26 April 2019
EMA/CHMP/220699/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ultomiris

International non-proprietary name: ravulizumab

Procedure No. EMEA/H/C/004954/0000

Note

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

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Administrative information

Name of the medicinal product:	Ultomiris
Applicant:	Alexion Europe SAS 1-15 avenue Edouard Belin 92500 Rueil Malmaison FRANCE
Active substance:	RAVULIZUMAB
International Non-proprietary Name/Common Name:	ravulizumab
Pharmaco-therapeutic group (ATC Code):	immunosuppressants, selective immunosuppressants (L04AA43)
Therapeutic 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 (see section 5.1).
Pharmaceutical form(s):	Concentrate for solution for infusion
Strength(s):	300 mg
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

Abbreviation or Specialist Term	Explanation
ADA	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
aHUS	atypical haemolytic uremic syndrome
BLA	biologics license application
BTH	breakthrough haemolysis
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	Clearance
CPMP	Committee for Proprietary Medicinal Products
cRBC	chicken red blood cell
CSR	clinical study report
C5	complement component 5
ECL	electrochemiluminescence
EMA	European Medicines Agency
EOI	end of infusion
EORTC	European Organisation for the Research and Treatment of Cancer
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FcRn	Fc receptor
FDA	Food and Drug Administration
IV	intravenous(ly)
LDH	lactate dehydrogenase
LDH-N	normalization of lactate dehydrogenase levels
mAb	monoclonal antibody
NAb	neutralizing antidrug antibody
NIM	noninferiority margin
PD	pharmacodynamics
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PNH	paroxysmal nocturnal haemoglobinuria
Pop-PK	population-pharmacokinetics
q2w	once every 2 weeks
q8w	once every 8 weeks
q12w	once every 12 weeks
SAE	serious adverse event
TA	transfusion avoidance
TEAE	treatment-emergent adverse event
t_{max}	time to maximum observed serum concentration
ULN	upper limit of normal
Vc	central volume of distribution (compartmental model)
Vp	volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Alexion Europe SAS submitted on 27 June 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Ultomiris, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 December 2017.

Ultomiris was designated as an orphan medicinal product EU/3/16/1661 on 30 May 2016 in the following condition: Treatment of paroxysmal nocturnal haemoglobinuria.

The applicant applied for the following indication: treatment of adult patients with paroxysmal nocturnal haemoglobinuria.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0356/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0356/2017 was completed.

The PDCO issued an opinion on compliance for the PIP: EMA-C1-002077-PIP01-16-M01 and EMA-C2-002077-PIP01-16-M01

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Derogation(s) from market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant submitted a claim addressing the following derogation laid down in Article 8.3 of the Regulation (EC) No. 141/2000; the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the applicant.

New active Substance status

The applicant requested the active substance ravulizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Following the CHMP positive opinion on this marketing authorisation and at the time of the review of the orphan designation by the Committee for Orphan Medicinal Products (COMP), this product was withdrawn from the Community Register of designated orphan medicinal products on 11 June 2019 on request of the sponsor. The relevant orphan designation withdrawal assessment report can be found under the 'Assessment history' tab on the Agency's website ema.europa.eu/en/medicines/human/EPAR/ultomiris.

Protocol Assistance

The applicant received Protocol Assistance on 23 June 2016 (EMEA/H/SA/3331/1/2016/III), and 26 January 2017 (EMEA/H/SA/3331/1/FU/1/2016/PA/II) for the development programme supporting the indication for the IV formulation granted by the CHMP. The Protocol Assistance pertained to the following quality, non-clinical, and clinical aspects:

- The comparability strategy for the implementation of new drug substance manufacturing sites. The specification strategy. The process validation package for drug substance and drug product. The stability strategy for the drug substance and drug product.
- The completeness of the nonclinical development program.
- Appropriateness of the clinical pharmacology plan.
- The proposed single pivotal Phase 3, open-label, 26-week, randomized, active-controlled, multicentre study to evaluate the safety and efficacy of ALXN1210 versus eculizumab administered by IV infusion to 140 adult patients with PNH who are naïve to eculizumab treatment. The use of modelling and simulations to inform phase 3 dose selection. The co-primary efficacy endpoint of (i) Proportion of patients who do not require a transfusion through Week 26, and (ii) Haemolysis as directly measured by percent change from baseline in LDH levels at Week 26. The proposed inclusion and exclusion criteria. The sample size based on a non-inferiority design comparing patients treated with eculizumab to those treated with ALXN1210. The justification for an open-label design. Acceptability of a 26-week treatment duration. The size of safety database.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jorge Camarero Jiménez Co-Rapporteur: Agnes Gyurasics

The application was received by the EMA on	27 June 2018
The procedure started on	19 July 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	17 October 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	9 October 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	22 October 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 November 2018
The applicant submitted the responses to the CHMP consolidated List of	02 January 2019

Questions on	
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	12 February 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 February 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	28 February 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 March 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 April 2019
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	26 April 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

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.

PNH can occur at any age, although it is diagnosed most often during young adulthood, with diagnosis typically occurring in the 30s or 40s.

2.1.2. Epidemiology and risk factors, screening tools / prevention

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.

2.1.3. Biologic features

Paroxysmal nocturnal haemoglobinuria 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, 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 and chronic intravascular haemolysis.

2.1.4. Clinical presentation and diagnosis

PNH can present with multi-systemic manifestations related to chronic intravascular haemolysis, impaired bone marrow function, and thrombosis. The common clinical manifestations of PNH are haemolytic anaemia, venous thrombosis and deficient haematopoiesis. Excessive levels of cell-free plasma haemoglobin during intravascular haemolysis contribute to platelet activation, procoagulant activity and thromboembolism, the leading cause of mortality in these patients. Chronic severe anemia also frequently develops. Red blood counts are normochromic and normocytic unless iron deficiency has occurred from chronic iron loss in the urine. 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.

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.

The only available curative approach for PNH is allogeneic haematopoietic stem cell transplantation (HSCT). However, allogeneic HSCT is associated with high mortality and morbidity.

About the product

Ravulizumab is a monoclonal antibody 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.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a concentrate for solution for infusion containing 300 mg of ravulizumab as active substance.

Other ingredients are: sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, sodium chloride, polysorbate 80 and water for injections.

The product is available in a vial (Type I glass) with a stopper and a seal.

2.2.2. Active Substance

General Information

The active substance (INN: ravulizumab) is a recombinant humanized IgG2/4 monoclonal antibody consisting of two identical heavy chains and two identical light chains (human kappa) linked by disulfide bonds. Ravulizumab binds to complement component 5 (C5) and blocks its activation by complement pathway convertases, thereby preventing the release of the proinflammatory anaphylatoxin C5a and the formation of the terminal complement complex via C5b.

Ravulizumab was constructed by introducing four unique mutations into the heavy chain of eculizumab. Taken together these mutations are predicted to significantly increase the dissociation of ravulizumab:C5 complexes to free ravulizumab in the acidified environment of the early endosome after pinocytosis and to increase the fraction of free ravulizumab recycled from the early endosome back into the vascular compartment by FcRn. Thus, the antibody half-life is increased, allowing administration (in the maintenance phase) once every 8 weeks, compared to every 2 weeks for eculizumab.

Manufacture, process controls and characterisation

Description of the manufacturing process and process controls

Ravulizumab active substance is produced at two manufacturing sites: FUJIFILM Diosynth Biotechnologies U.S.A., Inc. (FDBU) and Patheon Biologics LLC (Patheon).

During the procedure a major objection was raised in relation to several GMP issues (missing/outdated documentation and lack of EU batch release site). Updated GMP certificates for the sites involved in the manufacturing process were requested. In response, the applicant provided updated GMP certificates or evidence of positive GMP status issued by US FDA for the sites in question. In addition, new sites were introduced to fulfil the requirement for batch control testing to be conducted in the EU.

Ravulizumab is manufactured in Chinese hamster ovary (CHO) cells at the bioreactor scale. The production starts with a single vial of the Working Cell Bank (WCB) and cultures are progressively expanded using growth medium through a series of cell culture steps. The cell culture and harvesting process comprises of three discrete steps (inoculum expansion, cell culture in production bioreactor, and primary recovery). Upon completion of the cell culture, cells and cell debris are removed. The clarified harvest is filtered prior to purification. There are some differences in the batch definition in the two manufacturing sites although the batch size is the same in the two manufacturing sites.

The purification process is designed to purify ravulizumab by removal of process and product related impurities from the clarified harvest using orthogonal purification steps, followed by concentration and formulation into bulk drug substance (BDS). It includes a series of chromatography steps and virus inactivation and removal steps.

Flow diagrams and Tables showing the manufacturing steps and the critical (CPP) and key process parameters (KPP), in process controls (IPC) and key process attributes (KPA) for each manufacturing step in the two facilities are provided in the dossier. A KPP is defined as a process parameter that should be controlled within a defined range and is essential for process performance. A KPP affects KPAs but does not affect product quality attributes. A non-key process parameter (NKPP) is a process parameter that has been demonstrated to be well controlled or has a wide acceptance limit.

Processes at FDBU and Patheon are not identical, but differ as follows:

- Inoculum step differences.
- The CPP, KPP, IPC and KPA established and their acceptance criteria are not always the same at the two sites.
- Differences in the timing and acceptance limits of the bioburden and endotoxin controls.
- Differences in hold times.
- Chromatography step differences.

The applicant was requested to justify if the differences in the parameters and acceptance criteria that have been established in the two manufacturing sites are equally effective in the control of the manufacturing processes. The applicant was also requested to explain if the differences in acceptance limits for bioburden and endotoxin are not compromising the control of these two parameters in the two manufacturing sites. The applicant clarified that the differences between Patheon and FDBU are due to facility specific risk assessments and alignment with site policies/definitions. Further justifications were provided by the applicant in relation to the bioburden and endotoxin control and these were found acceptable.

It was also demonstrated in comparability studies that the production of ravulizumab is equally effective at both sites.

Control of Materials

The applicant has described all the raw materials used in the manufacture of ravulizumab, the quality of each component and the supplier quality management system. Critical raw materials have been identified and the specification of those raw materials has been provided. No biological sourced materials are used in the manufacturing process other than the CHO cell line, and one media component. The applicant has performed a risk assessment in relation to the media component concluding that the viral safety is assured. This is endorsed.

The applicant has thoroughly described the development genetics, the gene construct and the rationale for the gene construct. A two tiered cell banking system has been established with a master cell bank

(MCB) and a working cell bank. Extensive characterisation of the MCB, WCB and cells at the limit of *in vitro* cell age (LIVCA) has been performed in compliance with ICH Q5A and ICH Q5D. Clonality and genetic stability of the production cell line is demonstrated by several methods. All tests were performed according to current guidelines, and all the results obtained ensure that both cell banks meet all required specifications.

The applicant has presented their strategy for a continuous supply of the bank cells including a protocol for introducing new working cell banks, and has confirmed that the master cell bank is stored at two remote sites to ensure continuous and interrupted production of biopharmaceuticals

Process validation

Manufacturing process validation studies performed at FDBU and at Patheon are provided. For validation of the FDBU process, the studies were performed on an adequate number of active substance batches. The process validation studies for Patheon process were also performed on an adequate number of active substance batches. For validation studies, samples were taken to monitor the critical process parameters (CPP), key process parameters (KPP) and key process attributes (KPA). KPAs were monitored to demonstrate consistency of the process. Bioburden and endotoxin samples were taken to demonstrate microbial control of the process.

All the steps of cell culture, harvest and purification have been validated. The results showed that all the steps perform in a consistent, controlled, and reproducible manner.

Reprocessing is proposed for two filtration steps. Validations of these reprocessing steps have been performed. The studies performed showed that, in both cases, there is no impact in process performance or product quality after refiltration.

Studies were performed at FDBU and at Patheon to determine the ability of selected steps in the manufacturing processes to remove process related impurities. The data from these studies showed the reduction in impurities throughout the active substance manufacturing process. Based on the results, the applicant proposes the discontinuation of in-process testing for some impurities as well as discontinuation of release testing for some others. This proposal is found acceptable.

Studies were performed to determine the ability of selected steps in the ravulizumab manufacturing processes to remove product related impurities. This was done by measuring levels of selected impurities in samples collected from the process intermediate steps. The studies were performed on three at-scale batches at FDBU and three at Patheon. The results showed that the product related impurities are consistent and at low levels. They will be monitored at active substance release.

Resin re-use studies support the proposed resin re-use limits.

A membrane re-use protocol is provided in the dossier to determine the final re-use limit.

The steps in the manufacturing process where process hold times occur were validated at scale. The results showed that these process intermediate pools can be held out to the maximum times indicated without adversely impacting the biochemical/biophysical stability or microbiological integrity of the pools. The applicant commits to provide at scale biochemical stability data post-approval.

A shipping validation study was performed that confirm the ability of the shipping containers to maintain the correct temperature during shipment of the active substance.

Manufacturing process development

The initial manufacturing process (Process A) was optimized and scaled up to prepare for advanced clinical development and demand (Process B). In anticipation of commercialization, the manufacturing

process was transferred and scaled up and validated as the commercial process. Additional changes to the process were made to improve impurity clearance.

Studies supporting the changes made to Process B manufacturing process throughout clinical manufacturing process were performed and are presented in the dossier.

A quality target profile for ravulizumab has been developed defining the characteristics of a product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the finished product. Certain attributes such as those for composition, strength, appearance and adventitious agents were designated as mandatory CQA due to their high criticality to product efficacy, safety or regulatory considerations. For all other attributes, a risk assessment in accordance with ICH Q9 Quality Risk Management was completed to classify the attributes of ravulizumab in relation to the potential to affect biological activity, PK, immunogenicity and safety. A composite risk score was calculated by multiplying the highest impact score to the attribute by the uncertainty score. Those which have been found to have an impact have been designated as CQA.

A process control strategy for the active substance has been developed to ensure the robust manufacture and ensure consistent product quality.

The risk assessment output supported determination of whether multivariate or univariate Design of Experiment (DOE) studies were required, or if no study was required. From these studies, an impact ratio (threshold value for parameter classification) was calculated.

The impact ratio provides a measure of the amount of risk associated with a process parameter, exceeding a set threshold for which increases the likelihood of the product not meeting pre-established acceptable limits of process performance attributes and CQAs.

The applicant indicates that upon transfer to each manufacturing site, the parameter classification was reevaluated and in some cases refined based on facility specific risk assessments (e.g. FMEA, criticality assessment) and to align with site policy/definitions.

Process characterisation studies of all the manufacturing steps at small scale are presented in the dossier.

A comprehensive comparability evaluation has been completed to demonstrate that active substance batches manufactured at all sites and scales throughout development are comparable to the active substance manufactured by the validated processes. Due to limited inventory of the clinical active substance at the time of the study, in some cases, corresponding finished product material was used. Since the finished product is filled into glass vials with no further formulation, there is no expected impact on the comparability evaluation. This evaluation included an extensive battery of comprehensive and orthogonal tests that encompass product release and characterisation tests including head-to-head testing wherever appropriate of clinical batches compared to three batches manufactured by the validated manufacturing processes.

