30 March 2023
EMA/201701/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ultomiris

International non-proprietary name: ravulizumab

Procedure No. EMEA/H/C/004954/X/0027/G

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

ADA antidrug antibody

ADE adverse device effect

ADL activities of daily living

AE adverse event

AESI adverse event of special interest

aHUS atypical hemolytic uremic syndrome

BP blood pressure

BTH breakthrough hemolysis

C5 complement component 5

CAC complement amplifying condition

CFR Code of Federal Regulations

CI confidence interval

CIOMS Council for International Organizations of Medical Sciences

CMP Clinical Monitoring Plan

COVID-19 coronavirus disease 2019

CRF case report form

CRO contract research organization

CSR clinical study report

Ctrough trough serum concentration

E (total number of) events

ECG electrocardiogram

eCRF electronic case report form

e-diary electronic diary

eGFR estimated glomerular filtration rate

EORTC European Organisation for Research and Treatment of Cancer

ET early termination

FACIT-Fatigue Functional Assessment of Chronic Illness Therapy-Fatigue scale

FAS Full Analysis Set

GCP Good Clinical Practice

HIPAA Health Insurance Portability and Accountability Act

HRQoL health-related quality of life

ICF informed consent form

ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IEC Independent Ethics Committee

IRB Institutional Review Board

ISO International Organization for Standardization

IV intravenous(ly)

LDH lactate dehydrogenase

LSM least squares mean

mAb monoclonal antibody

MAVE major adverse vascular event

MedDRA Medical Dictionary for Regulatory Activities

NO nitric oxide

OBDS on-body delivery system

PD pharmacodynamic(s)

PK pharmacokinetic(s)

PNH paroxysmal nocturnal hemoglobinuria

pRBC packed red blood cell(s)

PY patient-years

QTcF QT interval corrected for heart rate using Fridericia's formula

qw every week

q8w once every 8 weeks

QLQ-C30 Quality of Life Questionnaire - Core 30 scale

QoL quality of life

RBC red blood cell

SAE serious adverse event

SAP Statistical Analysis Plan

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2

SC subcutaneous(ly)

SMQ Standardised MedDRA Query

SoA schedule of activities

SOC System Organ Class

TASQ Treatment Administration Satisfaction Questionnaire

ULN upper limit of normal

1. Background information on the procedure

1.1. Submission of the dossier

Alexion Europe SAS submitted on 15 February 2022 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation:

Variation(s) requested		Type
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Extension application to introduce a new pharmaceutical form (solution for injection) associated with new strength (245 mg), pharmaceutical form and route of administration (subcutaneous use), grouped with a type II variation (C.I.4) to align the Summary of product characteristics and Labelling of Ultomiris intravenous formulation (IV) with the proposed Ultomiris subcutaneous formulation (SC). The RMP (version 7.0) is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.3.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0239/2021 and P/0238/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP C2-001943- PIP01-16-M06 and C3-002077-PIP01-16-M04 was completed.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report, addressing the possible similarity with authorised orphan medicinal products. Assessment of these claims is appended.

1.5. Scientific advice

The MAH received Scientific advice from the CHMP on the development for the indication from the CHMP on 14 September 2017 (EMEA/H/SA/3331/1/FU/2/2017/PA/III) and 26 August 2018 (EMEA/H/SA/3331/3/FU/1/2018/PA1). The Scientific advice pertained to quality, non-clinical, and clinical aspects.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Blanca Garcia-Ochoa Co-Rapporteur: N/A

The application was received by the EMA on	15 February 2022
The procedure started on	24 March 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 June 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	21 July 2022
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	21 July 2022
The MAH submitted the responses to the CHMP consolidated List of Questions on	11 August 2022
The PRAC Rapporteur circulated the PRAC Rapporteur's Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	19 September 2022
The CHMP Rapporteur circulated the CHMP Rapporteur's Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	23 September 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 September 2022
– The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	13 October 2022
The MAH submitted the responses to the CHMP List of Outstanding Issues on	21 December 2022
The CHMP Rapporteur circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	16 January 2023
The CHMP agreed on a second list of outstanding issues in writing to be sent to the MAH on	26 January 2023
The MAH submitted the responses to the second CHMP List of Outstanding Issues on	28 February 2023
The CHMP Rapporteur circulated the Assessment Report on the responses to the second List of Outstanding Issues to all CHMP members on	16 March 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ultomiris on	30 March 2023
The CHMP adopted a report on similarity of Ultomiris with Aspaveli and Soliris on	30 March 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The MAH is submitting a Marketing Authorisation Extension Application for the addition of a new strength (245 mg/3.5 mL; 70 mg/ mL) and route of administration (subcutaneous use) for Ultomiris (ravulizumab) for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) or atypical haemolytic uremic syndrome (aHUS).

The following indications for the subcutaneous formulation were initially proposed:

Ultomiris subcutaneous formulation (Ultomiris SC) is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH):

- *in patients with haemolysis with clinical symptom(s) indicative of high disease activity.*
- *in patients who are currently treated with eculizumab or with ravulizumab intravenous formulation (Ultomiris IV).*

Ultomiris SC is indicated in the treatment of adult patients with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or are currently treated with eculizumab or ravulizumab IV.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Paroxysmal nocturnal haemoglobinuria (PNH) is a very rare and life-threatening disease in which uncontrolled complement activation leads to systemic complications, principally through intravascular haemolysis and thrombophilia.

The prevalence of PNH is estimated at 15.9 cases per million individuals in Europe and occurs more frequently in Asia than in western countries. The median age of PNH onset is the early to mid 30s; however, patients of all ages may develop the disease (Schrezenmeier, 2014; Socie, 1996).

Patients with PNH are at risk of substantial morbidity and mortality. Before the availability of eculizumab, mortality in several cohorts of patients with PNH approached 35% at 5 years, with a median survival of 10 years after diagnosis (de Latour, 2008; Hillmen, 1995; Socie, 1996). Patients with PNH have a decreased quality of life (QoL), which may include the inability to support themselves and social isolation due to debilitating fatigue, chronic pain, poor physical function, shortness of breath, abdominal pain, erectile dysfunction, frequent therapeutic interventions and hospitalization (Weitz, 2012).

Atypical haemolytic uremic syndrome (aHUS; ICD-10 classification: D58.8) is a rare, progressive, and life-threatening disorder characterized by haemolytic anaemia, thrombocytopenia, acute renal injury, and extra-renal complications (Muus, 2013; Noris, 2009; Sellier-Leclerc, 2007). aHUS prevalence in the age group of 20 years or younger was described ranging from 2.2 to 9.4 per million population, while the only study that reported prevalence in all ages showed a prevalence of 4.9 per million population (Yan, 2020).

Most cases of aHUS are caused by uncontrolled complement activation due to genetic mutations in the alternative pathway of complement. More recently, mutations in the gene of coagulation system have also been identified in patients with aHUS. There is a dysregulation of the alternative pathway of

complement, resulting in uncontrolled complement activation (Campistol, 2015; Noris, 2009; Zuber, 2012; George 2014). This uncontrolled complement activation causes inflammation, endothelial activation and damage, and a prothrombotic/procoagulant state resulting in systemic thrombotic microangiopathy (TMA; Noris, 2009; Stahl, 2008; Karpman, 2006; Licht, 2009). Approximately 20% to 48% of patients are reported to have signs and symptoms of damage to extra-renal organs at presentation, including elevated liver or pancreatic enzymes, pericarditis, intra-alveolar hemorrhage, seizures, altered consciousness, and focal neurologic deficits (Loirat, 2011; Brodsky, 2015; Fidan, 2018; Fremeaux-Bacchi, 2013). In many cases, multiorgan dysfunction is associated with poor prognosis and necessitates critical care. It is classified as a thrombotic microangiopathy (TMA).

2.1.3. Biologic features, Aetiology and pathogenesis

Paroxysmal nocturnal haemoglobinuria (PNH) is caused by a somatic mutation of the phosphatidylinositol glycan A (PIG-A) gene, located in the X-chromosome, that leads to a lack of CD55 and CD59 (Hill, 2013), which are key, naturally occurring terminal complement inhibitor proteins on cell surfaces. The absence of these complement inhibitor proteins on the cell surface results in continuous activation of the alternative complement pathway, chronic intravascular haemolysis and an increased propensity for clot formation (Borowitz, 2010; Wyrick-Glatzel, 2006).

Atypical hemolytic uremic syndrome (aHUS) is a severe disorder that frequently has a genetic component and results from the overactivation of the alternative complement pathway (Raina R, 2019; Yoshida Y, 2019). The disease primarily affects kidney function and is characterized by hemolytic anemia, thrombocytopenia, and renal impairment (Noris M, 2005).

2.1.4. Clinical presentation, diagnosis and prognosis

PNH is a debilitating, and life-threatening disease in which uncontrolled terminal complement activation leads to systemic complications, principally through intravascular haemolysis and thrombophilia (Brodsky, 2014; Brodsky, 2015). Effective treatment of PNH requires immediate, complete, and sustained inhibition of terminal complement activity to block haemolysis and prevent thrombosis.

Anaemia in PNH is often multifactorial and can result from a combination of haemolysis and bone marrow failure.

Granulocytopenia and thrombocytopenia are common and reflect deficient haematopoiesis. Clinical haemoglobinuria is intermittent in most patients and never occurs in some, but haemosidenuria is usually present.

Thromboembolic events are the leading cause of death in patients with PNH, and pulmonary hypertension and end-organ damage of vital organs, such as the liver, kidneys, brain, and intestines, are sequelae of thromboembolic events.

aHUS is characterized by hemolytic anemia, thrombocytopenia, acute renal injury, and extra-renal complications (Muus, 2013; Noris, 2009; Sellier-Leclerc, 2007). The predominant underlying cause of aHUS is dysregulation of the alternative pathway of complement, resulting in uncontrolled complement activation (Campistol, 2015; Noris, 2009; Zuber, 2012; George 2014). The main objective of effective treatment for aHUS with complement-targeted therapy is to provide immediate, complete, and sustained inhibition of terminal complement activity to treat and maintain patients with complement mediated TMA.

2.1.5. Management

The only approved drug for PNH, eculizumab (Soliris), was approved in 2007 in the EU. Eculizumab is a selective, humanized mAb that specifically targets C5 of the terminal complement cascade, inhibiting its cleavage during complement activation into C5a and C5b. Prior to the introduction of eculizumab (Soliris), the treatment of PNH was mainly supportive, aiming to control the clinical manifestations of the disease (management of haemolysis, anaemia, thrombophilia, and bone marrow failure). This supportive treatment included blood transfusion, administration of erythropoiesis-stimulating agents, corticosteroids, or anabolic steroids, iron therapy, thrombosis prophylaxis, and thrombolytic therapy.

Although the only available curative approach for PNH is allogeneic haematopoietic stem cell transplantation (HSCT), it is not recommended as upfront therapy in the eculizumab era given the risks of transplant-related morbidity and mortality. HSCT is a reasonable therapeutic option in patients who do not respond to therapy with eculizumab or those patients who have severe pancytopenia due to underlying BMF. The transplant paradigm pursued is often with reduced-intensity conditioning regimens, as myeloablation is not required to eradicate the PNH clone. In the current scenario, the use of HSCT may be revisited in the future as patients and healthcare providers weigh the cost-benefit ratio of HSCT versus a lifetime anti-C5 therapy.

In the case of aHUS, the first approved treatment was eculizumab. When eculizumab was approved for aHUS in 2011, it was the first treatment for life-threatening complement-mediated TMA events. Prior to eculizumab, treatment of aHUS was limited to plasma therapy, though its clinical benefit had not been established. Since the approval of eculizumab, patients with aHUS are probably no longer treated with long-term plasma therapy, which can transiently maintain normal levels of hematologic measures while the underlying complement dysregulation and thrombotic microangiopathic processes likely persist (Loirat, 2010).

Ravulizumab IV was approved in 2019 for PNH and in 2020 for aHUS, with a more convenient administration schedule.

2.2. About the product

Ravulizumab is a human recombinant monoclonal antibody (mAb) IgG2/4K that specifically binds to the complement protein C5, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]) and preventing the generation of the C5b-9. By binding specifically to C5, ravulizumab antagonizes terminal complement-mediated inflammation, cell activation, and cell lysis while preserving the early components of complement pathway activation that are essential for opsonization of microorganisms and clearance of immune complexes (Pharmacotherapeutic group: Selective immunosuppressants; ATC code: L04AA43).This mechanism of action provides the therapeutic rationale for the use of ravulizumab to treat diseases in which activation of terminal complement plays an etiologic role.

Ultomiris (ravulizumab, 10 mg/mL, for IV use) was initially approved for the treatment of PNH in the EU in July 2019 (EU/1/19/1371/001) and was subsequently approved on 25 June 2020 for the treatment of patients with a body weight of 10 kg or above with aHUS who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab (EMEA/H/C/004954/II/0002). On 18 Nov 2020, a higher concentration (100 mg/mL) of ravulizumab was approved (EU/1/19/1371/002 and /003).

A subcutaneous administration (ravulizumab SC, 70 mg/mL) has been developed to provide an alternative route of administration for adult patients with PNH or aHUS. Ravulizumab SC provides an alternative route of administration for adult patients with PNH and aHUS. It is a drug-device

combination product (ravulizumab on-body delivery system, also referred to as ravulizumab SC) comprised of a prefilled cartridge containing 70 mg/mL ravulizumab (drug constituent) co-packaged with a single-use on-body injector (OBI, device constituent). In the context of combination product development and assessment, the primary mode of action of ravulizumab SC is the drug constituent, ravulizumab.

In the EU, the drug product (ravulizumab) of the drug-device combination (ravulizumab SC) is regulated as a medicinal product per directive 2001/83/EC, and the administration device (OBI) of ravulizumab SC is regulated as a medical device in accordance with Article 1(9) of the Medical Device Regulation (MDR) EU 2017/745.

2.3. Type of Application and aspects on development

Ultomiris® (ravulizumab, 10 mg/mL, for IV use) was initially approved for the treatment of PNH in the EU on 02 Jul 2019 (EU/1/19/1371/001) and was subsequently approved for the aHUS indication on 25 Jun 2020.

On 18 Nov 2020, a formulation with a new strength of ravulizumab, 100 mg/mL, was approved (EU/1/19/1371/002 and /003). On 01 Sep 2021, Ultomiris was approved for the PNH indication in paediatric patients with a body weight of 10 kg or above [EU/1/19/1371 - EMEA/H/C/004954/II/0010].

This extension of the Marketing Authorisation concerns a new route of administration (subcutaneous injection) associated with a new strength (245 mg/3.5 mL (70 mg/ mL)) for Ultomiris. The clinical development program for ravulizumab SC is based on Study ALXN1210-PNH-303, a randomized, parallel group, open-label, multicenter, study to establish the non-inferior pharmacokinetics (PK) of ravulizumab SC as compared to ravulizumab IV in adult patients with PNH who are clinically stable and have been treated with eculizumab for at least 3 months prior to study entry.

With regards to Ultomiris SC development, scientific advice was received on 14 Sep 2017 on the proposed clinical development and registration data package based on bridging the safety and efficacy data from Ultomiris IV on the basis of PK non-inferiority principles (EMEA/H/SA/3331/1/FU/2/2017/PA/III):

- The overall approach for development of the SC formulation of Ultomiris was endorsed by the Committee for Medicinal Products for Human Use (CHMP) and agreed that available nonclinical data were expected to be sufficient to support the authorization of the Ultomiris SC formulation.
- The proposed Phase 3 study design was considered adequate and acceptable. It was agreed that efficacy of the IV formulation of Ultomiris can be bridged to that of the SC formulation by establishing non-inferior PK exposure on the basis of trough concentration (Ctrough) between IV and SC formulations of Ultomiris, and that the non-inferior PK exposure as measured by Ctrough is an acceptable primary endpoint for the proposed registration trial.

A second follow-up scientific advice was received on 26 Jul 2018 on the proposed device development aspects for the Ultomiris SC formulation in the treatment of adult patients with PNH, administered using an OBDS (EMEA/H/SA/3331/3/FU/1/2018/PA/I). The CHMP:

- considered the proposed design of the human factor (HF) study acceptable to confirm the usability of the OBDS by simulating the in-use conditions.
- confirmed the proposed drug-device stability plan and design verification testing (DVT) strategy were appropriate for the Phase 3 clinical study.

- acknowledged the proposed device information to support registration of Ultomiris OBDS. However, the adequacy of the OBDS documentation will be decided at the time of the MAA assessment.

2.4. Quality aspects

2.4.1. Introduction

Alexion Europe SAS, the Marketing Authorisation Holder (MAH), submitted a Marketing Authorisation Extension Application to implement the addition of a new strength (245 mg/3.5 mL (70 mg/ mL)) and route of administration (subcutaneous use, SC) for Ultomiris (ravulizumab) for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) or atypical haemolytic uremic syndrome (aHUS).

Ultomiris On-Body Delivery System (OBDS) is comprised of a prefilled cartridge (PFC) containing 70 mg/mL ravulizumab co-packaged with a single-use on-body injector (West SmartDose 3.5 Injector), hereafter referred to as "ravulizumab SC" (245 mg/OBDS). The 70 mg/mL strength is obtained by dilution of the ravulizumab 100 mg/mL active substance approved for intravenous (IV) administration with the same excipients (EU/1/19/1371/002 and /003).

The finished product is presented as a sterile, preservative free, pH buffered, aqueous solution containing 70 mg/mL of ravulizumab as active substance. Other ingredients are: sodium phosphate, L-arginine, sucrose and polysorbate 80.

The product is available in a Crystal Zenith (CZ, cyclic-olefin polymer resin) cartridge barrel with a piston, Flurotec film coated septum, and polypropylene cap. The prefilled cartridge (PFC) is used with an on-body injector (OBI) for subcutaneous administration.

2.4.2. Active Substance

This section is not applicable as the submission does not introduce any changes in the active substance part.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and Pharmaceutical Development

Ravulizumab finished product is a solution for injection supplied as a sterile, preservative free, pH buffered, aqueous solution, in a single-dose prefilled cartridge with a single-use on-body injector (OBI). It contains ravulizumab at a concentration of 70 mg/mL (245 mg of ravulizumab/3.5 mL) in sodium phosphate, L-arginine, sucrose, and polysorbate 80, at pH 7.4.

The qualitative composition of the finished product is shown in table below.

Component (Formulation Concentration)	**Quality Standard**	**Function**	**Amount per PFC**
Ravulizumab (70 mg/mL)	In-House Standard	Active Ingredient	245 mg
Sodium phosphate monobasic monohydrate	USP, Ph. Eur.	Buffering Agent	
Sodium phosphate dibasic heptahydrate	USP, Ph. Eur.	Buffering Agent	

Component (Formulation Concentration)	Quality Standard	Function	Amount per PFC
L-arginine	USP, Ph. Eur., JP	Stabilizer	
Sucrose	NF, Ph. Eur., JP	Tonicifying agent and stabilizer	
Polysorbate 80	NF, Ph. Eur., JP	Surfactant	
Water for injection	USP, Ph. Eur., JP	Solvent	QS to 3.5 mL

The finished product container closure system consists of a Crystal Zenith (CZ, cyclic-olefin polymer resin) cartridge barrel with a piston, Flurotec film coated septum, and polypropylene cap. The prefilled cartridge (PFC) is used with an on-body injector (West SmartDose 3.5 Injector) to deliver the product for subcutaneous administration. The on-body injector is a compact, sterile, single-use, disposable, electro-mechanical (battery-powered, microprocessor-controlled) on-body injector with a 29-gauge integrated needle designed to be used together with a prefilled Crystal Zenith cartridge assembled with a piston and telescopic screw assembly.

The on-body injector component must comply with the Medical Device Regulation (EU) 2017/745. The applicant committed to provide the EU certificate of conformity with the response to the Day 120 list of questions or, at the latest, before the CHMP opinion. The EU certificate of conformity for the device component is, however, not yet available. Nevertheless, the applicant has included in the dossier detailed information on the on-body delivery system that support its suitability for the intended use. In addition, the MAH has the responsibility to ensure that the co-packaged device is CE marked in accordance with the relevant EU legislation on medical devices prior to placing the product on the market.

PFC

The finished product composition is the same used for the active substance. No additional formulation steps are included. All excipients are compendial grade and the finished product composition has no overages. Ravulizumab is compatible with all the excipients in the formulation, as demonstrated previously for the already authorised presentations of Ultomiris. There are no physicochemical characteristics or biological properties of the ravulizumab active substance and excipients which influence the performance or manufacturability of the ravulizumab finished product. The formulation of the finished product has remained unchanged during clinical development.

The finished product is manufactured by dilution of the 100 mg/mL active substance in formulation buffer to a target of 70 mg/mL followed by filtration with sterilizing grade filters. This sterile filtered solution is filled into a sterile container closure system, using a filling machine, and stoppered. All manufacturing steps are performed using aseptic techniques and qualified facilities.

The Quality Target Product Profile (QTPP) for ravulizumab and the definition of Critical Quality Attributes (CQA) were performed for the initial marketing authorisation of Ultomiris and remains the same for the SC 70 mg/mL strength. There were no major changes to the manufacturing process throughout clinical development.

The finished product manufacturing process is the commercial finished product manufacturing process. There have been no changes to the process between pre-PPQ (Process Performance Qualification) and commercial manufacturing. No critical process parameters (CPPs) were identified for the finished product manufacturing process after performing a Failure mode and effects analysis (FMEA) exercise. The commercial manufacturing process was validated, as it is described in *Section 3.2.P.3.5 Process Validation and/or Evaluation (3.5 mL/PFC)*. Comparability of the finished product pre- and post-PPQ

has been demonstrated through an analysis of release, extended characterisation and forced degradation studies (by temperature, deamidation and oxidation), using three pre-PPQ lots (the oldest, to add a level of additional robustness to the study) and three post-PPQ lots. Acceptance criteria were met for all assays and the profiles showed comparable peak profiles across all samples.

The finished product is filled into a Crystal Zenith (cyclic-olefin polymer resin) cartridge stoppered with a FluroTec coated piston. The suitability of the container closure system (CCS) is demonstrated by appropriate studies, including stability, light-protection by secondary packaging, chemical resistance, CCS integrity (high voltage leak detection method and the helium leak test), closure suitability and extractable / leachable studies performed on the PFC. Only two compounds were detected in the extractable study. The safety margins for these compounds demonstrate negligible health hazard, which justifies the lack of need for further leachable testing.

Ravulizumab SC is directly administered with the on-body delivery system from the PFC without dilution. Therefore, compatibility studies with other materials apart from the PFC are not required.

Overall, the studies on Pharmaceutical Development performed by the applicant are considered adequate to guarantee the quality of the product, its microbiological attributes, and its compatibility for the intended use.

OBDS

Ravulizumab on-body delivery system (OBDS) consists of the prefilled cartridge (PFC) containing ravulizumab and an on-body injector (OBI). The essential performance requirements were confirmed by design verification activities, demonstrating that the use of ravulizumab with the OBI is safe and effective.

The OBI is intended to be used to deliver through injection a fixed dose of ravulizumab from the PFC.

The assembly process for OBDS is performed with no changes to the process between pre-PPQ and commercial manufacturing. The potential impact of each manufacturing step on product quality was assessed by a FMEA. No CPPs were identified during this evaluation.

An extractable study was conducted on the fluid path assembly (Tygon tube, patient needle and cartridge needle) of the ravulizumab OBDS to evaluate any potential leachables during dosing. Four types of compounds were detected and quantitated. The estimated safety margins for these compounds demonstrate negligible health hazard, which justifies the lack of need for further leachable testing.

The assembly process for ravulizumab OBDS includes the manual addition of a telescopic screw assembly (TSA) to the piston of the PFC. In order to demonstrate that this assembly process does not impact the integrity of the PFC components, supplemental study was successfully completed using the high voltage leak detection method (HVLD) on the PFC post-TSA assembly process on assembled ravulizumab OBDS.

The design inputs for the device constituent and combination product were properly established. Design outputs (specifications) are used for evaluation of the conformance to the design.

A design validation plan for ravulizumab OBDS was defined and executed successfully. Further, a design verification plan was performed to demonstrate that the design outputs meet the design input requirements. The acceptance criteria was based on a pre-defined confidence and reliability level, obtained by a risk-based approach. All Essential Performance Requirements (EPR) activities met their acceptance criteria.

The biological safety of the OBDS was evaluated by a biological risk assessment, including a biocompatibility testing (patient contacting and drug contacting portions of the device), an extractable

and leachables evaluation, and toxicological risk assessment. Results from these studies indicate that the likelihood of a toxic effect from the OBDS is negligible and can be considered safe for the intended use.

A few design enhancements were made from the clinical to the commercial version of ravulizumab OBDS, including modifications to the hardware, software and user interface. A technical assessment was performed to compare the functional performance before and after design enhancements. The assessment included design inputs, design verification and design validation. Based on this analysis, the differences between clinical and commercial presentations would not impact device performance or drug exposure.

A risk analysis was performed, focused on the drug-device interactions and the risk associated with ravulizumab OBDS. The risk analysis methods used included a preliminary hazard analysis and FMEAs, from the use, process and system design perspective. Identified risks were evaluated and were mitigated to acceptable levels by implementing risk control measures. The individual risks had been reduced as far as possible, concluding that the expected benefit of receiving the therapy outweighs each individual risk.

Finally, the potential impact on patient satisfaction was quantified using a patient reported outcome tool, i.e. Treatment Administration Satisfaction Questionnaire (TASQ) score, demonstrating a higher value for the proposed SC route of administration.

2.4.3.2. Manufacture of the product and process controls

PFC

The ravulizumab 70 mg/mL finished product manufacturing site Patheon Italia S.p.A. (Monza) holds an appropriate MIA and GMP certificate of compliance.

The ravulizumab 70 mg/mL finished product manufacturing process starts with the receipt of Ravulizumab 100 mg/mL active substance. The active substance is diluted to a target of 70 mg/mL using formulation buffer. Thereafter, the finished product is bioburden filtered prior to sterile filtration and aseptically filled into sterile cartridges, which are stoppered with rubber pistons.

Equipment and components were properly prepared and every individual step was adequately validated/qualified for the intended use.

As the finished product differs from the previously authorised presentation in strength (70 mg/mL) and container (PFC), a new risk assessment was performed to identify critical process parameters. The applicant confirmed that no CPP were identified for the finished product manufacturing process.

All major equipment was properly validated/qualified, including E-beam tunnel, autoclaves, vapour hydrogen peroxide (VHP) decontamination, sterile filtration and filling manifolds.

Sterility assurance validation was successfully completed performing three consecutive media fills simulations. During the media fills, the steps of a production fill are simulated under worst-case conditions. Re-qualification of the aseptic filling line is performed at least twice per year. Results demonstrate that aseptic conditions are maintained during the filling process.

Process Performance Qualification was successfully demonstrated with PPQ runs covering the minimum and maximum batch size range. All acceptance criteria were met.

Post PPQ minor changes were made. Verification studies to qualify these changes were successfully performed.

Filters were correctly validated for the microbial retention capacity. Process hold time and shipping conditions were properly qualified.

OBDS

An appropriate MIA and GMP certificate of compliance have been provided for the site performing OBDS manufacture (assembly). The on-body injector (OBI) is manufactured at a contract device manufacturer, holding a GMP certificate of compliance.

Tempered PFC is labelled and inspected, before the TSA is inserted into the piston of the PFC. Then, the labelled PFC-TSA assembly is placed into the blister pack containing the device (OBI), and later placed into a carton with the instruction for use (IFU) and package information leaflet (PIL).

Adequate controls are in place to ensure the consistent, robust manufacture of the combination product.

Process Performance Qualification was successfully demonstrated with PPQ runs. All acceptance criteria were met. Overall, the ravulizumab OBDS assembly process is capable of being executed in a consistent controlled manner.

2.4.3.3. Product specification, analytical procedures, batch analysis

PFC

The proposed specifications for the finished product (ravulizumab PFC) were derived from the specifications in place for the clinical studies, and it considers the authorised finished product formulated at 100 mg/mL. Release specifications are the same used for the authorised 100 mg/mL strength, adapted to the new strength for protein content, with the only exception of C5 binding. The applicant commits that the acceptance criterion will be reassessed when additional finished product release data are available and will be tightened if appropriate (Recommendation). This modification is considered acceptable.

The analytical procedures used for pre-filled cartridges are mostly the same methods described for the control of the authorized ravulizumab active substance. The analytical methods used specifically for the finished product were appropriately validated for their intended use or were qualified in accordance with the referenced Ph. Eur. monographs.

Characterisation of impurities is not required since there are no additional known process- or product-related impurities specific to the ravulizumab finished product that are not present in the active substance.

Release data from finished product product batches have been included in batch analysis. All batches comply with the specifications, demonstrating the consistency of the process and the uniformity of the finished product.

OBDS

The proposed specifications for the on-body delivery system were developed by systematic approach to define the essential performance requirement (EPR), based on the intended use, the identified use steps and the design input requirements. The approach used to set the specifications is considered appropriate.

The acceptance criteria proposed for each EPR were properly justified.

The analytical methods used to measure the EPR of the OBDS have been appropriately validated for their intended use.

Release data from finished product batches have been presented. All batches comply with the specifications, demonstrating the consistency of the process and the uniformity of the OBDS.

2.4.3.4. Stability of the product

PFC

The stability studies performed on Ravulizumab 3.5 mL/PFC are conducted according to ICH Q5C and ICH Q1E guidelines and are considered appropriate. Batches were placed in stability studies covering the standard cartridge storage (PFC) and the co-package with the OBDS.

Forced degradation and photostability studies have demonstrated ravulizumab sensitivity to light and elevated temperature. Stability indicating attributes have been properly identified by the accelerated stability data.

All available data from ravulizumab finished product stored at 2-8°C (long term storage conditions) meet acceptance criteria up to the latest time point available. Based on these data, the applicant proposes a shelf life of 24 months stored at 2-8°C protected from light. The shelf life could be extended after completion of stability studies, providing appropriate compliance with stability specifications. Any shelf life extension would be subject to a variation submission and assessment.

The post-approval stability protocol and commitment are similar to those approved for ravulizumab 10 and 100 mg/mL.

OBDS

The stability studies performed on the ravulizumab on-body delivery system (OBDS) are conducted according to ICH Q5C and ICH Q1E guidelines and include long-term (2-8°C) and accelerated (23-27°C) storage. Ravulizumab OBDS shelf life has been determined to be 24 months when stored at 2-8°C based on the constituent with the shortest shelf life (ravulizumab in PFC).

A trending comparison was performed pre- and post-activation of ravulizumab OBDS. Results of these studies demonstrate comparability of the stability profiles over the 24-month shelf life.

Ravulizumab OBDS Essential Performance Requirements (EPRs) are evaluated over the shelf life for ravulizumab OBDS, meeting acceptance criteria for the latest time point available.

The post-approval stability protocol and commitment are similar to those for ravulizumab 3.5 mL/PFC (storage at 2-8ºC by 24 months) but applied to EPRs.

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The current submission is intended to implement the addition of a new strength (245 mg/3.5 mL (70 mg/ mL)) and route of administration (subcutaneous use, SC). It also introduces a novel On-Body Delivery System (OBDS) for the SC administration, comprised of a prefilled cartridge (PFC) containing 70 mg/mL ravulizumab co-packaged with a single-use on-body injector (West SmartDose 3.5 Injector). The rationale for these changes is to offer an alternative route of administration for adult patients with PNH or aHUS.

The new strength is manufactured from the approved 100 mg/mL ravulizumab active substance and maintain the same formulation.

Ravulizumab finished product manufacture includes dilution of the 100 mg/mL active substance in formulation buffer, followed by filtration with sterilizing grade filters. The manufacturing process was validated by a process performance qualification (PPQ) study.

The ravulizumab finished product is filled into a Crystal Zenith (cyclic-olefin polymer resin) cartridge stoppered with a FluroTec coated piston.

Ravulizumab SC is directly administered with the OBDS from the PFC without dilution. The essential performance requirements (EPR) of the drug-device combination product were confirmed by design verification activities, demonstrating that the use of ravulizumab with OBI is safe and effective.

The on-body injector component must comply with the Medical Device Regulation (EU) 2017/745. The applicant has included in the dossier detailed information on the on-body delivery system that support its suitability for the intended use. In addition, the MAH has the responsibility to ensure that the co-packaged device is CE marked in accordance with the relevant EU legislation on medical devices prior to placing the product on the market.

The assembly process for the combination product is performed at ADMF. Design validation and verification plans were executed successfully. A biological risk assessment of the OBDS confirmed that the likelihood of a toxic effect is negligible and the OBDS can be considered safe for the intended use. Process Performance Qualification for ODBS assembly was successfully demonstrated with three consecutive PPQ runs.

In general, the quality of the product is good and the dossier is presented in a comprehensible manner.

At the time of the CHMP opinion, there was one unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertains to the review and tightening of the specification limit for C5 binding. This point is put forward and agreed as a recommendation for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The MAH is recommended to reassess the acceptance criterion for C5 binding in the finished product release specifications when additional finished product release data are available.

2.5. Non-clinical aspects

2.5.1. Introduction

Ultomiris (ravulizumab) is a humanized monoclonal antibody (mAb) that binds to and blocks complement mediated activation of complement component 5 (C5), thereby preventing the release of the proinflammatory anaphylatoxin C5a and formation of the terminal complement complex (TCC) via C5b. Approved in the 2018, is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) or atypical haemolytic uremic syndrome (aHUS).

This extension of the Marketing Authorisation concerns a new route of administration (subcutaneous injection) associated with a new strength (245 mg/3.5 mL (70 mg/ mL)) for Ultomiris.

A complete nonclinical information package was included in the original electronic CTD for ULTOMIRIS (ravulizumab IV), presented in 2018. Additional nonclinical studies were not performed to support the development of the new SC formulation.

A number of nonclinical pharmacology, PK, PD, and toxicology studies were conducted to support the clinical testing of ravulizumab IV in humans. The applicant claims that the systemic safety profile of ravulizumab SC has been well demonstrated from the non clinical toxicological testing conducted for the IV formulation.

An additional SC study in rabbits was performed to evaluate the local tolerability following single and repeated SC injections of ravulizumab. From the non clinical point of view this study is considered relevant for this application.

Two Protocol Assistance procedures were conducted with the EMA for ravulizumab SC, with EMA/CHMP/SAWP/581075/2017 and EMA/CHMP/SAWP/475997/2018 procedures containing non clinical advice.

2.5.2. Pharmacology

No additional nonclinical pharmacology studies have been submitted for ravulizumab SC.

2.5.3. Pharmacokinetics

No additional nonclinical PK studies have been submitted for ravulizumab SC.

2.5.4. Toxicology

A Local Irritation Study with Subcutaneous Formulation of ALXN1210, up to 15 days duration (GLP) in rabbits using the ALXN1210 SC formulation (batch 16R1501A) was provided in the original dossier.

2.5.4.1. Local tolerance

The test article was formulated at a higher concentration (100 mg/mL) with different excipients than the current IV formulation (10 mg/mL) being studied in human trials. The SC formulation was administered to NZW rabbits at doses of 0, 30, 60, or 100 mg/kg. The study had 2 phases: a single dose phase (Phase A) in which rabbits were dosed on Day 1 and necropsied on Day 2 or Day 15, and a repeat-dose phase (Phase B) in which rabbits were dosed on Days 1 and 8 and surviving animals were necropsied on Days 24 or 25. Rabbits in Phase B were intended to be dosed weekly for 4 weeks, but dosing was stopped

after Day 8 due to the onset of clinical signs. Assessment of toxicity was based on mortality, clinical observations, body weight, injection site dermal irritation scoring, immunohistochemistry evaluation, and anatomic and clinical pathology. Toxicokinetic and anti-drug antibody (ADA) assessments were conducted for the test article.

During Phase A, there were mild clinical signs of skin discoloration which occurred at the injection site within 4 to 6 hours post-dose in a limited number of animals at 100 mg/kg. Skin discoloration was observed in other areas of the body (ie, scrotal region) beginning on Day 8 in animals administered 60 or 100 mg/kg. There was evidence of an inflammatory/immune response at all dose levels as indicated by effects on fibrinogen, neutrophils, platelets, albumin, globulin, albumin/globulin ratios, activated partial thromboplastin time (aPTT), and/or cytokines (TNF-α, IL-6, IFN-γ, MCP-1 and IP-10). There were decreases in red cell mass and reticulocytes, with associated alterations to erythrocyte morphology typical of membrane injury. This collection of findings was likely multifactorial as related to erythroid suppression secondary to inflammation, and immune/complement-mediated erythrocyte injury. No histological findings were detected.

During Phase B, severe clinical signs of skin discoloration/blackening of the scrotal region, nose/muzzle and/or ears were observed in several animals approximately 3 days following the second dose administration. The most severely affected animals (7 animals) were euthanized in extremis due to the rapid progression and severity of the clinical signs. This included one animal in the 30 mg/kg/week, 2 animals in the 60 mg/kg/week, and 4 animals in the 100 mg/kg/week groups. One additional animal in the 30 mg/kg/week group was euthanized near the end of the study (Day 23).

The main findings in Phase B animals euthanized were moderate to marked renal injury and inflammatory effects as indicated by increases in urea nitrogen, creatinine, phosphorus, fibrinogen, IL-6, MCP-1, IP10, and/or neutrophils. Other findings consisted of mild to moderate decreases in red cell mass with concurrent evidence of regeneration and occasional spherocytosis. These findings were probably multifactorial in nature but largely test article-related and consistent with an immune complex/complement-mediated hemolytic component. Pathologic findings were focused on or around small to medium-sized blood vessels in multiple tissues. Macroscopic findings included discoloration of varying severities in a number of tissues (ears, skin, skin, subcutis, epididymides, and lung with bronchi). Vascular/perivascular inflammation, thrombi, with occasional necrosis and/or hemorrhage, were predominant in the peripheral skin but were also observed in visceral organs (ears, scrotum, injection sites, testes, epididymides, kidney, lungs, and heart).

Immunohistochemistry evaluations revealed granular deposits, which generally contained human Immunoglobulin G (IgG), rabbit IgG, rabbit Immunoglobulin M (IgM), and/or complement fraction, C3. The proximity between sites of granular immune complex deposition and sites of histopathology findings are suggestive of immune complex formation and/or deposition likely mediated the observed vascular/perivascular findings. Based on the spectrum of findings, these are most consistent with immune complex-mediated systemic disease.

2.5.5. Ecotoxicity/environmental risk assessment

According CHMP guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) with effective date of December 2006, states that vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted of environmental risk assessment because, due to their nature they are unlikely to result in significant risk to the environment. Due to the fact that ravulizumab is a monoclonal antibody and thus a protein, no Environmental Risk Assessment is provided.

2.5.6. Discussion on non-clinical aspects

A full nonclinical package was included in the original MAA for Ultomiris presented in 2018. No additional nonclinical data have been generated. This is considered acceptable.

It is agreed that the non-clinical systemic toxicity studies with the IV formulation are directly applicable to ravulizumab SC. Moreover, non-clinical efficacy from pharmacology studies can be extrapolated to the new route of administration. The potential risk of ravulizumab SC from a toxicological point of view concerns local tolerance and immunogenicity, which has been addressed in a local tolerance study using SC administration in rabbits. Toxicokinetics has been addressed in the same study.

