizumab in adults with PHN (N=261) and other two studies, one in adults (N=58) and one in paediatric patients (N=31) with aHUS, have been submitted. Therefore, a total of 362 patients have received, at least, one dose of ravulizumab within clinical trials.

All 13 patients received the four planned infusions up to the 26-week primary evaluation period with a mean treatment duration of 183.4 days. There were only two infusion interruptions but due to

technical issues, not related to treatment. The median treatment duration up to the 52-week evaluation period was 737 (341, 1107) days.

Eight eculizumab-treated patients were included, only one of them was <12 years old and below 40 kg weight, and four C5-inhibitor treatment-naive patients with, also one below 12 years and 34 kg. Overall, safety data of ravulizumab for PNH treatment are considered limited, especially for children (<12). Ravulizumab treatment is weight-based. In Study ALXN1210-PNH-304, 2 patients between 30 and 40 kg were included, 6 patients from 40 to 60 kg and 4 patients in the range 60-100 kg. No safety data for PNH patients under 30 kg is available.

During the Primary Evaluation Period, 83.3% (10/12) of patients experienced at least 1 AE (47 events) and 25% (3/12) of patients experienced any SAE. There were no deaths or discontinuations due to adverse events. The most common AEs, by SOC, were infections and infestations (9 patients, 75.0%) and gastrointestinal disorders (4 patients, 33.3%). Six patients reported upper respiratory tract infections (URTIs) during the Primary Evaluation Period and two reported abdominal pain. Three patients (25%) experienced Grade 3-4 AEs and details were submitted: one event of Grade 3 anaemia and two of infections.

Causality of AEs was established by the investigator and AEs were considered as related to treatment in four patients (33.3%). These were related to administration site conditions and device-related infection in one patient and to viral infections for the other two subjects.

The only AESI, based on previous data, for ravulizumab is meningococcal infection but none of the 12 patients analysed experienced this event up to the DBL. There were no changes to the frequency of ADRs with the inclusion of the 12 paediatric patients and no immunogenicity have been observed.

Supportive data, as mentioned, have been included to assess the safety profile of ravulizumab in these patients. In addition, data from 7 eculizumab studies in paediatric and adult patients with PNH or aHUS have been provided. Overall, ravulizumab safety profile in children and adolescents is based on 31 paediatric patients treated with ravulizumab for aHUS, 7 eculizumab treated paediatric patients for PNH and 28 eculizumab treated for aHUS.

For the pooled ravulizumab PNH studies, AEs incidences were similar to the ones observed in Study ALXN1210-PNH-304: 87.8% of patients experienced at least 1 TEAE, most of them Grade 1-2 and unrelated to treatment. No patients died or discontinued treatment during the primary evaluation period although 2 patients died during the extension period: due to lung cancer and pulmonary sepsis. In Study ALXN1210-PNH-201, 2 patients had meningococcal infections but the treatment was not interrupted. Regarding studies with aHUS patients, 98.6% experienced at least one TEAE, most of them also Grade 1-2 and unrelated to treatment. Four patients died in Study ALXN1210-aHUS-311 and 4 patients had SAEs that led to discontinuation. In the paediatric Study ALX1210-aHUS-312, one patient reported anaemia and one hypertensive crisis that led to discontinuation of treatment in the primary analysis. Hypertension was commonly reported across the aHUS studies.

Due to the limited available data (N=2), characterization of ravulizumab safety profile in children (<12 years) with PNH is difficult and needs to be mainly assessed on the basis of data from 22 paediatric patients enrolled in the aHUS study ALXN1210-312. In that study, 14 patients <20 kg of weight were included, a weight range that included no patients in Study ALXN1210-PNH-304.

Updated safety results from the 52-week evaluation period were provided during the procedure, these data accounted for a median treatment duration of 529 days for the treatment-naïve cohort (N=5) and 899 days for the eculizumab-experienced patients (N=8). Data from the 13th enrolled patient were included in this update, since this subject had not reached the primary evaluation period (26 weeks) at the first data cut-off. Overall, no relevant changes were identified in the ravulizumab safety profile in

this population with longer follow-up. All 13 patients experienced at least 1 treatment-emergent adverse event (TEAE), with 3 patients (23.1%) experiencing a total of 8 serious adverse events (SAEs). Abdominal pain, nasopharyngitis and headache were the most frequently reported adverse events (AEs), each experienced by 3 (23.1%) patients in total. One new SAE of breakthrough haemolysis (BTH) occurred in an eculizumab-experienced patient on Day 666. The SAE resolved and the investigator assessed the event as possibly related to the study drug since there was no complement activating condition for the BTH. As of 04 Mar 2021, no patient died and none discontinued the study due to AEs. No patient had meningococcal infection through the data cut-off date. No new ADRs were identified during this period. However, the MAH was asked to update the tabular safety information including this patient, up to the 52-week evaluation period in order to reflect these data on the assessment report.