Comparability also included forced degradation studies confirming that the rate and severity of degradation of the material was comparable. The comparability evaluation concluded that the clinical active substance is comparable to the material produced by the validated commercial manufacturing processes.

Characterisation

Physicochemical properties and biological properties of ravulizumab were characterised with a series of orthogonal techniques using the reference standard.

The expected amino acid sequence has been confirmed and the molecular mass analysis results are in conformity to the theoretically calculated figures. The charge profile was analysed. As the hinge region of ravulizumab is consistent with the IgG2 isotype, the disulphide bond isoforms have been analysed and a

profile resembling known IgG2 monoclonal antibodies has been recorded. The far and near UV circular dichroism spectra are similar to those of other IgG2 monoclonal antibodies. Thermal transitions were examined by differential scanning calorimetry at pH 7.0 (formulation buffer).

The consensus glycolysation site was identified and glycans have been thoroughly analysed. The predominant oligosaccharide is a fucosylated biantennary structure without terminal galactose. The extent of sialylation was found to be very low and no N-glycolyl neuraminic acid was detected.

Regarding biological activity, the pH-dependent binding kinetics of ravulizumab to C5 have been explored, and the inhibition of human complement haemolytic activity by the active substance has been demonstrated. Kinetics of FcRn binding of ravulizumab at pH 6.0 was examined, and binding was confirmed by an orthogonal method.

The impurities of ravulizumab active substance have been sufficiently characterised. Impurities were classified as process-related impurities and product-related impurities (charge variants and aggregates). Based on available data, the applicant concluded that routine testing for any of the process additives was not necessary.

Concerning product related impurities, the aggregate fraction was found to consist of dimers. Charge variants were analysed. Isolated fractions were examined.

Overall, the description of ravulizumab characterisation is adequate.

Specification

The release and stability specification for the active substance includes tests for appearance, osmolality, pH, protein concentration, identity, purity/impurities, potency, bioburden and endotoxin.

Specifications were based in historical batch data and in the analysis of the release data using a mean evaluation for the prediction of commercial specifications. However with this adjustment some specifications are broader that expected from the data obtained in batch release of batches used for clinical studies. The applicant agreed during the procedure to tighten some of the limits and for others the applicant made a commitment to review the limit once further commercial scale batches have been manufactured.

Analytical methods

In general, the analytical procedure descriptions are appropriate and the methods are adecuately validated or qualified.

Batch analysis

An analysis of the consistency of release and characterisation data generated for active substance batches manufactured during clinical development through process validation indicates that the process performance qualification batches are consistent to historical ravulizumab batches.

Reference Standards

During the development three ravulizumab reference standards have been generated, interim reference standard 1 and 2 and the current reference standard. Release testing and extended characterisation has been performed for all the reference standards. The initial reference standard was qualified using batch release testing and characterisation data. Bridging studies have been performed for the qualification of subsequent reference standards, including batch release testing and extended characterisation

The applicant has submitted the qualification and stability protocol for future reference standards.

During the procedure a major objection was raised regarding the storage of the reference standard at 2-8ºC and the lack of assurance that the potency of the reference standard is maintained under these

storage conditions. In response, the applicant provided further evidence of the stability of the reference standard. In addition, the acceptance criteria of the re-qualification protocol were tightened and the shelf-life of the current reference standard was shortened. The applicant also committed to implement a 2-tier reference standard program to include frozen storage of a primary reference standard to minimize loss of potency.

Stability

The stability studies proposed and performed on the active substance for the control of changes in identity, purity and potency are considered in general appropriate. Pre-clinical, engineering and clinical batches produced by different manufacturing processes (A and B), different manufacturers and produced at different scales have been placed on stability studies under long-term and accelerated conditions.

A 50 ml scaled-down version of the active substance bioprocess container is used in the stability studies, using the same product contact material.

Real time data for several batches have been provided. Data from studies under accelerated conditions has been provided.

Stability studies under stress conditions (agitation, temperature, oxidation, deamidation, acid and base hydrolysis as well as freeze-thaw cycling and glycation) have been also performed, while photostability of ravulizumab was evaluated using finished product material.

The proposed active substance shelf-life, protected from light, is supported by real time data and considered acceptable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is supplied as a sterile aqueous solution for intravenous administration containing ravulizumab at a concentration of 10 mg/ml in sodium phosphate, sodium chloride and polysorbate 80 in a stoppered 30 ml glass vial. The finished product is intended to be diluted with commercially available normal saline (0.9% sodium chloride) followed by administration by intravenous infusion.

The quantitative and qualitative composition of the finished product is presented in Table 2.

Table 1 Finished product composition

Component (Formulation Concentration)	Quality Standard	Function
ravulizumab (10 mg/mL)	In-house	Active ingredient
Sodium dihydrogen phosphate dihydrate	USP, Ph. Eur.	pH buffer
Disodium phosphate dihydrate	USP, Ph. Eur.	pH buffer
Sodium chloride	USP, Ph. Eur., JP	Tonicity modifier
Polysorbate 80	NF, Ph. Eur., JP	Surfactant
Water for injections	USP, Ph. Eur., JP	Solvent

The formulation of the finished product is the same formulation used for the active substance, and has remained unchanged during clinical development. The formulation components were selected based on

the widespread use in monoclonal antibody products intended for administration by intravenous (IV) infusion and are supported by long-term and accelerated stability data.

All excipients are compendial grade and comply with the corresponding Ph. Eur. monographs:

- sodium phosphate buffer system to maintain the pH of the DP solution at 7.0.
- sodium chloride to make the solution isotonic with the physiology of the bloodstream.
- polysorbate 80 is added as surfactant to enhance the stability of ravulizumab, preventing protein aggregation.

The finished product composition has no overages. Vials are filled with a 1.75 ml overfill to ensure an adequate extractable volume.

The finished product is manufactured by filtration of the active substance, followed by filling into a prepared sterile depyrogenated container closure system, and then sealing the filled and stoppered vials. All manufacturing steps are performed using aseptic techniques in qualified facilities, appropriately monitored, with qualified equipment.

The finished product manufacturing process has been developed along three manufacturing facilities with minor changes. The most relevant modification, taking place at the last facility transfer, consisted of a change in vial size and fill volume, keeping all other characteristics unaltered. An exhaustive comparability and manufacturing equivalency assessment has been performed, demonstrating the consistency of the process to produce a finished product with the required quality.

The primary container closure system consists of a 30 mL USP/Ph. Eur. Type I glass vial with a 20 mm stopper, and aluminium seal with a flip-off cap. The vial and stopper are compliant with all applicable requirements defined by the current Ph. Eur. 3.2.1. The selection of the primary container closure components was made on the basis of results of various physical, chemical, and functional testing of the components. The suitability of the primary packaging materials is properly demonstrated.

A summary of the risk assessment for elemental impurities in accordance with ICH Q3D has been provided and supports negligible risk health hazard for elemental impurities.

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.

Manufacture of the product and process controls

The finished product manufacturing is a standard process that begins with pooling of the active substance through a bioburden reduction filter into the compounding vessel. Once the pooling process is complete, the active substance is sterile filtered and aseptically filled into sterile, depyrogenated vials using an automated filling machine.

The finished product is processed continuously from active substance pooling and mixing through to aseptic filling and storage without any process intermediates. Parameters and in-process controls have been defined for every individual process step, including equipment and component preparation, pooling and stirring, sterile filtration, aseptic filling and capping.

A finished product batch size range has been validated, allowing the use of one or two active substance batches per finished product batch. Validation of the manufacturing process has been successfully performed, in accordance with FDA and EMA guidelines, demonstrating the suitability and robustness of the process to produce ravulizumab finished product consistently meeting critical quality attribute requirements that reflect product quality. The validation program includes sterilisation and depyrogenation of equipment and components (vial washer, autoclaves, depyrogenation tunnel, sterile

filtration and filling manifolds), sterility assurance validation, process qualification using 4 batches (assessing all process parameters, in-process controls and release tests on the finished product), and specific validation studies for filters (bubble point, rinsing, filter membrane compatibility, microbial retention, and extractable substances), finished product mixing, hold times and finished product shipment. The allowable time out of refrigeration during finished product manufacturing was determined. Requalification strategies have been properly described.

All excipients comply with current monographs and are supplied with the corresponding certificate of analysis. No excipients of human or animal origin, or novel excipients, are used in the ravulizumab finished product manufacturing process.

Product specification

The release and stability specification for the finished product includes tests for appearance, osmolality, pH, protein concentration, identity, purity/impurities, potency, endotoxin, sterility, container closure integrity, particulates and extractable volume.

The proposed specifications for the finished product were developed by evaluation of the historical data from all clinical finished product batches, including process validation batches, using a mean evaluation. During the procedure, the applicant was asked to justify the specification for visible particles and to narrow the acceptance criteria of several parameters that are considered too wide. The applicant stated that only product free of particles pass the examination and that any deviation from this will be reported in line with Ph. Eur. 2031 requirement. In addition, the applicant agreed to tighten the acceptance criteria for some of the specification parameters. The applicant also commits to re-evaluate the finished product specification after data from a statistically significant number of batches manufactured by the validated process are available and to tighten the acceptance criteria if appropriate.

Analytical methods

The analytical methods used specifically for the finished product comply with current Pharmacopeia and have been appropriately validated for their intended use, in accordance with the referenced Ph. Eur. monographs.

Batch analysis

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

Reference materials

The reference standard information for the finished product is the same as described for active substance.

Stability of the product

The stability studies performed on the finished product were carried out in accordance with ICH Q5C. Finished product batches produced at different manufacturing sites and with different fill volumes have been placed on stability studies under long-term (2 – 8ºC) and accelerated (23 - 27ºC) conditions.

Long term and accelerated stability data has been provided.

A photostability study demonstrated that the finished product is photosensitive in its primary container, but that the secondary packaging appropriately protects it from light.

An in-use compatibility exercise was performed to evaluate compatibility of the finished product with commonly used IV containers and IV sets, as well as the impact on transportation of the diluted finished product in the IV container. Results from these studies confirm the chemical and physical stability of the

diluted product of up to 6 hours at ambient (23-27°C) temperature, or refrigerated (2-8°C) up to 24 hours.

The applicant was requested to provide additional data to support the 30 months shelf-life proposed initially. The applicant updated the stability data and established a shelf-life of 24 months.

The proposed shelf-life of 24 months at 2 – 8ºC is supported by real time data generated with the intended commercial presentation (300 mg/30 ml) and is considered acceptable.

Post approval change management protocol(s)

The following post approval change management protocols (PAMCPs) are included in the dossier:

- Addition of a new active substance testing site.
- Extension of Shelf-Life.

The PACMPs include a description of changes, a risk assessment of the change impact on the product quality, the specific tests and studies to be performed, the control strategy, the process validation, the supportive data, the conditions to be fulfilled prior to implementation of the change and the data to be reported under the protocol.

Adventitious agents

The assessment of viral adventitious agents is in line with current EU guidelines. From the validation study of virus removal, three steps are considered to be effective – low pH virus inactivation, anion exchange chromatography II and virus filtration. The results and summaries of each virus removal validation step are presented and the provided information is considered adequate. The applicant also provided a summary compiling the global effect of all steps in the removal/inactivation of viruses.

A production medium used may be of synthetic or biologic origin depending on the supplier. A risk assessment has been completed which concludes no risk to product quality or viral safety. The applicant confirmed compliance with the “Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" (EMA/410/01 rev. 3).

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Two major objections were raised during the procedure, one concerning the maintenance of the potency of the reference standard at the storage temperature of 2-8ºC and the second concerning GMP issues.

With regard to the reference standard the applicant provided further evidence of the stability of the reference standard. In addition, the acceptance criteria of the re-qualification protocol were tightened and the shelf-life of the current reference standard was limited to 2 years. The applicant also committed to implement a 2-tier reference standard program to include frozen storage of a primary reference standard to minimize loss of potency.

In response to the major objection on GMP issues, the applicant provided updated GMP certificates or evidence of positive GMP status issued by US FDA for the sites in question. In addition, new sites were introduced to fulfil the requirement for batch control testing to be conducted in the EU.

2.2.5. 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. Data have been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended several points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant has designed and conducted non-clinical studies to prove the mechanism of action and compare the properties of ALXN1210 with those of eculizumab as well as to characterize whether any off-target binding and action can be revealed for ALXN1210.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The Applicant has conducted three primary pharmacodynamic studies in order to characterize the pharmacodynamic properties of ALXN1210.

Epitope mapping to assess cross-reactivity to C5 from other species – Study RTR-0006v1.0

Epitope mapping studies conducted with ALXN1210 confirmed the binding site of ALXN1210 on human C5 and identified 4 critical residues. Subsequent in vitro binding studies and haemolytic activity assays showed that ALXN1210 did not display any detectable specific binding to the recombinant C5 variant, nor did ALXN1210 block in vitro haemolysis in reactions containing the variant. In addition, ALXN1210 showed no pharmacologic activity on haemolysis in serum from any non-human species tested (10 NHP and 13 non primate mammals).

ALXN1210 differs from eculizumab at 4 amino acid substitutions in the heavy chain.

Effects of pH on ALXN1210 binding to C5 and FcRn – Study RTR-0003v1.0

In vitro binding studies of ALXN1210 to human C5 and FcRn compared to eculizumab showed that ALXN1210 maintains a high affinity binding to C5 at pH7.4 that is sufficient to deliver complete terminal complement inhibition equivalent to eculizumab, whereas in an acidified environment amino acid substitutions significantly attenuate antigen-mediated clearance by increasing dissociation of antibody:C5 complexes. Therefore, it is expected that in the acidified environment of the early endosome after pinocytosis (pH~6.0) K_D of ALXN1210 would increase compared to eculizumab, but maintaining a high affinity binding affinity to C5 in the vascular compartment (pH 7.4) and increasing the fraction of antibody recycled from the early endosome back into the vascular compartment by FcRn. Neither ALXN1210 nor eculizumab showed any detectable specific binding to FcRn at pH 7.4.
The two amino acid substitutions in the first and second complementarity determining regions (CDRs) of the heavy chain variable region, weaken the affinity dissociation constant (KD) of ALXN1210 for C5 by ~ 17-fold at pH 7.4 and ~ 36-fold at pH 6.0 compared with eculizumab.