The SC formulation of ravulizumab did not show any relevant local adverse effects when administered as a single injection, or prior to the development of anti-drug antibodies. However, the repeated SC administration caused severe immune response-related adverse events in rabbits indicative of a systemic, type III hypersensitivity response with an immune complex etiology, attributed to the development of ADAs as the applicant states. It is widely acknowledged that immunogenicity and hypersensitivity reactions to human biopharmaceuticals in animals are not predictive of the potential for these effects in humans (see ICH S6(R1)), consequently these findings have questionable relevance for patients. Use of alternative species are not warranted since ravulizumab does not exhibit pharmacologic activity or cross reactivity with any non-human animal species tested, including cynomolgus monkey, thus no additional non-clinical studies are required. Immunogenicity has been study in the clinical trials with ravulizumab SC.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, ravulizumab is not expected to pose a risk to the environment.

In conclusion, available non-clinical data are sufficient to support the authorisation of the ravulizumab SC formulation.

2.5.7. Conclusion on the non-clinical aspects

The CHMP considers that the available non-clinical data are sufficient to support the authorisation of the ravulizumab SC formulation.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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**

The Ultomiris SC clinical program comprises 3 clinical studies: one Phase 3 registrational pharmacokinetic (PK)/pharmacodynamic (PD), efficacy and safety study in adult patients with PNH (Study ALXN1210-PNH-303) and 2 supportive Phase 1 PK and safety studies in healthy adult subjects (Studies ALXN1210-HV-105 and ALXN1210-SC-101).

Data from these studies are included in the current clinical pharmacology analyses.

Table 1 **Summary of Studies Contributing Data to the PK, PD, and Immunogenicity Analyses for the Ravulizumab SC Development Program**

Study Identifier: (Population)	Study Description	Number of Participants	Duration of PK/PD/ADA Data Coverage
ALXN1210-SC-101 (Healthy adult subjects)	Phase 1, randomized, single center, single dose study to assess the safety, tolerability, immunogenicity, PK, PD, and absolute bioavailability of a single dose of ravulizumab SC (400 mg; double-blinded and placebo-controlled) compared with ravulizumab IV (400 mg; open-label).	Total: 42 Ravulizumab SC: 24 IV: 12 Placebo SC: 6	Single dose Followed through 200 days post dose
ALXN1210-HV-105 (Healthy adult subjects)	Phase 1, partially randomized, single center, sequential cohort, single ascending dose study to assess the safety, tolerability, PK, PD, immunogenicity, and absolute and relative bioavailability of ravulizumab SC coadministered with rHuPH20 compared with a single dose of ravulizumab SC or a single dose of ravulizumab IV.	Total: 49 Ravulizumab: SC 400 mg: 7 SC 500 mg + rHuPH20 10000 units: 12 SC 1000 mg + rHuPH20 20000 units: 12 SC 2000 mg + rHuPH20 40000 units: 12 IV 400 mg: 6	Single dose Followed through 200 days post dose
ALXN1210-PNH-303 (Adult patients with PNH who were clinically stable and previously treated with eculizumab for at least 3 months prior to study entry)	Phase 3, randomized, parallel-group, multicenter, open-label to compare the PK of ravulizumab SC administered via an OBI with ravulizumab IV.	PK Analysis Set: Total: 113 SC: 70; IV: 43 PD Analysis Set: Total: 129 SC: 84; IV: 45 SC Treated Full Analysis Set: SC/SC: 84 IV/SC: 44	PK and PD Analysis Sets: up to Day 71 SC Treated Full Analysis Set: through 1 year of SC treatment

Abbreviations: ADA = antidrug antibody; IV = intravenous; OBI = on-body injector; PD = pharmacodynamic; PK = pharmacokinetic; PNH = paroxysmal nocturnal hemoglobinuria; rHuPH20 = recombinant human hyaluronidase PH20; SAD = single ascending dose; SC = subcutaneous

2.6.2. Clinical pharmacology

Bioavailability studies and related analytical methods

The bioavailability of ravulizumab SC was assessed in healthy adult subjects in clinical Studies ALXN1210-SC-101 (assessed previously) and ALXN1210-HV-105.

The quantitation of ravulizumab in plasma from study ALXN1210-HV-105 is considered fully validated and it is acceptable.

The relative bioavailability Study ALXN1210-HV-105 demonstrate that the absolute bioavailability of ravulizumab SC administered alone was approximately 64%, and when co-administered with rHuPH20 resulted in a mean increased absolute bioavailability of ravulizumab SC of approximately 22%. However, after completion of this study, ravulizumab SC co-administered with rHuPH20 was not considered for further development.

2.6.2.1. Pharmacokinetics

Absorption

Study ALXN1210-PNH-303 is an ongoing Phase 3, randomized, open-label, parallel-group, multicenter study to evaluate PK non-inferiority of ravulizumab SC administered via an OBI compared with ravulizumab IV in adult patients with PNH who are clinically stable and have been previously treated with eculizumab for at least 3 months prior to study entry. The primary objective of this study was to evaluate the PK non-inferiority of ravulizumab SC versus ravulizumab IV based on the Day 71 C_{trough}.

Mean steady-state trough concentrations for the SC and IV groups were approximately 34% and 57% higher than those observed on Day 71, respectively.

Table 2 **Descriptive Statistics of Steady-State Exposure Parameters of Ravulizumab (Study ALXN1210-PNH-303)**

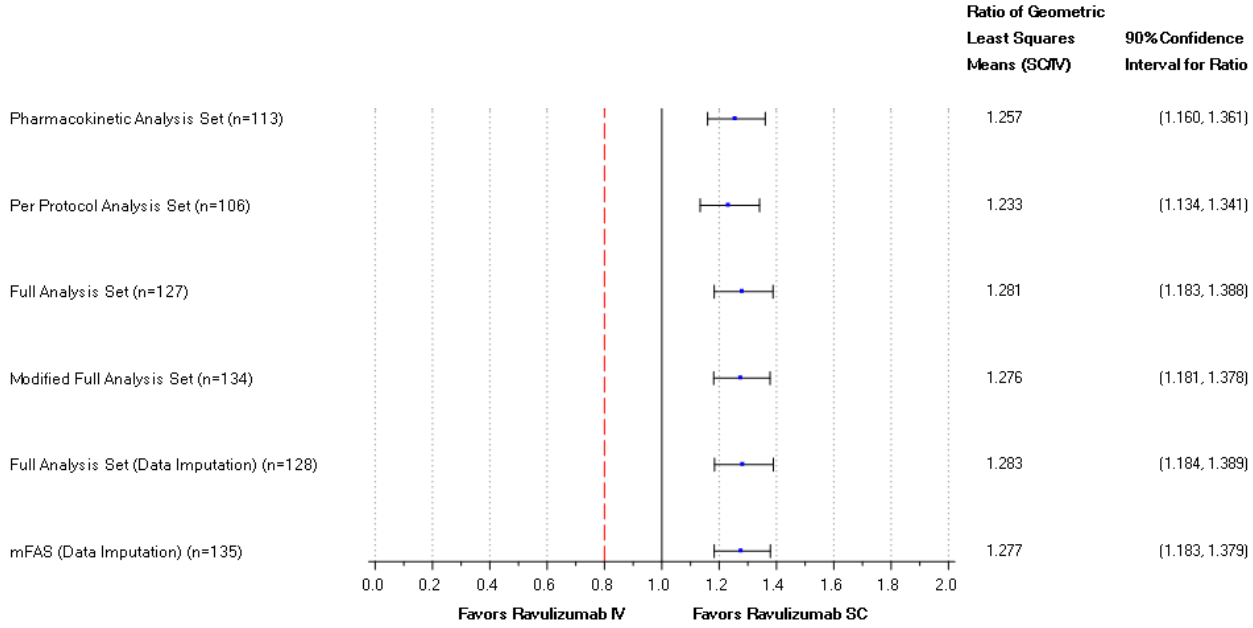
Parameters Statistic	Ravulizumab SC/SC Group (N = 84)	Ravulizumab IV/SC Group (N = 45[a])	Overall (N = 129)
$C_{trough,ss}$ (µg/mL)			
Mean (SD)	778 (204)	708 (164)	754 (193)
Median (CV%)	775 (26.3)	696 (23.2)	750 (25.7)
[Min, max]	[389, 1250]	[439, 1040]	[389, 1250]
$C_{max,ss}$ (µg/mL)			
Mean (SD)	797 (208)	727 (165)	773 (196)
Median (CV%)	793 (26.1)	715 (22.7)	763 (25.4)
[Min, max]	[404, 1290]	[445, 1060]	[404, 1290]
$C_{avg,ss}$ (µg/mL)			
Mean (SD)	791 (207)	721 (165)	766 (195)
Median (CV%)	786 (26.1)	708 (22.9)	761 (25.5)
[Min, max]	[399, 1270]	[443, 1060]	[399, 1270]
AUC_{ss} (µg.h/mL)			
Mean (SD)	133000 (34700)	121000 (27700)	129000 (32800)
Median (CV%)	132000 (26.1)	119000 (22.9)	128000 (25.5)
[Min, max]	[67000, 214000]	[74400, 177000]	[67000, 214000]

[a] One patient randomized to ravulizumab IV withdrew from the study during the 10-week Randomized Treatment Period and, thus, never received ravulizumab SC treatment. Bayesian estimates of F, Ka, and Tlag were allocated for this patient in order to derive steady-state exposure parameters following SC dosing.

Abbreviations: AUC_{ss} = area under the curve under steady-state conditions (ie, 1 week); $C_{avg,ss}$ = average concentration under steady state conditions; $C_{max,ss}$ = maximum serum concentrations under steady-state conditions; $C_{trough,ss}$ = trough concentrations under steady state conditions; CV=coefficient of variation; F = bioavailability; IV = intravenous; Ka = rate constant of absorption; SC = subcutaneous; SD=standard deviation; Tlag = absorption lag time

Source: SC PK/PD EU Report Table 7

Figure 1: Forest Plot of Day 71 Serum Ravulizumab Concentration by Population - Analysis of Variance (ANOVA): Noninferiority By Analysis Set (Study ALXN1210-PNH-303)



Notes: n is representative of the number of patients in each analysis set with available data. Each tail is representative of the 90% confidence interval for that analysis set. The null hypothesis that the ratio of geometric means of Day 71 C_{trough} between the SC group and the IV group was less than or equal to the noninferiority margin of 0.8 will fail to be rejected if the lower bound (left tail) crosses the noninferiority margin represented by the red dashed line.

Abbreviations: IV = intravenous; C_{trough} = concentration at the end of the dosage interval; mFAS = modified Full Analysis Set; PK = pharmacokinetic; SC = subcutaneous

Source: ALXN1210-PNH-303 CSR Figure 14.2.1.1.16

Elimination

The elimination of ravulizumab was similar between the SC and IV routes of administration. Following a single dose of ravulizumab SC; the median (range) time to maximum observed serum concentration (t_{max}) was 169.8 (96.0 to 508.1) hours following SC injection. The geometric mean (coefficient of variation [CV]%) terminal elimination half-life ($t_{½}$) was similar at 31.3 (13.6) days and 29.9 (15.4) days for ravulizumab SC and IV administration, respectively.

Pharmacokinetic in the target population

A total of 185 subjects were treated with ravulizumab IV or SC across study ALXN1210-SC-101, ALXN1210-HV-105 and ALXN1210-PNH-303. Healthy subjects (ALXN1210-SC-101 and ALXN1210-HV-105) received single IV or SC doses or ravulizumab and patients with PNH (ALXN1210-PNH-303) received IV or SC doses during the randomized treatment period (10 weeks) and SC doses during the extension period (refer to Table 1). Of these 185 subjects, 7 subjects from clinical site 0657 in study ALXN1210-PNH-303 (6 for the SC and 1 for the IV) were removed from the analysis due to critical findings related to deficiencies in source documentation and principal investigator oversight, as well as 4 major findings. As a result, a total of 178 subjects were included in the population PK analysis.

Table 4 **Baseline Characteristics of Ravulizumab PK Population**

Characteristics	ALXN1210-SC-101 (N=36)	ALXN1210-HV-105 (N=13)	ALXN1210-PNH-303 (N=129)	Overall (N=178)
Sex				
Female	12 (33.3%)	2 (15.4%)	69 (53.5%)	83 (46.6%)
Male	24 (66.7%)	11 (84.6%)	60 (46.5%)	95 (53.4%)
Race				
White	25 (69.4%)	7 (53.8%)	78 (60.5%)	110 (61.8%)
Black or African American	5 (13.9%)	3 (23.1%)	3 (2.3%)	11 (6.2%)
Asian	4 (11.1%)	1 (7.7%)	2 (1.6%)	7 (3.9%)
Hispanic or Latino	2 (5.6%)	0 (0%)	22 (17.1%)	24 (13.5%)
Other	0 (0%)	2 (15.4%)	4 (3.1%)	6 (3.4%)
Not Reported	0 (0%)	0 (0%)	20 (15.5%)	20 (11.2%)
Ethnicity				
Not Hispanic or Latino	34 (94.4%)	13 (100%)	107 (82.9%)	154 (86.5%)
Hispanic or Latino	2 (5.6%)	0 (0%)	22 (17.1%)	24 (13.5%)
Age (years)				
Mean (SD)	35.2 (7.90)	29.2 (6.08)	45.7 (14.0)	42.3 (13.7)
Median (CV%)	33.0 (22.5)	28.0 (20.8)	44.0 (30.7)	39.5 (32.4)
[Min, Max]	[25.0, 49.0]	[20.0, 38.0]	[18.0, 79.0]	[18.0, 79.0]
Height (cm)				
Mean (SD)	173 (8.54)	179 (9.21)	168 (9.27)	170 (9.60)
Median (CV%)	173 (4.9)	178 (5.1)	169 (5.5)	170 (5.6)
[Min, Max]	[153, 192]	[167, 196]	[149, 188]	[149, 196]
Body Weight (kg)				
Mean (SD)	72.6 (12.4)	77.6 (9.67)	72.9 (12.6)	73.2 (12.4)
Median (CV%)	75.1 (17.1)	77.8 (12.5)	72.3 (17.3)	73.2 (16.9)
[Min, Max]	[50.7, 94.1]	[60.3, 90.4]	[43.5, 98.4]	[43.5, 98.4]
BMI (kg/m^2)				
Mean (SD)	24.2 (3.27)	24.2 (2.30)	25.8 (4.41)	25.4 (4.13)
Median (CV%)	24.6 (13.5)	24.5 (9.5)	25.5 (17.1)	25.4 (16.3)
[Min, Max]	[18.7, 29.7]	[20.0, 27.6]	[17.7, 38.8]	[17.7, 38.8]

Abbreviations: CV = coefficient of variation; Min = minimum; Max = maximum; SD = standard deviation; BMI = body mass index.

Table 3 **Baseline Characteristics of Ravulizumab PK Population – Continuous Covariates – Hemoglobin, Hematocrit, Free C5, and Lactate Dehydrogenase**

Characteristics	Healthy Subjects* (N=49)	ALXN1210-PNH-303 (N=129)
Hemoglobin (g/L)		
Mean (SD)	144 (10.6)	112 (20.2)
Median (CV%)	143 (7.4)	112 (18.1)
[Min, Max]	[121, 171]	[58.0, 160]
Free C5 (µg/mL)		
Mean (SD)	81.5 (18.0)	0.341 (2.94)
Median (CV%)	81.2 (22.1)	0.00915 (860.9)
[Min, Max]	[27.9, 126]	[0.00915, 32.1]
LDH (U/L)		
Mean (SD)	160 (22.3)	253 (81.0)
Median (CV%)	158 (13.9)	238 (32.0)
[Min, Max]	[129, 249]	[90.0, 574]

Abbreviations: CV = coefficient of variation; Min = minimum; Max = maximum; SD = standard deviation; LDH = lactate dehydrogenase

* Healthy subjects from study ALXN1210-SC-101 (N=36) and ALXN1210-HV-105 (N=13)

Final population PK model

Final population PK parameter estimates of ravulizumab as well as between-subject variability (BSV) and residual error parameters are presented in Table and figures below.

Table 5 **Final Population PK Model: Ravulizumab Parameter and Covariate Estimates**

Parameter	Estimate[a]	RSE (%)	BSV[b] (%)	Shrinkage (%)
CL (L/h)	**0.00281** x $(BW/70)^{0.865}$ x $(HGB/121)^{-0.361}$ x 1.50 if Healthy Subjects	**3.15**	**19.5**	**2.15**
Q (L/h)	**0.0190** x $(BW/70)^{0.865}$	**10.2**	**NA**	**NA**
Vc (L)	**3.18** x $(BW/70)^{1.26}$ x $(BMI/25)^{-0.698}$ x $(HG/121)^{-0.283}$	**1.47**	**11.2**	**18.7**
Vp (L)	**1.84** x $(BW/70)^{1.26}$ x $(BMI/25)^{-0.698}$	**3.44**	**21.7**	**27.4**
Ka (h^{-1})	**0.00948**	**10.5**	**86.6**	**32.1**
Lag (h)	**1.12**	**12.7**	**NA**	**NA**
F	**0.794** x 0.837 if Study ALXN1210-SC-101 x 0.864 if Study ALXN1210-HV-105 x 0.931 if SC injection in the abdomen x 0.864 if SC injection in the arm	**3.31**	**NA**	**NA**
Residual Error				
Assay Conversion Factor 1	0.560	22.4	NA	NA
Assay Conversion Factor 2	1.12	4.31	NA	NA
Proportional (%)	10.9	3.32	NA	NA
Additive (µg/mL)	0.569	33.2	NA	NA
Proportional (Avanza) (%)	7.67	5.02	NA	NA
Additive (Avanza) (µg/mL)	0.301	22.4	NA	NA

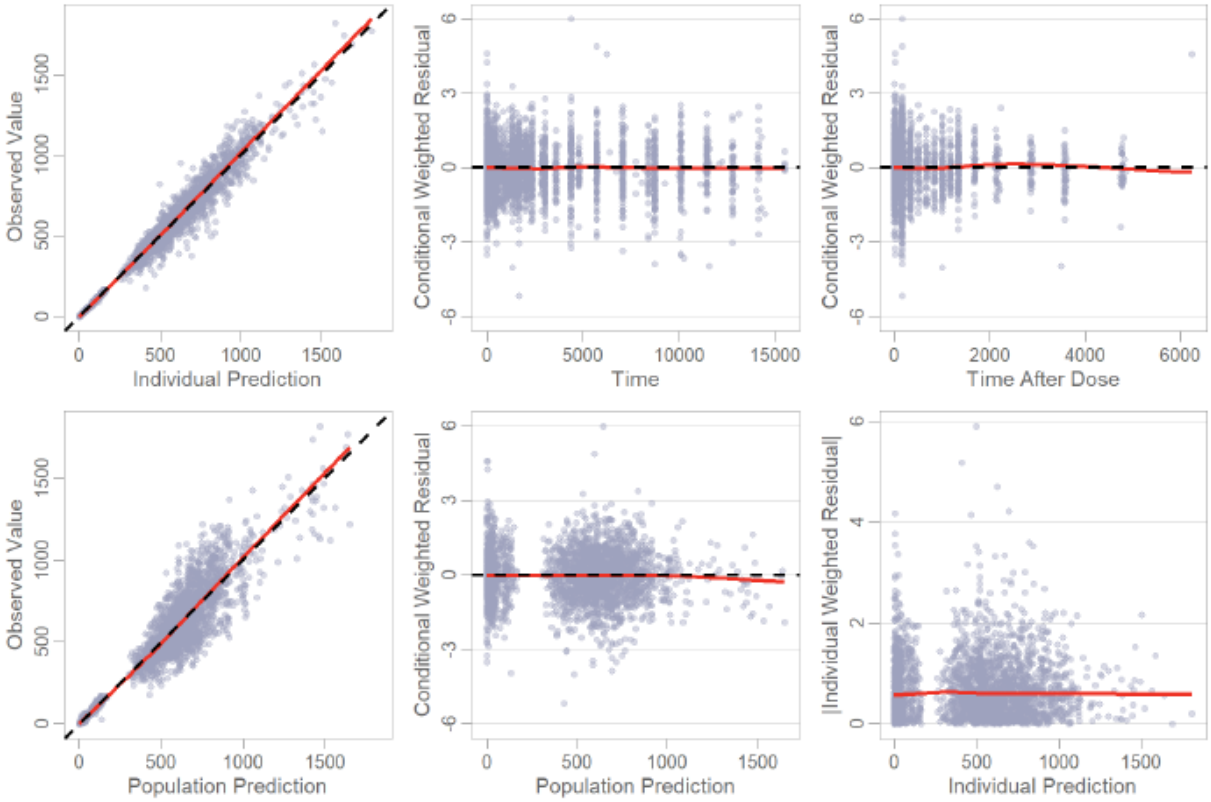
Note: Parameters are for a typical 70-kg male patient with PNH, with a BMI of 25.0 kg/m^2 and a baseline hemoglobin level of 122 g/L who received a SC injection in the thigh (or multiple/missing) for which PK concentrations of ravulizumab were analyzed with the PPD assay (study ALXN1210-PNH-303).

[a] Parameter estimates are back-transformed from the log-transformed domain. Additional PK parameters including bootstrap estimates and parameter correlations are presented in Appendix 2 (Section 11.8.1 and 11.8.2).

[b] BSV is presented as the standard deviation of the random effect (η_i), with the % coefficient of variation (100 x $(\exp(\omega^2)-1)^{0.5}$) in parentheses.

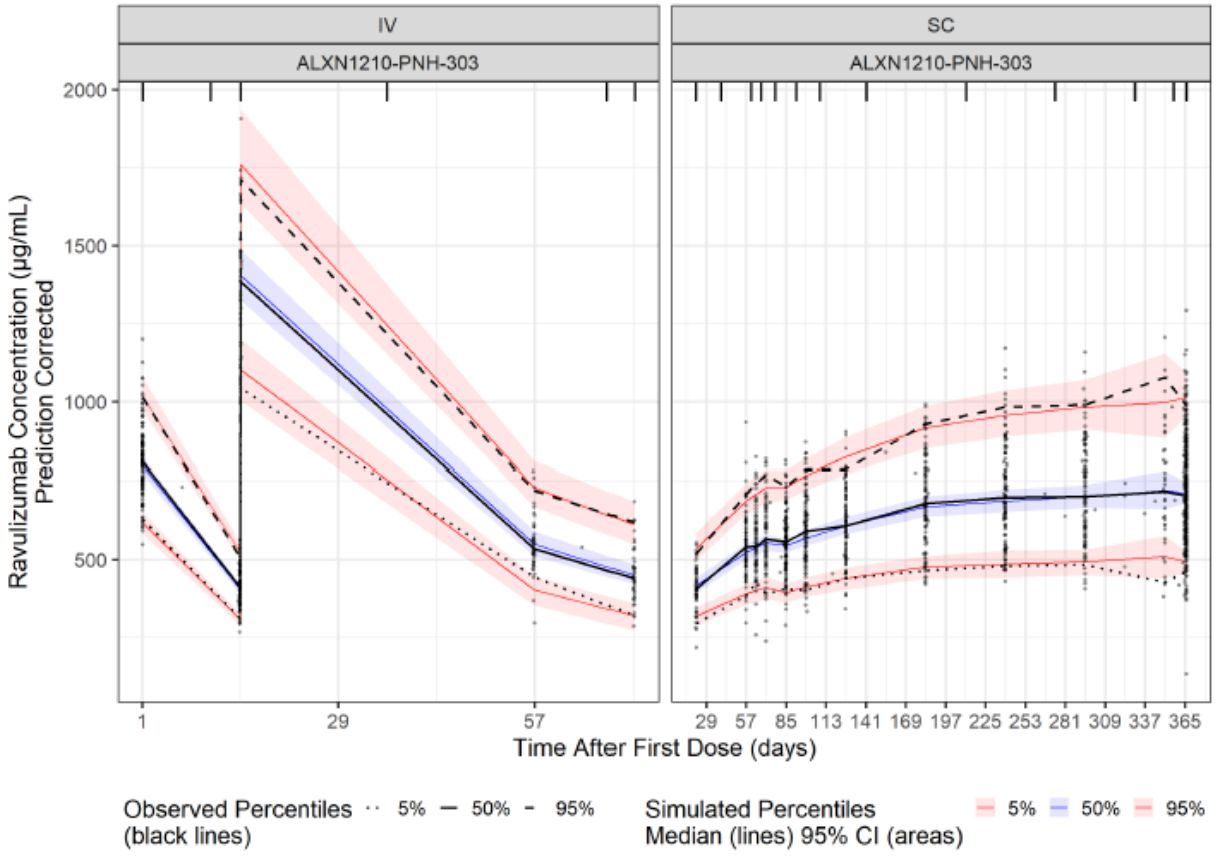
Abbreviations: BSV = between-subject variability; CI = confidence interval; CL = clearance; Ka = rate constant of absorption; F = bioavailability, NA = not applicable; Q = intercompartmental clearance; RSE = relative standard error; Vc = volume of distribution of the central compartment; Vp = volume of distribution of the peripheral compartment.

Figure 2 **Final Population PK Model of Ravulizumab: Goodness of Fit**



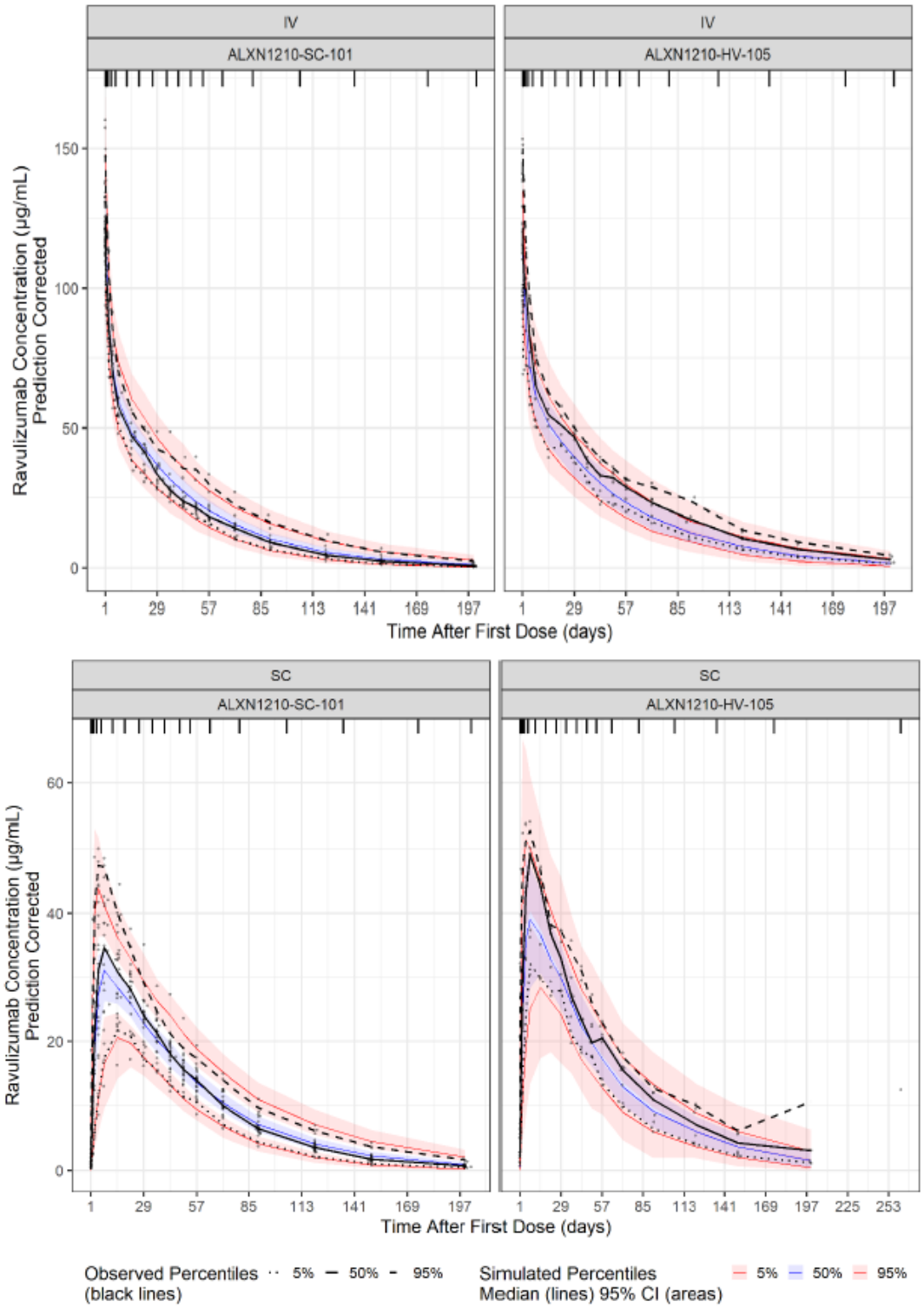
Abbreviations: IDENT = line of identity; LOESS = locally weighted scatter-plot smoothing; PK = pharmacokinetics.

Figure 3 **Final Population PK Model of Ravulizumab: Prediction-Corrected Visual Predictive Check Plots– Study ALXN1210-PNH-303**



Notes: The prediction-corrected VPC (pcVPC) retains the visual interpretation of the traditional VPC while removing the variability that arises from binning across independent variables by normalizing the observed and simulated dependent variable based on the typical population prediction for the median independent variable in the bin.
Abbreviations: PK = pharmacokinetics; VPC = visual predictive check.

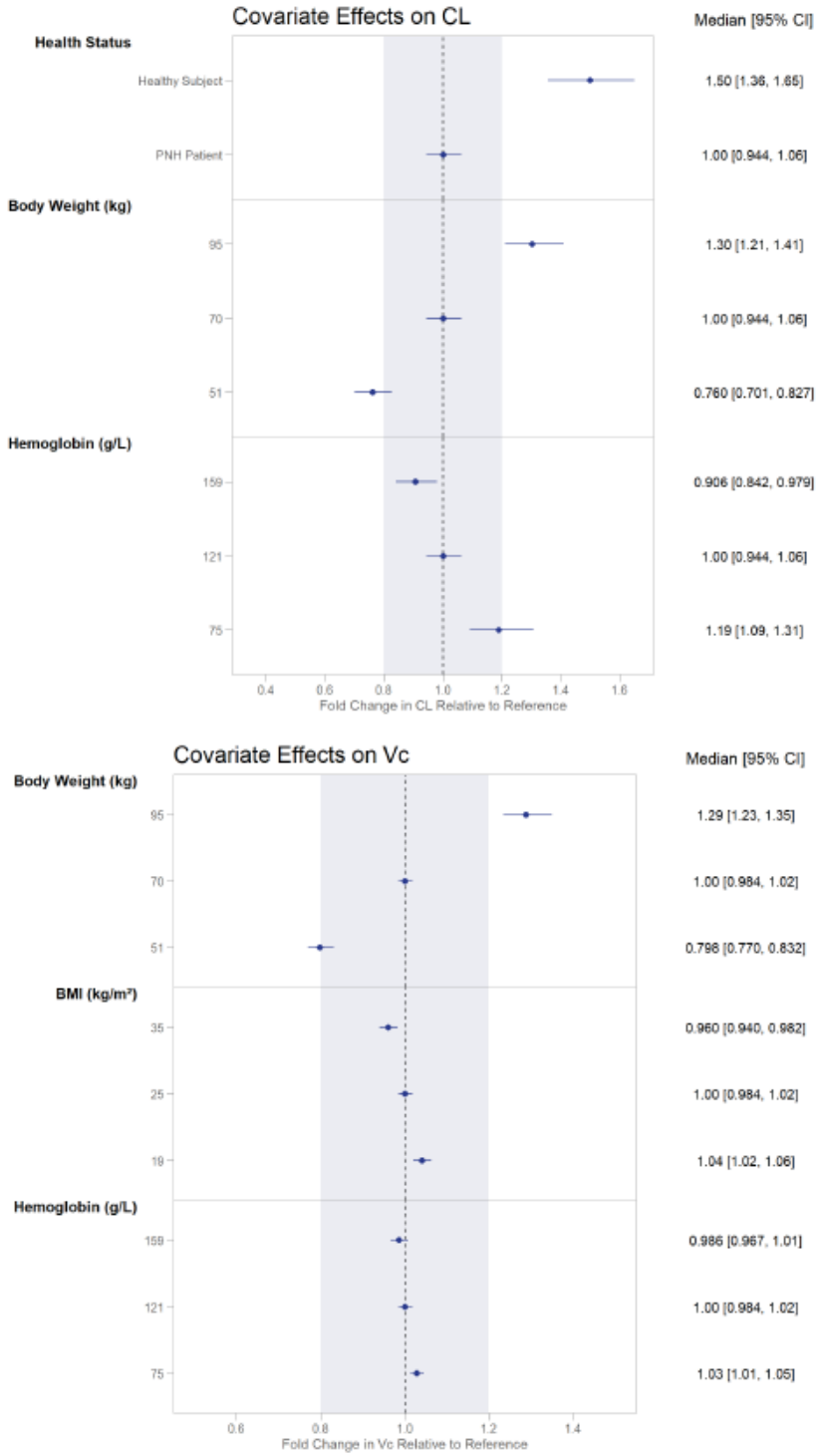
Figure 4 **Final Population PK Model of Ravulizumab: Prediction-Corrected Visual Predictive Check Plots – Study ALXN1210-SC-101 and ALXN1210-HV-105**



Abbreviations: PK = pharmacokinetics; VPC = visual predictive check.

The effect of specific covariates on the CL and Vc of ravulizumab relative to the reference population is presented in Figure below.

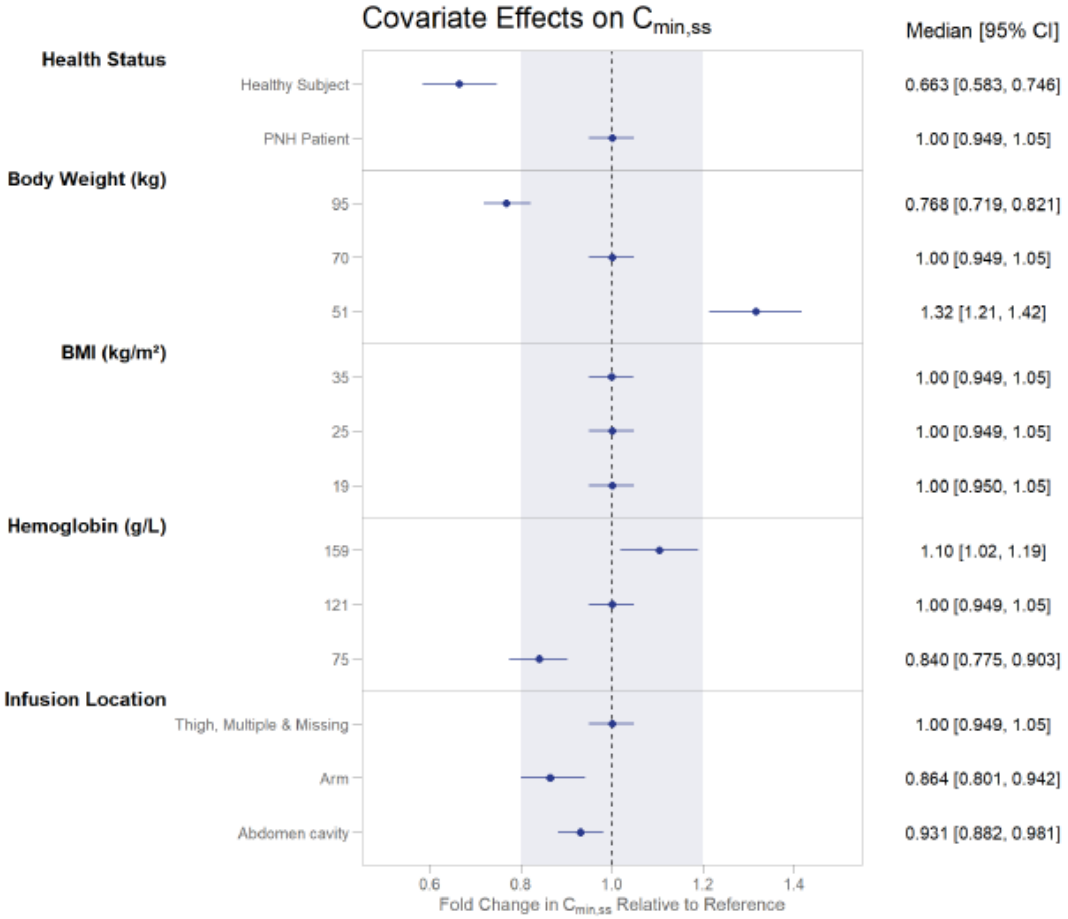
Figure 5 **Forest Plot: Impact of Covariates on the CL and Vc of Ravulizumab**



Reference: A typical 70-kg male patient with PNH, with a BMI of 25.0 kg/m^2 and who received SC dosing in the thigh with a baseline hemoglobin level of 121 g/L for which PK concentrations of ravulizumab were analyzed with the PPD assay (study ALXN1210-PNH-303).

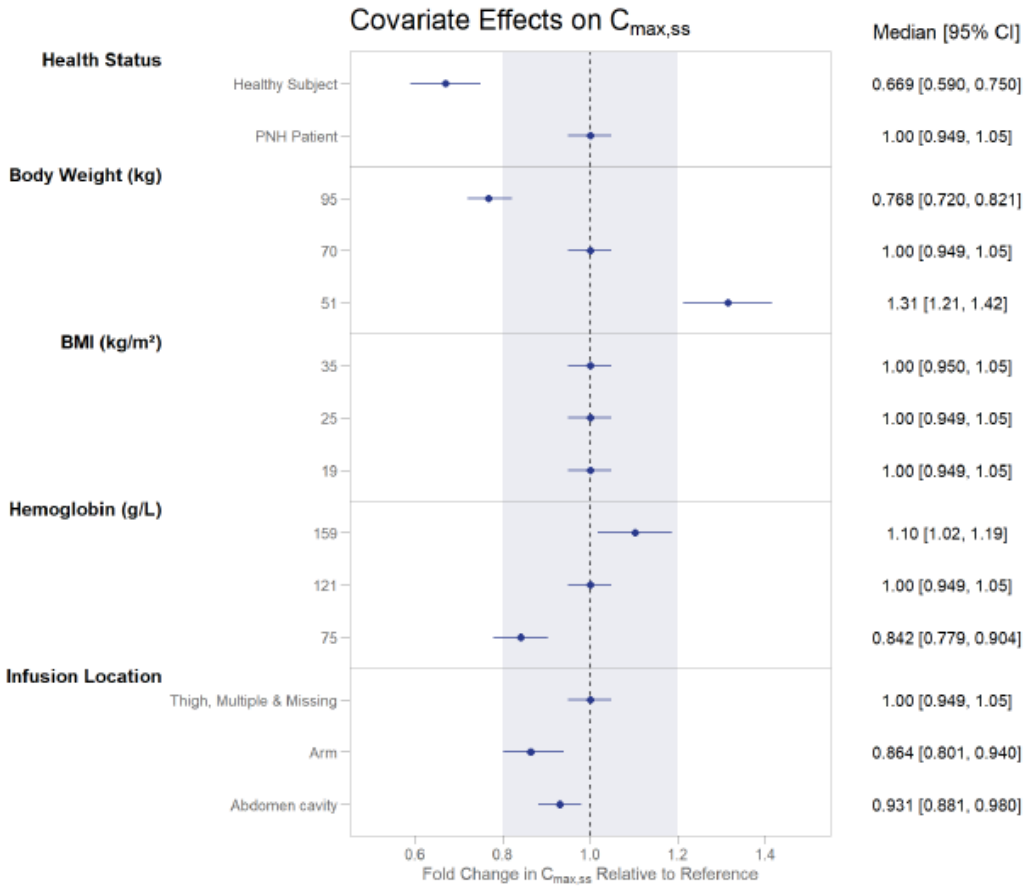
The most important covariates describing variability in CL were body weight and hemoglobin. The most important covariate describing variability in Vc was body weight. The effect of specific covariates on the Cmin,ss and Cmax,ss of ravulizumab following SC dosing with the OBDS relative to the reference population are presented in the Figures below.