No patients had antidrug antibodies (ADA) positive response through Day 911 visit of ravulizumab

Treatment and no relevant differences regarding laboratory parameters were observed.

Overall, no relevant differences have been found between safety data from Study ALXN1210-PNH-304 and previous studies with ravulizumab or eculizumab. No new adverse reactions have been identified.

2.5.2. Conclusions on clinical safety

Ravulizumab safety data for paediatric patients with PNH, based on Study ALXN1210-PNH-304, is in line with that reported during treatment of adults with PNH and adults and children with aHUS. The frequency of AEs was consistent with the reported in the previous studies. There were no deaths, no treatment discontinuations and no cases of meningococcal infections up to the primary evaluation period. No new safety concerns were identified.

However there is limited safety data in PNH children under 12 years and no data for patients <30 kg weight. Also, long-term safety data would allow confirming the observed effects.

Overall evaluation of the cumulative data regarding the important identified risk/potential risks of meningococcal infections associated with ravulizumab treatment, the benefit-risk balance of ravulizumab continues to be positive and favourable for the chronic treatment of patients with complement-mediated disorders including PNH and aHUS under the recommended conditions of use.

The following measures are considered necessary to address issues related to safety:

The observational study M07-001: Paroxysmal Nocturnal Hemoglobinuria (PNH) Registry as cat. 3 additional PV activity in the RMP studies patients of any age will collect and evaluate further safety data. Primary analyses assess safety endpoints, including occurrence and time to first event for the following: meningococcal infections, infections with serious outcomes, formation of HAHA or ADA to SOLIRIS / ULTOMIRIS, malignancy, thrombotic events, pulmonary hypertension, impaired renal function, serious haemolysis, pregnancies, infusion reactions, targeted adverse events, bone marrow transplant, and mortality. In addition, all serious adverse events, regardless of causality, will be collected to search for unknown safety concerns. Secondary analyses will include descriptions of patient populations, PNH specific treatments, concomitant medications, progression of disease, PNH clone sites, clinical symptoms, and clinical outcomes.

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 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 2.1 is acceptable. The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content:

Safety concerns

Table 23: 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 24: Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 – required additional pharmacovigilance activities				
PNH extension safety study in treatment naïve patients ALXN1210-PNH-301 Ongoing	To evaluate the safety and efficacy of ALXN1210 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 Ongoing	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" Ongoing	To collect and evaluate safety data specific to the use of SOLIRIS / ULTOMIRIS and to collect data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in SOLIRIS / ULTOMIRIS and non-SOLIRIS /	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	Interim data analysis	Every 2 years interim data analysis report

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	ULTOMIRIS treated patients.			
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 25: 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 – PNH/aHUS Parent's Information Brochure – Patient 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 – PNH Parent'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 Additional risk minimisation measures Educational materials – PNH/aHUS Physician's Guide – PNH/aHUS Patient's Information Brochure – PNH/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 – PNH/aHUS Parent's Information Brochure
Malignancies and haematologic abnormalities in PNH patients	Routine risk minimisation measures None proposed Additional risk minimisation measures: – PNH Physician's Guide – PNH Patient's Information Brochure – PNH Parent's Information Brochure

Safety Concern	Risk Minimisation Measures
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

Abbreviations: aHUS = atypical haemolytic uraemic syndrome; PNH = paroxysmal nocturnal haemoglobinuria; PL = package leaflet; SmPC = summary of product characteristics.

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 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- the PIL is sufficiently similar in both content and layout to the currently approved one, based on previous user consultation assessed:
    - Initial MAA of Ultomiris user consultation,
    - Both user bridging testing carried out as part of the subsequent Type II variation to extend Ultomiris indication to patients with atypical haemolytic uremic syndrome and the marketing authorisation extension application to add 2 new presentations of Ultomiris (300 mg/3 mL and 1,100 mg/11 mL)

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Treatment of adult and paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH):

- in patients with haemolysis with clinical symptom(s) indicative of high disease activity.
- in patients who are clinically stable after having been treated with eculizumab for at least the past 6 months (see section 5.1).

3.1.2. Available therapies and unmet medical need

Terminal complement inhibitor and allogenic bone marrow transplantation are the only widely effective therapies for patients with classical PNH.

Eculizumab was the first C5 inhibitor to be evaluated as treatment option in paediatric patients with PNH. Eculizumab (Soliris), is humanized monoclonal antibody (mAb) that specifically targets C5 of the terminal complement cascade, which was first approved in the EU in 2007. Eculizumab is the only approved medicinal product for PNH in children in the EU.