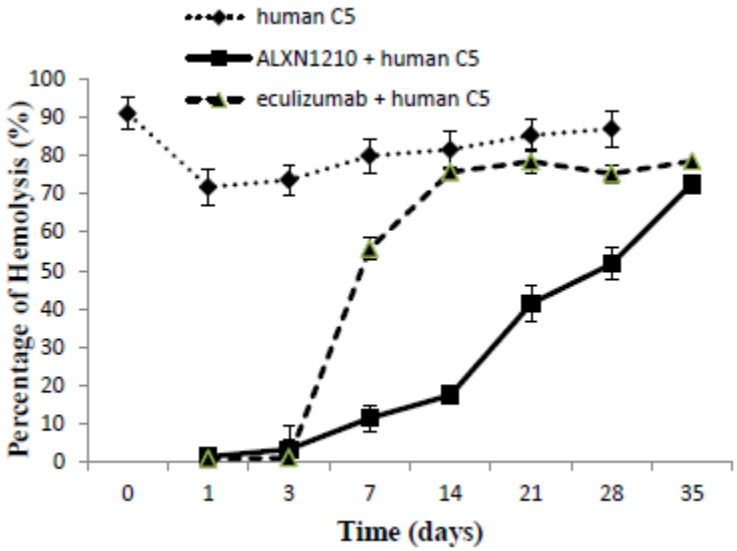
The two mutations in the third heavy chain constant region domain (CH3), strengthen the affinity of ALXN1210 for FcRn by ~ 10-fold at pH 6.0 compared to eculizumab.

Taken together these changes in binding to both C5 and FcRn are predicted to significantly attenuate TMDD by increasing dissociation of antibody:C5 complexes to free antibody in the acidified environment of the early endosome after pinocytosis, and to increase the fraction of antibody recycled from the early endosome back into the vascular compartment by FcRn.

Comparison of PK/PD of ALXN1210 and eculizumab in an *in vivo* NOD-scid mice model – Study RTR-0008v1.0

The findings from this study suggest that in the presence of human C5, ALXN1210 showed more than three-fold extension in half-life compared with eculizumab. In addition, the serum half-life of ALXN1210 relative to eculizumab resulted in increased PD, as evidenced by prolonged haemolytic inhibition. The difference in PK/PD profile of ALXN1210 and eculizumab was attributed to attenuation of antigen-mediated clearance through the mutations in the heavy chain CDRs of ALXN1210.

Figure 1: Percentage of Haemolytic Activity in the Presence and Absence of ALXN1210 and Eculizumab in the NOD-scid Mice



Haemolysis inhibition was complete for both eculizumab and ALXN1210 for 3 days. The haemolysis inhibitory effect of eculizumab declined rapidly after 3 days and completely disappeared by day 14 while ALXN1210 still retained 83% of haemolysis inhibitory effect on day 14 and showed reasonable effectiveness through 28 days. These data prove that the mutations in the heavy chain CDRs of ALXN1210 attenuated the antigen-mediated clearance thus provided significantly longer effectiveness on the haemolysis inhibition.

Secondary pharmacodynamic studies

Assessment Fc effector functions of ALXN1210 in vitro – study RTR 0005v1.0

The studies described examine the binding of three humanized antibodies, ALXN1210, eculizumab and h5G1.1-IgG1 to molecules known to be mediators of antibody effector function. ALXN1210, eculizumab and h5G1.1-IgG1 are closely related antibodies. All three are humanized antibody antagonists of terminal complement binding the same epitope on human complement component C5 and preventing its cleavage during complement activation into its active metabolites, C5a and C5b.

Binding experiments using ELISA, SPR and biolayer interferometry all indicate that the amino acid substitutions introduced into ALXN1210 do not appear to alter its binding affinity for FcγRI, FcγRIIb/c, FcγRIIIa, FcγRIIIb or C1q, relative to eculizumab. The ~ 2 fold increase in signal for ALXN1210 over eculizumab in an ELISA designed to measure mulivalent binding to FcγRIIa is not corroborated by increases in affinity under monovalent conditions. Given the weaker affinities overall for monovalent FcγRs, diminished signal relative to the IgG1 isotype observed under multivalent conditions and lack of detectable binding to C1q, combined with the soluble nature of the antigen itself, it is highly unlikely to be capable of initiating ADCC or CDC through these effector molecules.

Table 2: Summary of interactions between ALXN1210, Eculizumab, h5G1.1-IgG1 and FcγRs or C1q

	FcγRI (K_D)	FcγRIIa (K_D)	FcγRIIb/c (K_D)	FcγRIIIa (K_D)	FcγRIIIb (K_D)	C1q (K_D)
ALXN1210						
ELISA	-	++	-	-	-	
SPR Steady state kinetics	3.75 µM	2.31 µM	8.09 µM	7.23 µM	3.33 µM	
Biolayer Interferometry						-
Eculizumab						
ELISA	-	++	-	-	-	
SPR Steady state kinetics	3.78 µM	2.58 µM	9.84 µM	6.78 µM	3.49 µM	
Biolayer Interferometry						-
h5G1.1-IgG1						
ELISA	++	+++	++	-	+	
SPR Steady state kinetics / single cycle kinetics	0.123 µM	0.80 µM	3.06 µM	0.85 µM	1.89 µM	
Biolayer Interferometry						+++

Tissue cross-reactivity studies 20039106 and 20039107 (GLP)

A Tissue Cross-Reactivity Study of Fluoresceinated ALXN1210 in Normal Human Tissues – study 20039106;

A Tissue Cross-Reactivity Study of Fluoresceinated ALXN1210 in Normal Non-Human Primate (Cynomolgus Monkey) Tissues – study 20039107

The objective *of these studies* was to determine the potential cross-reactivity of fluoresceinated ALXN1210, a monoclonal antibody directed against human C5, with cryosections of *human and non-human primate (cynomolgus monkey)* tissues. In order to detect binding, the fluoresceinated test article, designated ALXN1210-FITC, was applied to cryosections of *normal human tissues (3 donors per tissue) or cynomolgus monkey tissues (2 donors per tissue)* at two concentrations (20 and 2 µg/mL). In addition, the test article was substituted with a monoclonal antibody which has a different antigenic specificity from that of the test article (control article), designated OX-90G2G4-FITC. Other controls were produced by omission of the test or control articles from the assay (assay control).

Tissue staining in cynomolgus monkey tissues was almost undetectable while in human tissues only C5 secreting cells showed some positivity. Any sign of staining in human tissues that do not secrete C5 or non-human tissues might have been an artefact or some cross-reactivity with Fc rec

Safety pharmacology programme

In vitro safety pharmacology studies have not been performed (see discussion on non-clinical aspects).

Pharmacodynamic drug interactions

No PD drug interaction studies have been performed (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

Limited nonclinical PK evaluation of ALXN1210 was conducted. ALXN1210 shows almost exclusive specificity to human C5; therefore, PK data from nonclinical studies are of limited value.

Two non-clinical studies assessing PK and TK of ravulizumab following a single intravenous (IV) injection to cynomolgus monkeys or single and repeated subcutaneous (SC) doses in New Zealand White rabbits were completed.

Absorption

Following a single SC administration to rabbits at 30, 60 or 100 mg/kg, systemic exposure (Cmax and AUC0-168) of ravulizumab increased in a dose proportional manner. Observed median Tmax ranged from 48 to 72 hours suggesting a slow absorption of ravulizumab from injection site. There were no PK differences by sex (**Study 1727-050**).

Figure 2: Mean concentration-time profile of ravulizumab following a single subcutaneous administration to rabbits at 30, 60 or 100 mg/kg

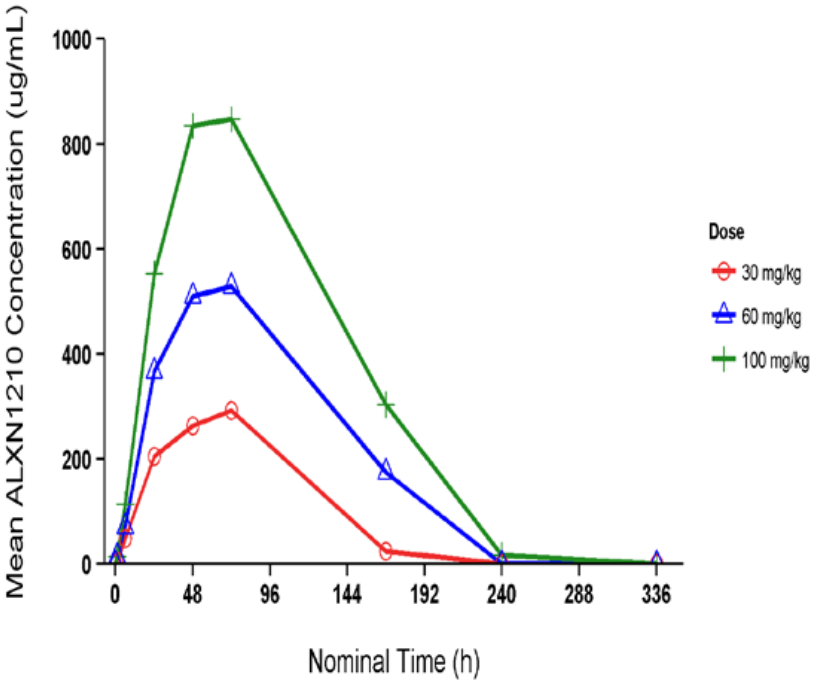


Table 3: The main pharmacokinetic parameters after a single administration of ravulizumab

Study ID	Species	N	Dose (mg/kg)	Route	Anal	Cmax (µg/mL)	Tmax (h)	$AUC_{0-\infty}$ (h*µg/mL)
A	Cynomolgus monkey	4	60	IV infusion	ECL	1680±269	2 (end of infusion)	579,000 ±113,000
		4	150	IV	ECL	4300±340	2 (end of	1,120,000

				infusion			infusion)	±285,000
		6	30	SC	ECL	292±54.4	72	27,600±6,730*
B	Rabbit	6	60	SC	ECL	552±48.6	60	52,500±17,700*
		6	100	SC	ECL	894±127	48	92,500±20,300*

Study ID	Species	N	Dose (mg/kg)	Route	Anal.	t½ (h)	Vss (mL/kg)	Clt (mL/h/kg)
A	Cynomolgus monkey	4	60	IV infusion	ECL	537±81.7	64.3±7.53	0.103±0.0191
		4	150	IV infusion	ECL	240±346	59.7±22.0	0.141±0.0377

* AUC_{0-168}

Study A: 1727-009 - A 16-week pharmacokinetic study of ALXN1210 following a single intravenous infusion dose in the cynomolgus monkey, Study Report, MPI Research, Inc., 2014

Study B: 1727-050 – A single dose and repeat dose subcutaneous irritation study in Rabbits, Study Report, MPI Research, Inc., 2016

Following a single SC administration to rabbits at 30, 60 or 100 mg/kg, systemic exposure (Cmax and AUC0-168) of ravulizumab increased in a dose proportional manner. Observed median Tmax ranged from 48 to 72 hours suggesting a slow absorption of ravulizumab from injection site. There were no PK differences by sex.

Distribution

No distribution data have been submitted by the applicant (see discussion on non-clinical aspects).

Metabolism

No metabolism data have been submitted by the applicant (see discussion on non-clinical aspects).

Excretion

No excretion data have been submitted by the applicant (see discussion on non-clinical aspects).

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity studies were performed with ALXN1210 (see discussion on non-clinical aspects).

Repeat dose toxicity

No repeat dose toxicity studies were performed with ALXN1210 because it does not display detectable anti-C5 activity in nonhuman serum and therefore no relevant species for toxicity testing exist. Instead, a repeat-dose toxicity study in mice was performed using BB5.1, a murine anti-mouse C5 surrogate antibody.

In a four week dose range finding study in mice, BB5.1 mAb was administered to female mice by IV route, once, twice, or three times weekly resulting in weekly dose levels of 30, 60 or 90 mg/kg. Controls received vehicle three times weekly. Neither treatment-related clinical signs nor effects on body weight or body weight change were observed. Serum analysis indicated similar extents of serum complement inhibition (mean haemolysis <20%, on days 8, 15, 23 and 29) for mice treated with BB5.1 mAb at 60 versus 90 mg/kg/week. Since the extent of haemolytic prevention was so similar at both 60 and 90 mg/kg, and greater at these doses than at 30 mg/kg/day (34±12% haemolysis day 8, 20%±13% day 15, <20% days 22 and 29), the recommended high dose of BB5.1 mAb in subsequent future toxicity studies in mice was 60 mg/kg/week.

A twenty-six week study evaluated the toxicity of BB5.1 mAb when administered once or twice weekly by IV injection to mice for 26 weeks followed by a 4-week recovery period (15-25 mice/sex/group). No unscheduled deaths occurred in the 30 mg/kg/wk dose group. Nine unscheduled deaths occurred during the study (4 in controls, and 5 in high dose group); none were related to treatment. Treatment did not affect any of the toxicity parameters examined. Serum analysis indicated that the extent of mean % haemolysis decreased from pre-treatment levels of 70-80 % to below 20 % in treated mice at weeks 12 and 25. Although results were similar for both treated mice groups, the mean % haemolysis was slightly less for the 60 mg/kg/week mice in most instances. Following a four-week recovery period, the mean % haemolysis approximated pre-study values for both treatment groups.

Genotoxicity

No genotoxicity studies were performed with ALXN1210.

Carcinogenicity

No carcinogenicity studies were performed. Nonclinical studies utilizing the murine surrogate molecule of C5 blockade, BB5.1 were performed; in these studies no specific carcinogenicity risks were observed.

Reproduction Toxicity

No reproductive and developmental toxicity studies were performed with ALXN1210. Instead, reproductive toxicity studies in mice were performed using BB5.1, a murine anti-mouse C5 surrogate antibody.

Fertility and early embryonic development

BB5.1 was administered IV to male and female CD-1 mice prior to mating until termination (males) or through early gestation (females) at 30 or 60 mg/kg/week (25/sex/group). Clinical observations, body weight and food consumption were evaluated. Treated males were paired with treated females during the mating period. On GD13, surviving pregnant and nonpregnant females were necropsied.

There were no treatment-related mortalities or clinical observations or necropsy findings. BB5.1 had no effect on reproductive performance, although there was a slight depression in the mean absolute and relative prostate weights of the 60 mg/kg/week males. Sperm count and motility were not affected. There were no remarkable changes in any of the C-section parameters indicating that BB5.1 had no effect on implantation or embryo-fetal viability.

Haemolytic activity was assessed in blood samples taken from females on GD12 and from males during week 4 and 10. Analysis of haemolytic activity showed that the mean percent haemolysis was generally ≤50% in the treated groups, indicating systemic exposure to BB5.1.

Based on the results of this study, the NOAEL for male toxicity was determined to be 60 mg/kg/week, while the No Observed Effect Level (NOEL) for female toxicity, male and female fertility, and embryo-fetal viability was determined to be ≥60 mg/kg/week.

Embryo-fœtal development

BB5.1 was administered intravenously to pregnant mice during the period of organogenesis (GD6-GD15) at 30, 60 mg/kg/week (25/group). Clinical observations, body weight and food consumption were evaluated. Mice were necropsied on GD18. Uteri were evaluated for number of live and dead foetuses and resorptions, and the ovaries were examined for the number of corpora lutea. Foetuses were weighed, sexed, and evaluated for external, visceral, and skeletal abnormalities.