Figure 6: Forest Plot: Impact of Covariates on the $C_{min,ss}$ of Ravulizumab



Reference: A typical 70-kg male patient with PNH, with a BMI of 25.0 kg/m^2 and who received SC dosing in the thigh with a baseline hemoglobin level of 121 g/L for which PK concentrations of ravulizumab were analyzed with the PPD assay (study ALXN1210-PNH-303).

Figure 6 **Forest Plot: Impact of Covariates on the $C_{max,ss}$ of Ravulizumab**

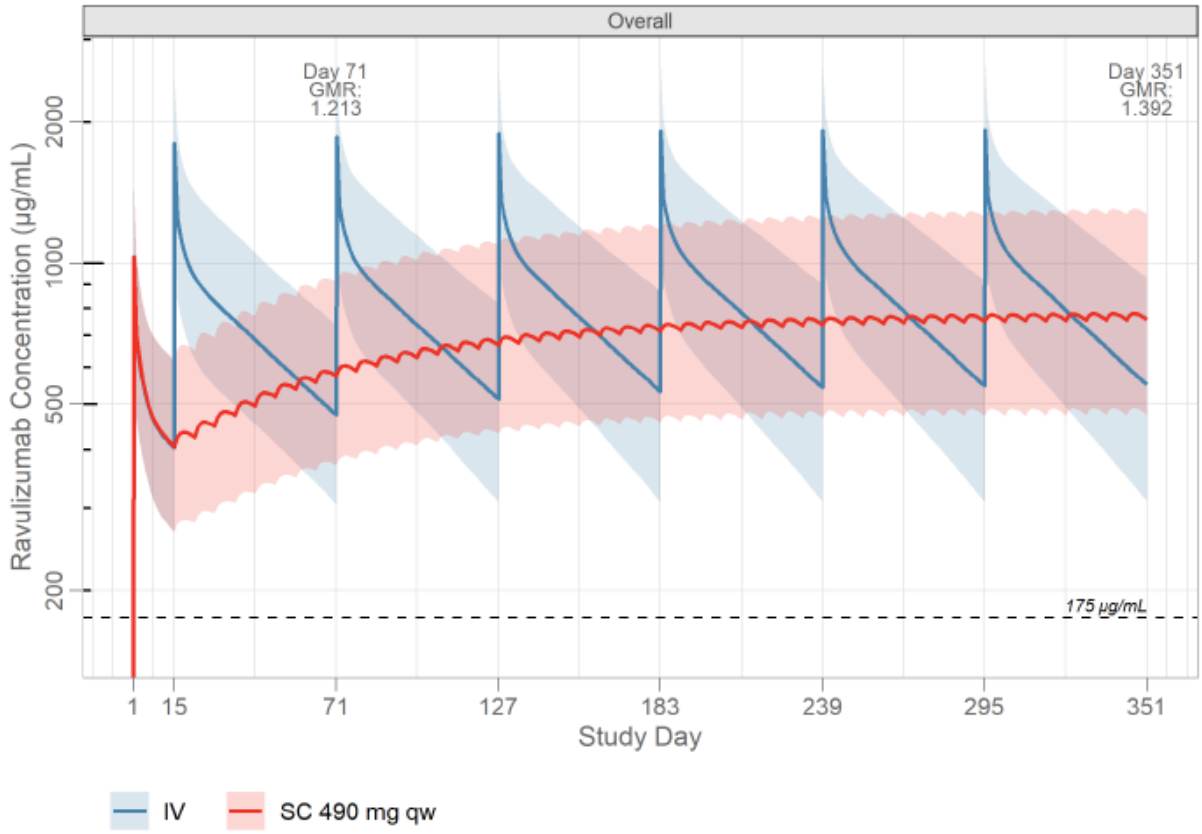


Reference: A typical 70-kg male patient with PNH, with a BMI of 25.0 kg/m^2 and who received SC dosing in the thigh with a baseline hemoglobin level of 121 g/L for which PK concentrations of ravulizumab were analyzed with the PPD assay (study ALXN1210-PNH-303).

Steady-state concentrations of ravulizumab following IV and SC dosing

The final population PK model was used to perform simulations in order to assess steady state concentration profiles following dosing over 1 year (i.e., no switch from IV to SC on Day 71). Model-predicted mean (95% prediction interval) concentration-times profiles of ravulizumab following SC and IV are presented in Figure below.

Figure 8 **Model-Predicted Mean (95% Prediction Interval) Concentration-Times Profiles of Ravulizumab Following SC and IV Dosing - Overall**



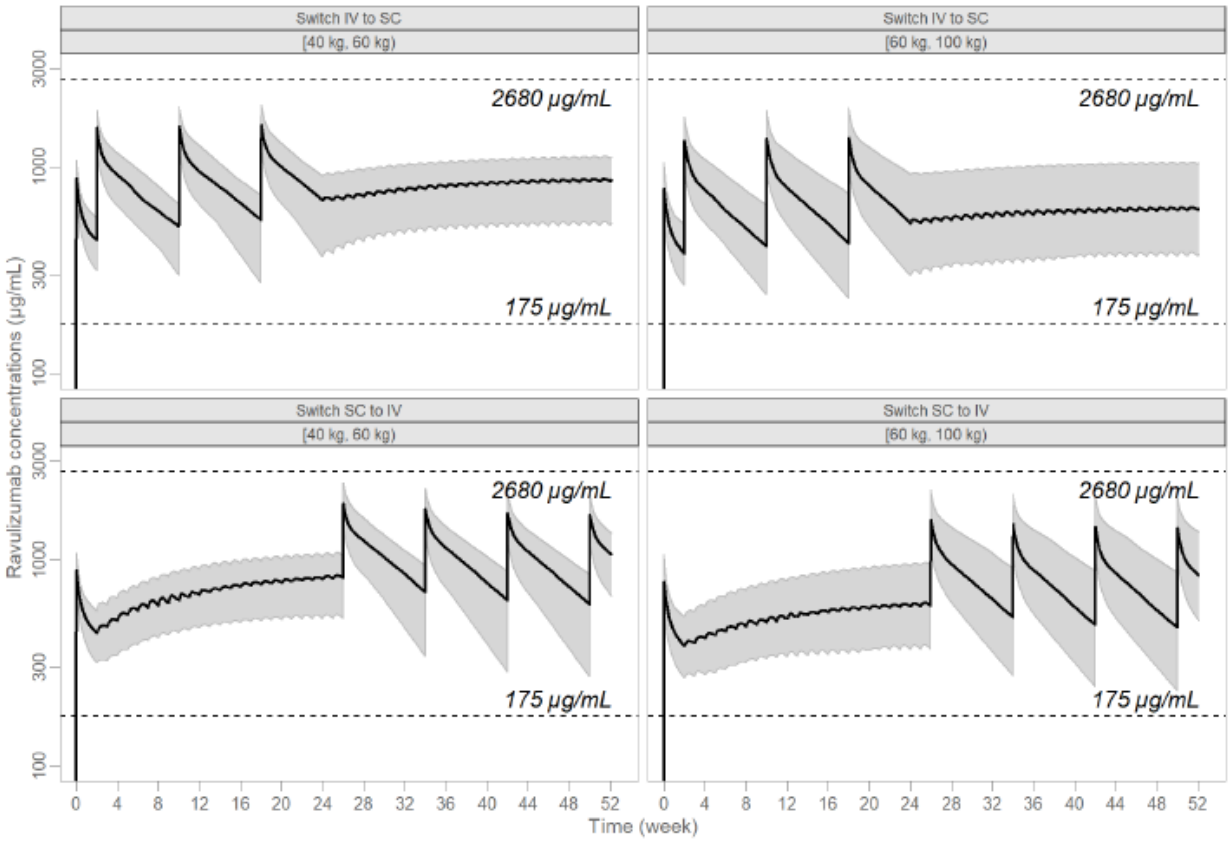
GMR = geometric mean ratio.
Note: SC simulations assumed 44% dosing in the thigh, 39% dosing in the abdomen and 17% dosing in the arm.

Based on model-predicted concentrations, the geometric mean ratio (GMR) for the SC to IV comparison on Day 1 and 351 (steady state) were 1.213 and 1.392, respectively. The GMR on Day 71 based on model-predicted concentrations is consistent with the reported GMR with an ANOVA model for the stage 1 analysis (1.176) and for the weighted overall results (1.257).

Switching from IV to SC and SC to IV

The final population PK model was used to perform simulations in order to assess the impact of switching from IV to SC and from SC to IV. Simulations were performed following achievement of steady state concentrations of ravulizumab following IV and SC administration (i.e., 6 months). Model-Predicted Mean (95% Prediction Interval) concentration-time profiles are presented in Figure below.

Figure 9 **Simulations: Switching from IV to SC and from SC to IV**



IV to SC switch: On Day 1 (Week 0), all patients received an IV loading dose of ravulizumab (2400 mg for patients ≥ 40 to < 60 kg and 2700 mg for patients ≥ 60 to < 100 kg). Starting on Day 15 (Week 2) patients received 3000 mg (≥ 40 to < 60 kg) and 3300 mg (≥ 60 to < 100 kg) q8w for 6 months (i.e., 3 doses). Patients switched to qw SC dosing (490 mg) afterward.

SC to IV switch: On Day 1 (Week 0), all patients received an IV loading dose of ravulizumab (2400 mg for patients ≥ 40 to < 60 kg and 2700 mg for patients ≥ 60 to < 100 kg). Starting on Day 15 (Week 2) patients received qw SC dosing (490 mg) for 6 months. Patients then switched to IV dosing as follows: 3000 mg (≥ 40 to < 60 kg) and 3300 mg (≥ 60 to < 100 kg) q8w.

The 95% prediction interval of concentration-time profiles of ravulizumab following a switch from IV to SC or from SC to IV were contained within 175 and 2680 µg/mL in patients with body weight ≥ 40 to <60 kg and ≥ 60 to <100 kg.

Body-weight >100 kg

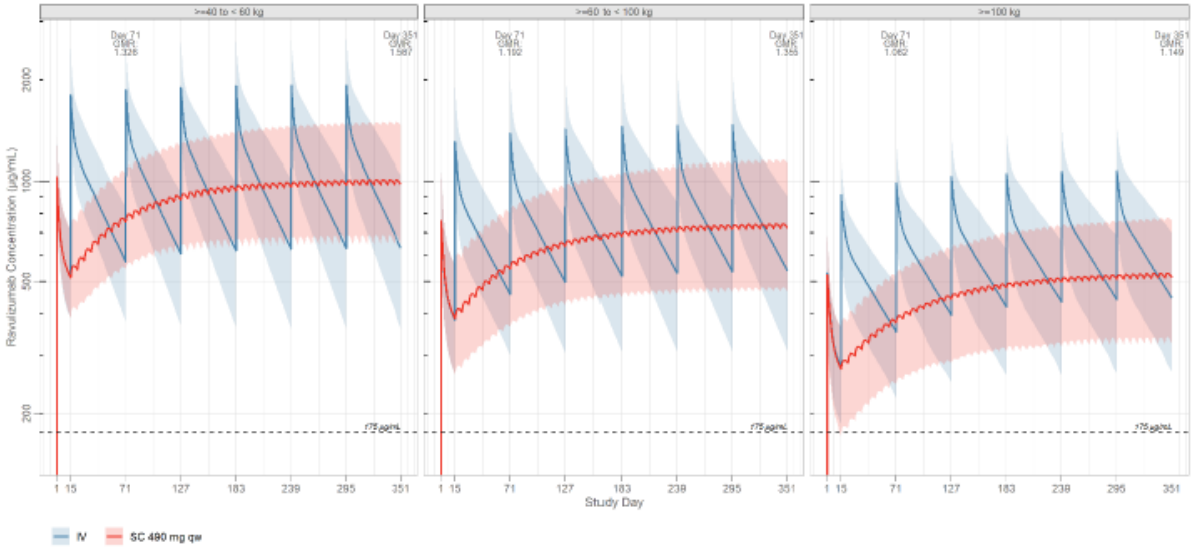
The final population PK model was used to perform simulations in virtual patients with body weight ≥100 kg with body weight-BMI matched information. Descriptive statistics of demographics parameters in adult patients with body weight ≥100 kg are presented in Table below.

Table 6 **Demographics Parameters in Adult Patients with Body Weight ≥100 kg**

Demographics	≥100 kg (N=1000)
Weight (kg)	
Mean (SD)	114 (11.8)
Median [min, max]	110 [100, 157]
Age (years)	
Mean (SD)	45.8 (15.7)
Median [min, max]	45.1 [18.0, 80.0]
BMI (kg/m²)	
Mean (SD)	38.7 (5.98)
Median [min, max]	37.9 [26.3, 65.2]

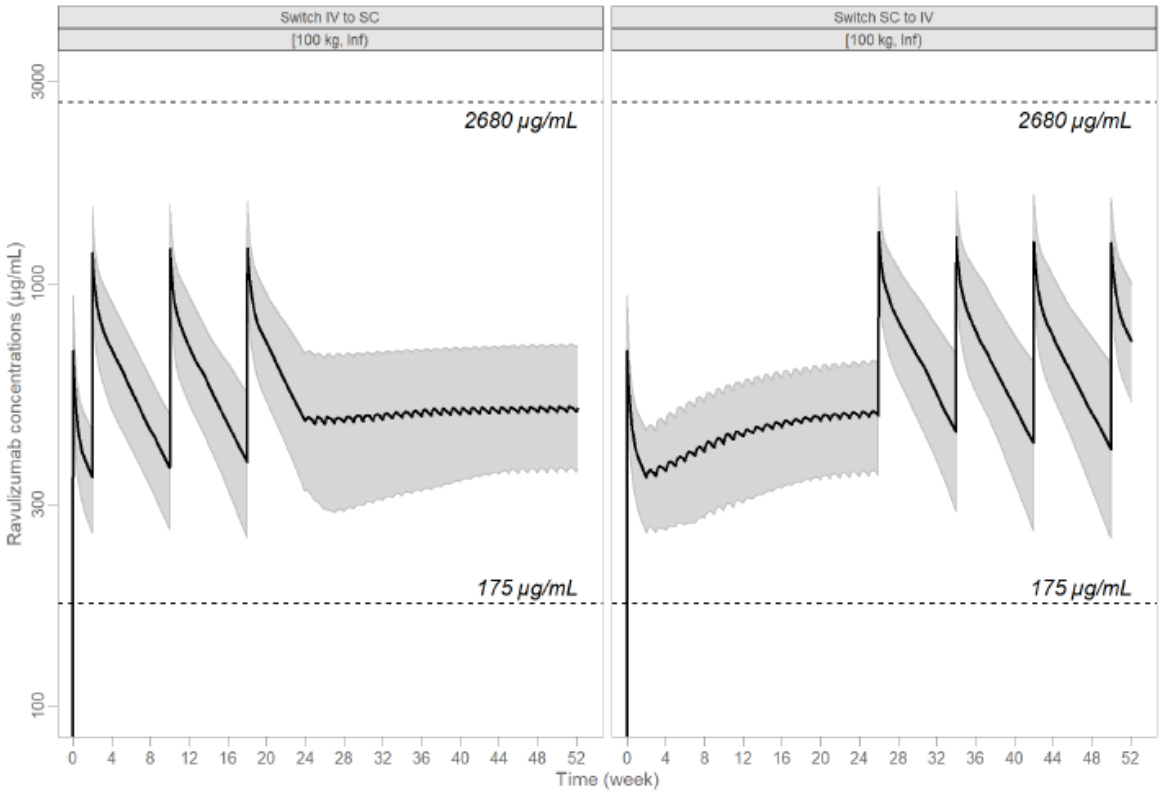
Model-predicted mean (95% prediction interval) concentration-times profiles of ravulizumab following SC and IV dosing in patients ≥100 kg relative to other body weight groups was derived assuming that patients would have received IV and SC regimens for 1 year (i.e., no switch from IV to SC on Day 71) in order to assess the extent of accumulation. Simulations results are presented in Figure below.

Figure 10 **: Model-Predicted Mean (95% Prediction Interval) Concentration-Times Profiles of Ravulizumab Following SC and IV Dosing in Patients with Body Weight ≥100 kg Relative to Other Weight Groups**



GMR = geometric mean ratio.
Note: SC simulations assumed 44% dosing in the thigh, 39% dosing in the abdomen and 17% dosing in the arm.

Figure 11 **Simulations: Model-Predicted Mean (95% Prediction Interval) - Switching from IV to SC and from SC to IV – Patients with Body Weight ≥ 100 kg**



IV to SC switch: On Day 1 (Week 0), all patients received an IV loading dose of ravulizumab (3000 mg for patients ≥ 100 kg). Starting on Day 15 (Week 2) patients received 3600 mg ≥ 100 kg) q8w for 6 months (i.e., 3 doses). Patients switched to qw SC dosing (490 mg) afterward.

SC to IV switch: On Day 1 (Week 0), all patients received an IV loading dose of ravulizumab (3000 mg for patients ≥100 kg). Starting on Day 15 (Week 2) patients received qw SC dosing (490 mg) for 6 months. Patients then switched to IV dosing as follows: 3600 mg (≥ 100 kg) q8w.

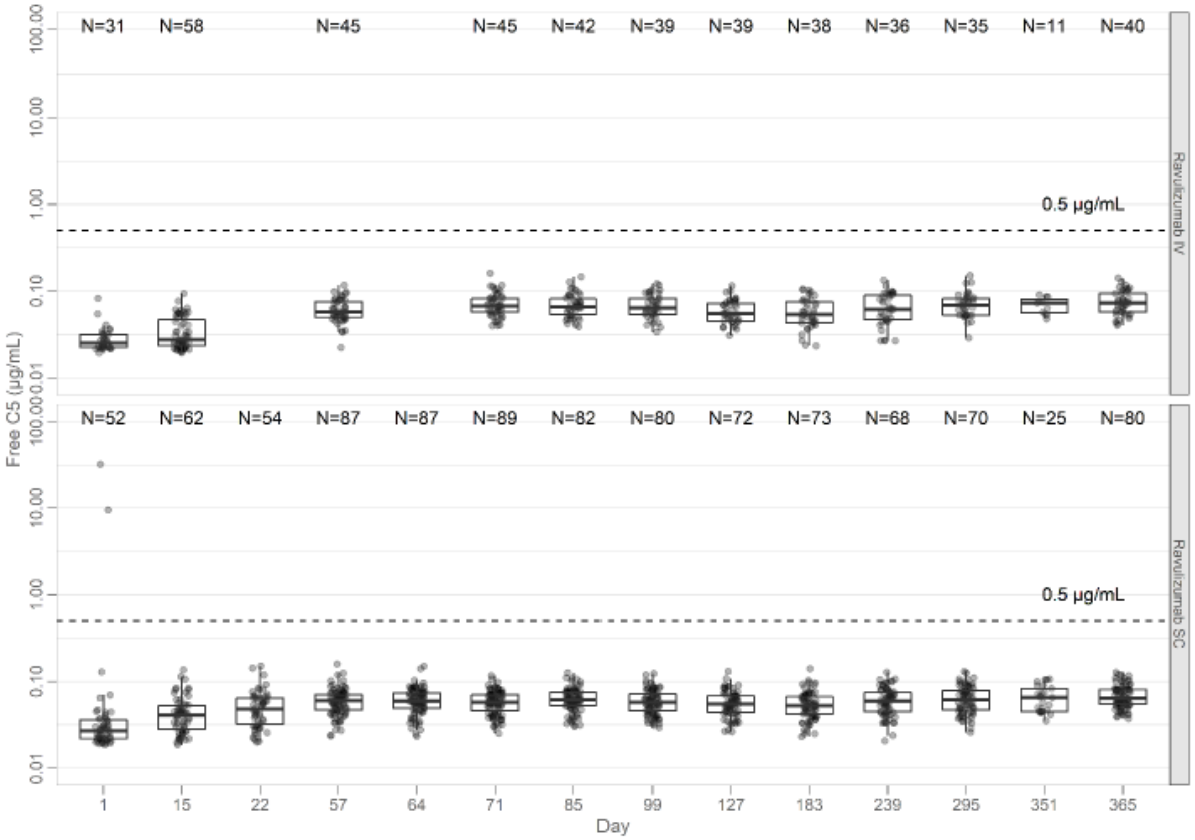
2.6.2.2. Pharmacodynamics

Exposure-response relationship

Exposure-efficacy

Longitudinal concentrations of free C5 (semi-log scale) in patient randomized to the IV and SC treatment arms in study ALXN1210-PNH-303 are presented in Figure below.

Figure 12 : **Longitudinal Profiles of Free C5 in Patient Randomized to the IV and SC Treatment Arms - ALXN1210-PNH-303**



Note: Ravulizumab IV Arm = IV on Day 1 and 15, and qw SC on Day 71 onward; Ravulizumab SC Arm = IV on Day 1 and qw SC dosing on Day 15 onward

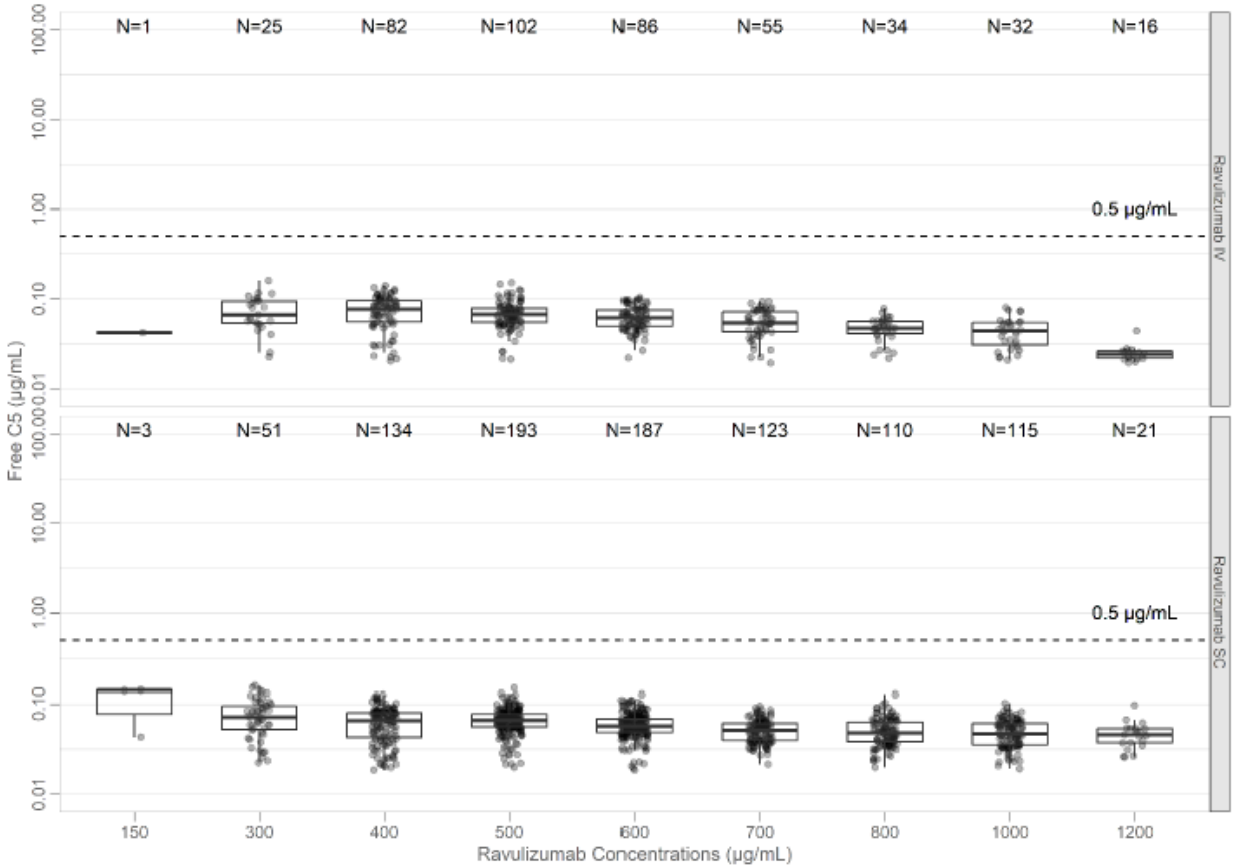
Patients with PNH currently treated with eculizumab were enrolled in study ALXN1210-PNH-303. As a result, all free C5 concentrations prior to ravulizumab dosing on Day 1 were below 0.5 µg/mL due to residual concentrations of eculizumab, with the exception of 2 subjects.

Following IV dosing on Day 1 and 15 in the IV treatment arm, all free C5 concentrations were below 0.5 µg/mL. All free C5 concentrations were maintained below 0.5 µg/mL following initiation of SC dosing on Day 71 and onward.

For the SC treatment arm, all free C5 concentrations were below 0.5 µg/mL following IV dosing on Day 1. All free C5 concentrations were maintained below 0.5 µg/mL following initiation of SC dosing on Day 15 and onward.

The PK/PD relationship between ravulizumab concentrations and serum free C5 concentrations is presented in Figure below.

Figure 13 **PK/PD Relationship – Ravulizumab and Free F5 Concentration - ALXN1210-PNH-303**



Ravulizumab IV Arm = IV on Day 1 and 15, and qw SC on Day 71 onward; Ravulizumab SC Arm = IV on Day 1 and qw SC dosing on Day 15 onward.
Note: A ±50 ng/mL binning was used for boxplots between 300 and 800 (e.g., the 500 boxplot covers 450-550 ng/mL). The first bin (150 ng/mL) has concentrations less than 250 ng/mL. The bin 1000 ng/mL cover 850-1100 ng/mL, and the last bin (1200 ng/mL) cover > 1100 ng/mL.
Note: the two predose sample on Day 1 with free C5 above 0.5 µg/mL were associated with ravulizumab concentrations of zero (BLQ)

All concentrations of ravulizumab in Study ALXN1210-PNH-303 for IV and SC treatment arms were associated with free C5 concentrations below 0.5 µg/mL.

Exposure-safety

The safety population was described as a patient who received at least 1 SC dose and one measurable concentration of ravulizumab. One patient in the ravulizumab IV arm only received IV doses on Day 1 and 15. As a result, the exposure-safety analysis included a total of 128 patients. A summary of TEAEs that occurred in ≥ 5% of the ravulizumab-treated population in Study ALXN1210-PNH-303 is presented in Table below.

Table 7 **Summary of Treatment-emergent Adverse Events Occurring in Greater Than or Equal to 5% of the Ravulizumab-treated Population in Study ALXN1210-PNH-303**

TEAE	Frequency	Percent (%)
Any systemic TEAE following SC Dose	113	88.3%
COVID-19	18	14.1%
Headache	18	14.1%
Pyrexia	14	10.9%
Asthenia	12	9.4%
Diarrhoea	12	9.4%
Nasopharyngitis	12	9.4%
Anaemia	10	7.8%
Abdominal pain	9	7.0%
Back pain	8	6.3%
Haemolysis	8	6.3%
Arthralgia	7	5.5%

[a] Percent is out of N = 128 patients from study ALXN1210-PNH-303. TEAE = treatment emergent adverse effect

A total of 113 (88.3%) patients experienced any systemic TEAEs following SC dose. COVID-19, headache, and pyrexia were the only TEAEs observed in more than 10% of patients in Study ALXN1210-PNH-303.

Table 8 **Probability of TEAEs as a Function of Ravulizumab Maximum Concentration at Steady State in Study ALXN1210-PNH-303**

TEAE	$C_{max,ss}$ Q1 404 – 599 µg/mL (N = 32)	Q2 599 – 763 µg/mL (N = 32)	Q3 763 – 911 µg/mL (N = 32)	Q4 911 – 1286 µg/mL (N = 32)	Overall (N = 128)
Any systemic TEAE following SC Dose					
n	30	28	28	27	113
%	93.8%	87.5%	87.5%	84.4%	88.3%
95% CI	[79.2% – 99.2%]	[71.0% – 96.5%]	[71.0% – 96.5%]	[67.2% – 94.7%]	[81.4% – 93.3%]
COVID-19					
n	8	2	5	3	18
%	25.0%	6.3%	15.6%	9.4%	14.1%
95% CI	[11.5% – 43.4%]	[0.8% – 20.8%]	[5.3% – 32.8%]	[2.0% – 25.0%]	[8.6% – 21.3%]
Headache					
n	6	4	2	6	18
%	18.8%	12.5%	6.3%	18.8%	14.1%
95% CI	[7.2% – 36.4%]	[3.5% – 29.0%]	[0.8% – 20.8%]	[7.2% – 36.4%]	[8.6% – 21.3%]
Pyrexia					
n	6	2	4	2	14
%	18.8%	6.3%	12.5%	6.3%	10.9%
95% CI	[7.2% – 36.4%]	[0.8% – 20.8%]	[3.5% – 29.0%]	[0.8% – 20.8%]	[6.1% – 17.7%]
Asthenia					
n	4	2	1	5	12
%	12.5%	6.3%	3.1%	15.6%	9.4%
95% CI	[3.5% – 29.0%]	[0.8% – 20.8%]	[0.1% – 16.2%]	[5.3% – 32.8%]	[4.9% – 15.8%]
Diarrhoea					
n	5	3	1	3	12
%	15.6%	9.4%	3.1%	9.4%	9.4%
95% CI	[5.3% – 32.8%]	[2.0% – 25.0%]	[0.1% – 16.2%]	[2.0% – 25.0%]	[4.9% – 15.8%]
Nasopharyngitis					
n	4	1	3	4	12
%	12.5%	3.1%	9.4%	12.5%	9.4%
95% CI	[3.5% – 29.0%]	[0.1% – 16.2%]	[2.0% – 25.0%]	[3.5% – 29.0%]	[4.9% – 15.8%]
Anaemia					
n	5	2	2	1	10
%	15.6%	6.3%	6.3%	3.1%	7.8%
95% CI	[5.3% – 32.8%]	[0.8% – 20.8%]	[0.8% – 20.8%]	[0.1% – 16.2%]	[3.8% – 13.9%]
Abdominal pain					
n	2	2	2	3	9
%	6.3%	6.3%	6.3%	9.4%	7.0%
95% CI	[0.8% – 20.8%]	[0.8% – 20.8%]	[0.8% – 20.8%]	[2.0% – 25.0%]	[3.3% – 12.9%]
Back pain					
n	1	2	2	3	8
%	3.1%	6.3%	6.3%	9.4%	6.3%
95% CI	[0.1% – 16.2%]	[0.8% – 20.8%]	[0.8% – 20.8%]	[2.0% – 25.0%]	[2.7% – 11.9%]
Haemolysis					
n	5	0	1	2	8
%	15.6%	0.0%	3.1%	6.3%	6.3%
95% CI	[5.3% – 32.8%]	[0.0% – 10.9%]	[0.1% – 16.2%]	[0.8% – 20.8%]	[2.7% – 11.9%]
Arthralgia					
n	1	3	1	2	7
%	3.1%	9.4%	3.1%	6.3%	5.5%
95% CI	[0.1% – 16.2%]	[2.0% – 25.0%]	[0.1% – 16.2%]	[0.8% – 20.8%]	[2.2% – 10.9%]

TEAE = treatment emergent adverse effect; Q1 = 1st quartile; Q2 = 2nd quartile; Q3 = 3rd quartile; Q4 = 4th quartile; CI = confidence interval

Note: 95% CI are calculated using the Clopper and Pearson method.

2.6.3. Discussion on clinical pharmacology

Bioavailability: The non-inferiority analysis of ravulizumab after SC vs. IV administration demonstrated that Ctrough concentrations are from 23-27% higher based on the dataset considered. The lower limit of the 90% CI of the GMR was higher than the unity, showing that statistically higher exposure is expected with the proposed dosing regimen compared to IV administration.

Elimination: The elimination of ravulizumab was similar between the SC and IV routes of administration.

Pharmacokinetics in the target population

A previously developed population PK model structure (two-compartment model with linear clearance) has been proposed including first order absorption process with absorption lag-time to describe the pharmacokinetic properties of ravulizumab after SC administration. Statistical covariate effects previously identified were considered for SC data, which is endorsed. Therefore, the modelling strategy is endorsed.

Overall, the model structure seems plausible and able to characterize the time-course of SC ravulizumab in PNH patients. However, minor discrepancies were observed in healthy volunteers based on the model performance from pc-VPC (Study ALX1210-HV-105), where the model clearly under-predicted the Cmax concentrations after SC administration, possibly due to a slight bias in the bioavailability estimation for the syringe pump compared to manual injection. Model performance in PNH patients (Study ALXN1210-PNH-303) did not show any major deviation due to the influence in the estimation of F from healthy volunteers.

The clinical relevance has been evaluated in Cmin,ss and Cmax,ss. Extreme body weight and healthy subjects vs patients did show clinically relevant changes in the exposure metrics, as previously observed for IV ravulizumab. However, clinically relevant changes in exposure (>20%) did not result in clinically meaningful limitations in terms of efficacy or safety, based on the model-based analysis that the applicant has provided. Based on the efficacy (175 micrograms/mL) and safety (2680 micrograms/mL) thresholds, the 95% prediction interval for each scenario did not overcame the therapeutic range, showing no compromise in terms of response.

Dose extrapolation of ravulizumab in aHUS patients

Regarding the extrapolation of qw ravulizumab SC maintenance dose of 490 mg in adult patients with aHUS, so far the evidence suggested similar PK behaviour across both disease conditions (aHUS and PNH) after IV administration. Despite no experimental PK evidence has been collected after SC administration, it is highly unexpected that differences in the absorption could be present due to differences in the disease conditions. Therefore, since no differences in ravulizumab disposition were detected after IV administration and similar exposure was demonstrated between SC and IV in PNH patients, it seems adequate to support the extrapolation of similar PK and PD behaviour of ravulizumab in aHUS patients.

Dose extrapolation of ravulizumab in complement inhibitor-naïve adult patients

The extrapolation of ravulizumab SC in complement inhibitor-naïve adult patients across all body weight groups seems adequate based on the previous evidence after ravulizumab IV administration.

Dose extrapolation of ravulizumab in patients with body weight ≥100 kg

Regarding the extrapolation of ravulizumab SC 490 mg in patients with body weight ≥100 kg, the applicant has conducted a simulation-based analysis to highlight that the predicted exposure in a virtual population with a median body weight of 110 kg will be above the efficacy threshold of 175

µg/mL. Body weight has been identified as a clinically relevant covariate on disposition parameters (CL, V, Q and Vp), showing clinically relevant changes in exposure (>20%) in patients with body weigh >95 kg and <51 kg (Figure 6 Population PK report). Therefore, differences in exposure have been quantitatively characterized and model-predicted exposure indicates that 90% of patients with body weight between 100 and 157 kg would show exposure levels above the efficacy threshold, which demonstrates the adequacy of the current posology.

Exposure-response relationship

The exposure-efficacy relationships between ravulizumab concentrations and serum free C5 concentrations did not identify any clinically relevant difference between patients from the IV and SC arms. All concentrations were below the efficacy threshold (0.5 micrograms/mL) after IV and SC, suggesting no differences in efficacy are expected.

The exposure-safety analysis did not identify any relevant difference in terms of treatment emergent adverse events or adverse device reaction after Cmax,ss ravulizumab concentrations.

2.6.4. Conclusions on clinical pharmacology

The characterization of the PK properties, immunogenicity and pharmacodynamic of SC ravulizumab has been developed in a clinical program that comprises 3 clinical studies (one Phase 3 and two Phase 1 studies).

The adequacy of the population PK model to characterize the time-course of ravulizumab after SC has been demonstrated in PNH patients and healthy volunteers. Similar structural population PK model as developed for IV administration has been applied, demonstrating adequate model performance. Based on it, model-based analysis to support the extrapolation of use in naïve PNH patients, patients with body weight >100 kg and inter-change between IV and SC administration can be considered informative to support its extrapolation. No differences in terms of response are expected based on the exposure predictions conducted in none of these scenarios.

The exposure-response analysis was evaluated over efficacy (serum free C5 concentrations) and safety endpoints, suggesting no differences between SC and IV administration. Therefore, no changes could be expected in the exposure-response profile in patients receiving SC vs. IV ravulizumab.

2.6.5. Clinical efficacy

Ultomiris SC is a drug-device combination product comprised of a PFC containing 70 mg/mL ravulizumab (drug constituent) co-packaged with a single-use administration on-body injection (OBI).

The Ultomiris SC clinical program comprises 3 clinical studies (Table below):

- one Phase 3 registrational pharmacokinetic (PK)/pharmacodynamic (PD), efficacy and safety study in adult patients with PNH (Study ALXN1210-PNH-303; N= 128), and
- 2 supportive Phase 1 PK and safety studies in healthy adult subjects (Studies ALXN1210-HV-105 (N=49) and ALXN1210-SC-101 (N=105)).

Table 9 . Ultomiris SC Clinical Program

Studies/Phase	Population	Number of Subjects/Patients	Duration of Treatment
ALXN1210-PNH-303/ Phase 3	Adult patients with PNH who were clinically stable after having been treated with eculizumab for at least 3 months prior to study entry	Total: 128 Ultomiris IV/SC[a]: 44 Ultomiris SC/SC[b]: 84	Minimum of 1 year
ALXN1210-SC-101/ Phase 1	Healthy adult subjects	Total: 42 Placebo: 6 Ultomiris IV: 12 Ultomiris SC: 24	NA (single dose)
ALXN1210-HV-105/ Phase 1	Healthy adult subjects	Total: 49 Ultomiris IV: 6 Ultomiris SC: 43	NA (single dose)

[a] IV/SC = patients randomized to the IV group during the Randomized Treatment Period and switched to receive Ultomiris SC during the Extension Period
[b] SC/SC = patients randomized to the SC group during the Randomized Treatment Period and continued to receive Ultomiris SC during the Extension Period
Abbreviations: IV = intravenous; NA = not applicable; PNH = paroxysmal nocturnal hemoglobinuria; SC = subcutaneous

2.6.5.1. Dose response study(ies)

No specific dose-finding studies have been reported.

A single dose of ravulizumab SC 400 mg, administered consecutively as 4 separate 100-mg injections, was evaluated in a Phase 1 healthy volunteer study and preliminary data indicated ravulizumab SC 400 mg was generally well-tolerated and without any safety concerns.

The proposed weekly dosing regimen of ravulizumab SC 490 mg to be evaluated in the Phase 3 study (Study ALXN1210-PNH-303) was identified by integrating the available Phase 1 PK data from Study ALXN1210-SC-101 and from the ravulizumab IV clinical development program using a modelling and simulation framework. A fixed SC maintenance dose of 490 mg for patients weighing ≥ 40 to < 100 kg starting 2 weeks following an IV loading dose was expected to maintain serum drug concentrations above the target concentration needed for complete inhibition of terminal complement in all adult patients weighing ≥ 40 to < 100 kg from the start of the treatment.