3.1.3. Main clinical studies

The main study in support of this submission is **study ALXN1210-PNH-304**. This is a Phase 3, open-label, single-arm study in paediatric patients (< 18 years and weighing ≥5 kg) with PNH. In this study both eculizumab-experienced and eculizumab treatment-naïve patients were included.

The study consisted on a 4-week screening period, a 26-week Primary Evaluation Period and an extension period of up to 4 years. Through the current submission, results from the Primary Evaluation Period have been provided, with a data cut-off of 27 May 2020. During the procedure, updated efficacy data through the Extension Period were submitted. Results presented below are from the Primary Evaluation Period.

The primary objective of the study was to assess PK and PD of ravulizumab in paediatric patients with PNH. Efficacy was a secondary objective in this study. Efficacy endpoints included percent change from baseline in LDH, transfusion avoidance, quality of life (using the Paediatric FACIT-Fatigue Questionnaire), stabilised haemoglobin, percent change in free haemoglobin and breakthrough haemolysis. All analyses were performed through the end of the Primary Evaluation Period (Day 183). Results presented are based on 13 patients (5 eculizumab-naïve and 8 eculizumab-experienced) in the study.

3.2. Favourable effects

Eculizumab-naïve patients

- The mean (SD) LDH percent (%) change from baseline was -47.91 (52.716).
- There were 3 (60%) patients who remained transfusions free at day 183.
- There were 3 (60%) patients who achieved haemoglobin stabilisation.
- Free C5 level normalised shortly after the first ravulizumab infusion and remained in the normal range during the 26 weeks of the study.

Eculizumab-experienced patients

- The mean (SD) LDH percent (%) change from baseline was +4.65 (44.70).
- All patients remained transfusions free at day 183.
- There were 6 (75%) patients who achieved haemoglobin stabilisation.

No events of breakthrough haemolysis were reported during the Primary Evaluation Period.

Less frequent IV infusions in 8-week-intervals may reduce the risk of missed doses and also may be associated with improved treatment adherence.

3.3. Uncertainties and limitations about favourable effects

One of the main limitations of this study is the lack of control arm and the limited sample size. However, due to the rarity of the disease in children, this design is acknowledged.

Clinical data in children <12 years are limited. Patients included in the study were between 9 and 17 years, with a median weight of 57.10 kg (range: 37.7, 72.0) and, even if in line with the agreed PIP, only two of them were under 12 years (1 eculizumab-naïve and 1 eculizumab-experienced).

Registry study M07-001 aims to collect and evaluate clinical outcomes and characterise the progression of PNH in Ultomiris treated PNH patients, including paediatric patients.

3.4. Unfavourable effects

All of the 13 patients reported at least one adverse event (AE) in Study ALXN1210-PNH-304 up to the 52-week evaluation period. Most AEs were Grade 1 or Grade 2 in severity. Five (38.5%) patients had AEs assessed by the Investigator to be related to study drug.

Three patients experienced 1 or more serious adverse events (SAEs) (device related sepsis, staphylococcal infection, multiple organ dysfunction syndrome, septic shock, and device related thrombosis in 1 patient; influenza A virus test positive in 1 patient; and viral upper respiratory tract infection [URTI] in 1 patient).

The most frequently reported AEs belonged to the Infections and infestations SOC (11 patients, 84.6%) and Gastrointestinal disorders SOC (6 patients, 46.2%). Abdominal pain and nasopharyngitis were each experienced by 3 (23.1%) patients. Most of the other AEs were reported by 1 patient each. Three (23.1%) patients experienced AEs of Grade 3: device-related sepsis, anaemia and influenza A virus test positive; and 2 (15.4%) patients reported any AE of a Grade 4 severity.

3.5. Uncertainties and limitations about unfavourable effects

Safety data provided is based on the 52-week evaluation period of Study ALXN1210-PNH-304 and no longer-term safety data for treatment of paediatric patients with PNH is available.

From the 13 patients included (eight previously treated with eculizumab and five treatment-naïve), only two patients were <12 years (the rest were adolescents) and no patients with <30 kg weight were included in the study so safety assessment rely on data reported from ravulizumab studies in paediatric patients with aHUS and adults with PNH.

Two patients had elevated LDH-level at Day 183 without any signs and/or symptoms of breakthrough haemolysis. None of them met the definition of breakthrough haemolysis (BTH) per protocol. Table-Top Haemolysis could not be assessed for the interim analysis supporting the initial submission and will be determined when conducting the analysis for final CSR.