No clinical signs were found in this study. A few external and soft tissue malformations were observed in different foetuses: a single incidence of umbilical hernia and 2 foetal incidences of retinal dysplasia (one fetus from 2 separate litters) were observed in mice treated with BB5.1 mAb at a dose of 60 mg/kg/week. No treatment-related fetal malformations were observed in mice treated with 30 mg/kg/week.

An exposure assessment was based on the degree of haemolytic activity in serum samples obtained; blood was collected prior to cesarean section on GD 18. Percentage haemolysis was highly variable in the treated groups although mean percentage haemolysis was ≤ 62.4% indicating systemic exposure.

The NOEL for maternal toxicity and embryo-foetal toxicity was determined to be ≥ 60 mg/kg/week, based on the lack of maternal and cesarean section findings at the highest dose of 60 mg/kg/. Based on the observed fetal soft tissue malformations at 60 mg/kg/week, the NOEL for developmental toxicity was determined to be 30 mg/kg/week.

However, an independent toxicology consultant (RTI Project No. 08412.007, attached to study 6709-105) was contracted to evaluate the findings of malformations in the 60 mg/kg/week dose group. Following a critical review of the report data and the teratology literature, the consultant concluded that the foetal malformations were unlikely to be treatment-related due to presence of umbilical hernia in one historical control database and the possibility of the malformations occurring by artifact during necropsy or processing. Therefore, the NOAEL for maternal toxicity and embryo-foetal toxicity was considered to be ≥ 60 mg/kg/week.

Prenatal and postnatal development, including maternal function

BB5.1 was intravenously administered to pregnant mice (37/group) at 30 or 60 mg/kg/week from GD6 to LD18 (lactation day). This study endpoints were clinical observations, body weight changes, food consumption and general health, as well as reproductive outcomes in the F0 and F1 generations. During lactation and post-weaning F1 litters were evaluated for growth and development. Necropsies were performed on F0 and F1 adults and F2 offspring, as appropriate.

Analysis of haemolytic activity showed that the mean percent haemolysis was lower in the treated groups compared to the control group, indicating systemic exposure to BB5.1. In the F0 generation there were no treatment-related mortalities, clinical findings or necropsy findings. Gestational and lactational body weights were not affected by BB5.1 mAb. No alterations were observed in the natural delivery and litter data from the F1 offspring, and in the F1 generation no treatment-related effects were observed, including overall reproductive performance.

The NOEL for maternal toxicity and F1 pup development and reproductive performance through to parturition of the F2 generation was determined to be ≥ 60 mg/kg/week.

Local Tolerance

Local tolerance studies were not performed with the current IV formulation of ALXN1210. However, no adverse injection site reactions were noted in the single dose IV PK study that was conducted with ALXN1210 in cynomolgus monkeys. In addition, local tolerance was evaluated within the repeat-dose toxicity study in mice using BB5.1, the mouse surrogate antibody and no adverse injection site reactions were noted either grossly or by histopathology.

A SC single and repeat-dose SC irritation study was conducted in rabbits. ALXN1210 administered subcutaneously caused a severe immune reaction after the second dose, leading to the premature sacrifice of several animals. However, these findings have questionable relevance for patients, as they were likely caused by the administration of a human protein to rabbits.

Other toxicity studies

Antigenicity

ADA formation was detected in PK studies in monkeys and local tolerance studies in rabbits. However, the induction of antibody formation in animals is not fully predictive of a potential for antibody formation in humans.

2.3.5. Ecotoxicity / environmental risk assessment

Ravulizumab is a monoclonal antibody. Therefore, according to the Guideline EMEA/CHMP/SWP/4447/00, it is not expected to pose a risk to the environment and it is exempted from environmental risk assessment.

2.3.6. Discussion on non-clinical aspects

ALXN1210 is a humanized monoclonal antibody (mAb) developed from the authorized eculizumab to bind and neutralize complement component 5 (C5).

Ravulizumab binds to complement component 5 (C5) and blocks its activation by complement pathway convertases, thereby preventing the release of the proinflammatory anaphylatoxin C5a and the formation of the terminal complement complex via C5b. To ensure the same specificity of ALXN1210 binding to C5, residues in the variable region that make direct contact with C5 were not altered from eculizumab. Furthermore, the engineered changes in affinity were tailored such that they are sufficient to attenuate antigen-mediated clearance and also preserve the ability to fully inhibit terminal complement activity under physiological conditions.

In vitro studies conducted with ALXN1210 confirmed the binding site of ALXN1210 on human C5; however binding of ALXN1210 to nonhuman C5 variants were not detected. In addition, ALXN1210 showed no pharmacologic activity on haemolysis in serum from any non-human species tested (10 NHP and 13 non primate mammals). When compared to eculizumab, it is expected that in the acidified environment of the early endosome after pinocytosis (pH~6.0) KD of ALXN1210 would increase compared to eculizumab, but maintaining a high affinity binding affinity to C5 in the vascular compartment (pH 7.4) and increasing the fraction of antibody recycled from the early endosome back into the vascular compartment by FcRn.

As the pharmacological target of ALXN1210, human C5 is only functional outside of the cells, in vitro testing with human cell lines would not be relevant. Additionally, clinical experience with use of eculizumab for long term C5 blockade has not shown any increased risk for CNS, cardiovascular, or respiratory effects.

In vivo pharmacology studies studies in a mice model showed that ALXN1210 has a significant longer half-life and PD effect than eculizumab.

Results from PK/PD studies conducted in a mouse PK model showed a significantly longer half-life of ravulizumab compared to eculizumab in the presence of human C5, suggesting that antigen-mediated clearance of ravulizumab was attenuated. Furthermore, the extended exposure of ravulizumab corresponded to extended duration of PD effect relative to eculizumab. However, since the analytical method used in this study was not validated, the PK results from this study cannot be regarded as usable for the evaluation of ravulizumab.

PK data after single dose administration were obtained in monkeys and rabbits. In the IV study in monkeys, only 2 animals/sex were in each group, which does not facilitate the interpretation of the results. Therefore, the Applicant is asked to explain the validity and robustness of these PK data. Upon evaluation of the clarification of this issue it was concluded that the study data is considered acceptable since it provides an acceptable approximation to the PK immunogenicity to the test compound despite the low numbers of animals used in the study. Cmax increased in a dose proportional manner, whereas AUC increased in a less than proportional manner, probably due to the presence of anti-human antibodies that could increase the clearance. ADAs were found in 75-100% of the ALXN1210 treated animals. However, the induction of antibody formation in animals is not predictive of a potential for antibody formation in humans. The bioanalytical methods used in this study were validated, but details of the validation are missing. Since the data submitted for clarification contains only a summary of results, and it was declared that no assay validation (in-study validation) was performed, the PK results from this study cannot be regarded as usable for the evaluation of ravulizumab. Since this validation cannot be supplemented, no further action is possible.

The study in rabbits was conducted by subcutaneous administration with a higher concentration than the clinical IV formulation and with different excipients, so the relevance of this study is limited. It was planned with a single dose and a repeated dose phase, but it was terminated earlier than planned due to limiting toxicity (see section 4.6 of this AR) and only TK data from single dose administration are available. In this study, Cmax and AUC increased in a dose proportional manner. The observed tmax ranged from 48 to 72 hours suggesting slow absorption of ALXN1210 from the injection site. There were no differences by sex. The incidence of ADA ranged from 83 to 100%; however as mentioned before this is not predictive of a potential immunogenicity in humans.

Overall, the PK data available with ALXN1210 are limited; however, as highlighted in the EMA scientific advice (EMA/CHMP/SAWP/403560/2016), given the lack of cross-reactivity with non-human tissues, the PK profile evaluation of ALXN1210 should be adequately assessed in humans.

The lack of safety pharmacology studies is considered acceptable.

General toxicity and reproductive toxicity studies were submitted and assessed in the Soliris (eculizumab) MAA and they were conducted with CD-1 mice using BB5.1, a murine anti-mouse surrogate antibody; therefore, the relevance of these studies is limited. This is considered acceptable due to the lack of cross-reactivity with non-human tissues of ALXN1210. However, findings regarding reproductive toxicity and local tolerance were detected.

In the repeated dose toxicity studies no signs of toxicity were seen. Pharmacodynamic activity (C5 blockade) was determined in serum through a cultured RBC haemolysis assay, with a decrease of the haemolytic activity from pre-treatment levels of 70-80% to below 20% in treated groups, confirming adequate exposure and biological activity.

No animal studies have been conducted to evaluate the genotoxic and carcinogenic potential of ravulizumab. The lack of these studies is acceptable as ICH S6 (R1) guideline indicates that nonclinical

carcinogenicity studies are not generally considered relevant to biotechnology products. ALXN1210 does not display detectable anti-C5 activity in serum from species normally used for such testing (mice and rats) and pharmacological profile of ALXN1210 does not show any proliferative, or growth factor like activities.

Animal reproductive toxicology studies have not been conducted with ravulizumab, but were conducted in mice with a murine surrogate complement inhibitory antibody, BB5.1. Reproductive toxicity studies showed no effect on reproductive performance, fertility markers and implantation or embryo-foetal viability. Haemolytic activity was assessed in these studies showing a dose-related exposure to BB5.1 mAb. No clear treatment-related effects or adverse effects were observed in the murine surrogate reproductive toxicology studies in mice. When maternal exposure to the antibody occurred during organogenesis, some external and soft tissue malformations were found; two cases of retinal dysplasia and one case of umbilical hernia were observed among 230 offspring born to mothers exposed to the higher antibody dose (approximately 4 times the maximum recommended human ravulizumab dose, based on a body weight comparison). However, the exposure did not increase foetal loss or neonatal death. Although it was determined that it is unlikely that these findings are treatment-related; umbilical hernia and retinal dysplasia were assessed in the light of the current knowledge about the role of C5 in organogenesis (e.g. JD Leslie, R Mayor. Complement in animal development: Unexpected roles of a highly conserved pathway. Semin Immunol. 2013 Feb; 25(1): 39–46. doi: [10.1016/j.smim.2013.04.005]. Based on the literature review assessment, it was not proven that complement system, or specifically C5 blockade, may impact organogenesis in human retinas or umbilical herniation during development.

No specific non-clinical study on fertility has been conducted with ravulizumab.

Nonclinical reproductive toxicology studies conducted in mice with a murine surrogate molecule (BB5.1) identified no adverse effect on fertility of the treated females or males.

Regarding local tolerance, a detailed assessment of findings observed in the repeat-dose toxicology studies and a justification that the results of local tolerance study in mice is the basis for the assessment of human local tolerability. Animal and human studies indicated that the final ravulizumab clinical formulation has an acceptable local tolerance profile.

Aspects on the risk assessment for elemental impurities are satisfactorily addressed in accordance with ICH Q3D.

General repeated-dose toxicity and reproductive toxicity studies were already submitted and assessed in the Soliris (eculizumab) MAA. However, additional toxicity studies with a new murine surrogate mAb are not expected to add any relevant information to the toxicology profile characterization of ALXN1210.

2.3.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, pharmacologic and toxicological characterization is acceptable. Non-clinical data reveal no special hazard for humans based on nonclinical studies using a murine surrogate molecule, BB5.1, in mice.

2.4. Clinical aspects

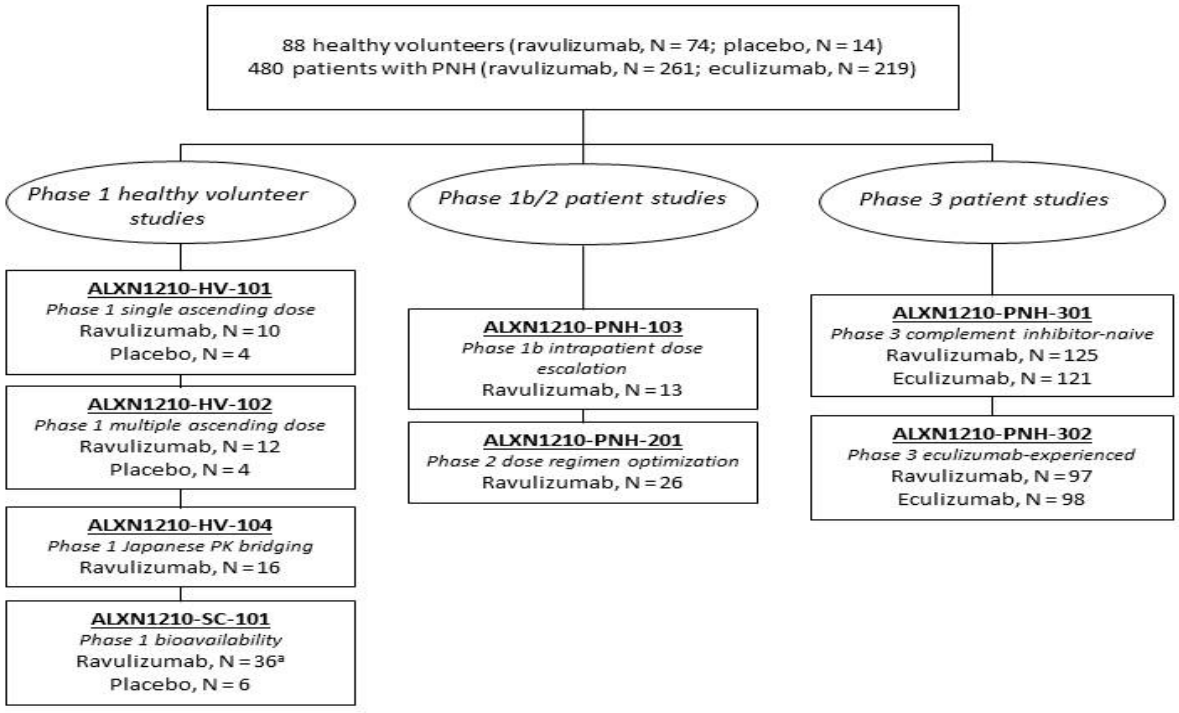
2.4.1. Introduction

GCP

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

The applicant 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.

- **Figure 3: overview of clinical studies**



Note: In Study ALXN1210-SC-101 ravulizumab/placebo were administered by either IV or SC route.
[a] *Ravulizumab SC, N = 24; ravulizumab IV, N = 12. Abbreviations: IV = intravenous; SC = subcutaneous*

Four Phase I studies were conducted in healthy volunteers to collect data on safety, tolerability, immunogenicity, PK and PD. A Phase 1b and a Phase 2 dose escalation studies were conducted for dose selection in patients with PNH who were naïve to complement inhibitor treatment. Two Phase 3 studies were conducted as pivotal studies, one in patients with PNH who were naïve to complement inhibitor treatment and other in patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months.

2.4.2. Pharmacokinetics

Absorption

Ravulizumab is a solution administered by IV infusion. Because the route of administration is an IV infusion and the dosage form is a solution, 100% of the administered dose is considered bioavailable. The time to maximum observed serum concentration (t_{max}) is expected at the end of infusion (EOI); however, because of the long terminal elimination half-life of ravulizumab and variability, the observed t_{max} in

clinical trials occurred either at or soon after EOI. Therapeutic steady-state drug concentrations are reached after the first dose.