2.6.5.2. Main study(ies)

A Phase 3, Randomized, Parallel-Group, Multicenter, Open-Label, Pharmacokinetic, Noninferiority Study of Ravulizumab Administered Subcutaneously Versus Intravenously in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria Currently Treated With Eculizumab

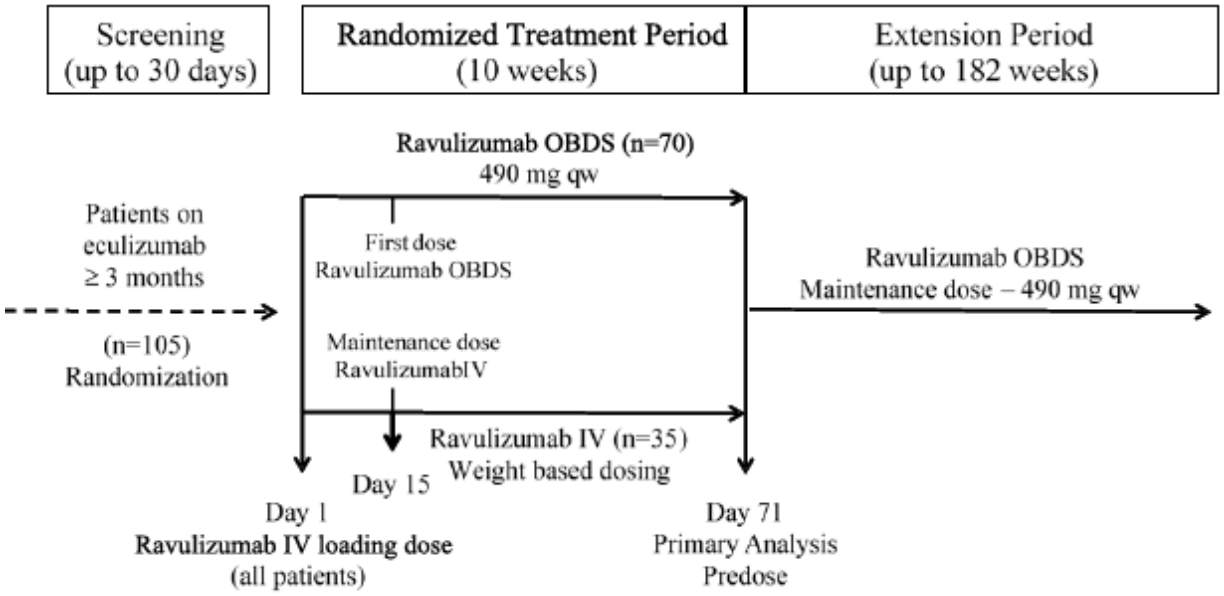
This study was also designed to assess the performance of the ravulizumab OBDS drug/device product (is a drug/device combination product, also referred to as ravulizumab on-body delivery system).

The study consists of an up to a **30-day Screening Period**, a **10-week Randomized Treatment Period**, and an **Extension Period of up to 172 weeks** or until the product is registered or approved (in accordance with country-specific regulations), whichever occurred first. A safety follow-up consisting of a phone call occurs 30 days after the last dose of ravulizumab.

Patients were stratified by weight group (≥40 kg to <60 kg and ≥60 kg to <100 kg) and then randomized in a 2:1 ratio to receive either ravulizumab SC or ravulizumab IV.

During the Randomized Treatment Period, patients assigned to the ravulizumab SC group received a weight-based loading dose of ravulizumab IV on Day 1, followed by maintenance doses of ravulizumab SC on Day 15 and every week (qw) thereafter through completion of the Randomized Treatment Period (Day 71). Patients assigned to the ravulizumab IV group received a weight-based loading dose of ravulizumab IV on Day 1 followed by a maintenance dose of ravulizumab IV on Day 15. After completion of the Randomized Treatment Period (Day 71), all patients received ravulizumab SC qw during the Extension Period.

Figure 14 Schematic of Randomized Treatment Period and SC Treatment in Study ALXN1210-PNH-



Ravulizumab SC dosage: Day 1 loading dose (IV) = 2400 mg for patients weighing ≥ 40 kg to < 60 kg and 2700 mg for patients weighing ≥ 60 kg to < 100 kg; Day 15 and all subsequent SC doses = 490 mg qw for all patients.
Ravulizumab IV dosage: Day 1 loading dose (IV) = 2400 mg for patients weighing ≥ 40 mg to < 60 kg and 2700 mg for patients weighing ≥ 60 kg to < 100 kg; Day 15 maintenance dose (IV) = 3000 mg for patients weighing ≥ 40 kg to < 60 kg, 3300 mg for patients weighing ≥ 60 kg to < 100 kg.
Extension Period maintenance doses (SC) = 490 mg qw for all patients.
Abbreviations: IV = intravenous; OBDS = on-body delivery system; qw = every week; SC = subcutaneous.

Results from this study are available for the Randomized Treatment Period and ongoing Extension Period (02 Feb 2021 data cut-off date, which includes at least 52 weeks of SC treatment). This report is for the study period from 05 Mar 2019 (first patient randomized) to 02 Feb 2021 (last patient last visit Day 365).

Methods

- **Study Participants**

Key inclusion criteria: ≥ 18 years of age with body weight ≥ 40 to < 100 kg; documented diagnosis of PNH confirmed by high-sensitivity flow cytometry evaluation; treated with eculizumab ≥ 3 months prior to study entry; lactate dehydrogenase (LDH) levels ≤ 1.5 × upper limit of normal (ULN) at Screening; and vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug.

Key exclusion criteria: more than 1 LDH value > 2 × ULN within the 3 months prior to study entry; major adverse vascular event (MAVE) in the 6 months prior to study entry; platelet count <30,000/mm3 (30 × 109/L); or absolute neutrophil count < 500/µL (0.5 × 109/L) at Screening.

- **Treatments**

Ravulizumab OBDS was supplied in a kit, comprising 245 mg of ravulizumab SC in a sterile, single-use, prefilled cartridge assembly copackaged with a single-use injector. Two kits will be used to deliver the full 490 mg dose of ravulizumab SC.

Ravulizumab IV loading and maintenance doses were based on patient body weight prior to dosing at each dosing visit.

***Table 10** Study Drug Dosing*

Treatment Group	Randomized Treatment Period (10 weeks)		Extension Period (up to 182 weeks)
Ravulizumab SC	**Loading Dose on Day 1:** Ravulizumab IV 2400 mg[a] or Ravulizumab IV 2700 mg[b]	**SC Doses on Days 15, 22, 29, 36, 43, 50, 57, and 64:** Ravulizumab SC 490 mg[c] (2 ravulizumab OBDS kits per weekly dose)	**Maintenance Doses on Day 71 and qw through Day 1275:** Ravulizumab SC 490 mg[d] (2 ravulizumab OBDS kits per weekly dose)
Ravulizumab IV		**Maintenance Dose on Day 15:** Ravulizumab IV 3000 mg[a] or Ravulizumab IV 3300 mg[b]	

[a] Weight group ≥ 40 to < 60 kg.
[b] Weight group ≥ 60 to < 100 kg.
[c] On Day 15, patients who randomized to the ravulizumab SC group will self-administer ravulizumab SC in the clinic with oversight by trained study site personnel as part of the required training program for at-home self-administration. On Days 29, 43, 57, and 64, ravulizumab SC will be self-administered by the patient in the clinic with oversight by trained study site personnel. On Days 22, 36, and 50, ravulizumab dosing can be self-administered by the patient at home. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic at these visits.
[d] Self-administered by the patient at home or self-administered in the clinic with oversight by trained study site personnel on scheduled visit days. With approval from the Sponsor, the patient can self-administer ravulizumab SC at the clinic on dosing days that are not scheduled in-clinic visits. On Day 71, patients who had been randomized to the ravulizumab IV group will self-administer ravulizumab SC in the clinic with oversight by trained study site personnel as part of the required training program for at-home self-administration.
Abbreviations: IV = intravenous; OBDS = on-body delivery system; qw = every week; SC = subcutaneous.

Day 71 is the end of the **Randomized Treatment Period** and the beginning of the Extension Period.

All Day 71 assessments completed prior to dosing are considered part of the Randomized Treatment Period. Dosing on Day 71 is the start of the Extension Period.

During the **Extension Period**:

- Patients who had been randomized to the ravulizumab SC group will continue to receive 490 mg of ravulizumab SC using 2 OBDS kits on Day 71 and qw thereafter through the end of the Extension Period (up to Day 1275).
- Patients who had been randomized to the ravulizumab IV group will switch to 490 mg of ravulizumab SC using 2 OBDS kits on Day 71 and qw thereafter through the end of the Extension Period (up to Day 1275).

- **Objectives**

Objectives	Endpoints
Primary	**Primary PK endpoint**
To evaluate PK noninferiority of ravulizumab SC versus ravulizumab IV in adult patients with PNH	Day 71 serum ravulizumab C_{trough}
Secondary	**PK Endpoint**
To characterize PK of ravulizumab SC	C_{trough} over time
	PD Endpoint
To characterize PD of ravulizumab SC	Free serum C5 concentrations over time
	Immunogenicity Endpoint
To characterize immunogenicity of ravulizumab SC	Incidence of treatment-emergent ADAs over time
	HRQoL and Treatment Satisfaction Endpoints
To evaluate HRQoL and treatment satisfaction on ravulizumab SC	• Change in FACIT-Fatigue Scale, Version 4, from Baseline to Day 183 • Change in EORTC QLQ-C30 Version 3.0, from Baseline to Day 183 • Reported treatment satisfaction and patient preference as measured by the TASQ score at Baseline and Day 183
	Safety Endpoints
To evaluate safety of ravulizumab SC and ravulizumab OBDS	• Change in physical examinations, vital signs, electrocardiograms, laboratory assessments over time • Incidence of adverse events and serious adverse events • Incidence of adverse device effects and serious adverse device effects
	Efficacy Endpoints
To evaluate efficacy of ravulizumab SC	• Change over time in LDH • Incidence of breakthrough hemolysis • Achievement of transfusion avoidance • Achievement of stabilized hemoglobin
	Performance Endpoint
To assess performance of ravulizumab OBDS	• Reported outcome of attempted full-dose administration (including device failure/malfunction)

Abbreviations: ADA = antidrug antibody; C5 = complement component 5; C_{trough} = pre-dose concentration; EORTC = European Organisation for Research and Treatment of Cancer; FACIT = Functional Assessment of Chronic Illness Therapy; HRQoL = health-related quality of life; IV = intravenous; LDH = lactate dehydrogenase; OBDS = on-body delivery system; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PNH = paroxysmal nocturnal hemoglobinuria; QLQ C30 = Quality of Life Questionnaire-Core 30 Scale; SC = subcutaneous; TASQ = Treatment Administration Satisfaction Questionnaire.

Hypothesis: *No inferiority*

- **Outcomes/endpoints**

Primary endpoint:

The primary objective is to demonstrate the non-inferiority in Day 71 serum ravulizumab Ctrough of ravulizumab subcutaneous (SC) administration compared with ravulizumab intravenous (IV) administration.

Secondary endpoints

Regarding efficacy endpoints, they are described below in the following tables:

Table 11 Study ALXN1210-PNH-303 Efficacy Objectives and Endpoints

Objectives	**Endpoints**
To evaluate efficacy of ravulizumab SC	• Change in LDH over time • Incidence of BTH • Achievement of transfusion avoidance • Achievement of stabilized hemoglobin • Change in clinical manifestations of PNH over time • Change in reticulocyte count over time • Change in eGFR over time • Change in PNH RBC clone size over time
To evaluate HRQoL and treatment satisfaction on ravulizumab SC	• Change in FACIT-Fatigue Scale, Version 4, from Baseline to Day 183 • Change in EORTC QLQ-C30 Version 3.0, from Baseline to Day 183 • Reported treatment satisfaction and patient preference as measured by the TASQ score at Baseline and Day 183

Abbreviations: BTH = breakthrough hemolysis; eGFR = estimated glomerular filtration; EORTC = European Organisation for Research and Treatment of Cancer; FACIT = Functional Assessment of Chronic Illness Therapy; HRQoL = health-related quality of life; LDH = lactate dehydrogenase; PNH = paroxysmal nocturnal hemoglobinuria; QLQ-C30 = Quality of Life Questionnaire - Core 30 scale; RBC = red blood cells; SC = subcutaneous; TASQ = Treatment Administration Satisfaction Questionnaire
Source: ALXN1210-PNH-303 CSR Section 2

Table 12 Efficacy and HRQoL Assessments

Assessment	**Definition/Details**
LDH and other disease-related laboratory parameters	• LDH value • Reticulocyte count • eGFR calculated using the Modification of Diet in Renal Disease formula • PNH RBC clone size evaluated by high sensitivity flow cytometry
Breakthrough hemolysis	At least 1 new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], MAVE including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN as assessed by the central laboratory.
Transfusion avoidance	Patients who remained transfusion free and did not require a transfusion after the first dose of study drug
Stabilized hemoglobin	Avoidance of a ≥ 2 g/dL decrease in hemoglobin level from Baseline in the absence of transfusion from Baseline to the end of the period of interest.
Clinical manifestations of PNH	Investigator or designee assessed each patient for signs and symptoms of PNH, which may include the following: fatigue, chest pain, abdominal pain, dyspnea, dysphagia, erectile dysfunction, and red/dark urine or hemoglobinuria.
FACIT-Fatigue scale	13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function over the preceding 7 days; total scores range from 0 to 52 with higher score indicating better HRQoL (Version 4.0).

Table 12 Efficacy and HRQoL Assessments

Assessment	Definition/Details
EORTC QLQ-C30	Includes the following subscales: global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social activity), symptom scales (fatigue, nausea and vomiting, and pain), and single items (dyspnea, insomnia, loss of appetite), constipation, diarrhea, and financial difficulties); each subscale has a range of 0% to 100%, with a high score representing a higher response level. Thus, a high score for a functional scale represents a high level of functioning, but a high score for a symptom scale represents a high level of symptomatology/problem (Version 3.0).
TASQ-IV and TASQ-SC	A validated (Doll, 2021; Theodore-Oklota, 2016) questionnaire that assesses patients' perceptions and satisfaction with eculizumab IV (TASQ-IV) or ravulizumab SC (TASQ-SC) treatment administration routes, which includes 5 domains: physical impact, psychological impact, impact on activities of daily living, convenience, and satisfaction. Each domain offers up to 5 response options with lower scores indicating a more positive response; scoring is completed by summing each of the 5 domains.

Abbreviations: eGFR = estimated glomerular filtration rate; EORTC = European Organisation for Research and Treatment of Cancer; FACIT = Functional Assessment of Chronic Illness Therapy; HRQoL = health-related quality of life; IV = intravenous; LDH = lactate dehydrogenase; MAVE = major adverse vascular event; PNH = paroxysmal nocturnal hemoglobinuria; QLQ-C30 = Quality of Life Questionnaire - Core 30 Scale; QoL = quality of life; RBC = red blood cells; SC = subcutaneous; TASQ = Treatment Administration Satisfaction Questionnaire; ULN = upper limit of normal

Source: ALXN1210-PNH-303 CSR Table 6

- **Sample size**

Assuming the ratio of the geometric means of Ctrough (SC/IV) is 1.03 and the coefficient of variation (CV) is 0.4 (or, equivalently, difference of means is 0.03 and standard deviation is 0.39), 62 patients in the ravulizumab SC group and 31 patients in the ravulizumab IV comparison group will achieve 90% power to detect non-inferiority, using a one-sided test at an alpha level of 0.05 and a PK non-inferiority margin (NIM) of 0.8 (or, equivalently, -0.22 for the difference of means).

The alpha level and NIM are based on recommendations in guidance documents "Statistical Approaches to Establishing Bioequivalence" and "Guideline on the Investigation of Bioequivalence", from the US Food and Drug Administration and European Medicines Agency, respectively. This sample size is increased to 105 patients (70 patients in the ravulizumab SC group and 35 patients in the ravulizumab IV group) to account for the possibility that approximately 10% of patients may not meet the criteria for inclusion in the PK analysis set. An interim analysis to evaluate futility and perform a sample size re-estimation was planned.

- **Randomisation and Blinding (masking)**

Randomization

Each patient was randomly assigned to a treatment group in a 2:1 ratio (SC:IV) using a centralized interactive web response system. Patients were stratified by weight groups (≥ 40 to < 60 kg and ≥ 60 to < 100 kg).

Blinding:

This is an open-label study.

- **Statistical methods**

Analysis populations

Table 13 Analysis Sets

Analysis Sets[a]	Modified Analysis Sets (Include All Sites)	Description	Analyses
Enrolled Analysis Set	NA	All patients who had signed informed consent and who were randomized	Disposition summaries and important protocol deviations
PK Analysis Set	NA	All patients who had evaluable[b] PK data for whom: • All doses up to Day 64 were compliant with the planned dose and the protocol-specified dosing time windows • The predose PK sample on Day 71 was collected within ± 3 hours from the nominal time of the first dose on Day 1	Primary analysis
PD Analysis Set	NA	All patients who received at least 1 dose of ravulizumab and who had evaluable PD data	All PD analyses
Per Protocol Analysis Set	NA	All patients in the PK analysis set who also satisfied all of the prespecified criteria outlined in Appendix 16.1.9 SAP Section 6.4	Sensitivity analyses performed by repeating the primary analysis on the Per Protocol Analysis Set
Full Analysis Set (FAS)[c]	Modified Full Analysis Set[c]	All patients in the Enrolled Analysis Set who received at least 1 dose of ravulizumab	Secondary efficacy endpoints; additional sensitivity analyses were performed by repeating the primary analysis on the FAS
SC Treated Full Analysis Set[c]	Modified SC Treated Full Analysis Set[c]	All patients in the FAS who received at least 1 dose of ravulizumab SC	All efficacy, PK, and PD analyses that started from the first exposure to SC treatment used the SC Treated Full Analysis Set analysis set
Safety Analysis Set[d]	Modified Safety Analysis Set[d]	All patients who received at least 1 dose of ravulizumab	Safety analyses
SC Treated Safety Analysis Set[d]	Modified SC Treated Safety Analysis Set[d]	All patients in the Safety Analysis Set who received at least 1 dose of SC ravulizumab	All safety and immunogenicity analyses that start from the first exposure to SC treatment used the SC Treated Safety Analysis Set

[a] All patients (n = 7) from 1 site were excluded from the primary PK, PD, Per Protocol, FAS, SC Treated FAS, Safety, and SC Treated Safety analysis sets due to important source document deviations and findings related to deficiencies in Investigator oversight (Section 4.2.2). The patients were included in a Modified Full Analysis Set, Modified Safety Analysis Set, and Modified SC Treated Safety Analysis Set.
[b] Evaluable PK data were defined as non-missing results generated from samples that complied with sample integrity requirements during sample collection, storage, shipment, and bioanalysis.
[c] Patients were analyzed according to the treatment they were randomized to receive.
[d] Patients were analyzed according to the treatment they actually received (must have received that treatment for all of their treatment administration visits).
Abbreviations: FAS = Full Analysis Set; NA = not applicable; PD = pharmacodynamic; PK = pharmacokinetic; SC= subcutaneous

Statistical hypothesis

The alternative hypothesis (HA) is that the Day 71 Ctrough concentration of patients treated with ravulizumab SC via an OBDS is non-inferior to that of patients treated with ravulizumab IV:

$$H_0: \mu_{SC} - \mu_{IV} \leq \delta \text{ vs. } H_A: \mu_{SC} - \mu_{IV} > \delta$$

Were δ is the non-inferiority margin.

Primary Analysis:

The primary analysis was based on the PK analysis set. The primary endpoint is the Day 71 serum ravulizumab Ctrough. While non-inferiority is not being assessed at the interim, descriptive statistics

and the point estimate are used for the sample size re-estimation and futility analysis.

Futility Analysis

When approximately 50% (minimum n=51) of the planned patients have been assessed for the primary endpoint, the primary efficacy interim analysis is conducted. The initial part of the analysis was to assess futility in order to allow the Sponsor to stop the study early if it is unlikely to lead to a significant final result. Following the futility assessment, but using the same set of patients and data, an interim sample size re-estimation analysis to reassess the required size of the study based on estimation of the primary endpoint was performed.

The above analysis provides information to determine whether early stopping for futility is warranted based on the expected treatment effect at the time of the interim analysis.

A nonbinding futility boundary based on conditional power for non-inferiority (CPni) of 20% is used so that if the Sponsor decides to continue the study, even if the futility boundary is crossed, there will be no impact to the primary analysis Type I error rate. The interim analysis is constructed to control the probability of overall type 1 error at 0.05, 1-sided. On the Z-scale the efficacy boundary at final analysis is c=1.645, as computed in EAST 6.4.

Table 14 Criteria for Futility Analysis and Sample Size Re-estimation

	Decision
CPni ≤ 20%	Consider stopping for futility
20% < CPni < CPmin%	Continue to N=105
CPmin% ≤ CPni < 90%	Increase to smaller of N=144 or N needed for CPni=90%
90% ≤ CPni	Continue to N=105

Abbreviations: CPmin = lower bound of the conditional power for noninferiority for the promising zone; CPni = conditional power for noninferiority; N = number of patients.

Effect of Interim Analysis on Final Analysis

Since the sample size may be increased in a data-dependent manner after the interim analysis, use of the conventional Z-statistic at the final analysis may lead to inflation of type 1 error as demonstrated by Cui et al. (1999). These authors have shown that one way to control for such type 1 error inflation is to use a weighted combination test, in which the independent increments of the Z-statistics of the 2 stages are combined by pre-specified weights that are computed based on the planned stage 1 and stage 2 sample sizes, n_1 and n_2 (with or without sample size increase). This weighted combination test is henceforth referred to as the CHW test. In the present case, the study is designed to have an interim analysis at approximately 50% information. The CHW test will use weights that equal:

$$w_1 = \sqrt{\left(\frac{n1}{n1+n2}\right)} \text{ for stage 1 and } w_2 = \sqrt{\left(\frac{n2}{n1+n2}\right)} \text{ for stage 2.}$$

CHW Test Statistic

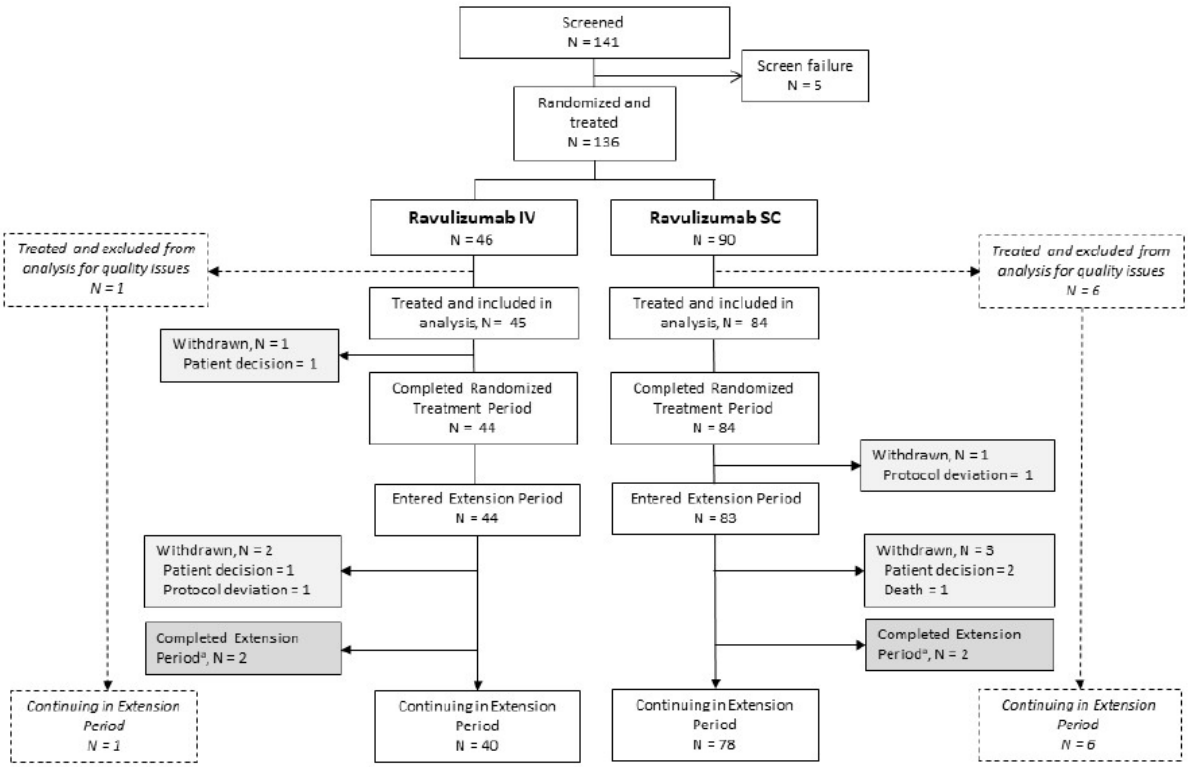
The final CHW test statistic is:

$$z_1 = t_1 - \frac{\delta_0}{SE(\hat{\delta}_1)} \text{ and } z_2 = t_2 - \frac{\delta_0}{SE(\hat{\delta}_2)}.$$

Statistical significance is reached (p-value for non-inferiority ≤.05) at the final analysis if , $Z_{CHW} > c$ where c is the efficacy boundary at final analysis, 1.645

Results

- **Participant flow**



Note: All patients (n = 7) from 1 site were excluded from the primary PK, PD, Per Protocol, FAS, SC Treated FAS, Safety, and SC Treated Safety Analysis Sets due to important source documentation deviations and findings related to deficiencies in Investigator oversight (Section 4.2.2).

[a] Four patients completed the Extension Period and opted not to continue when the duration of the study was extended with the implementation of Protocol Amendment 4.

Abbreviations: FAS = Full Analysis Set; IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; SC = subcutaneous

Source: Table 14.1.2.1.7, Table 14.1.2.1.8, Table 14.1.2.2.1.6, Table 14.1.2.2.2.6, Listing 16.2.1.1.6, and Listing 16.2.1.2.6

- **Recruitment**

  - Study initiation date: 05 mar 2019 (first patient randomized)
  - Primary completion date: 14 April 2020 (las patient Day 71 visit)
  - Interim Data Cut-off date: 02 Feb 2021 (las patient Day 365 visit)

The analysis presented in this report are based on a database lock date of 02 April 2021.

Locations: This study is being conducted at 51 centers that enrolled patients in 14 countries (Australia, Austria, Belgium, Brazil, Canada, Finland, France, Italy, Netherlands, Russia, Spain, Sweden, Turkey, USA).

- **Conduct of the study**

Since the original protocol (dated 25 June 2018), 4 global amendments have been made to the protocol. A summary of changes in the conduct of the study that were implemented by protocol amendments is provided in the Table below.

The Administrative Letter dated 26 May 2020 provided clarification that the duration of the Extension Period is up to 172 weeks, for a total study treatment duration of up to 3.5 years (182 weeks).

Table 15 Summary of Protocol Changes

Amendment Number	Summary of Key Changes in the Amendment
Amendment 1 (Global) 01 Aug 2018	• Removed free hemoglobin testing • Added restriction on ova donation for female patients
Amendment 2 (Global) 20 Sep 2018	• Modified the criteria for the assessment of causality of AEs by the Investigator • Added data collection for the documentation of medication errors occurring with the use of ravulizumab OBDS as ADEs
Amendment 3 (Global) 17 May 2019	• Removed 3 in-clinic study visits for patients in the ravulizumab SC treatment group during the Randomized Treatment Period and replaced with self-administration of ravulizumab SC by the patient in the home setting to reduce the patient burden • Provided additional information required by ISO guidelines for investigational devices • Decreased length of time on eculizumab prior to study entry from 6 months to 3 months • Decreased the period in which patient may have experienced LDH values > 2 × ULN from 6 months to 3 months • Clarified that the QoL instruments will be administered and recorded on paper rather than using an e-diary
Amendment 4 (Global) 19 Nov 2019	• Increased the total study treatment duration to up to 3.5 years (182 weeks) • Revised the definition for the PK analysis set based on an assessment of compliance with the dosing and PK sampling windows specified in the Schedule of Activities and on PK simulations conducted to confirm permitted dosing and sampling windows • Clarified the timing of doses and PK/PD sample collection after Day 1 • Updated definitions of overdose for ravulizumab administered via IV infusion and via the ravulizumab OBDS • Clarified the definition of ADE

Abbreviations: ADE = adverse device effect; AE = adverse event; e-diary = electronic diary; ISO = International Organization for Standardization; IV = intravenous; LDH = lactate dehydrogenase; OBDS = on-body delivery system; PD = pharmacodynamic; PK = pharmacokinetic; QoL = quality of life; SC = subcutaneous; ULN = upper limit of normal

Protocol deviations:

Important deviations were reported by 39% (3/136) of patients, with the incidence evenly distributed across treatment groups. Details on each type of deviation are provided below.

To ensure the quality of the study results, all patients from a noncompliant investigative site were excluded from analyses due to important source documentation deviations and findings related to deficiencies in Investigator oversight.

Table 16 Patients With Important Protocol Deviations as of Data Cut-off Date (Enrolled Analysis Set)

Study Period Type of Deviation	Ravulizumab IV (N = 46) n (%)		Ravulizumab SC (N = 90) n (%)		Total (N = 136) n (%)	
	Overall	COVID-19 Related	Overall	COVID-19 Related	Overall	COVID-19 Related
Overall Study	**18 (39.1)**	**0**	**35 (38.9)**	**3 (3.3)**	**53 (39.0)**	**3 (2.2)**
Eligibility and entry criteria	7 (15.2)	0	13 (14.4)	0	20 (14.7)	0
Investigational product	4 (8.7)	0	9 (10.0)[a]	0	13 (9.6)[a]	0
Informed consent	5 (10.9)	0	7 (7.8)	0	12 (8.8)	0
Study procedures/test	3 (6.5)[b, c]	0	9 (10.0)[a, b,c]	3 (3.3)	12 (8.8)[a,b,c]	3 (2.2)
Source document	1 (2.2)	0	8 (8.9)	0	9 (6.6)	0
Safety reporting	2 (4.3)[b]	0	5 (5.6)[b]	0	7 (5.1)[b]	0
Visit schedule	1 (2.2)[c]	0	4 (4.4)[c]	1 (1.1)	5 (3.7)[c]	1 (0.7)
Laboratory assessment	1 (2.2)	0	3 (3.3)	0	4 (2.9)	0
Concomitant medications	1 (2.2)	0	0	0	1 (0.7)	0
Other	3 (6.5)	0	2 (2.2)	0	5 (3.7)	0
Screening and Randomized Treatment Period	**13 (28.3)**	**0**	**28 (31.1)**	**3 (3.3)**	**41 (30.1)**	**3 (2.2)**
Eligibility and entry criteria	7 (15.2)	0	13 (14.4)	0	20 (14.7)	0
Investigational product	2 (4.3)	0	6 (6.7)	0	8 (5.9)	0
Study procedures/test	2 (4.3)	0	6 (6.7)	3 (3.3)	8 (5.9)	3 (2.2)
Source document	1 (2.2)	0	6 (6.7)	0	7 (5.1)	0
Visit schedule	1 (2.2)	0	3 (3.3)	1 (1.1)	4 (2.9)	1 (0.7)
Informed consent	1 (2.2)	0	2 (2.2)	0	3 (2.2)	0
Laboratory assessment	0	0	3 (3.3)	0	3 (2.2)	0
Safety reporting	1 (2.2)	0	1 (1.1)	0	2 (1.5)	0
Other	2 (4.3)	0	1 (1.1)	0	3 (2.2)	0
Extension Period	**8 (17.4)**	**0**	**14 (15.6)**	**0**	**22 (16.2)**	**0**
Informed consent	4 (8.7)	0	5 (5.6)	0	9 (6.6)	0
Investigational product	2 (4.3)	0	3 (3.3)[a]	0	5 (3.7)[a]	0
Safety reporting	1 (2.2)[b]	0	4 (4.4)[b]	0	5 (3.7)[b]	0
Study procedures/test	1 (2.2)[b,c]	0	3 (3.3)[a,b,c]	0	4 (2.9)[a,b,c]	0
Source document	0	0	3 (3.3)	0	3 (2.2)	0
Concomitant medications	1 (2.2)	0	0	0	1 (0.7)	0
Laboratory assessment	1 (2.2)	0	0	0	1 (0.7)	0
Visit schedule	0	0	1 (1.1)	0	1 (0.7)	0
Other	1 (2.2)	0	1 (1.1)	0	2 (1.5)	0

Note: Percentages (%) are based on the total number of randomized patients in each column. Protocol deviations due to COVID-19 are also presented in the overall column.

[a] Two patients had investigational product related important deviations that were incorrectly categorized to "Study procedure/test".

[b] Two patients had safety related important deviations that were incorrectly categorized to "Study procedure/test".

[c] Two patients had study/procedure test related important deviations that were incorrectly categorized to "Visit Schedule".

Abbreviations: COVID-19 = coronavirus disease 2019; IV = intravenous; SC = subcutaneous

Source: Table 14.1.2.4.1.6, Table 14.1.2.4.2.6, Table 14.1.2.4.3.6, and Listing 16.2.2.1.1.10

Although 20 patients had important protocol deviations classified in the eligibility and entry criteria category, these deviations did not affect the interpretation of the study results.

Important protocol deviations leading to exclusion from analysis sets:

Seven patients from 1 site (Site 0657) had important protocol deviations related to source documentation (eg, clinical research associate was not able to confirm the traceability, accuracy, and validity of source document[s] against the eCRF due to multiple sources).

The important protocol deviations noted at this site were further evaluated during a 'for-cause' audit resulting in the exclusion of the patients enrolled at this site from the primary PK Analysis Set, FAS, PD Analysis Set, Safety Analysis Set, SC Treated FAS, and the SC Treated Safety Analysis Set.

- **Baseline data**

Demographic characteristics

Table 17 Demographics and Baseline Characteristics (Full Analysis Set)

Variable	Ravulizumab IV (N = 45)	Ravulizumab SC (N = 84)	Total (N = 129)
Sex, n (%)			
Male	20 (44.4)	40 (47.6)	60 (46.5)
Female	25 (55.6)	44 (52.4)	69 (53.5)
Ethnicity, n (%)			
Not Hispanic or Latino	29 (64.4)	53 (63.1)	82 (63.6)
Hispanic or Latino	7 (15.6)	15 (17.9)	22 (17.1)
Not reported	6 (13.3)	12 (14.3)	18 (14.0)
Unknown	3 (6.7)	4 (4.8)	7 (5.4)
Race, n (%)[a]			
White	29 (64.4)	63 (75.0)	92 (71.3)
Not reported	6 (13.3)	13 (15.5)	19 (14.7)
Black or African American	4 (8.9)	3 (3.6)	7 (5.4)
Other	2 (4.4)	4 (4.8)	6 (4.7)
Asian	2 (4.4)	0	2 (1.6)
Non-Japanese descent	2 (4.4)	0	2 (1.6)
Unknown	1 (2.2)	1 (1.2)	2 (1.6)
American Indian or Alaska Native	1 (2.2)	0	1 (0.8)
Age (years) at informed consent			
Mean (SD)	46.4 (13.22)	45.3 (14.47)	45.7 (14.00)
Median	44.0	42.5	44.0
Min, max	24, 77	18, 79	18, 79
Age at informed consent, n (%)			
18 to 65 years	41 (91.1)	75 (89.3)	116 (89.9)
> 65 years	4 (8.9)	9 (10.7)	13 (10.1)
Baseline weight (kg)			
Mean (SD)	73.68 (12.655)	72.52 (12.611)	72.92 (12.589)
Median	73.00	72.15	72.30
Min, max	52.0, 98.4	43.5, 98.0	43.5, 98.4
Baseline weight, n (%)			
≥ 40 to < 60 kg	8 (17.8)	13 (15.5)	21 (16.3)
≥ 60 to < 100 kg	37 (82.2)	71 (84.5)	108 (83.7)

[a] Patients may have been counted in more than one category for race.
Abbreviations: IV = intravenous; SC = subcutaneous
Source: Table 14.1.1.1.1

Medical history:

The medical/surgical history and baseline physical examination findings were comparable (<20% difference) between the treatment groups and consistent with entry criteria and target population. The most frequently reported conditions and procedures (reported in ≥ 5% of total patients) included hypertension (18.6%), cholecystectomy (9.3%), cholelithiasis (7.0%), bone marrow failure (6.2%), appendectomy (6.2%), and anxiety (5.4%).

Disease history and characteristics

Table 18 Disease Characteristics (FAS)

Variable Category	Ravulizumab IV (N = 45)	Ravulizumab SC (N = 84)	Total (N = 129)
Method of PNH diagnosis, n (%)			
Flow cytometry and/or FLAER	42 (93.3)	79 (94.0)	121 (93.8)
Other	3 (6.7)	5 (6.0)	8 (6.2)
Years from PNH diagnosis to informed consent			
n	45	84	129
Mean (SD)	9.23 (6.335)	8.89 (6.536)	9.01 (6.444)
Median	7.90	7.45	7.50
Min, max	0.6, 29.0	0.8, 33.0	0.6, 33.0
PNH clone size at Screening			
PNH RBC Type II clone size, (%)			
n	34	63	97
Mean (SD)	16.34 (23.703)	10.63 (17.342)	12.64 (19.870)
Median	5.65	3.30	3.80
Min, max	0.3, 88.9	0.0, 68.1	0.0, 88.9
PNH RBC Type III clone size, (%)			
n	44	81	125
Mean (SD)	38.48 (27.309)	31.18 (26.900)	33.75 (27.161)
Median	34.70	23.30	26.10
Min, max	3.8, 97.3	0.0, 98.0	0.0, 98.0
Total PNH RBC clone size, (%)			
n	35	65	100
Mean (SD)	54.97 (33.389)	44.78 (34.558)	48.35 (34.333)
Median	62.60	32.40	41.75
Min, max	4.1, 98.7	0.9, 100.0	0.9, 100.0
Total granulocyte clone size, (%)			
n	45	82	127
Mean (SD)	83.18 (20.577)	73.95 (27.476)	77.22 (25.551)
Median	92.40	82.00	88.30
Min, max	27.4, 99.7	4.1, 99.8	4.1, 99.8
Total monocyte clone size, (%)			
n	45	83	128
Mean (SD)	85.66 (18.578)	77.21 (26.555)	80.18 (24.316)
Median	93.60	90.40	91.70
Min, max	28.0, 99.8	5.0, 99.7	5.0, 99.8

Abbreviations: FLAER = fluorescein-labeled proaerolysin; IV = intravenous; max = maximum; min = minimum; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; SC = subcutaneous; SD = standard deviation
Source: Table 14.1.3.1.1, Listing 16.2.4.1.10, and Listing 16.2.6.2.3.9

In this study population of patients with stable disease, 18.6% of patients (24/129) had a history of packed red blood cell (pRBC) transfusions in the year prior to first dose of study intervention. The percentage of patients receiving pRBC transfusions within 1 year prior to first dose was 24.4% in the IV group and 15.5% in the SC group.

The mean number of transfusions within 1 year prior to first dose was higher in the ravulizumab SC group than in the ravulizumab IV group, as was the mean number of units transfused. This difference was attributable to 1 heavily transfusion-dependent patient in the ravulizumab SC group.