Data with longer follow-up could be of interest taking into account this is a chronic treatment, as some important risks were identified in the extension period of different ravulizumab studies. The observational study M07-001: Paroxysmal Nocturnal Hemoglobinuria (PNH) Registry as cat. 3 additional PV activity in the RMP studies patients of any age will collect and evaluate further safety data (see RMP).

3.6. Effects Table

Table 26 Effects Table for treatment with ravulizumab in paediatric patients with PNH (data cut-off: 04 Mar 2021)

Effect	Short description	Unit	Complement inhibitor naïve (n=5)	Ecu exp (n=8)	Uncertainties / Strength of evidence	References
Favourable effects*						
%LDH	Percentage change in LDH from baseline to Day 183 (Week 26)	Mean (SD)	-47.91 (52.716)	+4.65 (44.70)	Clinical data in children (i.e. <12 years) are limited. Patients included in the study were between 9 and 17 years, only two of them were under 12 years (1 eculizumab-naïve and 1 eculizumab-experienced) The lack of control arm and the limited sample size, hinder the appropriate interpretation of the results. Due to the rarity of the disease in children, this design is acknowledged.	
TA	Transfusion avoidance	n (%)	3 (60)	8 (100)		
HGB-S	Haemoglobin stabilization	n (%)	3 (60)	6 (75)		
Unfavourable effects						
AEs	Adverse events	%	100	100	Safety data provided is based on the 52-week evaluation period of Study ALXN1210-PNH-304. No long-term safety data for treatment of paediatric patients with PNH have been provided.	
Related AEs	Adverse events related to study drug	%	20	62.5		
Grade 3 AEs	Adverse events of grade 3	%	20	25		
Grade 4 AEs	Adverse events of grade 4	%	20	12.5		
SAEs	Serious adverse events	%	20	37.5		
Infections and infestations	Common adverse event	%	80	87.5		

Efficacy data presented are based on the Primary Evaluation Period (Day 183).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Results of the study ALXN1210-PNH-304 showed a response in paediatric patients with PNH. However, data are based on patients between 9 and 17 years and a body weight over 30 kg. Therefore, there are no clinical data in children with PNH and a lower weight. In order to further support the proposed posology in patients with PNH weighting < 30 kg the MAH has performed an extrapolation exercise of PK/PD data from adult patients with PNH and paediatric/adult patients with aHUS to paediatric patients with PNH.

Overall, the safety profile of ravulizumab in paediatric patients with PNH appears consistent with that observed in adult patients with PNH and paediatric and adult patients with aHUS.

3.7.2. Balance of benefits and risks

The observed benefit is considered to outweigh the unfavourable effects of ravulizumab in paediatric patients with PNH. However, data are based on a low number of patients and no experimental data are available in patients weighting <30 kg.

Complete complement C5-inhibition was developed/maintained for all of them as assessed by the free C5 level measurements showing that the PD endpoint of the study was reached for all patients. Overall, LDH level was mainly declined in eculizumab-naive patients and the baseline of lowered LDH-level was maintained in the eculizumab-experienced ones. Efficacy has also been observed in terms of transfusions avoidance and haemoglobin stabilisation, although data in complement inhibitor-naïve patients are even more limited.

Safety characteristics of ravulizumab seem to be similar to that observed in adult PNH as well as in adult and paediatric aHUS studies.

Less frequent IV infusions in 8-week-intervals may reduce the risk of missed doses and also may be associated with improved treatment adherence.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Ultomiris in the applied indication of treatment of paediatric PNH patients 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 for Ultomiris to include treatment of paroxysmal nocturnal haemoglobinuria (PNH) in paediatric patients with a body weight of 10 kg or above; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, Annex II is updated to reflect the agreed educational material (addition of a "Parent guide"). Version 2.1 of the RMP has also been submitted, in order to include the new indication.

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

Amendments to the marketing authorisation

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

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.

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

The educational and controlled distribution programmes are 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 or use Ultomiris have access to/are provided with the following educational package to be disseminated through professional bodies:

- Physician educational material
- Patient/parent 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 safety concerns 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 meningitis.
  - 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. Male patients should not father a child or donate sperm 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 malignancies and haematologic abnormalities in PNH patients and 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 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 and aHUS registries
  - 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
- A Patient card

- **The patient guide** shall contain the following key messages:
  - To address the safety concerns 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. Male patients should not father a child or donate sperm 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 and aHUS registries.
- **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 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 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.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0399/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

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 'Ultomiris-H-C-004954-II-0010'

Attachments

1. SmPC, Annex II, Labelling, Package Leaflet (changes highlighted) as adopted by the CHMP on 22 July 2021.