Bioequivalence

The to-be-marketed ravulizumab drug product is a 10 mg/mL formulation for IV administration; all current clinical studies have utilized this formulation. This drug product is diluted to 5 mg/ml using 0.9% sodium chloride solution for injection prior to administration.

Influence of food

Given that ravulizumab is IV administered, there is no anticipated interaction with food.

Distribution

After a single dose administration of ravulizumab in healthy volunteers (Study ALXN1210-HV-101) the geometric mean Cmax (%CV) of ALXN1210 was 78.5 (10.2%) µg/ml following the 200-mg dose, and 139 (16.2%) µg/ml following the 400-mg dose. The observed median (range) Tmax was 2.4 (0.8 to 4.2) hours for the 200-mg dose, and 0.66 (0.59 to 1.2) hours for the 400-mg dose. Geometric mean (%CV) AUC∞ was 47,300 (13.9%) µg x h/mL for the 200-mg dose, and 80,400 (21.0%) µg x h/ml for the 400-mg dose.

In Study ALXN1210-HV-102, the maximal concentrations of ALXN1210 generally increased following each successive dose for the 400–mg and the 800–mg groups. The geometric mean maximum observed serum concentrations (Cmax) (geometric %CV) of ALXN1210 following the first dose were 133.4 (20.9%) and 269.8 (15.1%) µg/ml for the 400–mg and 800–mg groups, respectively. After the fifth dose, the geometric mean Cmax (geometric %CV) values were 208.2 (15.6%) and 452.2 (10.9%) µg/ml for the 400–mg and 800–mg groups, respectively. Consistent with the Cmax, the geometric mean Ctrough (geometric %CV) values were 32.9 (11.5%), and 71.9 (13.2%) µg/mL after the first dose and increased to 95.4 (13.0%), and 233.5 (14.4%) µg/ml after the fifth dose for the 400–mg and 800–mg groups, respectively. The median (range) tmax from all 5 periods was 1.08 (0.58 to 24.00) hours and 1.67 (1.17 to 8.00) hours for the 400–mg and 800–mg groups, respectively.

Geometric mean AUCτ increased following each infusion for both the 400–mg and 800–mg dose groups. The geometric mean AUCτ (geometric %CV) values of ALXN1210 after the first dose were 36781.9 (12.6%) and 78638.4 (12.1%) µg*h/ml for the 400–mg and 800–mg groups, respectively. After the fifth dose, the geometric mean AUCτ (geometric %CV) increased to 84623.4 (13.5%) and 196755.3 (9.3%) µg*h/ml for the 400–mg and 800–mg groups, respectively.

Following the fifth dose, the geometric mean total clearance (CL) was similar between doses, at 0.005 and 0.004 L/h for the 400–mg and 800–mg groups, respectively. The geometric mean Vss (geometric %CV) values were consistent at 5.8 (18.9%) and 5.2 (9.6%) L for the 400–mg and 800–mg dose groups, respectively. The median (range) half-lives (t½) were 31.3 (29.5 to 35.0) and 33.5 (27.3 to 42.6) days for the 400–mg and 800–mg dose groups, respectively.

The mean (SD) estimates for the central volume of distribution (Vc) and intercompartmental volume of distribution (Vp) in healthy adult subjects (Study ALXN1210-HV-102; N = 12) from the Final Pop-PK model are 3.25 L (0.36) and 2.18 L (0.25), respectively. The mean (SD) estimates for Vc and Vp in patients with PNH from the Phase 3 studies (N = 222) from the Final Pop-PK model are 3.45 L (0.65) and 1.91 L (0.32), respectively. No meaningful difference was noted between healthy adult subjects and patients with PNH.

The mean (standard deviation [SD]) volume of distribution at steady state for patients with PNH on the studied weight-based dose regimen was 5.34 (0.92) L.

Elimination

After a single dose administration of ravulizumab in healthy volunteers (Study ALXN1210-HV-101) the geometric mean t½ (%CV) was 32.4 (16.2%) days, and 30.8 (10.2%) days for the 200-mg and 400-mg doses, respectively.

After repeated drug administration (Study ALXN1210-HV-102) the median t½ were 31.3 days and 33.5 days for the 400-mg and 800-mg dose groups, respectively.

Ravulizumab contains only natural occurring amino acids and has no known active metabolites. The mean (SD) values for terminal elimination half-life and clearance of ravulizumab in patients with PNH are 49.7 (8.9) days and 0.003 (0.001) L/h, respectively.

Excretion

Due to the size of the molecule it is not expected that renal excretion may occur.

Metabolism

No data regarding the metabolism of the drug has been presented.

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

Dose proportionality and time dependencies

Dose proportionality

After a single dose administration of ravulizumab to healthy volunteers (Study ALXN1210-HV-101) geometric mean Cmax and AUC∞ indicate that exposures to 200 mg and 400 mg increased in a less than dose-proportional manner.

Table 4

Table 11: Geometric Mean Ratios, 90% Geometric Confidence Intervals and %CVs for Dose-Normalized (to 1 mg) AUC_t, AUC_∞, and C_{max} for ALXN1210 – Pharmacokinetic Population

			90% Geometric CI[b]		
Parameter	Dose Comparison	Ratio[a]	Lower	Upper	%CV
AUC_t	400 mg vs. 200 mg	85.91%	69.71%	105.87%	17.5%
AUC_∞	400 mg vs. 200 mg	85.06%	68.14%	106.17%	18.6%
C_{max}	400 mg vs. 200 mg	88.74%	74.89%	105.16%	14.2%

Abbreviations: AUC_t = area under the serum concentration versus time curve from time zero to the last quantifiable concentration; AUC_∞ = AUC from time zero to infinity; C_{max} = maximum observed serum concentration; CI = confidence interval; CV = coefficient of variation

[a] Calculated using least squares means according to the formula: $e^{(Difference)} \times 100$.

[b] 90% geometric confidence interval using ln-transformed data.

Source: Table 14.2.1.1

However, in Study ALXN1210-HV-102 a 2-fold increase in the dose from 400 mg to 800 mg led to an increase of approximately 2.1-fold in ALXN1210 exposure after a single dose administration. The median tmax after the ALXN1210 800–mg dose was approximately 0.5 hours longer (1.67hours) than the tmax after the 400-mg dose (1.08 hours). The mean CL and Vss were similar between the 400-mg and 800-mg doses of ALXN1210.

Dose proportional increases in Cmax, Ctrough, and AUCT were observed following administration of single and multiple doses of 400 mg and 800 mg of ALXN1210. Following once-every-28 days dosing, PK steady state evaluated on the basis of Ctrough was attained by Day 85. The geometric mean accumulation ratios for AUCT and Cmax following the fifth dose of ALXN1210 were 2.21 and 1.50, respectively, for the 400-mg dose group and 2.35 and 1.57, respectively, for the 800-mg dose group.

The results for PK dose proportionality for ALXN1210 using the power model are presented here:

Table 5: Pharmacokinetic Dose Proportionality – Power Model – Pharmacokinetic Population

Parameter	Period	Geometric Mean		Slope	90% Confidence Interval
		Cohort 1 400 mg	Cohort 2 800 mg		
AUC_τ (h*ug/mL)	1	36781.853	78638.360	1.057	0.870 – 1.243
	5	84623.383	196755.279	1.163	0.972 – 1.354
C_{max} (ug/mL)	1	133.355	269.808	0.977	0.705 – 1.249
	5	208.151	452.224	1.071	0.857 – 1.285
C_{trough} (ug/mL)	1	32.899	71.907	1.086	0.887 – 1.285
	5	95.362	233.512	1.230	1.002 – 1.457

Abbreviations: AUC_τ = area under the serum concentration-time curve to the end of the dosing interval; C_{max} = maximum observed serum concentration; C_{trough} = minimum observed serum concentration. Source: Table 14.2.1.4

The Period 5 C_{trough} value is the observed concentration 28 days after the Period 5 dose.

Over the studied dose (200 to 5400 mg) and regimen range (up to every 12 weeks [q12w] dosing), the final population PK (Pop PK) modeling results have shown that ravulizumab exhibited dose-proportional and time-linear.

Time dependency

This point has been evaluated in the popPK model and the results did not point towards a time dependency in the pharmacokinetics of ravulizumab.

Intra- and inter-individual variability

In healthy volunteers variability of critical PK parameters between 10- 20% while in patients somewhat large in the 20- 30% range.

Table 6: Mean ± SD (%CV) PK Parameters of Ravulizumab After the First Loading Dose and the Last Maintenance Dose to Complement Inhibitor-Naïve Patients with PNH (Study ALXN1210-PNH-301)

PK Parameter	Dosing Period	Ravulizumab All Patients		Ravulizumab ≥ 40 to < 60 kg		Ravulizumab ≥ 60 to < 100 kg		Ravulizumab ≥ 100 kg	
		n	Mean ± SD (%CV)	n	Mean ± SD (%CV)	n	Mean ± SD (%CV)	n	Mean ± SD (%CV)
C_{max} (µg/mL)	LD	125	771.4 ± 165.9 (21.5)	41	846.7 ± 174.3 (20.6)	79	740.3 ± 146.6 (19.8)	5	645.0 ± 181.3 (28.1)
	Last MD	124[a]	1378.5 ± 275.9 (20.0)	41	1528.8 ± 279.5 (18.3)	77[a]	1292.9 ± 242.8 (18.8)	6	1450.0 ± 219.0 (15.1)
C_{trough} (µg/mL)	LD	125	391.2 ± 136.8 (35.0)	41	424.15 ± 116.2 (27.4)	79	377.8 ± 146.3 (38.7)	5	333.6 ± 93.3 (28.0)
	Last MD	124[a]	472.7 ± 157.9 (33.4)	41	548.3 ± 168.0 (30.6)	77[a]	438.8 ± 139.3 (31.7)	6	391.8 ± 143.8 (36.7)

Table 7: Mean ± SD (%CV) PK Parameters of Ravulizumab After the First Loading Dose and the Last Maintenance Dose to Eculizumab-Experienced Patients with PNH (Study ALXN1210-PNH-302)

PK Parameter	Dosing Period	Ravulizumab All Patients)		Ravulizumab ≥ 40 to < 60 kg		Ravulizumab ≥ 60 to < 100 kg		Ravulizumab ≥ 100 kg	
		n	Mean ± SD (%CV)	n	Mean ± SD (%CV)	n	Mean ± SD (%CV)	n	Mean ± SD (%CV)
C_{max} (µg/mL)	LD	95[a]	842.9 ± 203.5 (24.1)	26	903.2 ± 150.4 (16.7)	62[a]	823.1 ± 216.0 (26.2)	7	794.7 ± 239.7 (30.2)
	Last MD	95[a]	1386.3 ± 268.4 (19.4)	27	1561.1 ± 261.3 (16.7)	60[a]	1349.7 ± 233.0 (17.3)	8	1071.1 ± 115.9 (10.8)
C_{trough} (µg/mL)	LD	96	405.4 ± 121.2 (29.9)	26	448.2 ± 151.4 (33.8)	63	394.5 ± 108.3 (27.5)	7	344.3 ± 50.3 (14.6)
	Last MD	95[a]	500.8 ± 143.2 (28.6)	27	560.7 ± 135.2 (24.1)	60[a]	484.1 ± 143.1 (29.6)	8	423.5 ± 108.7 (25.7)

Pharmacokinetics in target population

Final Pop-PK parameter estimates of ravulizumab as well as between-subject variability and residual error parameters are presented in Table 2.1.8.6

Table 8: Final Population-PK Model: Ravulizumab Parameter and Covariate Estimates

Parameter	Model Term	Typical Values		Bootstrap	
		Estimate	95% CI	Median	95% CI
CL (L/h)		0.00369	0.00355 – 0.00383	0.00369	0.00357 – 0.00382
Sex	× if Female	0.821	0.778 – 0.867	0.821	0.777 – 0.866
Disease state	× if Healthy	1.31	1.20 – 1.42	1.31	1.21 – 1.40
Body weight	× (WTBL/70) $^{\theta}$	0.652	0.523 – 0.780	0.650	0.518 – 0.775
Haemoglobi	× (HGBBASE/101) $^{\theta}$	-0.446	-0.598 – -0.293	-0.440	-0.583 – -0.284
Q (L/h)		0.0158	0.0139 – 0.0180	0.0159	0.0139 – 0.0182
Body Weight	× (WTBL/70) $^{\theta}$	0.652	0.523 – 0.780	0.650	0.518 – 0.775
Vc (L/h)		3.45	3.39 – 3.51	3.45	3.40 – 3.51
Body Weight	× (WTBL/70) $^{\theta}$	1.05	0.922 – 1.18	1.05	0.923 – 1.18
BMI	× (BMIBL/24.2) $^{\theta}$	-0.508	-0.695 – -0.322	-0.507	-0.694 – -0.316
Haemoglobin	× (HGBBASE/101) $^{\theta}$	-0.357	-0.440 – -0.275	-0.361	-0.438 – -0.278
Vp (L/h)		1.94	1.86 – 2.03	1.94	1.86 – 2.02
Body Weight	× (WTBL/70) $^{\theta}$	1.05	0.922 – 1.18	1.05	0.923 – 1.18
BMI	× (BMIBL/24.2) $^{\theta}$	-0.508	-0.695 – -0.322	-0.507	-0.694 – -0.316

Between-Subject Variability

Parameter	Model Term	Estimate	95% CI	CV (%)	Shrinkage (%)	Bootstrap	
						Median	95% CI
On CL	ω = SD ($\eta_{Vc,\,i}$)	0.204	0.184 – 0.225	20.6	4.23	0.203	0.184 – 0.223
On Vc	ω = SD($\eta_{Vc,i}$)	0.130	0.113 – 0.146	13.0	12.2	0.128	0.112 – 0.144
Correlation CL, Vc	ω = Corr($\eta_{CL,i}$, $\eta_{Vc,i}$)	0.243	0.109 – 0.376	NA	NA	0.241	0.0982 – 0.371

Residual Error

Parameter	Model Term	Estimate	95% CI	Bootstrap	
				Median	95% CI
Proportional Error (%)	σ = SD($\varepsilon_{i,j}$)	15.6	14.4 – 16.9	15.6	14.5 – 16.9
Assay	× θ if Avanza	0.832	0.739 – 0.926	0.836	0.746 – 0.932

Overall, the final Pop-PK model was deemed to be appropriately specified, with population typical values and covariate effects estimated with good precision. Using this Final Pop-PK model, post-hoc individual terminal elimination half-life estimates were derived. The estimated mean (SD) terminal elimination half-life of ravulizumab in 222 Phase 3 patients with PNH is 49.7 (8.9) days.