Table 19 Packed Red Blood Cell/Whole Blood Transfusions within 1 Year Prior to First Dose (FAS)

Variable Category	Ravulizumab IV (N = 45)	Ravulizumab SC (N = 84)	Total (N = 129)
Number of patients with pRBC/whole blood transfusions within 1 year prior to first dose, n (%)	11 (24.4)	13 (15.5)	24 (18.6)
pRBC/whole blood transfusions within 1 year prior to first dose			
Total	20	36	56
Mean (SD)	1.8 (1.54)	2.8 (2.45)	2.3 (2.10)
Median	1.0	2.0	2.0
Min, max	1, 6	1, 10	1, 10
Units of pRBC/whole blood transfused within 1 year prior to first dose			
Total	34	46	80
Mean (SD)	3.1 (3.27)	3.8 (2.62)	3.5 (2.91)
Median	2.0	3.5	2.0
Min, max	1, 12	1, 11	1, 12

Note: Percentages were based on the total number of patients in each group.
Abbreviations: IV = intravenous; pRBC = packed red blood cells; SC = subcutaneous
Source: Table 14.1.3.2.1

Table 20 PNH Medical History: PNH-Associated Conditions Diagnosed at Any Time Prior to Informed Consent (FAS)

PNH-Associated Conditions, n (%)	Ravulizumab IV (N = 45)	Ravulizumab SC (N = 84)	Total (N = 129)
Patients with any PNH-associated conditions prior to informed consent	41 (91.1)	78 (92.9)	119 (92.2)
Anemia	28 (62.2)	57 (67.9)	85 (65.9)
Hematuria or hemoglobinuria	17 (37.8)	31 (36.9)	48 (37.2)
Aplastic anemia	17 (37.8)	29 (34.5)	46 (35.7)
Other[a]	9 (20.0)	8 (9.5)	17 (13.2)
Renal failure	3 (6.7)	7 (8.3)	10 (7.8)
Myelodysplastic syndrome	4 (8.9)	5 (6.0)	9 (7.0)
Pregnancy complication	2 (4.4)	5 (6.0)	7 (5.4)

Note: Patients may have been counted in more than 1 category. Percentages were based on the total number of patients in each group.
[a] Reasons for the "Other" category are detailed in Listing 16.2.4.3.1.10.
Abbreviations: IV = intravenous; PNH = paroxysmal nocturnal hemoglobinuria; SC = subcutaneous
Source: Table 14.1.3.4.1

Table 21 Major Adverse Vascular Events History (FAS)

MAVE Categories, n (%)	Ravulizumab IV (N = 45)	Ravulizumab SC (N = 84)	Total (N = 129)
Patients with a history of MAVE	17 (37.8)	26 (31.0)	43 (33.3)
Hepatic/portal vein thrombosis (Budd-Chiari Syndrome)	5 (11.1)	7 (8.3)	12 (9.3)
Thrombophlebitis/deep vein thrombosis	6 (13.3)	6 (7.1)	12 (9.3)
Other	3 (6.7)	7 (8.3)	10 (7.8)
Cerebral arterial occlusion/cerebrovascular accident	4 (8.9)	5 (6.0)	9 (7.0)
Pulmonary embolus	3 (6.7)	3 (3.6)	6 (4.7)
Mesenteric/visceral vein thrombosis or infarction	0	4 (4.8)	4 (3.1)
Myocardial infarction	0	3 (3.6)	3 (2.3)
Renal vein thrombosis	0	3 (3.6)	3 (2.3)
Transient ischemic attack	0	2 (2.4)	2 (1.6)
Acute peripheral vascular occlusion	0	1 (1.2)	1 (0.8)
Amputation (non-traumatic; non-diabetic)	0	1 (1.2)	1 (0.8)
Cerebral venous occlusion	1 (2.2)	0	1 (0.8)
Mesenteric/visceral arterial thrombosis or infarction	0	1 (1.2)	1 (0.8)

Note: Percentages were based on the total number of patients in each group.
Abbreviations: IV = intravenous; MAVE = major adverse vascular event; SC = subcutaneous
Source: Table 14.1.3.5.1

- **Numbers analysed**

Table 22 Analysis Data Sets – Randomization Period

	Ravulizumab IV n (%)	Ravulizumab SC n (%)	Total n (%)
Enrolled Analysis Set (number of randomized patients)	46	90	136
Full Analysis Set, n (%)	45 (97.8)	84 (93.3)	129 (94.9)
Excluded from Full Analysis Set[a]	1 (2.2)	6 (6.7)	7 (5.1)
Safety Analysis Set, n (%)	45 (97.8)	84 (93.3)	129 (94.9)
Excluded from the Safety Analysis Set[a]	1 (2.2)	6 (6.7)	7 (5.1)
PD Analysis Set, n (%)	45 (97.8)	84 (93.3)	129 (94.9)
Excluded from the PD Analysis Set[a]	1 (2.2)	6 (6.7)	7 (5.1)
PK Analysis Set, n (%)	43 (93.5)	70 (77.8)	113 (83.1)
Excluded from the PK Analysis Set	3 (6.5)	20 (22.2)	23 (16.9)
Reason excluded[b]			
• Protocol deviation	2	13	15
○ Site non-compliance[a]	1	6	7
○ Any dose taken out of the protocol-specified window[c]	0	5	5
○ Day 71 predose PK sample collected out of the protocol-specified window[d]	1	2	3
○ Full dose not received at any visit	0	1	1
○ Temperature excursion impacting dose viability	0	1	1
• Dosing errors	0	9	9
○ Partial dose at any visit resulting in patient receiving more than 2 kits to achieve a full dose administration	0	9	9
• Patient withdrawal from study prior to Day 71	1	0	1
Per Protocol Analysis Set, n (%)	40 (87.0)	66 (73.3)	106 (77.9)
Excluded from the Per Protocol Analysis Set[a]	6 (13.0)	24 (26.7)	30 (22.1)

Note: Definitions for the analysis sets are provided in Section 3.7.1. a All patients (n = 7) from 1 site were excluded from the primary PK, PD, Per Protocol, FAS, SC Treated FAS, Safety, and SC Treated Safety analysis sets due to important source document deviations and findings related to deficiencies in Investigator oversight (Section 4.2.2). b A patient may have more than 1 reason leading to exclusion from the PK analysis set. c The window for dosing to be compliant for inclusion in the PK Analysis set was ± 3 hours at Days

15, 57, 64 and ± 6 hours at Days 22, 29, 36, 43 and 50 from the Day 1 nominal dose time. d The window for the pre-dose PK sample collection on Day 71 is ± 3 hours from the Day 1 nominal dose time. Abbreviations: FAS = Full Analysis Set; IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; SC = subcutaneous. Source: Table 14.1.2.3.6 and Table 14.1.2.4.6

Of the **136 randomized patients**, 113 patients were included in the PK Analysis Set (primary analysis set).

The PK, PD, Per Protocol, Full Analysis Set (FAS), SC Treated FAS, Safety, and SC Treated Safety Analysis Sets, **exclude 7 participants** (1 IV group and 6 SC group) from a single site due to important source documentation deviations and site non-compliance. The FAS, Safety Set, and PD Set were identical.

Table 23 Analysis Data Sets – SC Treatment Period

	Ravulizumab IV/SC (N = 46) n (%)	Ravulizumab SC/SC (N = 90) n (%)	Total (N = 136) n (%)
Number of patients in the SC Treated Safety Analysis Set[a]	44 (95.7)	84 (93.3)	128 (94.1)
Number of patients in the SC Treated Full Analysis Set[a]	44 (95.7)	84 (93.3)	128 (94.1)

Note: Definitions for the analysis sets are provided in Section 3.7.1.
[a] All patients (n = 7) from 1 site were excluded from the primary PK, PD, Per Protocol, FAS, SC Treated FAS, Safety, and SC Treated Safety analysis sets due to important source document deviations and findings related to deficiencies in Investigator oversight (Section 4.2.2).
Abbreviations: FAS = Full Analysis Set; IV = intravenous; PD = pharmacodynamic; PK = pharmacokinetic; SC = subcutaneous
Source: Table 14.1.2.3.6

- **Outcomes and estimation**

Primary Objective: PK Non-inferiority

This is to demonstrate the non-inferiority in Day 71 serum ravulizumab Ctrough of ravulizumab subcutaneous (SC) administration compared with ravulizumab intravenous (IV) administration.

This point is discussed in the clinical Pharmacology section.

Secondary Endpoints

Efficacy – Randomized Treatment Period

Efficacy results for the Randomized Treatment Period (through Day 71) are presented for the FAS.

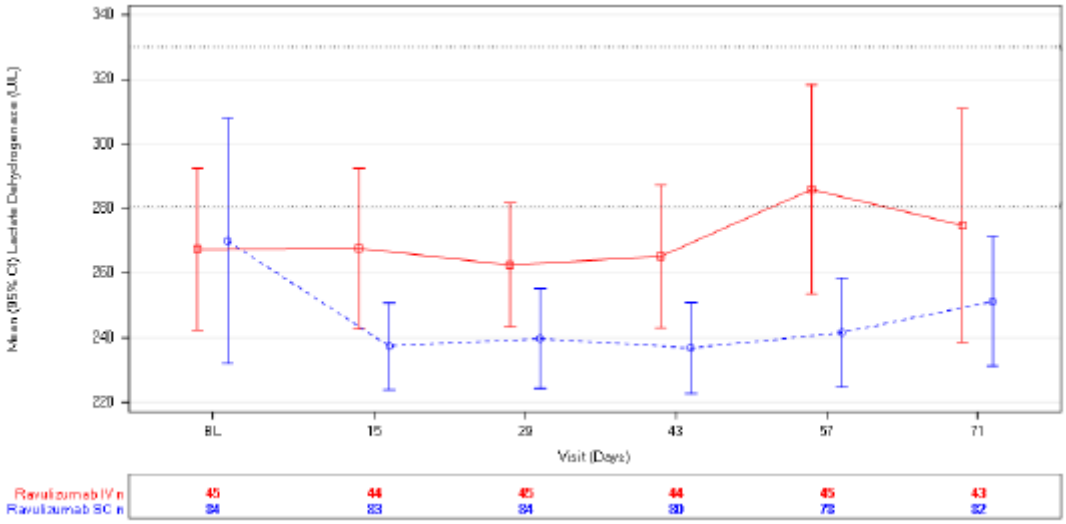
Efficacy analyses and results using the Modified FAS, which included the 7 patients from the non-compliant site, were similar when compared with the FAS for all of the efficacy endpoints.

Lactate Dehydrogenase (LDH)

During the Randomized Treatment Period, mean LDH levels remained stable over time in both treatment groups for the FAS.

Mean percent change in LDH from baseline to Day 71 was 2.57% for the SC group and 5.73% for the IV group.

Figure 15 LDH (U/L) Mean (95% CI) Values During Randomized Treatment Period (FAS)



Note: Baseline was defined as the last assessment from the central laboratory prior to first dose of study drug. Dotted horizontal lines indicate the ULN. ULN for male = 281 (U/L); ULN for female = 330 (U/L). Abbreviations: BL = baseline; CI = confidence interval; IV = intravenous; LDH = lactate dehydrogenase; SC = subcutaneous; ULN = upper limit of the normal range. Source: Figure 14.2.2.1.1.1

Breakthrough hemolysis

Breakthrough hemolysis was defined as having at least 1 new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], MAVE (including thrombosis), dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN as assessed by the central laboratory.

Two patients experienced BTH during the Randomized Treatment Period (through Day 71): 1 patient in the IV group at Day 57 and 1 patient in the SC group at Day 71.

The events of BTH were reviewed in an effort to evaluate the etiological factors involved, including time-matched PD parameters and/or presence of an infection or other potential complement amplifying condition (CAC), such as trauma, surgery, or pregnancy (Brodsky, 2017; Risitano, 2012; Sharma, 2015). Adverse events temporally associated with the onset of BTH were also reviewed for each patient to evaluate for potential infections or other CAC.

Neither of these events of BTH were associated with suboptimal C5 inhibition (defined as free C5 ≥ 0.5 µg/mL). Note that the patient in the IV group experiencing BTH on Day 57 did not have a free C5 sample obtained at the Day 57 visit; however, this patient showed complete C5 control at all other sampling time points. The patient in the SC group had a Grade 1 viral infection from Days 55 to 65 prior to the BTH event that was reported on Day 71.

Transfusion avoidance

The majority of patients in both treatment groups in the FAS avoided pRBC transfusion during the Randomized Treatment Period (IV group: 86.7%; SC group: 94.0%).

Stabilized haemoglobin

The majority of patients in both treatment groups in the FAS maintained stabilized haemoglobin during the Randomized Treatment Period (IV group: 81.8%; SC group: 93.6%). Stabilized haemoglobin was defined as the avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 71.

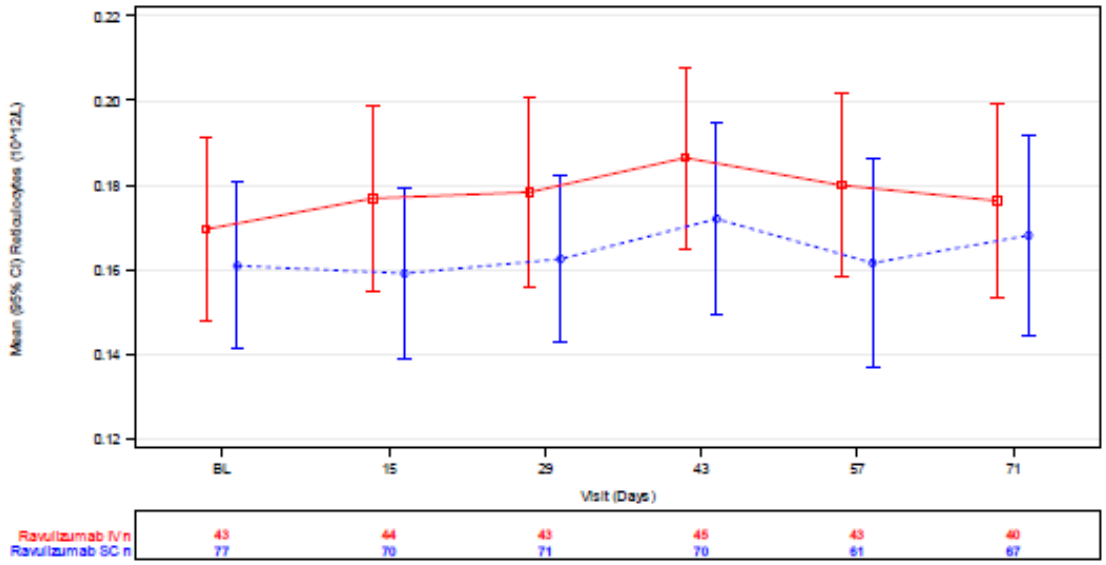
Clinical manifestations of PNH

During the Randomized Treatment Period, the percentage of patients with any clinical manifestations of PNH was similar in both treatment groups in the FAS (IV group: 46.7%; SC group: 47.6%). Fatigue was the most common symptom (IV group: 18/21 [85.7%]; SC group: 34/40 [85%]).

Reticulocyte count

During the Randomized Treatment Period, reticulocyte count levels remained stable over time in both treatment groups for the FAS.

Figure 16 Reticulocyte Count (1012/L) Mean (95% CI) Values During Randomized Treatment Period (FAS)

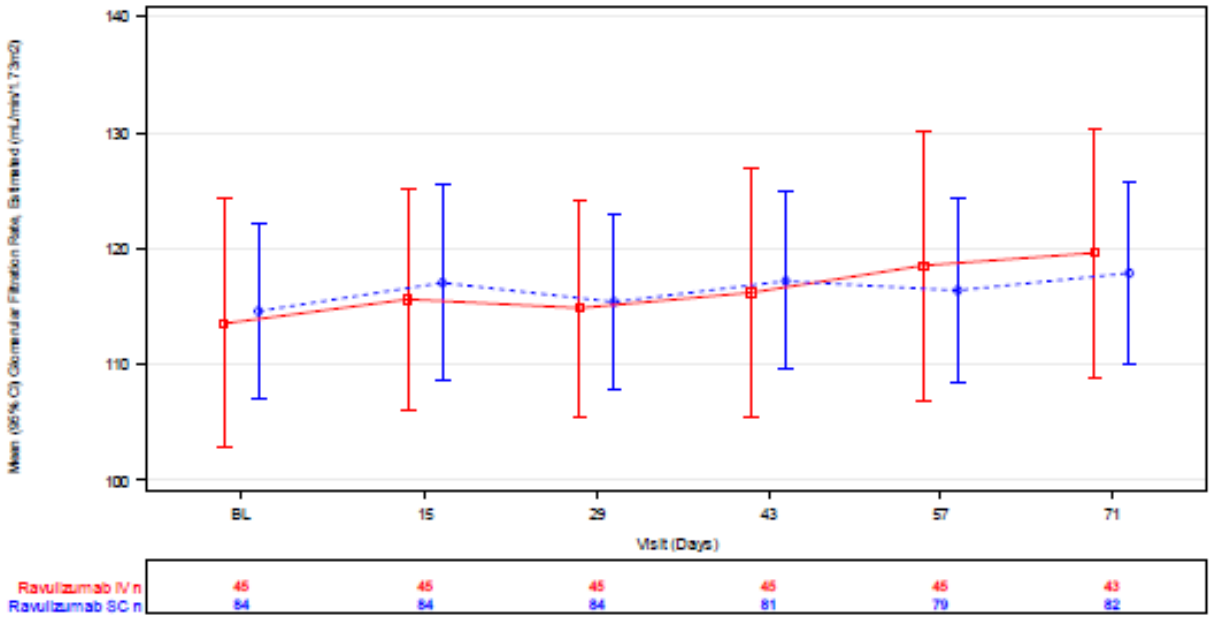


Note: Baseline was defined as the last assessment from the central laboratory prior to first dose of study drug.
Abbreviations: BL = baseline; CI = confidence interval; IV = intravenous; SC = subcutaneous
Source: Figure 14.2.2.2.1.1

Estimated Glomerular Filtration Rate

During the Randomized Treatment Period, eGFR levels remained stable over time in both treatment groups for the FAS.

Figure 17 Estimated Glomerular Filtration Rate (mL/min/1.73m2) Mean (95% CI) Values During the Randomized Treatment Period (FAS)



Note: Change and percentage change were summarized only for patients who had data at Baseline and the specified time point. Baseline was defined as the last assessment from the central laboratory prior to first study drug dose.
Abbreviations: BL = baseline; CI = confidence interval; IV = intravenous; SC = subcutaneous
Source: Figure 14.2.2.4.1.1

PNH RBC Clone Size

Mean total PNH RBC clone size was similar between the treatment groups at baseline and remained stable over time in both treatment groups for the FAS during the Randomized Treatment Period.

HRQoL and Treatment Administration Satisfaction – Randomized Treatment Period

FACIT-Fatigue

The mean FACIT-Fatigue subscale scores at baseline were similar between the treatment groups (IV group: 42.10; SC group: 40.29) and remained stable over time in both treatment groups for the FAS during the Randomized Treatment Period.

The percentages of patients with a change of ≥ +3 points at Day 71 compared to baseline in FACIT-Fatigue subscale score were similar in both treatment groups (IV group: 27.3%; SC group: 35.0%).

EORTC QLQ-C30

Mean EORTC Quality of Life Questionnaire - Core 30 scale (QLQ-C30) global health status scores were similar between the treatment groups at baseline (IV group: 73.15, SC group: 74.07) and remained stable in both treatment groups over time for the FAS during the Randomized Treatment Period.

At baseline, for both treatment groups, mean EORTC QLQ-C30 subscale scores reflected a patient population with stable disease: Global Health Status and Physical Functioning subscale scores were high, ranging from 73% to 83% across treatment groups, and Fatigue subscale scores were low, ranging from 25% to 27%).

Treatment Administration Satisfaction

The TASQ is a 19-item validated questionnaire designed to assess patients' perception and satisfaction with treatment administration routes (Doll, 2021). The TASQ scores treatment administration

satisfaction across 5 domains: physical impact, psychological impact, impact on ADL, convenience, and satisfaction. Each domain offers up to 5 response options with lower scores indicating a more positive response. Scoring is completed by summing each of the 5 domains.

Two versions of the TASQ were administered to patients:

- The TASQ-IV: based on the patient's most recent *eculizumab IV* administration
- The TASQ-SC: based on the patient's most recent *ravulizumab SC* administration

At baseline, mean total TASQ scores for the IV route of administration for eculizumab were similar between the treatment groups (Table 19). At the end of the Randomized Treatment Period (Day 71), the mean (SD) change from baseline in total TASQ score was -7.00 (34.581) for the IV group and -70.54 (70.522) for the SC group.

Table 24 Main results of efficacy endpoints – Randomized Treatment Period (Full Analysis Set)

Efficacy Endpoint	Randomized Treatment Period (Day 71)	
	IV (N = 45)	SC (N = 84)
LDH % change from baseline	(N = 43)	(N = 82)
Mean (SD)	5.73 (29.716)	2.57 (33.883)
Range	[-42.6, 174.1]	[-82.6, 179.5]
Breakthrough hemolysis[a]		
n (%)	1 (2.2)	1 (1.2)
95% CI	[0.06, 11.77]	[0.03, 6.46]
Transfusion avoidance		
n (%)	39 (86.7)	79 (94.0)
95% CI	[73.21, 94.95]	[86.65, 98.04]
Hemoglobin stabilization	(N = 44)	(N = 78)
n (%)	36 (81.8)	73 (93.6)
95% CI	[67.29, 91.81]	[85.67, 97.89]
FACIT-Fatigue change from baseline	(N = 44)	(N = 80)
Mean (SD)	-0.83 (7.378)	1.21 (7.882)
Range	[-26.0, 15.4]	[-32.0, 33.0]

[a] Breakthrough hemolysis (BTH) is defined as at least 1 new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], MAVE including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH $\geq 2 \times$ ULN as assessed by the central laboratory. There were no BTH events associated with free C5 level ≥ 0.5 µg/mL. The patient in the IV group who experienced BTH during the Randomized Treatment Period did not have a free C5 sample obtained at the Day 57 visit; however, all other sampling time points showed complete C5 control.

Abbreviations: C5 = complement component 5; CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy; IV = intravenous; LDH = lactate dehydrogenase; MAVE = major adverse vascular event; SC = subcutaneous; ULN = upper limit of normal

Efficacy - SC Treatment

Table 25 Main results of efficacy endpoints – SC Treatment Period (SC Treated Full Analysis Set)

Efficacy Endpoint	SC Treatment (Day 351)		
	IV/SC (N = 44)	SC/SC (N = 84)	Total SC (N = 128)
LDH % change from baseline Mean (SD) 95% CI	(N = 34) -0.83 (17.225) [-6.843, 5.178]	(N = 73) 1.74 (21.905) [-3.371, 6.851]	(N = 107) 0.92 (20.488) [-3.004, 4.85]
Breakthrough hemolysis[a] n (%) 95% CI	 2 (4.5%) [0.56, 15.47]	 3 (3.6) [0.74, 10.08]	 5 (3.9) [1.28, 8.88]
Transfusion avoidance n (%) 95% CI	 35 (79.5) [64.70, 90.20]	 72 (85.7) [76.38, 92.39]	 107 (83.6) [76.02, 89.55]
Hemoglobin stabilization n (%) 95% CI	(N = 44) 32 (72.7) [57.21, 85.04]	(N = 79) 66 (83.5) [73.51, 90.94]	(N = 123) 98 (79.7) [71.48, 86.39]
FACIT-Fatigue change from baseline Mean (SD) 95% CI	NA	(N = 70) 2.57 (7.178) [0.86, 4.28]	(N = 70) 2.57 (7.178) [0.86, 4.28]

[a] Breakthrough hemolysis (BTH) is defined as at least 1 new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], MAVE including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN as assessed by the central laboratory. There were no BTH events associated with free C5 level ≥ 0.5 µg/mL.

Abbreviations: C5 = complement component 5; CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy; IV = intravenous; LDH = lactate dehydrogenase; MAVE = major adverse vascular event; SC = subcutaneous; ULN = upper limit of normal

- **Ancillary analyses**

Subgroup analyses were performed stratified by weight group (≥40 kg to <60 kg and ≥60 kg to <100kg). Due to the small proportion of patients in the ≥40 to <60 kg weight group (16% of total patients in the FAS), no conclusions can be made for the subgroup analyses.

- **Summary of main efficacy results**

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 26 Summary of Efficacy for trial <trial>

Title: A Phase 3, Randomized, Parallel-Group, Multicenter, Open-Label, Pharmacokinetic, Noninferiority Study of Ravulizumab Administered Subcutaneously Versus Intravenously in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria Currently Treated With Eculizumab	
Study identifier	ALXN1210-PNH-303 EudraCT number 2017-002370-39
Design	Randomized, Open-label, parallel-group multicentre study

	Duration of main phase: Duration of screening phase: Duration of Extension phase:		10 weeks Up to 30 days Up to 172 weeks
Hypothesis	Pharmacokinetic (PK) non-inferiority		
Treatments groups	Ravulizumab IV		ravulizumab IV loading dose on Day 1 and a ravulizumab IV maintenance dose on Day 15, in accordance with approved ravulizumab dosing regimen. N = 46 patients
	Ravulizumab SC		ravulizumab SC group received a weight-based loading dose of ravulizumab IV on Day 1 followed by maintenance doses of ravulizumab SC on Day 15 and once weekly thereafter for a total of 10 weeks of study treatment. N = 90 patients
Endpoints and definitions	Primary endpoint (PK)	Day 71 serum ravulizumab Ctrough	Serum ravulizumab concentration readout from blood sample collected at Day 71 pre-dose
	Efficacy endpoints (Secondary)	Change in Lactate dehydrogenase (LDH) over time	LDH value
		Incidence of breakthrough haemolysis	At least 1 new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnoea], anaemia [haemoglobin < 10 g/dL], MAVE including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN as assessed by the central laboratory.
		Achievement of transfusion avoidance	Patients who remained transfusion free and did not require a transfusion after the first dose of study drug
		Achievement of stabilized haemoglobin	Avoidance of a ≥ 2 g/dL decrease in haemoglobin level from Baseline in the absence of transfusion from Baseline to the end of the period of interest.
		Clinical manifestations of PNH over time	Investigator or designee assessed each patient for signs and symptoms of PNH, which may include the following: fatigue, chest pain, abdominal pain, dyspnoea, dysphagia, erectile dysfunction, and red/dark urine or haemoglobinuria.
		Change in reticulocyte count over time	Reticulocyte count
		Change in eGFR over time	eGFR calculated using the Modification of Diet in Renal Disease formula
		Change in PNH RBC clone size over time	PNH RBC clone size evaluated by high sensitivity flow cytometry

		Change in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Subscale Score	13-item questionnaire to assess self-reported fatigue and its impact upon daily activities and function over the preceding 7 days
		Change in Treatment Administration Satisfaction Questionnaire (IV/SC)	19-Item questionnaire to assess patient perceptions and satisfaction with eculizumab IV (TASQ-IV) or ravulizumab SC (TASQ-SC) treatment.
	PK/PD endpoints	Ctrough over time	Summarized over time using descriptive statistics for continuous parameters
		Free serum C5 concentrations over time	Summarized over time using descriptive statistics for continuous parameters
Database lock	02 Apr 2021 (with a 02 Feb 2021 [last patient Day 365 visit] 52-week data cutoff date)		

Results and Analysis

Analysis description	**Primary PK Analysis**		
Analysis population and time point description	PK Analysis Set (defined as all participants who had evaluable PK data for whom: • All doses up to Day 64 were compliant with the planned dose and the protocol-specified dosing time windows • The pre-dose PK sample on Day 71 was collected within ± 3 hours from the nominal time of the first dose on Day 1) Time point: Day 71		
Descriptive statistics and estimate variability	Treatment group	Ravulizumab IV	Ravulizumab SC
	Number of subjects	43	70
	Day 71 serum ravulizumab Ctrough (µg/mL)		
	Mean	457.58	578.70
	Standard Deviation	108.491	140.819
Effect estimate per comparison	Primary endpoint: Day 71 serum ravulizumab Ctrough	Comparison groups	Ravulizumab SC vs Ravulizumab IV
		Geometric mean least squares mean ratio	1.257
		90% Confidence interval	1.160, 1.361
		P-value (ANOVA)	< 0.0001

Notes	The PK Analysis Set excluded 23 patients (IV=3, SC=20): 9 patients due to dosing errors; 1 patient who withdrew from the study prior to Day 71; 7 patients due to important deviations and findings related to deficiencies in source documentation and Investigator oversight; and 8 patients due to other important protocol deviations that resulted in non-evaluable PK data. Treatment with ravulizumab SC achieved statistically significant PK non-inferiority compared with ravulizumab IV treatment for the primary endpoint, Day 71 trough concentration (C_{trough}), as shown by a geometric least squares mean ratio of 1.257 (90% confidence interval [CI]: 1.160, 1.361) at Day 71, where the lower bound of the 90% CI was greater than the prespecified non-inferiority boundary of 0.80. In addition, the PK non-inferiority of SC versus IV was consistent across all pre-specified sensitivity analyses.		
Analysis description	**Secondary efficacy analysis**		
Analysis population and time point description	**Randomized Treatment Period** Full Analysis Set (all randomized participants [except for those 7 participants from the incompliant site] who received at least 1 dose of ravulizumab) Timepoint: Study Day 71		
Descriptive statistics and estimate variability	Treatment group	Ravulizumab IV	Ravulizumab SC
	Number of subjects	45	84
	Percent change in LDH from Baseline		
	Mean	5.73	2.57
	Standard Deviation	29.716	33.883
	Incidence of breakthrough haemolysis through Day 71		
	Number of participants (%)	1 (2.2)	1 (1.2)
	95% CI	0.06, 11.77	0.03, 6.46
	Achievement of transfusion avoidance through		
	Number of participants (%)	39 (86.7)	79 (94.0)
	95% CI	73.21, 94.95	86.65, 98.04
	Achievement of stabilized haemoglobin through Day 71		
	Number of participants (%)	36 (81.8)	73 (93.6)
	95% CI	67.29, 91.81	85.67, 97.89
	Any clinical manifestations of PNH through Day 71		

	Number (%) of participants	21 (46.7)	40 (47.6)
	95% CI	31.66, 62.13	36.60, 58.81
	Percent change in reticulocyte count from Baseline to Day 71		
	Mean	3.115	5.234
	Standard Deviation	18.7636	22.6450
	Percent change in eGFR from Baseline to Day 71		
	Mean	9.24	3.65
	Standard Deviation	20.019	16.157
	Percent change in total PNH RBC clone size from Baseline to Day 71		
	Mean	-0.36	0.22
	Standard Deviation	12.291	10.907
	Change in FACIT-Fatigue Subscale Score from Baseline to Day 71		
	Mean	-0.83	1.21
	Standard Deviation	7.378	7.882
	Change in Total TASQ-IV/SC score from Baseline to Day 71		
	Mean	-7.00	-70.54
	Standard Deviation	34.581	70.522
Notes	All patients (n = 7) from 1 site were excluded from the primary Randomized Treatment Period (Day 71) efficacy analyses due to important source document deviations and findings related to deficiencies in Investigator oversight.		

2.6.5.3. Clinical studies in special populations

Table 27: Elderly Age Categories

	Age 65-74 (Older subjects number / total number)	Age 75-84 (Older subjects number / total number)	Age 85+ (Older subjects number / total number)
Controlled Trials (ALXN1210-PNH-303)	10/129	4/129	0/129
Non Controlled Trials	N/A	N/A	N/A

Abbreviation: N/A = not applicable Source: Table EMA.Q15.1.2

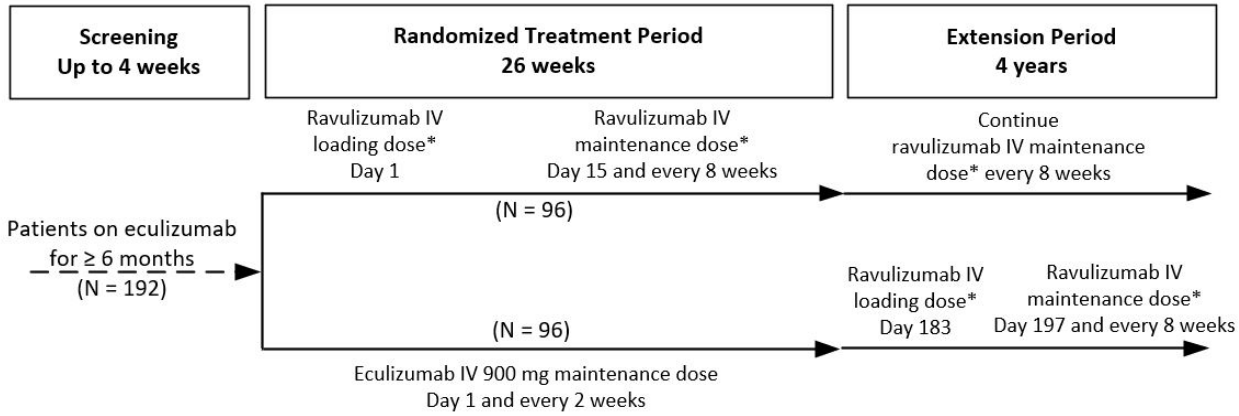
2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

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

Key efficacy results from Study ALXN1210-PNH-303 and Study ALXN1210-PNH-302 are compared in this section to support the similar efficacy observed with ravulizumab SC and ravulizumab IV treatment. Both studies enrolled eculizumab-experienced patients with PNH. Data are compared at 6 months of treatment, which was the primary endpoint for Study ALXN1210-PNH-302.

Figure 18 Study Design Schema for Study ALXN1210-PNH-302



** Ravulizumab IV loading dose = 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 mg for patients weighing ≥ 100 kg; maintenance dose = 3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg.*

Abbreviation: IV = intravenous

Table 28 Key Demographic and Baseline Characteristics in Eculizumab-experienced Adult Patients with PNH (Study ALXN1210-PNH-303 FAS and Study ALXN1210-PNH-302 FAS)

Characteristic	Study ALXN1210-PNH-303 Ravulizumab SC (N = 129)[a]	Study ALXN1210-PNH-302 Ravulizumab IV (N = 97)
Sex, n (%)		
Male	60 (46.5)	50 (51.5)
Female	69 (53.5)	47 (48.5)
Race, n (%)		
Asian	2 (1.6)	23 (23.7)
White	92 (71.3)	50 (51.5)
Black or African American	7 (5.4)	5 (5.2)
American Indian or Alaska Native	1 (0.8)	0
Other	6 (4.7)	2 (2.1)
Not reported	19 (14.7)	13 (13.4)
Unknown	2 (1.6)	3 (3.1)
Age (years)[b]		
Mean (SD)	45.7 (14.00)	46.6 (14.41)
Median	44.0	45.0
Min, max	18, 79	18, 79
Body weight (kg) category, n (%)		
≥ 40 to < 60	21 (16.3)	27 (27.8)
≥ 60 to < 100	108 (83.7)	62 (63.9)
≥ 100	0	8 (8.2)
LDH (U/L) at Baseline[c]		
n	128	97
Mean (SD)	250.5 (85.71)	228.01 (48.712)
Median	236.5	224.00
Min, max	95, 836[d]	135.0, 383.5
Number of patients with pRBC/whole blood transfusions within 12 months prior to first dose, n (%)	24 (18.6)	13 (13.4)

[a] *Baseline demographics include data for the 129 patients in the FAS; 128 patients are included in the SC Treated Full Analysis Set since 1 patient in the IV group withdrew from the study prior to receiving SC treatment in the Extension Period.*
[b] *Age at informed consent was reported in Study ALXN1210-PNH-303; age at first study drug infusion was reported in Study ALXN1210-PNH-302.*
[c] *SC Baseline is shown for Study ALXN1210-PNH-303.*
[d] *Patient 0523-801 had a Day 71 LDH value of 836 U/L, which was considered the patient's baseline value for SC treatment.*
Abbreviations: FAS = Full Analysis Set; IV = intravenous; LDH = lactate dehydrogenase; max = maximum, min = minimum; pRBC = packed red blood cell; SC = subcutaneous
Source: ALXN1210-PNH-302 CSR Table 14.1.1.1.1, Table 14.1.3.1.1, and Table 14.1.3.2.1; ALXN1210-PNH-303 CSR Table 14.1.1.1.1, Table 14.1.3.2.1, and Table 14.2.2.1.3.14

Table 29 Efficacy Results at 6 Months in Eculizumab-experienced Adult Patients with PNH (ALXN1210-PNH-303 SC Treated Full Analysis Set and ALXN1210-PNH-302 FAS)

Key Efficacy Endpoint	Study ALXN1210-PNH-303 Ravulizumab SC[a] (N = 128)	Study ALXN1210-PNH-302 Ravulizumab IV (N = 97)
LDH % change from Baseline Mean (SD)	(N = 111) 4.63 (37.336)	(N = 95) -0.81 (13.845)
Breakthrough hemolysis n (%)	2 (1.6)	0
Transfusion avoidance n (%)	113 (88.3)	85 (87.6)

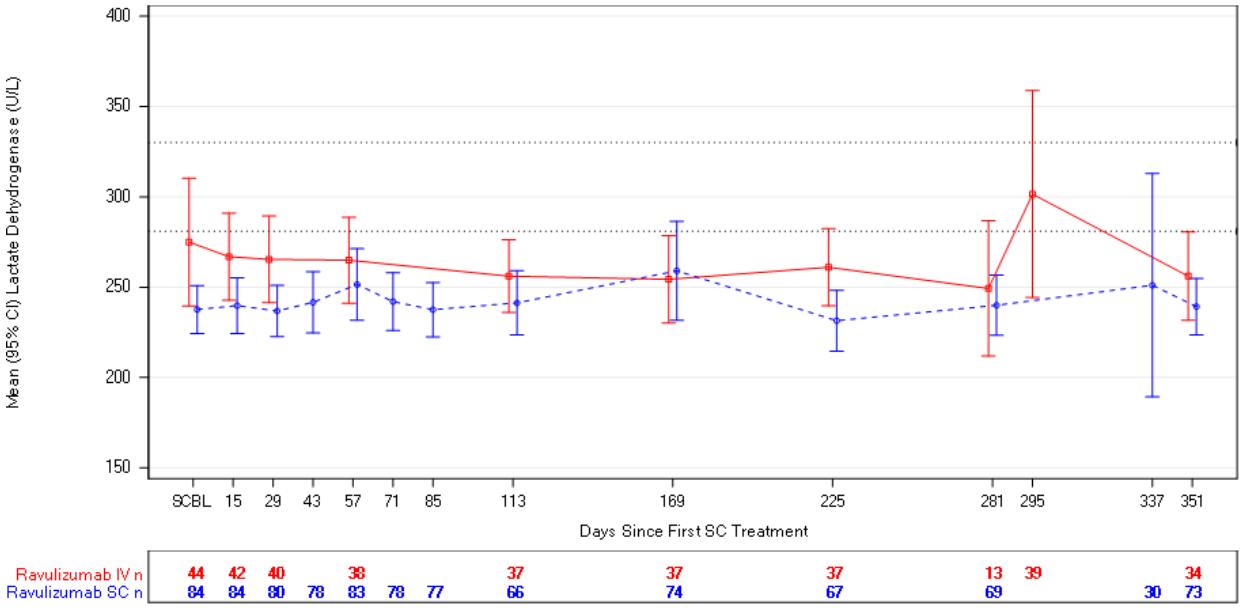
Key Efficacy Endpoint	Study ALXN1210-PNH-303 Ravulizumab SC[a] (N = 128)	Study ALXN1210-PNH-302 Ravulizumab IV (N = 97)
Achieved stabilized hemoglobin n (%)	(N = 123) 106 (86.2)	(N = 97) 74 (76.3)
FACIT-Fatigue change from Baseline Mean (SD)	(N = 107) 2.2 (7.61)	(N = 96) 1.59 (6.433)

Note: The 6-month timepoint is Day 183 for Study ALXN1210-PNH-302 and SC Day 169 for Study ALXN1210-PNH-303. Change and percentage change are summarized only for patients who have data at SC Baseline and SC Day 169. [a] Includes all patients in the SC Treated Full Analysis Set.
Abbreviations: FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; FAS = Full Analysis Set; IV = intravenous; LDH = lactate dehydrogenase; PNH = paroxysmal nocturnal hemoglobinuria; SC = subcutaneous; SD = standard deviation. Source: ALXN1210-PNH-302 CSR Table 14.2.1.3.1, Table 14.2.2.01.1, Table 14.2.2.13.1, Table 14.2.2.20.1, and Table 14.2.2.07.1; ALXN1210-PNH-303 CSR Table 14.2.2.1.3.14, Table 14.2.2.5.3.14, Table 14.2.2.6.3.14, Table 14.2.2.7.3.14, and Table 14.2.2.9.3.14

Persistence of Efficacy and/or Tolerance Effects

Efficacy data in Study ALXN1210-PNH-303 were analyzed up to the SC Day 351 visit. LDH levels remained stable over the duration of treatment with no evidence of loss of therapeutic effect over time. The mean percentage change in LDH from Baseline to SC Day 351 was 0.92%.