Table 9: Effect of Covariates on Ctroughss of Ravulizumab Relative to the Reference Population

Covariate Name	Covariate Value	Ratio Change in $C_{trough,ss}$ Relative to Reference	Bootstrap 95% CI
Sex	Male	0.877	[0.832, 0.926]
	Female	1.17	[1.11, 1.24]
Disease	PNH patient	1.00	[0.969, 1.04]
	Healthy volunteer	0.660	[0.584, 0.738]
Body weight at Baseline (kg)	40	1.16	[1.02, 1.32]
	50	1.06	[0.980, 1.15]
	60	1.07	[1.03, 1.13]
	70	1.00	[0.969, 1.04]
	80	0.940	[0.903, 0.983]
	90	0.888	[0.837, 0.946]
	100	0.920	[0.855, 0.996]
	110	0.878	[0.803, 0.962]
	120	0.841	[0.758, 0.933]
BMI (kg/m^2)	17.5	1.08	[1.04, 1.12]
	22.5	1.02	[0.986, 1.05]
	27.5	0.971	[0.934, 1.01]
	32.5	0.928	[0.884, 0.974]
	37.5	0.890	[0.833, 0.946]
Hemoglobin at Baseline (g/L)	60	0.753	[0.664, 0.857]
	80	0.883	[0.831, 0.939]
	100	0.996	[0.964, 1.03]
	120	1.10	[1.04, 1.16]
	140	1.20	[1.10, 1.30]
	160	1.29	[1.15, 1.43]

Note: Sensitivity analysis was performed by setting all covariates to median baseline values except for the covariate being tested. Sensitivity of simulated $C_{trough,ss}$ to the covariate being tested was performed by using values other than the median baseline value for the testing covariate.

Details on model parameters are presented in Appendix 2 (Section 11.3.10).

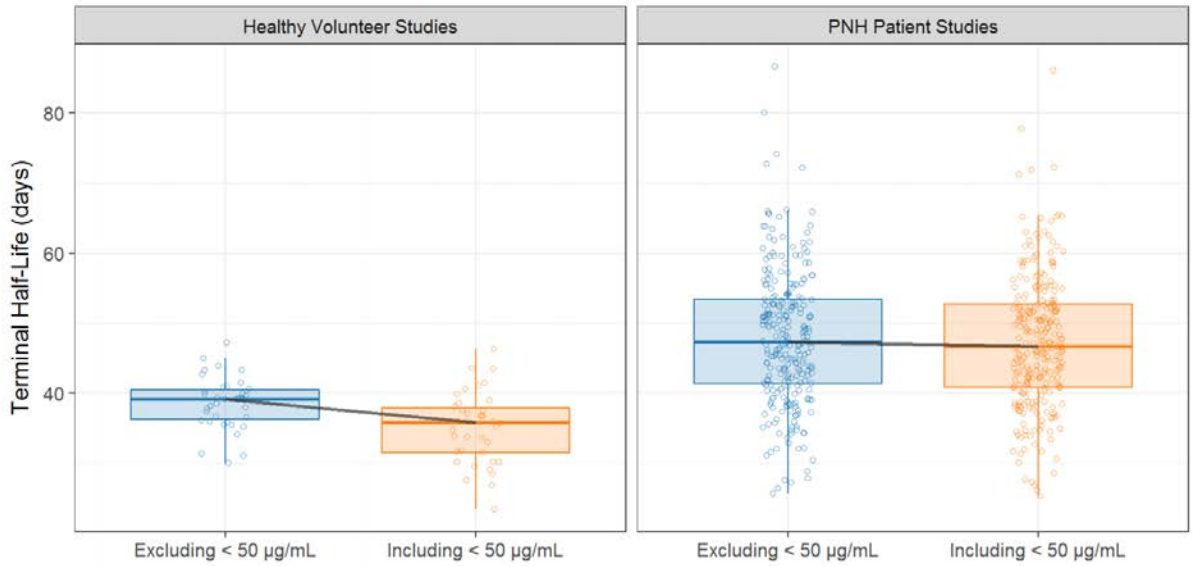
[a] The median baseline BMI value for the population was 24.2 kg/m^2.

[b] The median baseline hemoglobin value for the population was 101 g/L.

Abbreviations: BMI = body mass index; CI = confidence interval; $C_{trough,ss}$ = minimum concentrations under steady state conditions; PK = pharmacokinetic.

The MAH excluded from the analysis ravulizumab concentrations less than 50 μg/ml. Additional sensitivity analysis was carried out for assessing the impact of removing these low values from the PK dataset.

Figure 4: Final Population PK Model – Sensitivity Analysis Including Concentrations < 50 µg/mL



Special populations

- **Impaired renal function**

No study has been performed in patients with severe renal impairment.

It is expected that ravulizumab is metabolized as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways), with a similar elimination, thus no dose adjustment is deemed necessary in patients with renal impairment.

- **Impaired hepatic function**

No study has been performed in hepatic insufficiency.

Ravulizumab is not expected to undergo metabolism by hepatic metabolic enzymes or renal elimination.

- **Gender**

Population PK analysis revealed that females typical CL is approximately 18% lower than that observed in males.

This effect is not considered clinically relevant.

- **Race**

Study ALXN1210-HV-104 was a Phase 1, open-label, single ascending and multiple set dose study designed to evaluate the safety, tolerability, immunogenicity, PK, and PD of IV ravulizumab in healthy Japanese subjects.

Although mean Cmax and AUC values in Japanese healthy subjects seem to be slightly higher than those obtained in non-Japanese healthy subjects, this effect does not seem to be relevant considering that the target population in Europe is not this race.

- **Weight**

Patients with body weight between 40 to < 60 kg treated with a 3,000-mg MD q8w presented mean Ctrough,ss, Cmax,ss, and Cavg,ss values of approximately 20%, 17%, and 19% higher than patients with body weight between 60 to < 100 kg treated with a 3,300-mg MD q8w, respectively.

Patients with body weight ≥100 kg treated with a 3,600-mg MD q8w presented mean Ctrough,ss, Cmax,ss, and Cavg,ss values of 16%, 10%, and 14% lower than patients with body weight ≥ 60 to < 100 kg treated with a 3,300-mg MD q8w, respectively. These results confirmed the adequacy of the proposed dosing rationale based on weight.

- **Elderly**

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	25/261	6/261	0/261

Pharmacokinetic interaction studies

No drug-drug PK interaction studies have been presented.

It is unlikely that ravulizumab, as occurs with other mAB, interacts with small molecules or other biologics.

Pharmacokinetics using human biomaterials

N/A

2.4.3. Pharmacodynamics

Mechanism of action

Ravulizumab specifically binds to human complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b (the initiating subunit of the terminal complement complex [C5b-9]) during complement activation. This inhibition prevents the release of the proinflammatory mediator C5a and the formation of the cytolytic pore-forming membrane attack complex C5b-9 while preserving the proximal or early components of complement activation (eg, C3 and C3b) essential for the opsonization of microorganisms and clearance of immune complexes.

The hallmark of PNH disease activity is complement-mediated haemolysis. Paroxysmal nocturnal haemoglobinuria is caused by a somatic (acquired) mutation of the PIG-A gene that leads to a lack of CD55 and CD59, which are key, naturally occurring terminal complement inhibitor proteins on cell surfaces (Hill, 2013). The absence of these complement inhibitor proteins on the cell surface results in continuous activation of the alternative complement pathway and chronic intravascular haemolysis. Intravascular haemolysis releases free haemoglobin, resulting in nitric oxide consumption and persistent smooth muscle cell contraction, along with an increased risk of severe thromboembolism.

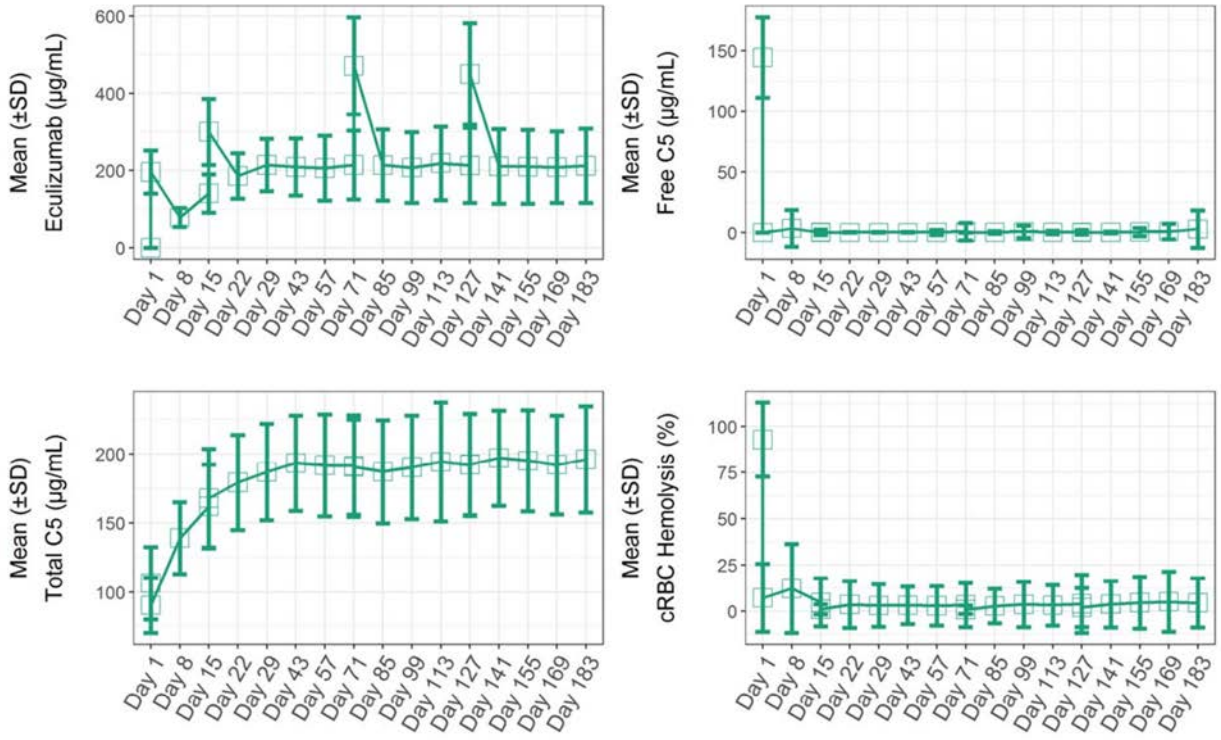
This mechanism of action provides the therapeutic rationale for the use of ravulizumab in PNH, in which uncontrolled complement activation is involved.

Primary and Secondary pharmacology

The primary pharmacological effect of ravulizumab is the decrease of LDH. A few variables were studied as secondary ones such as: mean total C5 concentration, mean free C5 concentration, chicken red blood cell haemolysis, complement C5b-9 concentrations, CPP and CAP activity and QT/QTc.

After single and oral doses of 200 and 400 mg of ravulizumab, mean total C5 concentrations decreased (%) from baseline a 15.42% and 14.10%, respectively. The administration of repeated doses of 400mg and 800 mg in healthy volunteers produced an increase of a 63.5% and 82.5% in total C5 concentrations. This effect was similar to that observed in the phase II studies, with mean increases around 55% (for maintenance doses of 1000 and 1600mg). However, higher maintenance doses of 2400 and 5400 mg only increased mean total C5 concentrations by 36.7 and 29.38%. This effect was characterized for a higher effect in the initial doses, and lower at later maintenance doses. The mean total effect in phase III studies is higher than in the phase II studies, and this decrease in the effect over time was not observed in phase III studies; however, the results from phase III studies have been presented for 183 days.

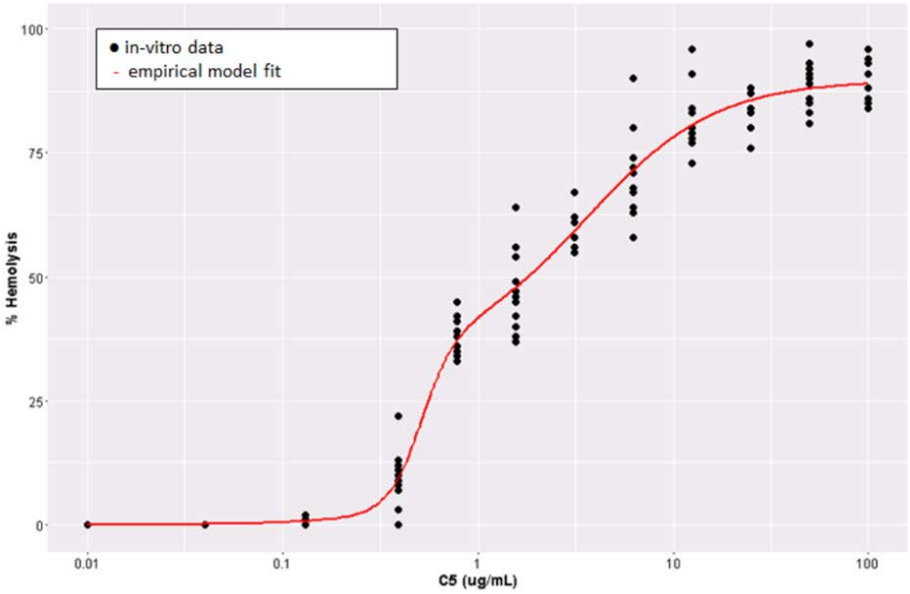
Figure 5: Exploratory Analysis – ALXN1210-PNH-301 - Mean (±SD) Concentration-Time of PK, Total C5 and cRBC –Eculizumab Arm (Linear Scale) – Overall



Ravulizumab decreased free C5 concentrations to values lower than 99% of the baseline value in phase I and phase II studies. In phase III studies, the proposed dosing schedule produced a decrease in free C5 concentrations to values lower than the target 5 microg/mL. The effect was observed for all the patients included in the studies, and for a period of time of up to 183 days. The results were compared to eculizumab, and although the mean results were similar, some of the patients in the eculizumab arm presented free C5 concentrations above the target concentration.

An in-vitro study 12 different C5 concentrations at 100, 50, 25, 12.5, 6.25, 3.13, 1.56, 0.78, 0.39, 0.13, 0.04 and 0.01µg/mL were prepared by spiking purified human C5 into C5 depleted human serum. A cRBC haemolysis response was assessed at each of the serum C5 concentration.

Figure 6: % cRBC Haemolysis vs. C5 Concentration



In phase I studies cRBC haemolysis followed a time course almost parallel to that observed for free C5 concentrations. In study ALXN1210-PNH-201 and ALXN1210-PNH-302 studies a decrease of the effect over time was observed. The decrease in the drug effect was more prominent after the last dose compared to the previous ones. Therefore, the applicant should explain whether this decrease in the effect on cRBC haemolysis might be pointing to a possible decrease of drug efficacy in the long term.

In phase I studies after a single oral dose of 200mg or 400 mg of ALXN1210 mean complement C5b-9 concentrations decreased between 28 and 43% and remained relatively stable up to 168 hours after the drug intake.

ALXN1210 produced a decrease of CPP and CAP activity of around a 95% of the baseline value after the administration of single oral doses of 200 mg or 400 mg. The baseline values were almost recovered by day 253 after multiple administrations of 400 mg and 800 mg.

Based on a PK-QT/QTc relationship, the changes observed in the pd variable do not seem to be related to the exposure to the drug.

Secondary pharmacology

No exposure-response relationships were observed for TEAEs observed in less than 10% of patients in Studies ALXN1210-PNH-301 and ALXN1210-PNH-302.

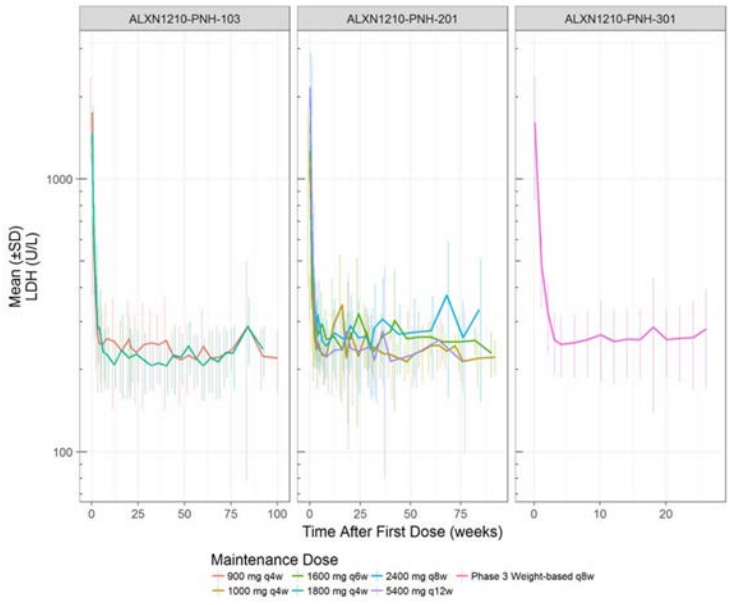
Pharmacodynamic interactions with other medicinal products

No interaction studies have been submitted.

Relationship between plasma concentration and effect

A total of 164 patients with PNH from 3 clinical studies (ALXN1210-PNH-103, ALXN1210- PNH-201, and ALXN1210-PNH-301) were included in the PK/PD analysis of LDH. Exploratory analyses were first performed to visually assess longitudinal profiles of LDH.

Figure 7: Mean (SD) Concentration-Time Profiles of LDH Following Administration of Ravulizumab



The response profile of LDH was characterized by a rapid onset after administration of the first dose of ravulizumab, and suppression of LDH concentrations was sustained during the maintenance phase of ravulizumab treatment. The majority of LDH levels remained within 468 U/L (ie, 2 x the upper limit of normal) for the whole study duration.

An indirect PK/PD response model (with a zero-order production of LDH response and inhibitory effect of ravulizumab on the zero-order production of LDH) previously provided an adequate description of the observed data (ALXN1210 Dose Rationale, 2016). The above indirect PK/PD model was used in a first step to assess the longitudinal profiles of LDH. Population PK/PD parameters are presented in Table 2.2.7.2

Table 10: Population PK/PD Analysis of LDH – Parameters Estimates

Parameters	Typical Values		Between-Subject Variability		
	Estimate[a]	RSE (%)	Estimate	RSE (%)	Shrinkage (%)
E_0 (U/L)	1404	3.87	0.447	6.96	6.84
I_{max} (fraction)	0.825	1.16	0.670	7.95	6.63
IC_{50}[b] (µg/mL)	21.0	NE	NA	NA	NA
IC_{95} (µg/mL)	146	13.4	NA	NA	NA
Hill coefficient	1.52	38.6	NA	NA	NA
K_{out} (h^{-1})	0.0101	2.77	NA	NA	NA
Proportional error (%)	19.9	6.39	NA	NA	NA

Note: E_0 and I_{max} were highly correlated (correlation estimate of 0.871).

[a] The I_{max} parameter estimate in the logit scale (1.55) was back-transformed to the normal scale. Other parameter estimates are back-transformed from the log-transformed domain. Other parameters are presented in Appendix 4 (Section 14.1.2).

[b] IC_{50} was estimated as a secondary model parameter.

Abbreviations: CI = confidence interval; E_0 = Baseline LDH; I_{max} = maximal reduction of LDH synthesis; IC_{50} = concentration of ravulizumab leading to half-maximal reduction of LDH synthesis; IC_{95} = concentration of ravulizumab leading to 95% of maximal reduction of LDH synthesis; K_{out} = LDH first-order elimination rate constant; NA = not applicable; NE = not estimated; RSE = relative standard error.

Typical Imax was 0.825, suggesting that the administration of ravulizumab is expected to suppress LDH levels through a maximum 82.5% inhibition of the synthesis rate (Kin) of LDH (ie, E0 * Kout). The mean IC95 derived with the PK/PD model was 146 µg/ml, suggesting a steep concentration effect relationship. Mean $Ctrough_{ss}$ in patients with body weight values ≥ 40 to < 60 kg, ≥ 60 to < 100 kg, and ≥ 100 kg were 3.9-, 3.2-, and 2.7-fold higher than the estimated IC95, respectively. Mean $Cavg_{ss}$ in patients with body weight values ≥ 40 to < 60 kg, ≥ 60 to < 100 kg, and ≥ 100 kg (refer to Table 14) were 6.0-, 5.0-, and 4.3-fold higher than the estimated IC95, respectively. Based on the above results, differences in exposure between males and females, and according to baseline haemoglobin levels were not deemed clinically relevant.

A total of 27 (<1%) LDH concentrations out of 2,954 measurement were associated with CWRES values >|4|. A sensitivity analysis was performed without concentrations associated with CWRES values >|4|. Typical E0, Imax, and Kout derived without concentrations associated with CWRES values >|4| were within 1% of those derived in the original analysis. The typical IC95 and Hill coefficient parameters derived without CWRES values >|4| were within 10% and 7%, respectively, of those derived in the original analysis (back-transformed scale).

In addition, a total of 11 (<1%) LDH concentrations were associated with coinciding complement-amplifying condition (CAC) episodes. A sensitivity analysis was performed without LDH samples associated with CAC episodes. Typical E0, Imax, and Kout values derived without samples associated with CAC episodes were within 1% of those derived in the original analysis. The typical Hill coefficient parameter estimated without LDH samples associated with CAC episodes was within 3% of that derived in the original analysis (back-transformed scale).

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics of ravulizumab has been based on six different studies (two phase I in healthy volunteers, two phase II studies performed in PNH, and two phase III studies in patients with PNH who received either ravulizumab or eculizumab).

As the route of ravulizumab administration is an intravenous infusion and the dosage form is a solution, 100 % of the administered dose is considered bioavailable. The time to maximum observed concentration (t_{max}) is expected at the end of infusion (EOI) or soon after EOI. Therapeutic steady-state drug concentrations are reached after the first dose. The mean (standard deviation [SD]) volume of distribution at steady state for patients with PNH on the studied weight-based dose regimen was 5.34 (0.92) L.

As an immunoglobulin gamma (IgG) monoclonal antibody, ravulizumab is expected to be metabolized in the same manner as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways), and is subject to similar elimination. Ravulizumab contains only natural occurring amino acids and has no known active metabolites. The mean (SD) values for terminal elimination half-life and clearance of ravulizumab in patients with PNH are 49.7 (8.9) days and 0.003 (0.001) L/h, respectively.

Over the studied dose and regimen range, ravulizumab exhibited dose proportional and time linear pharmacokinetics (PK).

When given the same dose, heavier patients with PNH had lower median serum ravulizumab concentrations compared with lighter patients. Weight-based dosing is proposed in SmPC section 4.2. No formal trial of the effect of sex, race, age (geriatric), hepatic or renal impairment on the pharmacokinetics of ravulizumab was conducted. However, based on population-PK assessment no impact of sex, age, race and hepatic or renal function on ravulizumab PK was identified in the studied healthy volunteers subjects and patients with PNH, and as a result, no dosing adjustment is considered necessary.

Two population pharmacokinetic models have been developed, the first one at EOP2, and the second one including data from phase III studies, as well as data from phase I and II - using two approaches: noncompartmental approach and population modelling approach. The first model developed was used to simulate different dose and dosing schedules. The final popPK model was used to confirm that the selected doses in phase 3 studies permitted to achieve the target concentrations. Moreover, the model was used as the input function for a popPKPD model of the primary pharmacology (percent of change on the LDH).

Secondary variables evaluated included free C5 concentrations, total C5 concentrations, chicken red blood cells haemolysis, complement C5b-9 concentrations, CPP and CAP activity and QT/QTc. Two of the secondary variables, total C5 concentrations and chicken red blood cells haemolysis showed a decrease of the drug effect over time up to 52 and 26 weeks were presented. Total C5 does not seem to change up to 52 weeks. The final model shows that the pharmacokinetics of ravulizumab depends on weight, BMI, haemoglobin and gender. Information regarding the qualification of the model has been adequately presented and the model fit has been accepted.

The drug produced inconsistent changes in total C5 concentrations when dose in considered, however these changes can be explained by the limited number of participants included in some cohorts, and the variability in the response. The effect over time showed a decrease in the effect of the drug at different maintenance regimens up to 26 weeks. However, new data of total C5 has shown that the effect is maintained up to 52 weeks. No data further than 26 weeks were presented for the chicken red blood cells haemolysis. The decrease in free C5 concentrations was higher than 99% in phase I and phase II studies. In the two phase III studies free C5 concentrations were maintained below the target concentration of 5 microg/mL in all studied patients up to 183 days. No data up to 52 weeks has been presented.

Two different analytical methods were used to quantify free C5 concentrations following ravulizumab and eculizumab treatments in the pivotal phase 3 trials. A cross-validation exercise revealed that the two methods provide statistically different results for the very same sample. So, difference between free C5 levels following ravulizumab and eculizumab treatments partly might be due to fact that different assay methods were used.

AlXN1210 produced a decrease of CPP and CAP activity of around a 95% of the baseline value after the administration of single oral doses of 200 mg or 400 mg. The baseline values were almost recovered by day 253 after multiple administrations of 400 mg and 800 mg.

Ravulizumab exhibited a low incidence of immunogenicity in patients with PNH (< 0.5%), However, it is not clear that anti-ravulizumab could have been detected in Phase 3 trials at all because the trough serum levels were above the drug tolerance levels of the applied ADA assays. As Table 2.1.2.6 shows the lowest drug tolerance limits are below trough levels.

Based on a PK-QT/QTc relationship, the changes observed in the pd variable do not seem to be related to the exposure to the drug.

2.4.5. Conclusions on clinical pharmacology

The data on clinical pharmacology aspects are considered adequate to support the marketing authorisation of Ultomiris. Relevant pharmacology information has been reflected in the SmPC section 5.2 and 4.2.

2.5. Clinical efficacy

2.5.1. Dose response studies

The Phase 1b and Phase 2 clinical studies evaluating ravulizumab were designed to evaluate safety and efficacy and explore dose and dosing regimens in patients with PNH. Adult patients with a documented diagnosis of PNH, elevated LDH (≥3 x ULN), and no prior use of complement inhibitors were eligible for enrolment.

Study ALXN1210-PNH-103 assessed a range of doses infused at 28-day intervals, and Study ALXN1210-PNH-201 assessed higher induction doses and longer dosing intervals.

Integrated population PK and PK PD/LDH analyses were performed using pooled data from these studies to characterize PK and covariates influencing PK, and to explore PK PD and PK LDH relationships for identifying the Phase 3 dosing regimen.

Additionally, these early phase studies included an Extension Period to explore the long term safety of ravulizumab in patients with PNH.

Table 11: Population Comparison Across Ravulizumab Phase1b and 2 Studies in Patients With PNH

Main Criteria for Eligibility at Screening	ALXN1210-PNH-103	ALXN1210-PNH-201
Adult ≥ 18 years of age	X	X
Documented diagnosis of PNH confirmed by HSFC evaluation of RBCs and WBCs	X	X
Complement inhibitor-naïve	X	X
Baseline LDH value: ≥ 3 × ULN ≥ 1.5 × ULN ≤ 1.5 × ULN	X	X

[a] *PNH signs and symptoms: fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (haemoglobin < 10 g/dL), history of a major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction; or history of pRBC transfusion due to PNH.*

Abbreviations: HSFC = high-sensitivity flow cytometry; LDH = lactate dehydrogenase; PNH = paroxysmal nocturnal haemoglobinuria; pRBC = packed red blood cell; RBC = red blood cell; ULN = upper limit of normal; WBC = white blood cell

Study ALXN1210-PNH-103 is a Phase 1b, open-label, multiple-dose, multicenter, intrapatient dose escalation study designed to explore the safety, tolerability, efficacy, PK/PD, and immunogenicity of ravulizumab in adult patients with PNH who were not previously treated with a complement inhibitor. Recruitment was conducted in South Korea and Australia. 13 patients were enrolled in this study. All 13 patients received 1 of 3 induction regimens of ravulizumab followed by maintenance doses of ravulizumab 900 mg (Cohort 1, N = 6) or ravulizumab 1800 mg (Cohort 2, N = 7) through Day 169, after which they entered an Extension Period of up to 3 years and continue treatment with ravulizumab. Initially, patients continued treatment with ravulizumab at the same maintenance dose and frequency as their randomized treatment assignment. After the start of the Phase 3 studies, all patients in the Phase 1b study changed to a body weight-based dosing regimen of ravulizumab IV 3000 to 3600 mg maintenance doses every 8 weeks (q8w).

Study ALXN1210-PNH-201 is a Phase 2, open-label, multiple-ascending dose study to evaluate the efficacy, safety, tolerability, immunogenicity, PK, and PD of ravulizumab administered IV to adult patients with PNH who had not been previously treated with a C5 complement inhibitor.

The study had 4 treatment cohorts, with at least 6 patients planned per cohort. Each cohort of patients received a different dose and dosing schedule of ravulizumab during the Treatment Period.

26 patients were enrolled in this study. All 26 patients received an induction regimen of ravulizumab followed by maintenance doses of 1000 mg every 4 weeks (q4w) (Cohort 1, N = 6), 1600 mg every 6 weeks (q6w) (Cohort 2, N = 6), 2400 mg q8w (Cohort 3, N = 7), and 5400 mg q12w (Cohort 4, N = 7). All 26 patients completed the 24-week Primary Evaluation Period (up to Day 253 for Cohorts 1 to 3 and up to Day 281 for Cohort 4) without dose adjustment or discontinuation, after which they entered an Extension Period of up to 5 years and continue treatment with ravulizumab. Initially, patients continued treatment with ravulizumab at the same maintenance dose and frequency as their randomized treatment assignment. After the start of the Phase 3 studies, all patients in the Phase 2 study changed to a body weight-based regimen of ravulizumab IV 3000 to 3600 mg maintenance doses q8w (except for Cohort 4 which remained on 5400 mg every 12 weeks [q12w]).