Figure 19 LDH (U/L) Mean (95% CI) Values Since First SC Treatment in Study ALXN1210-PNH-303 (SC Treated Full Analysis Set)



Abbreviations: BL = Baseline; CI = confidence interval; IV = intravenous; LDH = lactate dehydrogenase; SC = subcutaneous. Source: ALXN1210-PNH-303 CSR Figure 14.2.2.1.2.14

These results are consistent with observations made in studies in patients with PNH and aHUS treated with ravulizumab IV for up to 100 weeks:

- Long-term data available from the 39 patients who entered the Extension Periods of Phase 1b and Phase 2 Studies ALXN1210-PNH-103 and ALXN1210-PNH-201, respectively, indicate that patients with PNH continue to maintain efficacy up to 100 weeks in terms of LDH suppression and increase in hemoglobin value over time (PNH Adult IV). Additionally, data on LDH levels over 52 weeks of

treatment indicated similar maintenance of efficacy in the Phase 3 PNH studies (Kulasekararaj, 2019).

- The Phase 3 efficacy data from 56 adult patients with aHUS treated with ravulizumab showed sustained therapeutic effect during the 6-month Primary Evaluation Period. For patients continuing in the Extension Period, the sustained therapeutic effect was maintained through 52 weeks of treatment (ALXN1210 aHUS 311 52-week).

The cumulative ravulizumab experience as of 30 Jun 2021 comprises a clinical database of 2,036.5 patient-years, and a postmarketing database of approximately 3,996.7 patient-years (Ravulizumab Periodic Benefit Risk Evaluation Report [PBRER] #5). Loss of efficacy has not been observed with ravulizumab treatment.

Based on the posology support described in Section 4, efficacy in PNH or aHUS patients receiving ravulizumab SC treatment is expected to be similar to that observed following ravulizumab IV treatment.

2.6.5.6. Supportive study(ies)

Not applicable.

2.6.6. Discussion on clinical efficacy

The current submission for MA is supported by one parallel-group Phase 3 study (ALXN1210-PNH-303; N=129) for ravulizumab (ALXN1210) SC, based on bridging efficacy data from ALXN1210 IV on the basis of pharmacokinetic non-inferiority principles, for the treatment of PNH adult patients previously treated with eculizumab.

The following indication was initially proposed:

Ultomiris subcutaneous formulation (Ultomiris SC) is indicated in the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH):

- *in patients with haemolysis with clinical symptom(s) indicative of high disease activity.*
- *in patients who are currently treated with eculizumab or with ravulizumab intravenous formulation (Ultomiris IV).*

Ultomiris SC is indicated in the treatment of adult patients with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or are currently treated with eculizumab or ravulizumab IV.

The proposed posology is 490 mg once a week in adult patients with a body weigh ≥40 kg. Moreover, a ravulizumab IV loading dose is required prior to the initiation of ravulizumab SC for complement-inhibitor treatment-naïve patients or patients switching treatment from eculizumab.

The analyses presented in this report are based on a database lock date of 02 April 2021 (data cut-off date 2 Feb 2021).

Design and conduct of clinical studies

Study **ALXN1210-PNH-303** (N=128) is a randomized, parallel-group, open-label, multicenter Phase 3 study to establish the non-inferior PK of ravulizumab SC OBDS as compared to ravulizumab IV in adult patients with PNH who are clinically stable and have been treated with eculizumab for at least 3 months prior to study entry. Masking is not applicable, since the study is open-label. This is acceptable

for the ALXN1210-PNH-303 pivotal study, considering the different routes of administration (SC vs. IV).

The purpose of this study (ALXN1210-PNH-303) is to evaluate the pharmacokinetics, efficacy, tolerability and safety of the SC formulation of ravulizumab in adult patients with PNH whose disease is controlled by a standard treatment with eculizumab at the currently approved dose (900 mg IV every 14 days). The design of the proposed SC trial in adult patients with PNH consisted in an up to **30-day Screening Period**, a **10-week Randomized Treatment Period**, and an **Extension Period of up to 172 weeks** with PK non-inferiority primary and secondary endpoints at Week 10 (Day 71) and 26 (Day 183), respectively, followed by a 2-year extension period. Day 71 is the end of the Randomized Treatment Period and the beginning of the Extension Period.

The inclusion and exclusion criteria clearly define the target population. Of note, patients should have been treated with eculizumab for at least 3 months prior to study entry and had LDH levels ≤1.5 x ULN. Thus, there were no naïve patients in Study ALXN1210-PNH-303. Only patients with a body weight ≥40 to <100 kg were included in the study.

The proposed primary endpoint is PK exposure (as measured by Day 71 Ctrough as parameter for comparison) with ALXN1210 SC to be compared with ALXN1210 IV dosing to be registered in the treatment of PNH. Secondary endpoints include PK exposure non-inferiority as measured by Day 183 Ctrough, haemolysis as directly measured by LDH (the hallmark of PNH disease activity), breakthrough haemolysis, quality of life as measured by FACIT-fatigue, transfusion avoidance, and stabilized haemoglobin. Patient preference and satisfaction for treatment was also recorded at Day 183 of the study.

The study design was aimed at demonstrating non-inferiority of ravulizumab SC to ravulizumab IV, defined mainly by pharmacokinetics. The selection of efficacy endpoints is supported, and as expected, they are in line with the ones proposed in the previous studies of ravulizumab IV. The non-inferiority design is acceptable.

The proposed sample size is considered adequate. Additionally, stratification (by weight) and randomization (2:1 ratio, SC:IV) were used to minimize bias, and are as well supported. The European population is considered well represented.

The posology and rationale for the SC dosing regimen in the conducted study is overall agreed (see PK/PD section).

Efficacy data and additional analyses

A total of 136 patients were enrolled and treated (46 in the ravulizumab IV treatment group and 90 in the ravulizumab SC treatment group). Screening failure was reported for 5 patients. Seven patients (1 from the ravulizumab IV arm and 6 from the SC arm) from a single site were excluded due to important source documentation deviations (reported as quality issues), for both the FAS (understood as ITT population) and for the SC Treated Full Analysis Set (TFAS). These 7 patients were all enrolled in the same investigational site. Detailed information on the reasons that led to the exclusion of these patients has been provided and they were mainly related to the reliability of the data, affecting the ability to reconstruct and evaluate the activities performed by the site. Overall, considering that 7 patients were excluded from the FAS, the total number of patients would be 129. Of note, one patient in the ravulizumab IV arm did not complete the Randomised Treatment Period and therefore did not enter the Extension Period. As a result, the total number of patients that received ravulizumab SC is 128. The Per Protocol Analysis Set excluded 30 patients based on the pre-specified criteria outlined in the SAP (due to inclusion and exclusion criteria).

A single interim analysis (IA) was conducted when approximately 50% of the planned patients had been assessed for the primary endpoint. At the time of this IA, the MAH performed a sample size re-estimation. The main intention for this interim analysis was to evaluate futility and to study the possibility of increasing the sample size up to 144 patients. According to the documentation provided, the recommendation by the independent statistician was to make no adjustment to the planned sample size. However, even if the planned sample size was of 105 patients, a total of 136 patients were finally included in the study. The applicant provided a sensitivity analysis of the primary endpoint based on the 106 first enrolled patients (PK analysis set n=88) showing that the difference with respect to the originally submitted analysis was minimal and confirming that the over-enrolment had no impact on the final analysis.

The demographic and baseline characteristics were balanced across the treatment groups. Among the total population, 53.5% (69/129) of patients were female and 71.3% (92/129) of patients were White. The mean age was 45.7 years (18; 79) at enrolment with only 10.1% (13/129) of the patients >65 years, and most patients (83.7%; 108/129) were in the baseline weight category ≥60 kg to <100 kg. As required by the study inclusion criteria, all 129 patients had a history of eculizumab use for at least 3 months preceding study entry.

Among the total population, the median time from PNH diagnosis to informed consent was 7.5 years (range: 0.6; 33). Mean LDH values at baseline were similar between the treatment groups (IV group: 267 U/L [range: 90, 519]; SC group: 270 U/L [range: 125, 1260]). However, according to inclusion criteria patients should have LDH ≤1.5xULN (ULN=246 U/L) at Screening. Bearing in mind LDH values at baseline it seems that in some patients LDH value was >1.5xULN, and therefore might not be considered to have controlled PNH disease from prior eculizumab treatment. In this regard, the applicant has clarified that there were 8 patients with LDH values > 1.5 × ULN at baseline. However, at their Screening visit LDH values were ≤ 1.5 × ULN as required by protocol in all of the patients except for 1 male patient (1143-803) with a missing LDH value at Screening. According to the applicant, the missing LDH value was not discovered until after the patient entered the study and the patient was allowed to continue in the study. It can be assumed that data from an isolated patient would not have an impact in the study outcomes. However, the reported patients as noted above, even when meeting the inclusion criteria at the Screening visit do not actually fulfilled the criteria of controlled disease. As additional information regarding this issue, the applicant provided follow up efficacy data from 7 of these 8 patients with LDH values > 1.5 × ULN at baseline (the additional patient withdrew consent and this data are then not available). Overall clinical results of these patients were similar to the global population.

All patients had confirmed diagnosis of PNH at Screening to quantify the percentage of PNH cells (clone size) in the peripheral blood. Overall, the FAS population had a mean total PNH RBC clone size of 48.35%, mean total PNH granulocyte clone size of 77.22%, and mean total PNH monocyte clone size of 80.18%.

The mean number of transfusions within 1 year prior to first dose was higher in the ravulizumab SC group than in the ravulizumab IV group, as was the mean number of units transfused. This difference was attributable to 1 heavily transfusion-dependent patient in the ravulizumab SC group. A total of 43 (33.3%) patients had a history of major adverse vascular events.

Outcomes and estimation

Efficacy results for the Randomized Treatment Period (through Day 71) were presented for the FAS (n=129). Efficacy analyses and results using the modified FAS (n=136), which included the 7 patients from the non-compliant site, were similar when compared with the FAS for all of the efficacy endpoints.

During the Randomized Treatment Period, mean LDH levels remained stable over time in both treatment groups for the FAS. Mean percent change in LDH from baseline to Day 71 was 2.57% for the SC group and 5.73% for the IV group. A 3-5% mean change is within the range of normal variability for LDH values and not clinically significant.

Regarding Breakthrough Haemolysis (BTH), two patients experienced BTH during the Randomized Treatment Period (through Day 71): 1 patient in the IV group at Day 57 and 1 patient in the SC group at Day 71. Neither of these events of BTH were associated with suboptimal C5 inhibition (defined as free C5 ≥0.5 µg/mL).

The majority of patients in both treatment groups in the FAS avoided pRBC transfusion during the Randomized Treatment Period (IV group: 86.7%; SC group: 94.0%). Similarly, the majority of patients in both treatment groups in the FAS maintained stabilized haemoglobin during the Randomized Treatment Period (IV group: 81.8%; SC group: 93.6%). Results were aligned in the other secondary variables of efficacy: clinical manifestations of PHN, reticulocyte count, estimated glomerular filtration rate, PNH RBC clone size. Regarding HRQoL and treatment administration satisfaction, assessments were similar in both arms. Overall, it can be considered that there was an improved treatment satisfaction with the SC administration.

Subgroup analyses were performed stratified by weight group (≥40 kg to <60 kg and ≥60 kg to <100kg). Due to the small proportion of patients in the ≥40 to <60 kg weight group (16% of total patients in the FAS) it is difficult to extract conclusions in this subgroup.

Regarding special subpopulations, it should be noted that patients who weighed <40 Kg and ≥100 kg were excluded from the study. Additionally, only 10.1% (13/129) of the patients were >65 years.

The MAH has provided an additional comparison between key efficacy results from Study ALXN1210-PNH-303 and Study ALXN1210-PNH-302 to support the similar efficacy observed with ravulizumab SC and ravulizumab IV treatment. Both studies enrolled eculizumab-experienced patients with PNH. Data are compared at 6 months of treatment, which was the primary endpoint for Study ALXN1210-PNH-302. Although indirect comparisons are of limited value, the efficacy results for SC-treated patients from Study ALXN1210-PNH-303 appear consistent with those of IV-treated patients from Study ALXN1210-PNH-302, and these data are considered supportive.

Furthermore, additional data to confirm persistence of efficacy and tolerance effects have been provided: efficacy data in Study ALXN1210-PNH-303 were analysed up to the SC Day 351 visit. LDH levels remained stable over the duration of treatment with no evidence of loss of therapeutic effect over time, with a mean percentage change in LDH from Baseline to SC Day 351 of 0.92%. These results are consistent with observations made in studies in patients with PNH and aHUS treated with ravulizumab IV for up to 100 weeks. Other efficacy endpoints remained overall consistent throughout the extension period.

Overall, the reported results support efficacy in the target population. It is considered that efficacy results from Study ALXN1210-PNH-303 demonstrate that patients with PNH can be switched from eculizumab IV or Ultomiris IV to Ultomiris SC without loss of efficacy.

Wording of the indication

The MAH applied for an indication in adults with PNH and aHUS, including both patients newly diagnosed and patients previously treated with eculizumab. Extrapolation of data from the SC Phase 3 study in patients with PNH to the aHUS indication and treatment naïve patients was considered acceptable (see PK/PD section). However, since extrapolation is mainly based on data generated with ravulizumab IV and results of study ALXN1210-PNH-303, in which ravulizumab SC was compared with ravulizumab IV, it was requested that the indication for the SC formulation should be in line with that

of the IV formulation, since no further efficacy/safety data have been provided as part of this submission. The MAH amended the wording of the indication accordingly, also in line with what has been done in other approved medicinal products with a SC formulation. In addition, a minor change in the wording of the indication of the ravulizumab IV was included, to more clearly reflect the patient population in the aHUS indication (i.e. *'adult and paediatric'* patients), and the reference to section 5.1 was deleted, also in line with the approach taken for recently approved medicinal products.

The finally approved indications is

Ultomiris is indicated in the treatment of adult patients 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

Ultomiris is indicated in the treatment of adult patients with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab

Assessment of paediatric data on clinical efficacy

An indication in the paediatric patient population has not been requested. No efficacy and safety data are available with this new formulation and administration device in paediatric patients. This formulation should not be used in paediatric patients.

2.6.7. Conclusions on the clinical efficacy

The Study ALXN1210-PNH-303 met its primary endpoint, demonstrating non-inferiority of ravulizumab SC versus ravulizumab IV in terms of PK. From an efficacy point of view, results appear similar between both formulations.

2.6.8. Clinical safety

Table 30: Phase 3 Adult Clinical Studies Supporting the Safety of Ravulizumab

	Studies in PNH			**Study in aHUS**
	ALXN1210-PNH-303	**ALXN1210-PNH-301**	**ALXN1210-PNH-302**	**ALXN1210-aHUS-311**
Study design	Phase 3, open-label, noninferiority study of SC vs IV	Phase 3 open-label, active-control	Phase 3 open-label, active-control	Phase 3 open-label, single-arm efficacy and safety study
Patient population	Eculizumab-experienced	Complement inhibitor naïve	Eculizumab-experienced	Complement inhibitor treatment-naïve adolescents[a] and adult patients weighing ≥ 40 kg

	Studies in PNH			Study in aHUS
	ALXN1210-PNH-303	**ALXN1210-PNH-301**	**ALXN1210-PNH-302**	**ALXN1210-aHUS-311**
				with evidence of TMA
Study duration	Randomized Treatment Period: Days 1 to 71 Extension Period: Day 71 up to 172 weeks (approximately 3.3 years)	Primary Evaluation Period: 26 weeks (183 days) Extension Period: up to 5 years	Primary Evaluation Period: 26 weeks (183 days) Extension Period: up to 3 years[e]	Initial Evaluation Period: 26 weeks (183 days) Extension Period: up to 4.5 years
Ravulizumab treatment regimens during Primary Evaluation Period[f]	On Day 1: Loading dose of IV ≥ *40 to < 60 kg*: 2400 mg ≥ *60 to < 100 kg*: 2700 mg <u>Maintenance dosing</u> IV arm: Day 15 ≥ *40 to < 60 kg*: 3000 mg ≥ *60 to < 100 kg*: 3300 mg SC arm: Day 15 onwards q1w ≥ *40 to < 100 kg*: 490 mg[b]	On Day 1: ≥ *40 to < 60 kg*: 2400 mg ≥ *60 to < 100 kg*: 2700 mg ≥ *100 kg*: 3000 mg On Day 15 and q8w thereafter: ≥ *40 to < 60 kg:* 3000 mg ≥ *60 to < 100 kg:* 3300 mg ≥ *100 kg:* 3600 mg	On Day 1: ≥ *40 to < 60 kg*: 2400 mg ≥ *60 to < 100 kg*: 2700 mg ≥ *100 kg*: 3000 mg On Day 15 and q8w thereafter: ≥ *40 to < 60 kg:* 3000 mg ≥ *60 to < 100 kg:* 3300 mg ≥ *100 kg:* 3600 mg	On Day 1: ≥ *40 to < 60 kg*: 2400 mg ≥ *60 to < 100 kg*: 2700 mg ≥ *100 kg*: 3000 mg On Day 15 and q8w thereafter: ≥ *40 to < 60 kg:* 3000 mg ≥ *60 to < 100 kg:* 3300 mg ≥ *100 kg:* 3600 mg
Active comparator (eculizumab) treatment regimens during Primary Evaluation Period	NA	600 mg q1w for 4 doses, then 900 mg q2w thereafter	900 mg q2w	NA

	Studies in PNH			Study in aHUS
	ALXN1210-PNH-303	**ALXN1210-PNH-301**	**ALXN1210-PNH-302**	**ALXN1210-aHUS-311**
Ravulizumab treatment regimens during Extension Period	490 mg[b] q1w	Weight-based maintenance dose[d] q8w (patients switching from eculizumab received a weight-based loading[c] dose followed 2 weeks later by a weight-based maintenance dose q8w)	Weight-based maintenance dose[d] q8w (patients switching from eculizumab received a weight-based loading[c] dose followed 2 weeks later by a weight-based maintenance dose q8w)	Weight-based maintenance dose q8w
Study status	Randomized Treatment Period completed Extension Period ongoing	Primary Evaluation Period completed Extension Period ongoing	Primary Evaluation Period completed Extension Period ongoing	Initial Evaluation Period completed Extension Period ongoing
Safety Evaluation data cutoff	52-week data cutoff 02 Feb 2021	52-week data cutoff 04 Sep 2018	52-week data cutoff 07 Sep 2018	52-week data cutoff 02 Jul 2019
Data source	ALXN1210-PNH-303 CSR	ALXN1210-PNH-301 52-week data	ALXN1210-PNH-302 52-week data	ALXN1210-aHUS-311 52-week data

[a] Although enrollment of both adult and adolescent patients was planned, enrollment completed with only adult patient participation (aHUS IV Module 2.7.3 Table 1).
[b] Administered SC via 2 ravulizumab OBDS kits.
[c] Ravulizumab loading dose: 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 mg for patients weighing ≥ 100 kg.
[d] Ravulizumab maintenance dose: 3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg.
[e] Extension Period up to 4 years in Canada, Netherlands, and France
[f] Referred to as Randomized Treatment Period in Study ALXN1210-PNH-303 or Initial Evaluation Period in Study ALXN1210-aHUS-311
Abbreviations: aHUS = atypical hemolytic uremic syndrome; CSR = clinical study report; IV = intravenous; NA = not applicable; OBDS = on-body delivery system; PNH = paroxysmal nocturnal hemoglobinuria; q1w = once every week; q2w = every 2 weeks; q8w = every 8 weeks; SC = subcutaneous; TMA = thrombotic microangiopathy

Table 31: Phase 1 Clinical Studies in Healthy Subjects Supporting the Safety of Ravulizumab

	Study ALXN1210-HV-105[a]	**Study ALXN1210-SC-101[b]**
Study design	Phase 1, sequential cohort, single ascending dose study of ravulizumab SC coadministered with rHuPH20 compared with a single dose of ravulizumab IV or a single dose of ravulizumab SC.	Phase 1, partially-blinded, placebo-controlled, single dose study of ravulizumab SC (400 mg), and ravulizumab IV (400 mg)
Study duration	Single dose Followed through 200 days post dose	Single dose Followed through 200 days post dose

Study treatment regimens	Treatment cohorts • SC 400 mg • SC 500 mg + rHuPH20 10000 units • SC 1000 mg + rHuPH20 20000 units • SC 2000 mg + rHuPH20 40000 units • IV 400 mg	Treatment Cohorts • Ravulizumab SC 400 mg, • Ravulizumab IV 400 mg • Placebo
Study status	Completed	Completed
Data source	ALXN1210-HV-105 CSR	PNH Adult IV ALXN1210-SC-101 CSR

[a] *Only data from SC 400 mg cohort of Study ALXN1210-HV-105 are presented in the SCS as data from other cohorts of the study that included coadministration of ALXN1210 with rHuPH20 and ravulizumab IV are irrelevant for this SCS*
b Only data from SC 400 mg cohort of Study ALXN1210-SC-101 are discussed in this SCS as data from IV cohort have been discussed in PNH Adult IV Module 2.7.4
Abbreviations: CSR = clinical study report; HV = healthy volunteer; IV = intravenous; rHuPH20 = recombinant human hyaluronidase PH20; SC = subcutaneous; SCS = Summary of Clinical Safety

The overall safety evaluation is based on the pivotal study ALXN1210-PNH-303 and a comparison of data obtained through the 52-weeks data cutoff of ravulizumab SC treatment in Study ALXN1210-PNH-303 (hereafter referred to as SC group) versus pooled data from 52-weeks data cutoffs on ravulizumab IV treatment in 2 Phase 3 studies (ALXN1210-PNH-301 and ALXN1210-PNH-302, hereafter referred to as pooled IV group).

The ISS Safety Analysis Set that is used for the safety evaluation is defined as all patients who either received at least one dose of ravulizumab SC in the SC Treated Safety Analysis Set of Study ALXN1210-PNH-303 (excluding 7 patients from 1 site due to important source documentation deviations and site noncompliance) or received at least one dose of ravulizumab IV in the Safety Set of Study ALXN1210-PNH-301 or Study ALXN1210-PNH-302.

Safety data from the 52-weeks data cutoff from Study ALXN1210-aHUS-311 were also provided as supportive.

The 52-week data cutoff date applies to the last patient enrolled and all data available through the specific cutoff dates for each Phase 3 PNH and aHUS study are included

2.6.8.1. Patient exposure

ALXN1210-PNH-303

Randomized treatment period

All 45 patients in the IV group received the correct weight-based ravulizumab IV loading dose on Day 1 and maintenance dose on Day 15. The 84 patients in the SC group attempted a total of 672 SC dose administrations in the following locations: abdomen (n = 628), thigh (n = 425), and upper arm with help (n = 299).

One patient (IV group) had 2 infusion interruptions on Day 1 and Day 15, and 1 patient (SC group) had an IV loading dose infusion interruption on Day 1; all 3 infusions were interrupted to replace the micron filter and were restarted. None of the IV infusion interruptions were due to AEs.

It was noted that 1 patient missed the planned SC dose at Day 43 during the Randomized Treatment Period, but this patient actually received their SC dose on Day 42 which was recorded as an unscheduled visit; the patient had been hospitalized for an SAE of gastroenteritis on Day 40 that resolved on Day 43.

All 7 patients who were excluded from the Safety Analysis Set received all planned doses per the protocol during the Randomized Treatment Period.

During the Randomized Treatment Period, treatment compliance was 100% in the IV group and 98.8% in the SC group.

SC Treatment

While patients in both treatment groups received SC administration of ravulizumab during the Extension Period, patients randomized to the SC group also received 56 days of SC treatment during the Randomized Treatment Period (referred to as the SC/SC group). Patients randomized to receive ravulizumab IV during the Randomized Treatment Period had their first dose of ravulizumab SC at the start of the Extension Period (Day 71) (referred to as the IV/SC group).

As of the data cut-off date (02 Feb 2021), the mean duration of SC treatment was 486.4 days (range 37 to 709 days) and the maximum exposure to SC treatment was 709 days (Table below). The longer mean exposure in the SC/SC group reflects the 8-week IV dose regimen received by the IV/SC group during the Randomized Treatment Period.

Overall, the 128 patients in the SC Treated Safety Analysis Set had a total of 8,464 SC dose administration attempts and patients received the full dose in 99.9% of these dosing attempts.

The median total infusion time per site administration was 10 minutes.

Table 32 Treatment administration for Ravulizumab sc since first sc treatment (SC treatment safety analysis set)

Variable	Ravulizumab IV/SC (N = 44)	Ravulizumab SC/SC (N = 84)	Total (N = 128)
Total time under treatment effect (days)			
Mean (SD)	444.3 (107.07)	508.5 (113.95)	486.4 (115.34)
Median	457.0	520.0	488.5
Min, max[a]	37, 633	79, 709	37, 709
Total infusion time per site administration visit (mins)			
n	438	1508	1946
Mean (SD)	12.0 (12.81)	13.5 (24.37)	13.2 (22.30)
Median	10.0	10.0	10.0
Min, max[b]	7, 148	4, 419	4, 419
Infusion location			
Thigh	2222	4932	7154
Abdomen	2280	4445	6725
Upper arm (with help)	846	2201	3047

Note: Duration of study treatment effect (ie, the time a patient was at risk of reporting a treatment-related AE), was defined as the time from first dose of SC treatment through the data cutoff date (02 Feb 2021).

[a] Maximum exposure to SC treatment is greater than 1 year (365 days) since all safety and exposure data through the data cutoff date are included (ie, individual patients may have had different exposure duration).

[b] Maximum infusion time calculated from the time first kit administration to the last kit administration; patients who had longer infusion times required the use of multiple ODBS kits for full dose administration.

Abbreviations: AE = adverse event; IV = intravenous; max = maximum; min = minimum; OBDS = on-body delivery system; SC = subcutaneous; SD = standard deviation

Source: Table 14.3.1.1.4.1.12 and Table 14.3.1.1.3.1.12

Overall, the majority (90.6%) of patients had 100% treatment compliance since first SC treatment; 11 (8.6%) patients had ≥ 90% to < 100% treatment compliance; and 1 patient (SC group) had ≥ 70% to < 80% treatment compliance due to interruption of study treatment during hospitalization for bone marrow transplant.

Reasons for missed doses were collected for all doses administered at the study site and were not documented for home administration. Seven (5.5%) patients missed a planned SC dose at 11 time points during study drug administration performed at the site.

Three patients did not have reasons recorded for missed doses and 4 patients had reasons listed as "Other" (1 due to patient issues, 1 due to early termination [ET], 1 due to dosing received the prior day at home, and 1 patient missed 5 doses due to hospitalization and subsequently withdrew from the study). None of missed doses were due to the COVID-19 pandemic.

2.6.8.2. Adverse events

Randomized Treatment Period

During the 10-week Randomized Treatment in Study ALXN1210-PNH-303, the percentage of patients who experienced AEs was 60.0% in the IV group and 79.8% in the SC group.

When ADEs are excluded, the AE incidence was similar (IV group: 60.0%; SC group: 64.3%). The most commonly reported AE was headache (IV group: 8.9%; SC group: 13.1%).

Infusion reactions were experienced by 8 (17.8%) patients in the IV group and 38 (45.2%) patients in the SC group. Unrelated SAEs of neutropenia, lens dislocation, gastroenteritis, cervicobrachial syndrome, and urinary retention were reported by 1 patient each in the SC group, and cholecystitis was reported in the IV group.

Table 33 Overview of Treatment-Emergent Adverse Events during the Randomized Treatment Period- Safety Analysis Set

	Ravulizumab IV (N = 45)		Ravulizumab SC (N = 84)		Total (N = 129)	
	n (%)	E	n (%)	E	n (%)	E
Any AE	27 (60.0)	73	67 (79.8)	291	94 (72.9)	364
Any SAE	1 (2.2)	1	5 (6.0)	5	6 (4.7)	6
Death	0	0	0	0	0	0
AE leading to discontinuation of study drug	0	0	0	0	0	0
Any ADE[a]	NA	NA	39 (46.4)	110	39 (30.2)	110
Any serious ADE[a]	NA	NA	0	0	0	0
Patients with ADEs that were not device issues[a]	NA	NA	22 (26.2)	77	22 (17.1)	77
Patients with ADEs that were device issues[a]	NA	NA	21 (25.0)	33	21 (16.3)	33
AEs not associated with device/device use	27 (60.0)	73	54 (64.3)	181	81 (62.8)	254
AE by relationship to study treatment						
Related	7 (15.6)	16	31 (36.9)	136	38 (29.5)	152
Not related	23 (51.1)	57	52 (61.9)	155	75 (58.1)	212
AE by severity[b]						
Grade 1	21 (46.7)	51	64 (76.2)	251	85 (65.9)	302
Grade 2	14 (31.1)	19	20 (23.8)	35	34 (26.4)	54
Grade 3	2 (4.4)	3	3 (3.6)	4	5 (3.9)	7
Grade 4	0	0	1 (1.2)	1	1 (0.8)	1
Grade 5	0	0	0	0	0	0
SAE by relationship to study treatment						
Related	0	0	0	0	0	0
Not related	1 (2.2)	1	5 (6.0)	5	6 (4.7)	6
AEs of special interest	8 (17.8)	11	39 (46.4)	150	47 (36.4)	161
Infusion reactions[c]	8 (17.8)	11	38 (45.2)	149	46 (35.7)	160
Meningococcal infections	0	0	0	0	0	0
Other serious infections	0	0	1 (1.2)	1	1 (0.8)	1

Note: AEs were coded using MedDRA Version 23.1. ADEs are a subset of AEs.
a ADEs are noted as "not applicable" since patients in the IV group did not use the OBDS device.
b Severity of AEs was graded using CTCAE Version 4.03. Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = fatal.
c Infusion reactions are defined in Table 22.
Abbreviations: ADE = adverse device effect; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; E= number of events; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; OBDS = on-body delivery system; SAE = serious adverse event; SC = subcutaneous

Only safety data on ravulizumab SC treatment in Study ALXN1210-PNH-303 or ravulizumab IV treatment in Phase 3 PNH IV studies are presented and compared hereafter.

SC treatment

Through the 52-week data cut-off dates, the overall AE profiles were similar in the SC and the pooled IV groups, with similar rate of deaths and AEs leading to discontinuation of study drug.

No meningococcal infections were reported in either group.

Excluding AEs and serious adverse events, (SAEs) related to COVID-19, the percentage of patients with AEs and SAEs were similar in both SC and pooled IV groups.

Table 34 Overview of All Treatment-emergent Adverse Events and Serious Adverse Events by Delivery Mechanism (ISS Safety Analysis Set)

	Study ALXN1210-PNH-303 Ravulizumab SC (N = 128) PY = 161.7		Studies ALXN1210-PNH-301 and ALXN1210-PNH-302 Ravulizumab IV (N = 436) PY = 417.6	
	n (%)	E (Rate)	n (%)	E (Rate)
AE by relationship to study drug[a]				
Related AE	25 (19.5)	102 (63.1)	128 (29.4)	333 (79.7)
Unrelated AE	111 (86.7)	474 (293.1)	370 (84.9)	1829 (438.0)
AE by severity[b]				
Grade 1	96 (75.0)	380 (235.0)	325 (74.5)	1336 (319.9)
Grade 2	66 (51.6)	147 (90.9)	260 (59.6)	674 (161.4)
Grade 3	19 (14.8)	36 (22.3)	80 (18.3)	129 (30.9)
Grade 4	8 (6.3)	12 (7.4)	15 (3.4)	21 (5.0)
Grade 5	1 (0.8)	1 (0.6)	2 (0.5)	2 (0.5)
AE leading to study drug interruption	1 (0.8)	5 (3.1)	5 (1.1)	9 (2.2)
AE leading to study drug discontinuation	1 (0.8)	1 (0.6)	2 (0.5)	2 (0.5)
AE considered as a MAVE	0	0	6 (1.4)	6 (1.4)
Any AE not considered COVID-19 related	108 (84.4)	547 (338.3)	381 (87.4)	2162 (517.7)
AE of special interest	52 (40.6)	159 (98.3)	129 (29.6)	226 (54.1)
Any AE of special interest not considered COVID-19 related	49 (38.3)	151 (93.4)	129 (29.6)	226 (54.1)
Any serious adverse event (SAE)	26 (20.3)	44 (27.2)	51 (11.7)	75 (18.0)
SAE by relationship to study drug				
Related SAE	0	0	12 (2.8)	15 (3.6)
Unrelated SAE	26 (20.3)	44 (27.2)	39 (8.9)	60 (14.4)
SAE leading to study drug interruption	1 (0.8)	1 (0.6)	0	0
SAE leading to study drug discontinuation	0	0	2 (0.5)	2 (0.5)
SAE considered as a MAVE	0	0	3 (0.7)	3 (0.7)
Any SAE not considered COVID-19 related	21 (16.4)	36 (22.3)	51 (11.7)	75 (18.0)
Death	1 (0.8)	1 (0.6)	2 (0.5)	2 (0.5)

Note: The data cutoff dates are based on the 52-week data for Studies ALXN1210-PNH-303 (02 Feb 2021), ALXN1210-PNH-301 (04 Sep 2018), and ALXN1210-PNH-302 (07 Sep 2018).
Rate of AE adjusted by patient-years of exposure, defined as (number of events × 100)/total patient years (ie, rate/ 100 PY).
By default, AE refers to treatment-emergent AEs (TEAE); TEAEs were AEs with a start date and start time on or after the date and time of the first infusion of study drug. Adverse device effects were defined as AEs in Study ALXN1210-PNH-303 are summarized separately.
a Related AEs were defined as AEs that were related, possibly related, probably related, definitely related, or missing relationship to study drug. Not related AEs were defined as AEs that were unlikely or not related to study drug.
b Severity of AEs was graded using CTCAE Version 4.03. Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = fatal.
Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; CTCAE = Common Terminology Criteria for Adverse Events; E = number of events; ISS = Integrated Summary of Safety; IV = intravenous; MAVE = major adverse vascular events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; n = number of patients with data; PY = patient-years of exposure; SC = subcutaneous, SAE = serious adverse event
Source: ISS Table 14.3.1.1.1.2

Common Adverse Events

Randomised treatment period

Table 35 Treatment-emergent Adverse Events Experienced by 2 or More of All Patients During the Randomized Treatment Period (Safety Analysis Set)

System Organ Class Preferred Term	Ravulizumab IV (N = 45)		Ravulizumab SC (N = 84)		Total (N = 129)	
	n (%)	E	n (%)	E	n (%)	E
Patients with treatment-emergent AEs	27 (60.0)	73	67 (79.8)	291	94 (72.9)	364
Blood and lymphatic system disorders	2 (4.4)	2	3 (3.6)	7	5 (3.9)	9
Anaemia	0	0	2 (2.4)	3	2 (1.6)	3
Haemolysis	1 (2.2)	1	1 (1.2)	2	2 (1.6)	3
Neutropenia	0	0	2 (2.4)	2	2 (1.6)	2
Gastrointestinal disorders	7 (15.6)	15	17 (20.2)	34	24 (18.6)	49
Diarrhoea	2 (4.4)	2	11 (13.1)	12	13 (10.1)	14
Abdominal pain	3 (6.7)	3	5 (6.0)	7	8 (6.2)	10
Nausea	3 (6.7)	4	5 (6.0)	6	8 (6.2)	10
Vomiting	2 (4.4)	2	3 (3.6)	3	5 (3.9)	5
Toothache	1 (2.2)	1	1 (1.2)	1	2 (1.6)	2
General disorders and administration site conditions	1 (2.2)	1	33 (39.3)	119	34 (26.4)	120
Injection site erythema	0	0	5 (6.0)	19	5 (3.9)	19
Injection site reaction	0	0	5 (6.0)	16	5 (3.9)	16
Pyrexia	0	0	5 (6.0)	5	5 (3.9)	5
Asthenia	0	0	3 (3.6)	3	3 (2.3)	3
Fatigue	0	0	3 (3.6)	3	3 (2.3)	3
Influenza like illness	0	0	3 (3.6)	3	3 (2.3)	3
Medical device site erythema	0	0	3 (3.6)	4	3 (2.3)	4
Injection site pruritus	0	0	2 (2.4)	4	2 (1.6)	4
Injection site swelling	0	0	2 (2.4)	11	2 (1.6)	11
Medical device site bruise	0	0	2 (2.4)	2	2 (1.6)	2
Medical device site reaction	0	0	2 (2.4)	2	2 (1.6)	2
Swelling	0	0	2 (2.4)	9	2 (1.6)	9
Infections and infestations	9 (20.0)	11	20 (23.8)	22	29 (22.5)	33
Nasopharyngitis	2 (4.4)	2	5 (6.0)	5	7 (5.4)	7
Upper respiratory tract infection	2 (4.4)	2	2 (2.4)	2	4 (3.1)	4
Urinary tract infection	1 (2.2)	1	3 (3.6)	3	4 (3.1)	4
Influenza	1 (2.2)	1	2 (2.4)	2	3 (2.3)	3
Sinusitis	1 (2.2)	1	1 (1.2)	2	2 (1.6)	3
Viral infection	0	0	2 (2.4)	2	2 (1.6)	2
Metabolism and nutrition disorders	3 (6.7)	4	3 (3.6)	4	6 (4.7)	8
Decreased appetite	2 (4.4)	2	1 (1.2)	1	3 (2.3)	3
Vitamin B12 deficiency	1 (2.2)	1	2 (2.4)	2	3 (2.3)	3
Musculoskeletal and connective tissue disorders	7 (15.6)	7	10 (11.9)	15	17 (13.2)	22
Back pain	2 (4.4)	2	4 (4.8)	6	6 (4.7)	8
Pain in extremity	1 (2.2)	1	2 (2.4)	2	3 (2.3)	3
Arthralgia	1 (2.2)	1	1 (1.2)	1	2 (1.6)	2
Muscular weakness	1 (2.2)	1	1 (1.2)	1	2 (1.6)	2

System Organ Class Preferred Term	Ravulizumab IV (N = 45)		Ravulizumab SC (N = 84)		Total (N = 129)	
	n (%)	E	n (%)	E	n (%)	E
Nervous system disorders	7 (15.6)	9	14 (16.7)	22	21 (16.3)	31
Headache	4 (8.9)	5	11 (13.1)	16	15 (11.6)	21
Dizziness	2 (4.4)	2	1 (1.2)	1	3 (2.3)	3
Somnolence	0	0	2 (2.4)	2	2 (1.6)	2
Product issues	0	0	21 (25.0)	33	21 (16.3)	33
Device delivery system issue	0	0	13 (15.5)	18	13 (10.1)	18
Incorrect dose administered by device	0	0	10 (11.9)	12	10 (7.8)	12
Psychiatric disorders	0	0	6 (7.1)	6	6 (4.7)	6
Depression	0	0	2 (2.4)	2	2 (1.6)	2
Insomnia	0	0	2 (2.4)	2	2 (1.6)	2
Respiratory, thoracic and mediastinal disorders	5 (11.1)	5	1 (1.2)	1	6 (4.7)	6
Cough	4 (8.9)	4	0	0	4 (3.1)	4
Skin and subcutaneous tissue disorders	5 (11.1)	5	4 (4.8)	6	9 (7.0)	11
Rash	1 (2.2)	1	1 (1.2)	1	2 (1.6)	2
Vascular disorders	2 (4.4)	2	3 (3.6)	3	5 (3.9)	5
Hypertension	1 (2.2)	1	1 (1.2)	1	2 (1.6)	2

Note: Percentages were based on the total number of patients in each group. In summarizing n (%), if a patient had multiple events for a particular SOC or Preferred Term, he/she was counted only once for that SOC or Preferred Term. SOCs and Preferred Terms were coded using MedDRA version 23.1.

Abbreviations: E = total number of events; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; SC = subcutaneous, SOC =System Organ Class

SC treatment period

Among the most frequently reported TEAEs (SC vs pooled IV group; at least 10% incidence in any group) of headache (14.1% vs 23.2%), pyrexia (10.9% vs 8.9%), and nasopharyngitis (9.4% vs 14.2%), incidences of headache and nasopharyngitis, were less frequent in the SC group than in the pooled IV group.

The most frequently reported TEAEs decreased over time through the 52-week data cut-off date in both groups.

The incidence of Preferred Terms (PT) were balanced between the SC and pooled IV groups, except for COVID-19 infection-related AEs that were reported only in the SC group (a total of 23 patients). Given that Study ALXN1210-PNH-303 was conducted during the COVID-19 pandemic, the possibility of patients testing positive for COVID-19 was expected in the SC group as compared to the pooled IV group; in the pooled IV group, patients were treated in the PNH IV studies prior to the COVID-19 pandemic.

Incidences of upper respiratory tract infection (URTI) were lower in the SC group (18.8%) than in the pooled IV group (35.8%).

Among TEAEs (SC vs pooled IV group) assessed by the Investigator as related to study drug administration across both groups, headache (3.9% vs 10.1%), erythema (3.9% vs 0.2%), and nausea (0.8% vs 2.5%) were the most frequently reported. Despite the numerical differences in related TEAEs, the type of related TEAEs were similar and consistent with the known safety profile of ravulizumab.

Analysis of TEAEs by worst severity showed that most patients in both groups had Grade 1 or 2 severity AEs. In general, there was no evidence of increased severity of AEs in the SC group compared to the pooled IV group.

Table 36 Treatment-emergent Adverse Events Occurring ≥ 5% of Patients by Delivery Mechanism by MedDRA System Organ Class and Preferred Term (ISS Safety Analysis Set)

	Study ALXN1210-PNH-303 Ravulizumab SC (N = 128) PY = 161.7		**Studies ALXN1210-PNH-301 and ALXN1210-PNH-302 Ravulizumab IV (N = 436) PY = 417.6**	
	n (%)	**E (Rate)**	**n (%)**	**E (Rate)**
System Organ Class Preferred Term				
Blood and lymphatic system disorders Anaemia Haemolysis	14 (10.9) 10 (7.8) 8 (6.3)	29 (17.9) 17 (10.5) 12 (7.4)	30 (6.9) 21 (4.8) 12 (2.8)	40 (9.6) 27 (6.5) 13 (3.1)
Gastrointestinal disorders Abdominal pain Diarrhoea Nausea	21 (16.4) 9 (7.0) 12 (9.4) 6 (4.7)	34 (21.0) 14 (8.7) 13 (8.0) 7 (4.3)	85 (19.5) 33 (7.6) 37 (8.5) 35 (8.0)	128 (30.7) 41 (9.8) 45 (10.8) 42 (10.1)
General disorders and administration site conditions Pyrexia Asthenia Fatigue	28 (21.9) 14 (10.9) 12 (9.4) 5 (3.9)	39 (24.1) 20 (12.4) 13 (8.0) 6 (3.7)	80 (18.3) 39 (8.9) 5 (1.1) 40 (9.2)	102 (24.4) 43 (10.3) 5 (1.2) 54 (12.9)
Infections and infestations COVID-19 Nasopharyngitis Upper respiratory tract infection	34 (26.6) 18 (14.1) 12 (9.4) 5 (3.9)	41 (25.4) 22 (13.6) 14 (8.7) 5 (3.1)	123 (28.2) 0 62 (14.2) 70 (16.1)	182 (43.6) 0 93 (22.3) 89 (21.3)
Musculoskeletal and connective tissue disorders Back pain Arthralgia Pain in extremity	19 (14.8) 8 (6.3) 7 (5.5) 6 (4.7)	27 (16.7) 11 (6.8) 9 (5.6) 7 (4.3)	75 (17.2) 25 (5.7) 33 (7.6) 27 (6.2)	104 (24.9) 30 (7.2) 45 (10.8) 29 (6.9)
Nervous system disorders Headache Dizziness	24 (18.8) 18 (14.1) 6 (4.7)	31 (19.2) 25 (15.5) 6 (3.7)	116 (26.6) 101 (23.2) 22 (5.0)	171 (40.9) 147 (35.2) 24 (5.7)
Respiratory, thoracic and mediastinal disorders Cough	5 (3.9) 5 (3.9)	6 (3.7) 6 (3.7)	24 (5.5) 24 (5.5)	26 (6.2) 26 (6.2)

Note: Rate of AE adjusted by patient-years of exposure, defined as (number of events × 100)/total patient-years (ie, rate/ 100 PY).
The data cutoff dates are based on the 52-week data for Studies ALXN1210-PNH-303 (02 Feb 2021), ALXN1210-PNH-301 (04 Sep 2018), and ALXN1210-PNH-302 (07 Sep 2018).
Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; E = number of events; ISS = Integrated Summary of Safety; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; n = number of patients with data; PY = patient-years of exposure; SC = subcutaneous
Source: ISS Table 14.3.1.6.1.2

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

No deaths occurred during the Randomized Treatment Period. In the SC group, 1 patient died on Day 182 due to COVID-19; this event was assessed by the Investigator to be not related to the study drug.

In the pooled IV group, 2 patients died through the 52-week data cut-off date, both assessed by the Investigator as not related to the study drug (ALXN1210-PNH-301 52-week data)

- One patient died due to lung adenocarcinoma during the Extension Period following symptoms of lung cancer (blood-tinged sputum, cough, and wheezing) that developed during the Primary Evaluation Period.

- One patient died due to pulmonary sepsis during the Extension Period.

Other Serious Adverse Events

Randomised treatment period

Six patients experienced an SAE during the Randomized Treatment Period; 1 patient in the ravulizumab IV group experienced an SAE of cholecystitis and 5 patients in the ravulizumab SC group experienced SAEs of neutropenia, lens dislocation, gastroenteritis, cervicobrachial syndrome, and urinary retention. One patient (SC group) from the excluded site had an SAE of extravascular haemolysis. None of the SAEs were considered related to study treatment, and all events resolved.

SC treatment period

The percentage of patients with SAEs, excluding those related to COVID-19, was similar in both groups.

A total of 8 patients had COVID-19-related SAEs in the SC group: 6 patients had COVID-19, 1 patient had suspected COVID-19, and 1 patient had COVID-19 pneumonia. All SAEs related to COVID-19 were assessed as unrelated to the study drug by the Investigator. Based on the mechanism of action of ravulizumab, it does not appear that patients receiving ravulizumab treatment are at increased risk of developing COVID-19 infection.

The most frequently reported SAE across both groups was pyrexia (2 patients [1.6%] in SC vs 5 patients [1.1%] in pooled IV group). Other SAEs reported in at least 2 patients in either group were anaemia, haemolysis, aplastic anaemia, influenza, pneumonia, thrombocytopenia, and uterine leiomyoma; all other SAEs were reported in no more than 1 patient in either group.

The rate of study drug discontinuation (SC vs pooled IV group) due to SAEs was low (0 vs 2 SAEs in 2 patients).

Table 37 Serious Adverse Events by Delivery Mechanism by MedDRA System Organ Class and Preferred Term (ISS Safety Analysis Set)

	Study ALXN1210-PNH-303 Ravulizumab SC (N = 128) PY = 161.7		**Studies ALXN1210-PNH-301 and ALXN1210-PNH-302 Ravulizumab IV (N = 436) PY = 417.6**	
System Organ Class Preferred Term	**n (%)**	**E (Rate)**	**n (%)**	**E (Rate)**
Patients with at least 1 SAE	26 (20.3)	44 (27.2)	51 (11.7)	75 (18.0)
Blood and lymphatic system disorders	**8 (6.3)**	**13 (8.0)**	**12 (2.8)**	**16 (3.8)**
Anaemia	2 (1.6)	4 (2.5)	2 (0.5)	2 (0.5)
Haemolysis	2 (1.6)	2 (1.2)	2 (0.5)	2 (0.5)
Haemolytic anaemia	1 (0.8)	2 (1.2)	1 (0.2)	1 (0.2)
Neutropenia	1 (0.8)	2 (1.2)	1 (0.2)	2 (0.5)
Thrombocytopenia	2 (1.6)	2 (1.2)	1 (0.2)	1 (0.2)
Aplastic anaemia	1 (0.8)	1 (0.6)	5 (1.1)	7 (1.7)
Pancytopenia	0	0	1 (0.2)	1 (0.2)
Cardiac disorders	**0**	**0**	**2 (0.5)**	**2 (0.5)**
Left ventricular failure	0	0	1 (0.2)	1 (0.2)
Myocardial ischaemia	0	0	1 (0.2)	1 (0.2)
Eye disorders	**1 (0.8)**	**2 (1.2)**	**0**	**0**
Lens dislocation	1 (0.8)	2 (1.2)	0	0
Gastrointestinal disorders	**1 (0.8)**	**1 (0.6)**	**4 (0.9)**	**6 (1.4)**

	Study ALXN1210-PNH-303 Ravulizumab SC (N = 128) PY = 161.7		Studies ALXN1210-PNH-301 and ALXN1210-PNH-302 Ravulizumab IV (N = 436) PY = 417.6	
System Organ Class Preferred Term	**n (%)**	**E (Rate)**	**n (%)**	**E (Rate)**
Gastritis	1 (0.8)	1 (0.6)	0	0
Abdominal hernia	0	0	1 (0.2)	1 (0.2)
Colitis	0	0	1 (0.2)	3 (0.7)
Ileus	0	0	1 (0.2)	1 (0.2)
Toothache	0	0	1 (0.2)	1 (0.2)
General disorders and administration site conditions	**3 (2.3)**	**3 (1.9)**	**6 (1.4)**	**6 (1.4)**
Pyrexia	2 (1.6)	2 (1.2)	5 (1.1)	5 (1.2)
Chest pain	1 (0.8)	1 (0.6)	0	0
Hyperthermia	0	0	1 (0.2)	1 (0.2)
Hepatobiliary disorders	**2 (1.6)**	**2 (1.2)**	**4 (0.9)**	**4 (1.0)**
Cholangitis	1 (0.8)	1 (0.6)	0	0
Cholecystitis acute	1 (0.8)	1 (0.6)	0	0
Biliary colic	0	0	1 (0.2)	1 (0.2)
Cholecystitis	0	0	1 (0.2)	1 (0.2)
Cholelithiasis	0	0	1 (0.2)	1 (0.2)
Liver disorder	0	0	1 (0.2)	1 (0.2)
Infections and infestations	**14 (10.9)**	**15 (9.3)**	**18 (4.1)**	**21 (5.0)**
COVID-19	6 (4.7)	6 (3.7)	0	0
Bacterial infection	1 (0.8)	1 (0.6)	0	0
Bacterial sepsis	1 (0.8)	1 (0.6)	0	0
COVID-19 pneumonia	1 (0.8)	1 (0.6)	0	0
Gastroenteritis	1 (0.8)	1 (0.6)	1 (0.2)	1 (0.2)
Hepatitis viral	1 (0.8)	1 (0.6)	0	0
Salmonellosis	1 (0.8)	1 (0.6)	0	0
Sinusitis	1 (0.8)	1 (0.6)	0	0
Suspected COVID-19	1 (0.8)	1 (0.6)	0	0
Tubo-ovarian abscess	1 (0.8)	1 (0.6)	0	0
Abscess limb	0	0	1 (0.2)	1 (0.2)
Atypical pneumonia	0	0	1 (0.2)	1 (0.2)
Endometritis	0	0	1 (0.2)	1 (0.2)
Endophthalmitis	0	0	1 (0.2)	1 (0.2)
Fungal endocarditis	0	0	1 (0.2)	1 (0.2)
Herpes zoster	0	0	1 (0.2)	1 (0.2)
Infection	0	0	1 (0.2)	1 (0.2)
Influenza	0	0	3 (0.7)	3 (0.7)
Leptospirosis	0	0	1 (0.2)	1 (0.2)
Lower respiratory tract infection	0	0	1 (0.2)	1 (0.2)
Pharyngitis	0	0	1 (0.2)	1 (0.2)
Pneumonia	0	0	2 (0.5)	2 (0.5)
Pulmonary sepsis	0	0	1 (0.2)	1 (0.2)
Septic shock	0	0	1 (0.2)	1 (0.2)
Systemic infection	0	0	1 (0.2)	1 (0.2)
Upper respiratory tract infection	0	0	1 (0.2)	1 (0.2)
Viral upper respiratory tract infection	0	0	1 (0.2)	1 (0.2)
Injury, poisoning and procedural complications	**1 (0.8)**	**1 (0.6)**	**2 (0.5)**	**2 (0.5)**
Transfusion reaction	1 (0.8)	1 (0.6)	0	0
Skin laceration	0	0	1 (0.2)	1 (0.2)
Tibia fracture	0	0	1 (0.2)	1 (0.2)

	Study ALXN1210-PNH-303 Ravulizumab SC (N = 128) PY = 161.7		Studies ALXN1210-PNH-301 and ALXN1210-PNH-302 Ravulizumab IV (N = 436) PY = 417.6	
System Organ Class Preferred Term	**n (%)**	**E (Rate)**	**n (%)**	**E (Rate)**
Musculoskeletal and connective tissue disorders	**0**	**0**	**1 (0.2)**	**1 (0.2)**
Foot deformity	0	0	1 (0.2)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**3 (2.3)**	**4 (2.5)**	**4 (0.9)**	**8 (1.9)**
Basal cell carcinoma	1 (0.8)	2 (1.2)	0	0
Colon adenoma	1 (0.8)	1 (0.6)	0	0
Lung adenocarcinoma	1 (0.8)	1 (0.6)	1 (0.2)	1 (0.2)
Myelodysplastic syndrome	0	0	1 (0.2)	1 (0.2)
Uterine leiomyoma	0	0	2 (0.5)	6 (1.4)
Nervous system disorders	**1 (0.8)**	**1 (0.6)**	**2 (0.5)**	**2 (0.5)**
Cervicobrachial syndrome	1 (0.8)	1 (0.6)	0	0
Epilepsy	0	0	1 (0.2)	1 (0.2)
Migraine	0	0	1 (0.2)	1 (0.2)
Psychiatric disorders	1 (0.8)	1 (0.6)	1 (0.2)	1 (0.2)
Depression	1 (0.8)	1 (0.6)	1 (0.2)	1 (0.2)
Renal and urinary disorders	**0**	**0**	**2 (0.5)**	**2 (0.5)**
Acute kidney injury	0	0	1 (0.2)	1 (0.2)
Renal colic	0	0	1 (0.2)	1 (0.2)
Reproductive system and breast disorders	**1 (0.8)**	**1 (0.6)**	**0**	**0**
Adnexal torsion	1 (0.8)	1 (0.6)	0	0
Respiratory, thoracic, and mediastinal disorders	**0**	**0**	**1 (0.2)**	**1 (0.2)**
Respiratory failure	0	0	1 (0.2)	1 (0.2)
Vascular disorders	**0**	**0**	**3 (0.7)**	**3 (0.7)**
Deep vein thrombosis	0	0	1 (0.2)	1 (0.2)
Jugular vein thrombosis	0	0	1 (0.2)	1 (0.2)
Peripheral artery thrombosis	0	0	1 (0.2)	1 (0.2)

Note: Rate of AE adjusted by patient-years of exposure, defined as (number of events × 100)/total patient-years (ie, rate/ 100 PY).
AEs are coded using MedDRA Version 23.1.
The data cutoff dates are based on the 52-week data for Studies ALXN1210-PNH-303 (02 Feb 2021), ALXN1210-PNH-301 (04 Sep 2018), and ALXN1210-PNH-302 (07 Sep 2018).
Abbreviations: AE = adverse event; COVID-19 = coronavirus disease 2019; E = number of events; IV = intravenous; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; n = number of patients with data; PY = patient-years of exposure; SAE = serious adverse event; SC = subcutaneous
Source: ISS Table 14.3.1.5.1.2

Adverse Events of Special Interest

Adverse events of special interest (AESIs) included infusion reactions, meningococcal infections, other serious infections, and antidrug antibodies.

Randomised treatment period

Local (infusion site or injection site reactions), systemic (infusion-associated/infusion-related reactions), and immune-mediated reactions were evaluated during the Randomized Treatment Period.

Eight (17.8%) patients in the IV group and 38 (45.2%) patients in the SC group experienced infusion reactions during the Randomized Treatment Period. In the SC group, 30 (35.7%) patients experienced infusion reactions coded to the SOC of General Disorders and Administration Site Conditions under Preferred Terms such as injection site erythema, injection site reaction, fatigue, and medical device site erythema. Two events of drug hypersensitivity (both Grade 2 severity) were experienced by 1 patient, and 1 event of hypersensitivity (Grade 2) was experienced by another patient; both of these patients were ADA negative. An additional patient had an event coded as medical device site erythema (verbatim "sensitivity to device adhesive [mild erythema]").

No meningococcal infections were reported during the Randomized Treatment Period and no patients developed antidrug antibodies.

SC treatment period

The exposure-adjusted rates of infusion reactions (excluding ADEs) was 98.3 and 54.1 in the SC and pooled IV groups, respectively (Table below). The difference in the rates of infusion reactions between the SC and pooled IV groups are attributable to local infusion reactions (ie, injection site reactions) related to the SC mode of administration. It is important to note that the infusion reactions for ravulizumab SC administered via on-body injector (OBI) were defined and assessed differently from that of ravulizumab IV administration. Infusion reactions for ravulizumab IV included systemic reactions. Infusion reactions, for ravulizumab SC administered via OBI, included local reactions (which are injection site reactions localized to the site of SC administration) as well as systemic reactions.

In addition, COVID-19 related AESI was reported only in the SC group, which is a result of the pre-pandemic timing of the Studies ALXN1210-PNH-301 and ALXN1210-PNH-302. Otherwise, the rate of serious infections was consistent between the SC and pooled IV groups.

There were no meningococcal infections and no antidrug antibody (ADA)-positive results in Study ALXN1210-PNH-303.

The rates of infusion reactions decreased over time through the 52-week data cut-off date in both groups.

Table 38 Treatment-emergent Adverse Events of Special Interest up to Data Cutoff by Delivery Mechanism by MedDRA System Organ Class and Preferred Term (ISS Safety Analysis Set)

	Study ALXN1210-PNH-303 Ravulizumab SC (N = 128) PY = 161.7		**Studies ALXN1210-PNH-301 and ALXN1210-PNH-302 Ravulizumab IV (N = 436) PY = 417.6**	
Adverse Event of Interest Preferred Term	**n (%)**	**E (rate)**	**n (%)**	**E (rate)**
Patients with at least 1 AESI	52 (40.6)	159 (98.3)	129 (29.6)	226 (54.1)
Infusion reactions	48 (37.5)	144 (89.1)	121 (27.8)	205 (49.1)
Erythema	5 (3.9)	22 (13.6)	2 (0.5)	2 (0.5)
Headache	9 (7.0)	12 (7.4)	47 (10.8)	64 (15.3)
Swelling	1 (0.8)	10 (6.2)	0	0

Asthenia	8 (6.3)	9 (5.6)	2 (0.5)	2 (0.5)
Injection site erythema	1 (0.8)	8 (4.9)	0	0
Abdominal pain	5 (3.9)	7 (4.3)	4 (0.9)	4 (1.0)
Pyrexia	4 (3.1)	7 (4.3)	6 (1.4)	7 (1.7)
Fatigue	4 (3.1)	5 (3.1)	5 (1.1)	5 (1.2)
Injection site urticaria	1 (0.8)	5 (3.1)	0	0
Arthralgia	4 (3.1)	4 (2.5)	4 (0.9)	4 (1.0)
Influenza like illness	4 (3.1)	4 (2.5)	6 (1.4)	6 (1.4)
Cough	3 (2.3)	3 (1.9)	3 (0.7)	3 (0.7)
Diarrhoea	3 (2.3)	3 (1.9)	4 (0.9)	5 (1.2)
Dyspnoea	3 (2.3)	3 (1.9)	3 (0.7)	3 (0.7)
Injection site pruritus	1 (0.8)	3 (1.9)	0	0
Nausea	2 (1.6)	3 (1.9)	11 (2.5)	12 (2.9)
Abdominal pain lower	2 (1.6)	2 (1.2)	0	0
Abdominal pain upper	2 (1.6)	2 (1.2)	2 (0.5)	2 (0.5)
Chest pain	2 (1.6)	2 (1.2)	2 (0.5)	3 (0.7)
Dizziness	2 (1.6)	2 (1.2)	3 (0.7)	3 (0.7)
Drug hypersensitivity	1 (0.8)	2 (1.2)	2 (0.5)	2 (0.5)
Infusion site reaction	1 (0.8)	2 (1.2)	0	0
Myalgia	2 (1.6)	2 (1.2)	3 (0.7)	3 (0.7)
Pain	1 (0.8)	2 (1.2)	1 (0.2)	1 (0.2)
Pruritus	1 (0.8)	2 (1.2)	1 (0.2)	1 (0.2)
Rash	2 (1.6)	2 (1.2)	10 (2.3)	11 (2.6)
Skin induration	1 (0.8)	2 (1.2)	0	0
Abdominal distension	1 (0.8)	1 (0.6)	0	0
Anxiety	1 (0.8)	1 (0.6)	0	0
Chills	1 (0.8)	1 (0.6)	2 (0.5)	2 (0.5)
Eczema	1 (0.8)	1 (0.6)	3 (0.7)	3 (0.7)
Hypersensitivity	1 (0.8)	1 (0.6)	3 (0.7)	3 (0.7)
Hypertension	1 (0.8)	1 (0.6)	2 (0.5)	2 (0.5)
Injection site bruising	1 (0.8)	1 (0.6)	0	0
Macule	1 (0.8)	1 (0.6)	1 (0.2)	1 (0.2)
Oedema peripheral	1 (0.8)	1 (0.6)	1 (0.2)	1 (0.2)
Palpitations	1 (0.8)	1 (0.6)	5 (1.1)	5 (1.2)
Pustule	1 (0.8)	1 (0.6)	0	0
Tachycardia	1 (0.8)	1 (0.6)	0	0
Urticaria	1 (0.8)	1 (0.6)	1 (0.2)	1 (0.2)
Vomiting	1 (0.8)	1 (0.6)	1 (0.2)	1 (0.2)
Allergic transfusion reaction	0	0	1 (0.2)	1 (0.2)
Conjunctivitis allergic	0	0	1 (0.2)	1 (0.2)
Dermatitis	0	0	2 (0.5)	3 (0.7)
Dermatitis allergic	0	0	2 (0.5)	2 (0.5)
Infusion related reaction	0	0	5 (1.1)	7 (1.7)
Infusion site extravasation	0	0	1 (0.2)	1 (0.2)
Infusion site joint pain	0	0	1 (0.2)	1 (0.2)
Injection site pain	0	0	2 (0.5)	2 (0.5)
Rash macular	0	0	1 (0.2)	1 (0.2)
Rash maculo-papular	0	0	2 (0.5)	3 (0.7)
Rash pruritic	0	0	2 (0.5)	2 (0.5)
Rhinitis allergic	0	0	7 (1.6)	9 (2.2)
Skin lesion	0	0	2 (0.5)	2 (0.5)
Vaccination site pain	0	0	7 (1.6)	7 (1.7)
Vessel puncture site haematoma	0	0	1 (0.2)	1 (0.2)
Meningococcal infections	0	0	0	0

Other serious infections	14 (10.9)	15 (9.3)	18 (4.1)	21 (5.0)
COVID-19	6 (4.7)	6 (3.7)	0	0
Bacterial infection	1 (0.8)	1 (0.6)	0	0
Bacterial sepsis	1 (0.8)	1 (0.6)	0	0
COVID-19 pneumonia	1 (0.8)	1 (0.6)	0	0
Gastroenteritis	1 (0.8)	1 (0.6)	1 (0.2)	1 (0.2)
Hepatitis viral	1 (0.8)	1 (0.6)	0	0
Salmonellosis	1 (0.8)	1 (0.6)	0	0
Sinusitis	1 (0.8)	1 (0.6)	0	0
Suspected COVID-19	1 (0.8)	1 (0.6)	0	0
Tubo-ovarian abscess	1 (0.8)	1 (0.6)	0	0
Abscess limb	0	0	1 (0.2)	1 (0.2)
Atypical pneumonia	0	0	1 (0.2)	1 (0.2)
Endometritis	0	0	1 (0.2)	1 (0.2)
Endophthalmitis	0	0	1 (0.2)	1 (0.2)
Fungal endocarditis	0	0	1 (0.2)	1 (0.2)
Herpes zoster	0	0	1 (0.2)	1 (0.2)
Infection	0	0	1 (0.2)	1 (0.2)
Influenza	0	0	3 (0.7)	3 (0.7)
Leptospirosis	0	0	1 (0.2)	1 (0.2)
Lower respiratory tract infection	0	0	1 (0.2)	1 (0.2)
Pharyngitis	0	0	1 (0.2)	1 (0.2)
Pneumonia	0	0	2 (0.5)	2 (0.5)
Pulmonary sepsis	0	0	1 (0.2)	1 (0.2)
Septic shock	0	0	1 (0.2)	1 (0.2)
Systemic infection	0	0	1 (0.2)	1 (0.2)
Upper respiratory tract infection	0	0	1 (0.2)	1 (0.2)
Viral upper respiratory tract infection	0	0	1 (0.2)	1 (0.2)

Note: Rate of AE adjusted by patient-years of exposure, defined as (number of events × 100)/ total patient-years.
The data cutoff dates are based on the 52-week data for Studies ALXN1210-PNH-303 (02 Feb 2021), ALXN1210-PNH-301 (04 Sep 2018), and ALXN1210-PNH-302 (07 Sep 2018).
Abbreviations: AE = adverse event; AESI = adverse events of special interest; COVID-2019 = coronavirus disease 2019; E = number of events; IV = intravenous; ISS = Integrated Summary of Safety; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; n = number of patients with data; PY = patient-years of exposure; SC = subcutaneous
Source: ISS Table 14.3.1.7.1.2

Analysis of Adverse Events by Organ System or Syndrome

The most frequently reported SOCs (SC vs pooled IV group) included infections and infestations (26.6% vs 28.2%), general disorders and administrative site conditions (21.9% vs 18.3%), nervous system disorders (18.8% vs 26.6%), and gastrointestinal disorders (16.4% vs 19.5%).

Adverse Device Effects of Ravulizumab SC

Adverse device effects specific to ravulizumab SC in Study ALXN1210-PNH-303 are not included in analysis of AEs, although an overview is presented in this section:

Aside from ADEs associated with the SC route of administration, there were no other notable differences between ravulizumab SC and ravulizumab IV.

Local administration site reactions coded to the SOC of General Disorders and Administration Site Conditions were reported by 21.9% of patients.

The most frequently reported local administration site reactions (in > 3% of patients) included injection site reaction (4.7%), medical device site erythema (3.9%), infusion site erythema (3.1%), and injection site erythema (3.1%). Two patients experienced systemic reactions considered related to the study device (1 patient had procedural dizziness and 1 patient had a serious ADE of procedural hypotension).

Of the patients experiencing local administration site reactions, 2 (1.6%) patients had Grade 2 events, and 1 (0.8%) patient had a Grade 3 event (application site induration); all other events were Grade 1.

The incidence of local administration site reactions decreased over time (0 to 6 months: 197.4 E/100PY, > 6 to 12 months: 13.2 E/100PY). One or more ADEs relating to drug delivery (ie, no drug or less than full volume of the device administered; coded to the SOC of Product Issues) were reported for 91 (71.1%) patients.

The incidence of these ADEs decreased over time (0 to 6 months: 192.6 E/ 100 PY, > 6 to 12 months: 152.0 E/ 100 PY).

Although many patients had at least 1 ADE relating to drug delivery, full dose (490 mg) administration was achieved in 99.9% of ravulizumab SC administration attempts administered as patients were permitted to use more than 2 devices as needed.

The majority (97.6%) of full doses were administered per protocol using 2 OBDS device kits; few doses (2.4%) used more than 2 OBDS kits.

Table 39 Adverse Device Effects Since First SC Dose as of Data Cutoff Date (SC Treated Safety Analysis Set)

System Organ Class Preferred Term	Ravulizumab IV/SC (N = 44) PY = 50.5			Ravulizumab SC/SC (N = 84) PY = 111.3			Total (N = 128) PY = 161.7		
	n (%)	E	E/100 PY	n (%)	E	E/100 PY	n (%)	E	E/100 PY
Patients with ADEs	35 (79.5)	122	241.7	60 (71.4)	251	225.6	95 (74.2)	373	230.6
Patients with ADE Preferred Terms coded under the SOC of Product issues	35 (79.5)	90	178.3	56 (66.7)	148	133.0	91 (71.1)	238	147.2
Device delivery system issue	22 (50.0)	44	87.2	36 (42.9)	76	68.3	58 (45.3)	120	74.2
Incorrect dose administered by device	17 (38.6)	39	77.3	30 (35.7)	59	53.0	47 (36.7)	98	60.6
Drug dose omission by device	6 (13.6)	7	13.9	7 (8.3)	13	11.7	13 (10.2)	20	12.4
Patients with ADE Preferred Terms that were not coded under the SOC of Product issues	7 (15.9)	32	63.4	22 (26.2)	103	92.6	29 (22.7)	135	83.5
General disorders and administration site conditions	6 (13.6)	31	61.4	22 (26.2)	101	90.8	28 (21.9)	132	81.6
Injection site reaction	1 (2.3)	8	15.8	5 (6.0)	23	20.7	6 (4.7)	31	19.2
Medical device site erythema	2 (4.5)	7	13.9	3 (3.6)	4	3.6	5 (3.9)	11	6.8
Infusion site erythema	2 (4.5)	4	7.9	2 (2.4)	2	1.8	4 (3.1)	6	3.7
Injection site erythema	1 (2.3)	2	4.0	3 (3.6)	10	9.0	4 (3.1)	12	7.4
Medical device site rash	1 (2.3)	1	2.0	2 (2.4)	2	1.8	3 (2.3)	3	1.9
Medical device site reaction	1 (2.3)	1	2.0	2 (2.4)	2	1.8	3 (2.3)	3	1.9
Complication associated with device	2 (4.5)	2	4.0	0	0	0.0	2 (1.6)	2	1.2
Device allergy	0	0	0.0	2 (2.4)	2	1.8	2 (1.6)	2	1.2
Infusion site pain	0	0	0.0	2 (2.4)	4	3.6	2 (1.6)	4	2.5
Infusion site swelling	1 (2.3)	2	4.0	1 (1.2)	1	0.9	2 (1.6)	3	1.9
Injection site swelling	0	0	0.0	2 (2.4)	21	18.9	2 (1.6)	21	13.0
Medical device site bruise	0	0	0.0	2 (2.4)	2	1.8	2 (1.6)	2	1.2
Application site induration	0	0	0.0	1 (1.2)	1	0.9	1 (0.8)	1	0.6
Application site rash	0	0	0.0	1 (1.2)	1	0.9	1 (0.8)	1	0.6
Induration	0	0	0.0	1 (1.2)	2	1.8	1 (0.8)	2	1.2
Infusion site induration	0	0	0.0	1 (1.2)	1	0.9	1 (0.8)	1	0.6
Infusion site pruritus	1 (2.3)	2	4.0	0	0	0.0	1 (0.8)	2	1.2
Infusion site rash	1 (2.3)	2	4.0	0	0	0.0	1 (0.8)	2	1.2

System Organ Class Preferred Term	Ravulizumab IV/SC (N = 44) PY = 50.5			Ravulizumab SC/SC (N = 84) PY = 111.3			Total (N = 128) PY = 161.7		
	n (%)	E	E/100 PY	n (%)	E	E/100 PY	n (%)	E	E/100 PY
Infusion site reaction	0	0	0.0	1 (1.2)	3	2.7	1 (0.8)	3	1.9
Injection site haematoma	0	0	0.0	1 (1.2)	1	0.9	1 (0.8)	1	0.6
Injection site induration	0	0	0.0	1 (1.2)	1	0.9	1 (0.8)	1	0.6
Injection site inflammation	0	0	0.0	1 (1.2)	4	3.6	1 (0.8)	4	2.5
Injection site pain	0	0	0.0	1 (1.2)	4	3.6	1 (0.8)	4	2.5
Injection site pruritus	0	0	0.0	1 (1.2)	1	0.9	1 (0.8)	1	0.6
Injection site rash	0	0	0.0	1 (1.2)	2	1.8	1 (0.8)	2	1.2
Injection site urticaria	0	0	0.0	1 (1.2)	1	0.9	1 (0.8)	1	0.6
Medical device site haematoma	0	0	0.0	1 (1.2)	1	0.9	1 (0.8)	1	0.6
Medical device site induration	0	0	0.0	1 (1.2)	1	0.9	1 (0.8)	1	0.6
Medical device site pruritus	0	0	0.0	1 (1.2)	2	1.8	1 (0.8)	2	1.2
Swelling	0	0	0.0	1 (1.2)	2	1.8	1 (0.8)	2	1.2
Injury, poisoning and procedural complications	1 (2.3)	1	2.0	1 (1.2)	2	1.8	2 (1.6)	3	1.9
Procedural dizziness	1 (2.3)	1	2.0	0	0	0.0	1 (0.8)	1	0.6
Procedural hypotension	0	0	0.0	1 (1.2)	1	0.9	1 (0.8)	1	0.6
Product dose omission issue	0	0	0.0	1 (1.2)	1	0.9	1 (0.8)	1	0.6

Notes: E/100PY is the rate of AEs adjusted by 100 patient-years of exposure defined as (number of events*100/Total patient years). Patient-years was the total number of days since first SC treatment for all patients in the group divided by 365.25. Percentages (%) were based on the total number of patients in the SC group. In summarizing n (%), if a patient had multiple events for a particular SOC or Preferred Term, he/she was counted only once for that SOC or Preferred Term. SOCs and Preferred Terms were coded using MedDRA version 23.1.

Abbreviations: ADE = adverse device effect; AE = adverse event; E = total number of events; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; PY = patient-years; SC = subcutaneous; SOC = System Organ Class

Device performance

Full dose administration was achieved in 99.9% (8459/8464) of ravulizumab SC administration attempts. The majority (97.6%) of full doses (490 mg) were administered using 2 OBDS kits per the instructions for use.

A total of 17,165 devices were used during the course of the study. Full volume per device was delivered by 98.6% of the devices used during study (ie, 16,926 out of 17,165 devices).

Table: Device Performance Assessment for the OBDS Since First SC Dose as of Data Cutoff Date (SC Treated Safety Analysis Set)

Variable	Ravulizumab IV/SC (N = 44)	Ravulizumab SC/SC (N = 84)	Total (N = 128)
Total number of full dose administration attempts	2646	5818	8464
Actual number of full dose administrations	2646	5813	8459
Percentage of actual full dose administrations	100.0	99.9	99.9
Total number of devices used to achieve full dose, n (%)[a]			
2 devices were used to achieve full dose	2565 (96.9)	5692 (97.9)	8257 (97.6)
3 devices were used to achieve full dose	73 (2.8)	105 (1.8)	178 (2.1)
4 devices were used to achieve full dose	6 (0.2)	14 (0.2)	20 (0.2)
5 devices were used to achieve full dose	2 (0.1)	0	2 (< 0.1)
6 devices were used to achieve full dose	0	2 (< 0.1)	2 (< 0.1)
Actual number of less than full dose or no dose administrations	0	5	5
Total number of devices used when full dose not achieved, n (%)			
2 devices were used	0	2 (40.0)	2 (40.0)
3 devices were used	0	1 (20.0)	1 (20.0)
4 devices were used	0	2 (40.0)	2 (40.0)
Total number of devices attempted	5383	11782	17165
Total number of devices which delivered its full volume	5292	11634	16926
Percentage of devices with full volume delivery	98.3	98.7	98.6

Note: Full dose administration was defined as receiving the full volume from at least 2 OBDS devices. The number of full dose administration attempts and total devices used was determined based on the data recorded on the ravulizumab SC administration CRF (Listing 16.2.5.1.2.10).

[a] Denominator = total number of full dose administration attempts.

Abbreviations: CRF = case report form; IV = intravenous; OBDS = on body delivery system; SC = subcutaneous

Of the 17,165 devices attempted (roughly 134 devices per patient), complaints were reported for 298 (1.7%) devices. The root cause of approximately half (163/298) of the reported complaints was use error, 21 were due to confirmed technical defects, 28 were due to unknown defects, 65 were unable to be analysed since the device was not returned, and 21 had an ongoing investigation at the time of the data cutoff date.

Table 40 Device Complaints for the On Body Delivery System Since First SC Dose as of Data Cutoff Date (SC Treated Safety Analysis Set)

Variable	Ravulizumab IV/SC (N = 44)	Ravulizumab SC/SC (N = 84)	Total (N = 128)
Total number of devices attempted	5383	11782	17165
Devices with a reported complaint[a], n (%)	111 (2.1)	187 (1.6)	298 (1.7)
Devices with a confirmed technical defect[a], n (%)	7 (0.1)	14 (0.1)	21 (0.1)
Technical defects category, n (%)			
Battery contact issue caused the error	6 (0.1)	6 (0.1)	12 (0.1)
Damage / obstruction inside the motor	0	4 (< 0.1)	4 (< 0.1)
Error due to TSA failure/defect	0	3 (< 0.1)	3 (< 0.1)
Unit did not activate because the battery voltage was insufficient	0	1 (< 0.1)	1 (< 0.1)
Corrupted software	1 (< 0.1)	0	1 (< 0.1)
Devices with a use error[a], n (%)	61 (1.1)	102 (0.9)	163 (0.9)
Use error category, n (%)			
Door open – incomplete delivery	11 (0.2)	18 (0.2)	29 (0.2)
Door opened by user - complete delivery	4 (0.1)	17 (0.1)	21 (0.1)
Button pressed prior to secure skin placement	7 (0.1)	16 (0.1)	23 (0.1)
User misunderstood and took device off early	4 (0.1)	11 (0.1)	15 (0.1)
Door closed by patient before loading of the cartridge and could not be opened	3 (0.1)	8 (0.1)	11 (0.1)
Cartridge not fully inserted	12 (0.2)	6 (0.1)	18 (0.1)
Button not fully pressed	2 (< 0.1)	4 (< 0.1)	6 (< 0.1)
Device removed early	6 (0.1)	4 (< 0.1)	10 (0.1)
Device removed early - user misunderstood and took device off early	0	3 (< 0.1)	3 (< 0.1)
Patient does not wait 45 min for device to come to room temperature before activating device. Error noticed within 1 min of activation	2 (< 0.1)	3 (< 0.1)	5 (< 0.1)
Unknown	0	3 (< 0.1)	3 (< 0.1)
Button pressed by patient before removal of adhesive tabs	2 (< 0.1)	2 (< 0.1)	4 (< 0.1)
Delayed activation	2 (< 0.1)	2 (< 0.1)	4 (< 0.1)
Door off hinge - TSA did not nest properly	0	2 (< 0.1)	2 (< 0.1)
Customer handling	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)
Device removed from the skin prior to end of delivery.	0	1 (< 0.1)	1 (< 0.1)
User removed door from hinge since door was received closed	0	1 (< 0.1)	1 (< 0.1)
Door closed by user	2 (< 0.1)	0	2 (< 0.1)
Door closed and activation started before loading the cartridge	1 (< 0.1)	0	1 (< 0.1)
One or neither of the adhesive tabs were removed prior to applying device to the skin	1 (< 0.1)	0	1 (< 0.1)
User removed door from hinge - TSA did not nest properly	1 (< 0.1)	0	1 (< 0.1)
Devices with other/unknown defects[a], n (%)	43 (0.8)	71 (0.6)	114 (0.7)
Other/unknown defect category, n (%)			
N/A[b]	25 (0.5)	40 (0.3)	65 (0.4)
Unknown[c]	10 (0.2)	18 (0.2)	28 (0.2)
TBD - investigation in process	8 (0.1)	13 (0.1)	21 (0.1)

Notes: A confirmed technical defect refers to any confirmed device defect or malfunction not attributed to use error, whether or not dose delivery was affected. Use error refers to user action/lack of user action while using the device that leads to a different result than intended by the manufacturer or expected by the user. Other/unknown defect refers to everything else other than confirmed device defect or a use error. The source data for the reported complaints, confirmed technical defects, use errors, and other/unknown defects are the Investigations Department device complaints dataset. Total number of devices attempted is based on the data recorded on the ravulizumab SC administration CRF. a Denominator = total number of devices attempted. b N/A = no device was returned; unable to analyse. c Unknown = device was returned and the Investigations Department could not find a defect. Abbreviations: CRF = case report form; IV = intravenous; SC = subcutaneous; N/A = not available; TBD = to be determined; TSA = telescopic screw assembly

2.6.8.4. Laboratory findings

Pooled data analyses of laboratory parameters in the Pooled IV group were performed for data obtained during the Extension Period only when all patients were treated with ravulizumab. Due to the differences in patient population (treatment-naïve and eculizumab experienced) in Studies ALXN1210-PNH-301 and ALXN1210-PNH-302 during the Randomized Treatment Period (through Day 183) data are presented by individual studies.

There were no clinically significant changes in laboratory parameters across the Phase 3 PNH studies that were of safety concern.

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

Intrinsic Factors

Safety data analysed by intrinsic factors (age, sex, body weight, geographic region, and race) for the SC and pooled IV groups were presented.

Regarding subgroups, some of the subgroup categories (age > 65 years; body weight ≥ 100 kg; geographic regions of North America, Latin America, and Asia Pacific; racial groups of Black or African American and Other/Unknown) are represented by patient numbers too small to make any meaningful interpretation in the SC group.

With the consideration of these limitations, the subgroup analysis of the safety profile identified no sensitive subgroups that were considered to have an influence on the overall safety profile of ravulizumab SC treatment.

Extrinsic Factors

Safety analyses by extrinsic factors were not performed.

Use in Pregnancy and Lactation

Ravulizumab has not been studied in pregnant or lactating females.

In the SC group, 1 patient became pregnant during the Extension Period and had an elective abortion before informing site staff; the patient continued to remain on study treatment.

In the pooled IV group, 1 patient became pregnant (reported on Day 328). The patient delivered a healthy baby via 'Caesarean' section, with no complications.

Table 41 Overview of TEAEs in Various Age Groups in Study ALXN1210-PNH-303 (SC Treated Safety Analysis Set)

MedDRA Terms	**< 65 yr** (N=114) n (%)	**65-74 yr(N=10) n (%)**	**75-84 yr(N=4)n (%)**	**≥ 85 yr** (N=0) n (%)
Total AEs	114 (100)	9 (90.0)	4 (100)	0
Serious AEs - Total	31 (27.2)	4 (40.0)	3 (75.0)	0
Fatal	2 (1.8)	1 (10.0)	0	0
Hospitalization/Prolong existing hospitalization	30 (26.3)	4 (40.0)	3 (75.0)	0
Life-threatening	3 (2.6)	0	0	0

Disability/Incapacity	0	0	0	0
Other (Medically Significant)	4 (3.5)	0	0	0
AEs leading to study discontinuation	1 (0.9)	0	0	0
Psychiatric disorders	18 (15.8)	0	0	0
Nervous system disorders	34 (29.8)	3 (30.0)	0	0
Accidents and injuriesa	5 (4.4)	3 (30.0)	1 (25.0)	0
Cardiac disorders	4 (3.5)	1 (10.0)	0	0
Vascular disorders	7 (6.1)	0	0	0
Cerebrovascular disorders	1 (0.9)	0	0	0
Infections and infestations	81 (71.1)	8 (80.0)	3 (75.0)	0
Anticholinergic syndromea	27 (23.7)	3 (30.0)	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	9 (7.9)	1 (10.0)	1 (25.0)	0
Other AEs appearing more frequently in older patients (≥ 65 years)b				
Arthralgia	6 (5.3)	2 (20.0)	0	0
Ascites	0	1 (10.0)	0	0
Back pain	6 (5.3)	2 (20.0)	0	0
Chest pain	4 (3.5)	1 (10.0)	0	0
Cholecystitis	2 (1.8)	1 (10.0)	0	0
Cholecystitis acute	0	1 (10.0)	0	0
Constipation	5 (4.4)	1 (10.0)	0	0
Cough	5 (4.4)	1 (10.0)	0	0
Dental caries	0	1 (10.0)	0	0
Diarrhoea	12 (10.5)	2 (20.0)	1 (25.0)	0
Diverticulum intestinal	0	1 (10.0)	0	0
Drug hypersensitivity	0	1 (10.0)	0	0
Dysphonia	0	1 (10.0)	0	0
Dyspnoea	3 (2.6)	2 (20.0)	0	0
Dyspnoea exertional	0	0	1 (25.0)	0
Dysuria	1 (0.9)	1 (10.0)	0	0
Eyelid oedema	0	1 (10.0)	0	0
Flank pain	0	2 (20.0)	0	0
Gastric haemorrhage	0	0	1 (25.0)	0
Generalised oedema	0	1 (10.0)	0	0
Haemolysis	9 (7.9)	1 (10.0)	2 (50.0)	0
Haemorrhoidal haemorrhage	1 (0.9)	1 (10.0)	0	0
Haemorrhoids	3 (2.6)	1 (10.0)	0	0
Hyperfibrinogenaemia	0	0	1 (25.0)	0

Infusion site pain	1 (0.9)	1 (10.0)	0	0
Infusion site swelling	1 (0.9)	1 (10.0)	0	0
Inguinal hernia	0	1 (10.0)	0	0
Injection site erythema	3 (2.6)	2 (20.0)	0	0
Injection site haematoma	0	1 (10.0)	0	0
Injection site induration	0	1 (10.0)	0	0
Injection site pain	1 (0.9)	1 (10.0)	0	0
Injection site pruritus	1 (0.9)	1 (10.0)	0	0
Injection site reaction	5 (4.4)	1 (10.0)	0	0
Injection site swelling	1 (0.9)	1 (10.0)	0	0
Injection site urticaria	0	1 (10.0)	0	0
Medical device site induration	0	1 (10.0)	0	0
Muscle spasms	1 (0.9)	1 (10.0)	0	0
Musculoskeletal stiffness	0	1 (10.0)	0	0
Myalgia	4 (3.5)	1 (10.0)	0	0
Nausea	8 (7.0)	1 (10.0)	0	0
Osteoarthritis	0	1 (10.0)	1 (25.0)	0
Pain in extremity	7 (6.1)	1 (10.0)	0	0
Periodontal disease	2 (1.8)	1 (10.0)	0	0
Pruritus	0	1 (10.0)	0	0
Serum ferritin increased	0	1 (10.0)	0	0
Skin disorder	0	0	1 (25.0)	0
Skin ulcer	0	1 (10.0)	0	0
Toothache	5 (4.4)	1 (10.0)	1 (25.0)	0
Urticaria	1 (0.9)	1 (10.0)	0	0
Vomiting	6 (5.3)	1 (10.0)	0	0

Note: % = n/N*100; E=number of events. Treatment emergent AEs are AEs with a start date on or after first dose of SC treatment. In summarizing n(%), if a patient had multiple events for a particular PT, he/she is counted only once for that PT. AEs are coded using MedDRA Version 25.0. a Sponsor generated based on SMQ search. b Preferred terms that appear more frequently in the ≥65 years subgroup compared to the <65 years subgroup, based on percentage in the total arm, where the PT was not previously reported in the summary. Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event; SC = subcutaneous; SMQ = standard MedDRA query Source: Table EMA.Q17.2.12

2.6.8.7. Immunological events

Immunogenicity

Patients with PNH No treatment-emergent ADA-positive findings were observed after ravulizumab SC administration in any patient. This low ADA incidence rate is consistent with the low rates observed following ravulizumab IV treatment. As such, no impact of immunogenicity on safety was observed with SC administration.

In the pooled IV group, 1 patient had treatment-emergent positive ADA-positive finding through the 52-week data cutoff date (ALXN1210-PNH-301 52-week data). The ADA response was transient, with low titer and not positive for eculizumab cross reactivity. There were no neutralizing ADAs.

2.6.8.8. Safety related to drug-drug interactions and other interactions

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

2.6.8.9. Discontinuation due to adverse events

The rate of study drug discontinuation due to AEs by patients was low in both SC and pooled IV groups:

- One patient in the SC group discontinued study drug on Day 85 due to a non-serious AE of depression that began on Day 72 and subsequently withdrew from study on Day 85. The event was not considered to be related to the study drug by the Investigator.
- Two patients in the pooled IV group discontinued study drug during the Extension Period (lung adenocarcinoma and myelodysplastic syndrome) through the 52-week data cut-off date in the pooled IV group (ALXN1210-PNH-301 52-week data). Both AEs were assessed by the Investigator as not related to the study drug.

2.6.8.10. Post marketing experience

The estimated post-marketing exposure to ravulizumab IV since the first Marketing Authorization (21 Dec 2018) through 30 Jun 2021 was 3996.7 patient-years (PY) for the PNH and aHUS indications.

Meningococcal infection remains an important identified risk for ravulizumab IV based on the mechanism of action, findings from ravulizumab clinical studies, and long-term experience with eculizumab.

Three patients reported meningococcal infection in the postmarketing setting of ravulizumab IV (2 patients with serotype non-typeable and 1 patient with unknown serotype) with a reporting rate of approximately 0.08 per 100 PY [3 patients/3997 PY], between 197 to 322 days of the first dose of ravulizumab IV for PNH. This is within the rate observed in ravulizumab IV clinical studies (consistent with the overall meningococcal rate of 0.3 per 100 PY with eculizumab) and within the postmarketing meningococcal rate observed on eculizumab treatment. Administration of a meningococcal vaccination at least 2 weeks prior to the administration of ravulizumab IV was confirmed in all 3 patients.

Long-term post-marketing experience with eculizumab showed a consistent reporting rate 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. This is 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 as of 30 Jun 2021. Mitigation measures of the risk of meningococcal infections remain appropriate and effective.

A signal of hypersensitivity reactions was confirmed based on cumulative data review of the Standard MedDRA Query (SMQ) hypersensitivity. The signal of hypersensitivity reactions was confirmed as an identified risk. It is not considered an important risk because hypersensitivity reaction including anaphylaxis is a well-documented and well-characterized reaction associated with therapeutic proteins including monoclonal antibodies.

2.6.9. Discussion on clinical safety

The overall safety assessment is based on study ALXN1210 PNH 303 (including the Randomised Treatment Period and the Extension Period up to week 52) and a comparison of data obtained through the 52-weeks data cut-off (2 Feb 2021) of ravulizumab SC treatment in Study ALXN1210 PNH 303 (hereafter referred to as SC group) versus pooled data from 52-weeks data cut-offs on ravulizumab IV treatment in 2 Phase 3 studies (ALXN1210 PNH 301 and ALXN1210 PNH 302, hereafter referred to as pooled IV group). Safety is further supported by data from the 52-weeks data cut-off from Study ALXN1210 aHUS 311. The safety dataset is comprised by 129 patients treated with ravulizumab in study ALXN1210 PNH 303, 45 initially randomised to the IV arm and 84 to the SC arm during the Randomised Treatment Period. Of these, 128 patients received at least one dose of ravulizumab SC and represent the main safety dataset (SC Treated Safety Analysis Set).

Overall, demographic and baseline characteristics appear broadly balanced between the SC and pooled IV groups and were as expected based on the eligibility criteria in each study, except for race and body weight categories.

Regarding the main **Phase 3 Study ALXN1210-PNH-303** of ravulizumab SC OBDS in adult patients with paroxysmal nocturnal haemoglobinuria (PNH) (N= 128; IV/SC: 44 SC/SC:84), all patients in the IV group received the corresponding weight-based ravulizumab IV loading dose on Day 1 and maintenance dose on Day 15The 84 patients in the SC group attempted a total of 672 SC dose administrations. During the Randomized Treatment Period, treatment compliance was 100% in the IV group and 98.8% in the SC group.

A flat dose is proposed for the administration of ravulizumab SC and according to the PK results of the ALXN1210 PNH 303 study, a higher exposure could be expected with ravulizumab SC at the proposed dosing regimen compared with ravulizumab IV (see PK/PD section). In this regard, safety data according to weight ($\geqslant$ 40 kg to < 60 kg; $\geqslant$ 60 kg to < 100 kg) have been provided. Of note, the proportion of patients with TESAEs and TEAEs of Grade 4 was higher in the subgroup of patients with a lower weight although information on TESAEs and TEAEs of Grade 4 by weight did not show relevant issues.

Overall, the 128 patients in the SC Treated Safety Analysis Set had a total of 8,464 SC dose administration attempts and patients received the full dose in 99.9% of these dosing attempts, what is considered adequate. The median total infusion time per site administration was 10 minutes.

Regarding the main Phase 3 study **ALXN1210-PNH-303**, **during the 10-week Randomized Treatment Period**, the percentage of patients who experienced AEs was 60.0% in the IV group and 79.8% in the SC group. This difference appears to be driven mostly by the SOCs "General disorders and administration site conditions" (1 [2.2] ravulizumab IV vs. 33 [39.3%] ravulizumab SC) and "Product issues" (0 vs. 21 [25.0%], respectively), mainly device delivery system issue (13 patients) and incorrect dose administered device (10 patients). According to the MAH, when adverse device effects (ADEs) are excluded, the percentage of patients who experienced AEs was similar between the treatment groups (IV group: 60.0%; SC group: 64.3%). The most common AE was headache, which was reported by 8.9% of patients in the IV group and 13.1% of patients in the SC group. Of note, a higher incidence of diarrhoea was observed in the ravulizumab SC arm compared with the IV (11 [13.1%] vs 2 [4.4%]). Further, psychiatric disorders were reported in 6 (7.1%) patients in the ravulizumab SC arm while none in the IV arm. Psychiatric disorders included depression, insomnia (2 each), anxiety and daydreaming (1 each). Serious adverse events (SAEs) were reported in 5 (6.0%) patients in the ravulizumab SC arm vs 1 (2.2%) in the ravulizumab IV. None of these SAE was reported in more than one patient. SAEs reported included neutropenia, lens dislocation,

gastroenteritis, cervico-brachial syndrome, and urinary retention, reported by 1 patient each in the SC group, and cholecystitis was reported by 1 patient in the IV group.

Considering the SC group (n=128), after excluding AEs and SAEs related to COVID-19, the percentage of patients with AEs and SAEs were similar in both SC and pooled IV groups.

During SC Treatment as of data cut-off date, the **most common AEs** (reported by ≥ 10% of patients) were headache (14.1%), COVID-19 (14.1%), and pyrexia (10.9%).

Among TEAEs (SC vs. pooled IV group) assessed by the Investigator as related to study drug administration across both groups, headache (3.9% vs. 10.1%), erythema (3.9% vs. 0.2%), and nausea (0.8% vs. 2.5%) were the most frequently reported. Despite the numerical differences in related TEAEs, the type of related TEAEs were similar and consistent with the known safety profile of ravulizumab, and no relevant differences were shown between IV and SC ravulizumab. Additionally, analysis of TEAEs by worst severity showed that most patients in both groups had Grade 1 or 2 severity AEs. In general, there was no evidence of increased severity of AEs in the SC group compared to the pooled IV group. Asthenia was reported to be higher in the SC group compared to the poled IV group (SC 12/128 [9.4%] vs. IV 5/436 [1.1 %]), however a thorough review of the individual cases of asthenia did not reveal any safety concerns, being asthenia a very common symptom in PNH disease patients. As reported by the MAH, over long-term exposure as of Week 108 (2 year) for Study ALXN1210-PNH 303, there was a decreasing trend in the event rate of asthenia from 8.9 events per 100 patient-years for 0-12 months to 4.3 events per 100 patient years for the > 12 - 24 month time frame.

In study ALXN1210-PNH-303, **SAEs** were reported for 26 (20.3%) patients during SC treatment, including 8 patients with COVID-19 related SAEs (1 of them fatal, assessed as unrelated to study drug). One patient had 2 serious ADEs of application site induration and procedural hypotension assessed as related to the study device. One patient withdrew from study treatment due to an AE of depression (not related to study treatment). No meningococcal infections or MAVEs were reported.

In the pooled IV group, 2 patients died through the 52-week data cut-off date, both assessed by the Investigator as not related to the study drug (ALXN1210-PNH-301 52-week data).

The rate of study drug discontinuation (SC vs. pooled IV group) due to SAEs was low (0 vs. 2 SAEs in 2 patients).

Local administration site reactions were reported by 28 (21.9%) patients (2 patients had Grade 2 events, 1 patient had a Grade 3 event, and all other events were Grade 1). The most frequently reported local administration site reactions (>3% of patients) included injection site reaction (4.7%), medical device site erythema (3.9%), infusion site erythema (3.1%), and injection site erythema (3.1%). The incidence of local administration site reactions decreased over time (0 to 6 months: 197.4 events per 100 patient-years (E/100PY), >6 to 12 months: 13.2 E/100PY).

The rates of infusion reactions decreased over time through the 52-week data cut-off date in both groups. Of note, there were no meningococcal infections and no antidrug antibody (ADA)-positive results in Study ALXN1210-PNH-303.

During the procedure, long-term safety data up to Week 108 (data cut-off of 2 March 2022) have been provided. Overall, the safety profile of ravulizumab SC appears in line with the previously reported data although there was an increase in the overall incidence of SAEs and TEAEs of Grade 3 compared with the previous data cut-off. The incidence of some TEAEs was also higher (i.e. blood and lymphatic system disorders, gastrointestinal disorders, infections and infestations and pyrexia, among others), although this is not unexpected taking into account the longer treatment exposure. Notwithstanding,

the incidence of TEAEs, SAEs, ADEs and AEs of special interest seems to decrease over time. No additional relevant issues were identified.

With regards to de device performance, in 99.9% of cases, full dose administration was achieved. The majority (97.6%) of full doses (490 mg) were administered using 2 OBDS kits. There were also 202 administrations in which >2 kits were required for a full dose. Of the 17,165 devices attempted, complaints were reported for 298 (1.7%) devices. Of these, 21 were due to confirmed technical defects, 28 were due to unknown defects, 163 due to a use error and 114 due to other/unknown defects (65 were unable to be analysed since the device was not returned, and 21 had an ongoing investigation).

The fact that 2 kits (or more) are required to administer a full dose increases the complexity of the procedure albeit the generation of notable waste materials. During a scientific advice requested by the MAH in 2018 the possibility of developing a ready-to-use integral drug-device combination (DDC) was discussed. However, during the presubmission meeting prior to submission of this applications procedure the MAH stated that their intent has always been to develop ravulizumab SC as non-integral DDC.

Of note, according to the MAH, the injector of ravulizumab SC uses acrylic adhesive and therefore, for patients with a known allergy to acrylics adhesive, use of this product may result in an allergic reaction. A warning has been included in section 4.4. of the SmPC. Premedication can be considered and/or supportive measures should be instituted if signs of allergy appear.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

2.6.10. Conclusions on the clinical safety

The safety profile for ravulizumab SC, administered at a weekly flat dose of 490 mg, appears generally consistent with the well-characterized safety profile for ravulizumab IV. The SC formulation is associated with a higher incidence of administration site adverse events and adverse device effects, although most of them were mild.

No new clinically relevant safety concerns were identified for ravulizumab SC.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 42: Summary of Safety Concerns

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

Abbreviations: aHUS = atypical haemolytic uraemic syndrome; PNH = paroxysmal nocturnal haemoglobinuria; TMA = thrombotic microangiopathy.

2.7.2. Pharmacovigilance plan

Table 43: Ongoing and Planned Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 3 – required additional pharmacovigilance activities				
"A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Complement Inhibitor-Naïve Adult Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)" (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
"A Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) Currently 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	Dec 2022

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
"Paroxysmal Nocturnal Hemoglobinuria (PNH) Registry" M07-001 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 / ULTOMIRIS treated patients.	Meningococcal infection Serious haemolysis after drug discontinuation in PNH patients 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
"Atypical Hemolytic Uremic Syndrome (aHUS) Registry" (M11-001) 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
"Single Arm Study of ALXN1210 in Complement Inhibitor Treatment-Naïve Adult and Adolescent Patients with Atypical Hemolytic Uremic Syndrome (aHUS)" (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

Abbreviations: aHUS = atypical haemolytic uraemic syndrome; CSR = clinical study report; PNH = paroxysmal nocturnal haemoglobinuria; TMA = thrombotic microangiopathy.

2.7.3. Risk minimisation measures

Table 44: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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/gMG/NMOSD Physician's Guide – PNH/aHUS/gMG/NMOSD Patient's Information Brochure – PNH/aHUS Parent's Information Brochure – Patient card Controlled distribution Revaccination reminder	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific adverse reaction follow-up questionnaire **Additional pharmacovigilance activities:** – Study ALXN1210-PNH-301 (final study report date: Oct 2023) – Study ALXN1210-PNH-302 (final study report date: Dec 2022) – PNH registry (M07-001) – aHUS registry (M11-001) – Study ALXN1210-aHUS-311 (final study report date: Dec 2023)
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	**Additional pharmacovigilance activities:** – Study ALXN1210-PNH-301 (final study report date: Oct 2023) – Study ALXN1210-PNH-302 (final study report date: Dec 2022) – PNH registry (M07-001)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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	**Additional pharmacovigilance activities:** – aHUS registry (M11-001) – Study ALXN1210-aHUS-311 (final study report date: Dec 2023)
Immunogenicity	**Routine risk minimisation measures:** – SmPC sections 4.4 and 4.8 **Additional risk minimisation measures:** Educational materials – PNH/aHUS/gMG/NMOSD Physician's Guide – PNH/aHUS/gMG/NMOSD Patient's Information Brochure	**Additional pharmacovigilance activities:** – Study ALXN1210-PNH-301 (final study report date: Oct 2023) – Study ALXN1210-PNH-302 (final study report date: Dec 2022) – aHUS registry (M11-001) – Study ALXN1210-aHUS-311 (final study report date: Dec 2023)
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/gMG/NMOSD Physician's Guide – PNH/aHUS/gMG/NMOSD Patient's Information Brochure – PNH/aHUS Parent's Information Brochure	**Additional pharmacovigilance activities:** – Study ALXN1210-PNH-301 (final study report date: Oct 2023) – Study ALXN1210-PNH-302 (final study report date: Dec 2022) – PNH registry (M07-001) – aHUS registry (M11-001) – Study ALXN1210-aHUS-311 (final study report date: Dec 2023)
Malignancies and haematologic abnormalities in PNH patients	**Routine risk minimisation measures:** – None proposed **Additional risk minimisation measures:** Educational materials – PNH Physician's Guide – PNH Patient's Information Brochure	**Additional pharmacovigilance activities:** – Study ALXN1210-PNH-301 (final study report date: Oct 2023) – Study ALXN1210-PNH-302 (final study report date: Dec 2022) – PNH registry (M07-001)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
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/gMG/NMOSD Physician's Guide – PNH/aHUS/gMG/NMOSD Patient's Information Brochure	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** – Specific adverse reaction follow-up questionnaire **Additional pharmacovigilance activities:** – Study ALXN1210-PNH-301 (final study report date: Oct 2023) – Study ALXN1210-PNH-302 (final study report date: Dec 2022) – PNH registry (M07-001) – aHUS registry (M11-001) – Study ALXN1210-aHUS-311 (final study report date: Dec 2023)

Abbreviations: aHUS = atypical haemolytic uraemic syndrome; gMG = generalised myasthenia gravis, NMOSD = neuromyelitis optica spectrum disorder; PNH = paroxysmal nocturnal haemoglobinuria; PL = package leaflet; SmPC = summary of product characteristics.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 7.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

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.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

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

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

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The MAH is submitting a Marketing Authorisation Extension Application for the addition of a new strength (245 mg solution for injection) and route of administration (subcutaneous use) for Ultomiris (ravulizumab) for the treatment of adult patients with paroxysmal nocturnal haemoglobinuria (PNH) or atypical haemolytic uremic syndrome (aHUS).

The following indications have been agreed:

Ultomiris is indicated in the treatment of adult patients 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.*

Ultomiris is indicated in the treatment of adult patients with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.

The SC formulation is a drug-device combination product comprised of a prefilled cartridge (PFC) containing 245mg of ravulizumab co-packaged with a single-use on-body injector.

3.1.2. Available therapies and unmet medical need

The first treatment for PNH, eculizumab (Soliris), was approved in 2007 in the EU. Eculizumab is a selective, humanized mAb that specifically targets C5 of the terminal complement cascade, inhibiting its cleavage during complement activation into C5a and C5b. Prior to the introduction of eculizumab, the treatment of PNH was mainly supportive, aiming to control the clinical manifestations of the disease (management of haemolysis, anaemia, thrombophilia, and bone marrow failure). This supportive treatment included blood transfusion, administration of erythropoiesis-stimulating agents, corticosteroids, or anabolic steroids, iron therapy, thrombosis prophylaxis, and thrombolytic therapy.

Although the only available curative approach for PNH is allogeneic haematopoietic stem cell transplantation (HSCT), it is not recommended as upfront therapy in the eculizumab era given the risks of transplant-related morbidity and mortality. HSCT is a reasonable therapeutic option in patients who do not respond to therapy with eculizumab or those patients who have severe pancytopenia due

to underlying bone marrow failure. The transplant paradigm pursued is often with reduced-intensity conditioning regimens, as myeloablation is not required to eradicate the PNH clone.

When eculizumab was approved for aHUS in 2011, it was the first treatment approved for life-threatening complement-mediated TMA events. Prior to eculizumab, treatment of aHUS was limited to plasma therapy, and since its approval, patients with aHUS are probably no longer treated with long-term plasma therapy, which can transiently maintain normal levels of hematologic measures while the underlying complement dysregulation and thrombotic microangiopathic processes likely persist (Loirat, 2010).

Ravulizumab IV was approved in 2019 for PNH and in 2020 for aHUS, with a more convenient administration schedule. A subcutaneous administration (ravulizumab SC, 70 mg/mL) has been developed to provide an alternative route of administration for adult patients with PNH or aHUS, in which a chronic treatment is expected.

3.1.3. Main clinical studies

The main clinical study to support efficacy, safety and pharmacokinetics is the pivotal **ALXN1210-PNH-303 study**, a phase 3, randomized, parallel-group, multicenter, open-label, pharmacokinetic, non-inferiority study of ravulizumab sc versus iv in 129 adult patients with PNH currently treated with eculizumab.

This study was also designed to assess the performance of the ravulizumab on body delivery system (OBDS) drug/device product.

The study consists of an up to a 30-day screening period, a 10-week randomized treatment period, and an extension period of up to 172 weeks or until the product is registered or approved, whichever occurred first. Data provided are based on the randomised treatment period and the extension period up to 52 weeks.

Patients were stratified by weight group (≥40 kg to <60 kg and ≥60 kg to <100 kg) and then randomized in a 2:1 ratio to receive either ravulizumab SC or ravulizumab IV.

Additionally, two supportive Phase 1 PK and safety studies in healthy adult subjects (Studies ALXN1210-HV-105 (N=49) and ALXN1210-SC-101 (N=105)) fulfil the clinical program of Ultomiris sc.

3.2. Favourable effects

Primary endpoint

At the end of the Randomized Treatment Period (Day 71), the mean (percent coefficient of variation) Ctrough was 457.58 (23.7%) µg/mL in the IV group and 578.70 (24.3%) µg/mL in the SC group. The geometric least squares mean (LSM) ratio was 1.257 (90% CI: 1.160, 1.361) on Day 71.

Secondary endpoints

During the Randomized Treatment Period (through Day 71), efficacy endpoints remained stable in both the IV and SC groups.

- Mean percent change in LDH from Baseline to Day 71 was 2.57% for the SC group and 5.73% for the IV group.
- Breakthrough haemolysis (BTH) event incidence was low and similar between treatment groups (1 patient in each group).

A similar proportion of patients in each treatment group achieved transfusion avoidance (IV group: 86.7%; SC group: 94.0%) and stabilized haemoglobin (IV group: 81.8%; SC group: 93.6%).

Efficacy endpoints remained stable over time through 1 year of ravulizumab SC treatment in both the SC/SC group as well as the IV/SC group.

- LDH levels were maintained over time in both treatment groups. Mean percent change from Baseline to SC Day 351 in LDH was 0.9% (IV/SC group: -0.83%; SC/SC group: 1.7%).
- BTH events were infrequent: 5/128 (3.9%) (IV/SC group: 2 events; SC/SC group: 3 events). None were free complement component 5 (C5)-related.
- Transfusion avoidance was maintained in 83.6% of patients (IV/SC group: 79.5%; SC/SC group: 85.7%).
- Haemoglobin stabilization was achieved by 79.7% of patients (IV/SC group: 72.7%; SC/SC group: 83.5%).

3.3. Uncertainties and limitations about favourable effects

There are no critical limiting uncertainties regarding the efficacy results. The reported data seem to be consistent with the data from the IV formulation. As previously described, efficacy endpoints remained stable over time through 1 year of ravulizumab SC treatment in both the SC/SC group as well as the IV/SC group, what can be a prove that patients can switch from ravulizumab IV to ravulizumab SC without loss of efficacy.

3.4. Unfavourable effects

During the 10-week randomized treatment period:

- The percentage of patients who experienced AEs was 60% in the IV group and 79.8% in the SC group. When adverse device effects (ADEs) are excluded, the percentage of patients who experienced AEs was similar between the treatment groups (IV group: 60%; SC group: 64.3%).
- The most common AE was headache, which was reported by 8.9% of patients in the IV group and 13.1% of patients in the SC group.
- Serious adverse events (SAEs) were reported in 5 (6.0%) patients in the ravulizumab SC arm vs 1 (2.2%) in the ravulizumab IV. Unrelated SAEs of neutropenia, lens dislocation, gastroenteritis, cervicobrachial syndrome, and urinary retention were reported by 1 patient each in the SC group, and cholecystitis was reported by 1 patient in the IV group.

No patients had AEs leading to discontinuation of study treatment during the randomized treatment period.

During SC treatment as of data cut-off date:

- The most common AEs (reported by ≥ 10% of patients) were headache (14.1%), COVID-19 (14.1%), and pyrexia (10.9%).
- SAEs were reported for 27 (21.1%) patients, including 8 patients with COVID-19 related SAEs (1 fatal, assessed as unrelated to study drug). One patient had 2 serious ADEs of application site induration and procedural hypotension assessed as related to the study device. One patient withdrew from study treatment due to an AE of depression (not related to study treatment).
- No meningococcal infections or MAVEs were reported.

- Local administration site reactions were reported by 28 (21.9%) patients (2 patients had Grade 2 events, 1 patient had a Grade 3 event, and all other events were Grade 1).
    - The most frequently reported local administration site reactions (> 3% of patients) included injection site reaction (4.7%), medical device site erythema (3.9%), infusion site erythema (3.1%), and injection site erythema (3.1%).
    - The incidence of local administration site reactions decreased over time (0 to 6 months: 197.4 events per 100 patient-years (E/100PY), > 6 to 12 months: 13.2 E/100PY).

No deaths were reported related to the study drug.

All trends reported above, have been confirmed with the updated data from the 2 years data cut-off. No additional safety signals have been identified.

3.5. Uncertainties and limitations about unfavourable effects

The SC formulation is associated with a higher incidence of administration site adverse events and adverse device effects.

A flat dose is proposed for the administration of ravulizumab SC and according to the PK results of the ALXN1210 PNH 303 study, a higher exposure could be expected with ravulizumab SC compared with ravulizumab IV. Safety data according to weight showed a higher incidence of TESAEs and TEAEs of Grade 4 in the subgroup of patients with the lowest weight (i.e. ≥ 40 kg to < 60 kg). Further information on TESAEs and TEAEs of Grade 4 should be provided.

The ravulizumab SC formulation is administered by means of a device, a single-use on-body injector. For a full dose (i.e. 490 mg) 2 injectors/kits (or more) are required. This increases the complexity of the administration procedure albeit the generation of notable waste materials.

3.6. Effects Table

Table 45 Effects Table for ALXN1210-PNH-303 - phase 3, randomized, parallel-group, multicenter, open-label, pharmacokinetic, non-inferiority study of ravulizumab administered subcutaneously versus intravenously in adult patients with paroxysmal nocturnal haemoglobinuria currently treated with eculizumab (data cut-off 02 Feb 2021).

Effect	Short Description	Unit	Ravulizumab IV N= 45	Ravulizumab SC N= 84	Strength of evidence
Favourable Effects - randomized treatment period					
$C_{through}$	Day 71 serum ravulizumab Ctrough	µg/ml	457.58	578.70	Geometric least squares mean ratio: 1.257 (90%CI: 1.160, 1.361)
Percent change in LDH from Baseline to Day 71		Mean SD	5.73 29.716	2.57 33.883	Mean percent change from Baseline to SC Day 351 in LDH was 0.9% (IV/SC group: -0.83%; SC/SC group: 1.7%
Incidence of breakthrough haemolysis through Day 71		N (%) 95% CI	1 (2.2) 0.06, 11.77	1 (1.2) 0.03, 6.46	BTH events were infrequent through 1 year: 5/128 (3.9%) (IV/SC group: 2 events; SC/SC group: 3 events). None free complement component 5 (C5)-related.
Achievement of transfusion avoidance through Day 71		N (%) 95% CI	39 (86.7) 73.21, 94.95	79 (94.0) 86.65, 98.04	Transfusion avoidance was maintained through 1 year in 83.6% of patients (IV/SC group: 79.5%; SC/SC group: 85.7%).
Achievement of stabilized haemoglobin through Day 71		N (%) 95% CI	36 (81.8) 67.29, 91.81	73 (93.6) 85.67, 97.89	Hb stabilization through 1 year in 79.7% of patients (IV/SC group: 72.7%; SC/SC group: 83.5%).
Change in FACIT-Fatigue Subscale Score from Baseline to Day 71		Mean SD	-0.83 7.378	1.21 7.882	Change in FACIT through 1 year was 2.6 (7.18) for SC group

Effect	Short Description	Unit	Ravulizumab IV N= 45	Ravulizumab SC N= 84	Strength of evidence
Randomized Treatment Period: During the Randomized Treatment Period, following both treatments, all individual serum ravulizumab concentrations were >175 µg/mL, the previously established PK threshold for achieving and sustaining complete terminal complement inhibition. Immediate and complete inhibition of terminal complement free C5 (free C5 concentrations <0.5 µg/mL) was observed in all patients at all times during the Randomized Treatment Period for both treatment groups. **SC Treated Period:** A fixed weekly SC maintenance regimen achieved C_{trough} levels above the previously established free C5-based PK threshold (175 µg/mL) in all patients through 1 year of SC treatment. All individual serum free C5 concentrations obtained after first dose of ravulizumab SC in all patients were <0.5 µg/mL, the defined threshold for complete terminal complement inhibition through 1 year of SC treatment.					
Unfavourable Effects- randomized treatment period					
Any AE		N (%)	27 (60)	67 (79.8)	
Any SAE		N (%)	1 (2.2)	5 (6.0)	
Death		N (%)	0	0	
AE leading to discontinuation of study drug		N (%)	0	0	
AE Grade 4 AE Grade 5		N (%)	0 0	1 (1.2) 0	
SAE Related Not related		N (%)	 0 1 (2.2)	 0 5 (6.0)	
AESI Infusion reactions Other serious infections Meningococcal infections		N (%)	8 (17.8) 8 (17.8) 0 0	39 (46.4) 38 (45.2) 1 (1.2) 0	

Notes: Primary endpoint: PK analysis: Day 71 serum ravulizumab Ctrough (µg/mL)
The efficacy endpoints reported in the table above are secondary endpoints of the main study (ALXN1210-PNH-303).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Based on the results of study ALXN1210-PNH-303 non-inferiority of ravulizumab SC versus ravulizumab IV can be considered demonstrated in primary (PK) and secondary endpoints (efficacy)

and there is good concordance among the different efficacy endpoints. Of note, ravulizumab exposure appears to be higher when administered subcutaneously at the recommended flat dose compared with the IV administration.

Considering these results and the non-inferiority design ravulizumab SC offers an alternative option to patients with the added potential advantage of a more convenient and easier self-administration route as compared to the IV.

From a safety point of view, no major differences have been observed in the safety profile of ravulizumab SC compared to ravulizumab IV, apart from a higher incidence of adverse events related to the administration and drug device.

The MAH has applied for an indication in adults with PNH and aHUS, including both patients of newly diagnosis and patients previously treated with eculizumab. Data from the SC Phase 3 study in patients with PNH is intended to be used to extrapolate to the aHUS indication. Extrapolation of data to the aHUS indication and treatment naïve patients appears acceptable (see PK/PD section). However, since extrapolation is mainly based on data generated with ravulizumab IV and results of study ALXN1210-PNH-303, in which ravulizumab SC was compared with ravulizumab IV, the indication for the SC formulation was requested to be aligned with that of the IV formulation, since no further efficacy/safety data have been provided as part of this submission.

Further, since the PI of ravulizumab IV is being updated as part of this procedure to align it with the PI of the SC formulation, a minor change in the wording of the indication was proposed to more clearly reflect the patient population covered by the aHUS indication. Further, the cross-reference to section 5.1 has been deleted.

3.7.2. Balance of benefits and risks

Non-inferiority of ravulizumab SC to ravulizumab IV has been demonstrated in the current phase 3 trial in eculizumab pre-treated patients with PNH. The safety profile appears in line with the already known for ravulizumab IV although a higher incidence of AEs related to the administration were observed with the SC formulation, but overall mild and manageable. The SC formulation may offer an alternative route for patients.

It is considered that the favourable effects of ravulizumab SC outweigh the risks.

3.8. Conclusions

The overall benefit /risk balance of ravulizumab SC in the proposed indication is considered positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ultomiris is similar to Soliris within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Derogation(s) from market exclusivity

The CHMP by consensus is of the opinion that pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000 the following derogation laid down in Article 8.3 of the same Regulation apply:

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

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Ultomiris 245 mg, Solution for injection is favourable in the following indication(s):

Ultomiris is indicated in the treatment of adult patients 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.

Ultomiris is indicated in the treatment of adult patients with atypical haemolytic uremic syndrome (aHUS) who are complement inhibitor treatment-naïve or have received eculizumab for at least 3 months and have evidence of response to eculizumab.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Ultomiris subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

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 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, for intravenous formulation only) 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.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		**Type**	**Annexes affected**
X.02.V	Annex I_2.(e) Change or addition of a new route of administration	Line Extension	I, IIIA, IIIB and A
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A
X.02.IV	Annex I_2.(d) Change or addition of a new pharmaceutical form	Line Extension	I, IIIA, IIIB and A

Extension application to introduce a new pharmaceutical form (solution for injection) associated with new strength (245 mg) and route of administration (subcutaneous use), grouped with a type II variation (C.I.4) to align the Summary of product characteristics and Labelling of Ultomiris intravenous formulation (IV) with the proposed Ultomiris subcutaneous formulation (SC).
The RMP (version 7.0) is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.3.