Table 12: Selected Efficacy Results from Phase 1b and Phase 2 Studies

Efficacy Endpoint	Study ALXN1210-PNH-103			Study ALXN1210-PNH-201				
	Cohort 1 900 mg q4w (N = 6)	Cohort 2 1800 mg q4w (N = 7)	Overall (N = 13)	Cohort 1 1000 mg q4w (N = 6)	Cohort 2 1600 mg q6w (N = 6)	Cohort 3 2400 mg q8w (N = 7)	Cohort 4 5400 mg q12w (N = 7)	Overall (N = 26)
LDH % change from baseline to end of Primary Evaluation Period[a], mean (SD)	–85.952 (3.1897)	–84.736 (3.7736)	–85.297 (3.4289)	–72.85 (12.082)	–77.82 (6.474)	–84.96 (4.423)	–87.63 (6.923)	–81.23 (9.422)
Number (%) of patients with LDH ≤ 1.0 × ULN at end of Primary Evaluation Period[a]	4 (66.7)	4 (57.1)	8 (61.5)	3 (50.0)	1 (16.7)	3 (42.9)	4 (57.1)	11 (42.3)
Number (%) of patients with LDH ≤ 1.5 × ULN end of Primary Evaluation Period[a]	5 (83.3)	7 (100.0)	12 (92.3)	6 (100.0)	6 (100.0)	5 (71.4)	6 (85.7)	23 (88.5)
Number (%) of patients who received any pRBC transfusions from first dose of study drug to end of Primary Evaluation Period[a]	1 (16.7)	1 (14.3)	2 (15.4)	1 (16.7)	1 (16.7)	2 (28.6)	1 (14.3)	5 (19.2)
pRBC transfusions from first dose of study drug to end of Primary Evaluation Period[a], median (min, max)	2.0 (2, 2)	1.0 (1, 1)	1.5 (1, 2)	4.0 (4, 4)	21.0 (21, 21)	4.0 (1, 7)	1.0 (1, 1)	4.0 (1, 21)

Efficacy Endpoint	Study ALXN1210-PNH-103			Study ALXN1210-PNH-201				
	Cohort 1 900 mg q4w (N = 6)	Cohort 2 1800 mg q4w (N = 7)	Overall (N = 13)	Cohort 1 1000 mg q4w (N = 6)	Cohort 2 1600 mg q6w (N = 6)	Cohort 3 2400 mg q8w (N = 7)	Cohort 4 5400 mg q12w (N = 7)	Overall (N = 26)
Units of pRBC transfused from first dose of study drug to end of Primary Evaluation Period[a], median (min, max)	4.0 (4, 4)	2.0 (2, 2)	3.0 (2, 4)	8.0 (8, 8)	32.0 (32, 32)	8.0 (2, 14)	2.0 (2, 2)	8.0 (2, 32)
FACIT-Fatigue, change from baseline to end of Primary Evaluation Period[a], mean (SD)	6.3 (11.38)	13.9 (10.42)	10.4 (11.11)	9.8 (8.70)[b]	13.6 (11.01)[b]	12.3 (16.87)[b]	11.2 (8.64)[b]	10.6 (11.22)[b]

Abbreviations: FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; LDH = lactate dehydrogenase; min = minimum; max = maximum; PNH = paroxysmal nocturnal haemoglobinuria; pRBC = packed red blood cell; q4w = every 4 weeks; q6w = every 6 weeks; q8w = every 8 weeks; q12w = every 12 weeks; ULN = upper limit of normal

[a] *For Study ALXN1210-PNH-103, end of Primary Evaluation Period was Day 169; for Study ALXN1210-PNH-201, end of Primary Evaluation Period was Day 253 (Cohorts 1-3) or Day 281 (Cohort 4).*

[b] *For FACIT-Fatigue scores in Study ALXN1210-PNH-201, Cohort 1 n = 5, Cohort 2 n = 5, Cohort 3 n = 6, Cohort 4 n = 6, and Overall n = 23.*

The dosing regimen studied in the ravulizumab PNH Phase 3 studies was developed using modeling and simulation methods that utilized the Phase 1 and Phase 2 PK, PD, and LDH data over a wide range of doses and regimens in healthy volunteers and patients with PNH, and was subsequently confirmed on the basis of the Phase 3 safety and efficacy data.

The recommended body weight-based dosing regimen is a loading dose administered on Day 1 followed by q8w administration of the maintenance dose starting on Day 15. No modification of this dosing regimen is required for any special populations or demographic subgroups.

Table 13: Ravulizumab Weight-Based Dosing Regimen

Body Weight	Loading Dose (mg)	Maintenance Dose (mg)
≥ 40 to < 60 kg	2400	3000
≥ 60 to < 100 kg	2700	3300
≥ 100 kg	3000	3600

2.5.2. Main studies

Study ALXN1210-PNH-301, a Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Complement Inhibitor-Naïve Adult Patients With Paroxysmal Nocturnal Haemoglobinuria (PNH)

Methods

Study Participants

Patients in the complement inhibitor naïve study had active haemolysis as evidenced by the laboratory parameter of LDH ≥ 1.5 × the upper limit of normal (ULN) plus the presence of at least 1 clinical sign or symptom of active disease: fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (haemoglobin < 10 g/L), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. A majority (> 80%) of patients were transfusion-dependent at baseline.

Table 14: Summary of inclusion and exclusion criteria in both main studies:

Inclusion Criteria	
ALXN1210-PNH-301	**ALXN1210-PNH-302**
• Presence of 1 or more of the following PNH-related signs or symptoms within 3 months of screening: fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (haemoglobin < 10 g/dL), history of a major adverse vascular event (MAVE, including thrombosis), dysphagia, or erectile dysfunction; or history of pRBC transfusion due to PNH. • Lactate dehydrogenase level ≥ 1.5 × ULN at screening.	• Treated with eculizumab according to the labelled dosing recommendation for PNH for at least 6 months prior to Day 1. • LDH level ≤ 1.5 × the ULN at screening. Sample must have been obtained on a scheduled eculizumab dosing day prior to dose administration (ie, at trough eculizumab level) and analyzed by the central laboratory.
• Male or female, 18 years of age or older at the time of consent. • Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation (Borowitz, 2010) of RBCs and white blood cells (WBCs), with granulocyte or monocyte clone size of ≥ 5%. • All patients were required to have been vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiated study drug treatment less than 2 weeks after receiving a meningococcal vaccine were required to have received treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. • Female patients of childbearing potential and male patients with female partners of childbearing potential must have followed protocol-specified guidance for avoiding pregnancy while on treatment in this study and for 8 months after the last dose of study drug.	
Exclusion Criteria	
ALXN1210-PNH-301	**ALXN1210-PNH-302**
• **Current or previous treatment with a complement inhibitor.**	• LDH value > 2 × ULN in the 6 months prior to Day 1 • Major adverse vascular event (MAVE) in the 6 months prior to Day 1
• Platelet count < 30,000/mm3 (30 × 109/L) at creening. • Absolute neutrophil count (ANC) < 500/µL (0.5 × 109/L) at screening. • History of bone marrow transplantation. • Body weight < 40 kg at screening. • History of N. meningitidis infection. • History of unexplained, recurrent infection. • Active systemic bacterial, viral, or fungal infection within 14 days prior to study drug administration on Day 1. • Presence of fever ≥ 38° C (100.4° F) within 7 days prior to study drug administration on Day 1. • Human immunodeficiency virus (HIV) infection (evidenced by HIV type 1 or type 2 [HIV-1, HIV-2] antibody titer). • Immunized with a live-attenuated vaccine within 1 month prior to study drug administration on Day 1. • History of malignancy within 5 years of screening with the exception of nonmelanoma skin cancer or carcinoma in situ of the cervix that had been treated with no evidence of recurrence. • History of or ongoing major cardiac, pulmonary, renal, endocrine, or hepatic disease (eg, active hepatitis) that, in the opinion of the Investigator or Sponsor, precluded the patient's participation in an investigational clinical trial. • Unstable medical conditions (eg, myocardial ischemia, active gastrointestinal bleed, severe congestive heart failure, anticipated need for major surgery within 6 months of randomization, coexisting chronic anemia unrelated to PNH) that would have made the patient unlikely to tolerate the requirements of	

the protocol (eg, transfusion guidelines).

- Concomitant use of anticoagulants was prohibited if the patient was not on a stable regimen for at least 2 weeks prior to Day 1.
- History of hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins.
- Female patients who planned to become pregnant or were currently pregnant or breastfeeding.
- Female patients who had a positive pregnancy test result at screening or on Day 1.
- Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever was greater.
- Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of screening.
- Known medical or psychological condition(s) or risk factor that, in the opinion of the Investigator, might have interfered with the patient's full participation in the study, pose any additional risk for the patient, or confound the assessment of the patient or outcome of the study.

Treatments

During the 26-week Primary Evaluation Period, the following treatments were administered via IV infusion:

• Ravulizumab treatment group: weight-based loading dose on Day 1 followed by every 8 weeks (q8w) weight-based maintenance doses on Days 15, 71, and 127.

• Eculizumab treatment group: 600-mg induction doses on Days 1, 8, 15, and 22 followed by q2w 900-mg maintenance doses on Days 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169.

Ravulizumab Dosages for the Randomized Treatment Period

Body Weight	ALXN1210 Loading Dose (Day 1)	ALXN1210 Maintenance Dose (Days 15, 71, 127)
≥ 40 to < 60 kg	2400 mg	3000 mg
≥ 60 to < 100 kg	2700 mg	3300 mg
≥ 100 kg	3000 mg	3600 mg

After completion of all assessments on Day 183 of the Randomized Treatment Period, all patients had the opportunity to enter an Extension Period and receive ravulizumab until product registration or approval (in accordance with country-specific regulations) or for up to 2 years, whichever occurred first.

Objectives

Primary Objective:

- to assess the **non-inferiority** of ALXN1210 compared to eculizumab in adult patients with PNH who had never been treated with a complement inhibitor.

Non-inferiority was claimed if after 26 weeks of treatment (1) the lower bound of the 95% confidence interval (CI) for the difference (ALXN1210 - eculizumab) in transfusion avoidance (TA) rate was greater than -20%, and (2) the lower bound of the 95% CI for the odds ratio of ALXN1210 compared with eculizumab for lactate dehydrogenase normalization (LDH-N) was greater than 0.39.

Secondary objectives:

- To characterize the safety and tolerability of ALXN1210 in this patient population
- To evaluate the efficacy of ALXN1210 by additional efficacy measures
- To characterize the pharmacokinetics (PK)/pharmacodynamics (PD) and immunogenicity of ALXN1210
- To evaluate the long-term safety and efficacy of ALXN1210
- To evaluate the safety and efficacy in patients who switch from eculizumab to ALXN1210 in the Extension Period (data not included in this 26-week report of the Primary Evaluation Period)

Outcomes/endpoints

The following table summarizes the endpoints used in both Phase 3 studies:

Table 15: Primary and Secondary Endpoints in Ravulizumab PNH Phase 3 Studies

Study	Endpoint	Statistic for Treatment Comparison	NIM	Eculizumab Effect Preserved
ALXN1210-PNH-301	**Coprimary**			
	% Transfusion Avoidance	Difference in rate	-20%[a]	50%
	Normalization of LDH levels	Odds ratio	0.39[b,c]	50%
	Key Secondary			
	% Change in LDH	Difference in % change	20%[c]	75%
	Change in FACIT-Fatigue	Difference in change	-5[c]	50%
	% Breakthrough Haemolysis	Difference in rate	20%[c,d]	70%
	% Haemoglobin Stabilization	Difference in rate	-20%[c]	50%
ALXN1210-PNH-302	**Primary**			
	% Change in LDH	Difference in % change	15%[a]	89%
	Key Secondary			
	% Breakthrough Haemolysis	Difference in rate	20%[a,c]	51%
	Change in FACIT-Fatigue	Difference in change	-3[c]	50%
	% Transfusion Avoidance	Difference in rate	-20%[a]	60%
	% Haemoglobin Stabilization	Difference in rate	-20%[a]	56%

Note: The endpoints are presented in hierarchical testing order for non-inferiority (additional testing order for superiority is detailed in the SAP for each study).

[a] PNH Registry data were used to assess the non-inferiority margin (NIM).

[b] An NIM of 0.39 on the odds ratio scale which was derived from TRIUMPH clinical trial data where LDH-N was calculated to be 0.42 for eculizumab and 0.10 for placebo.

[c] TRIUMPH study data were used to assess NIM for Study ALXN1210-PNH-301. TRIUMPH and/or PNH registry data were used to assess NIM for Study ALXN1210-PNH-302.

[d] Phase 3 definition of breakthrough cannot be fully replicated in TRIUMPH due to incomplete collection of symptoms. NIM was established using LDH data from TRIUMPH and clinical judgment.

Abbreviations: FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; LDH = lactate dehydrogenase; NIM = non-inferiority margin; PNH = paroxysmal nocturnal haemoglobinuria; SAP = statistical analysis plan

Other Secondary endpoints

• Change in EORTC QLQ-C30 from baseline to Day 183 (Week 26)

• Time to first occurrence of LDH-N

• Total number of units of pRBCs transfused through Day 183 (Week 26)

• Change in clinical manifestations of PNH (fatigue, haemoglobinuria, abdominal pain, shortness of breath, chest pain, dysphagia, and erectile dysfunction) from baseline to Day 183 (Week 26)

• Proportion of patients experiencing MAVEs from baseline to Day 183 (Week 26)

Sample size

Approximately 214 patients were planned to be randomly assigned in a 1:1 ratio to receive ALXN1210 (N = 107) or eculizumab (N = 107) to ensure at least 193 evaluable patients (assumes no more than a 10% drop-out rate). The sample size estimation was based on a non-inferiority design comparing ALXN1210-treated patients with eculizumab-treated patients.

Coprimary endpoints of haemolysis as directly measured by LDH-N from Day 29 through Day 183 and the proportion of patients who achieve TA through Day 183 were used to assess non-inferiority. For the coprimary endpoint of LDH-N, using a non-inferiority margin (NIM) based on the relative benefit of eculizumab with respect to placebo of 0.39 and a type I error of 1-sided 2.5%, a minimum of 142 patients would have been expected to provide 80% power to demonstrate non-inferiority of ALXN1210 to eculizumab. The NIM was determined based on the TRIUMPH study, a randomized placebo- controlled study of eculizumab in patients with PNH (Hillmen, 2006). For the other co-primary endpoint of proportion of patients achieving TA through Day 183, using a NIM of -20% and a type I error of 1-sided 2.5%, a minimum of 193 patients would have been expected to provide 80% power to demonstrate non-inferiority between the treatment arms.

Table 16: Summary of Parameters Used in Estimating Sample Size With Coprimary Endpoints

Parameters	LDH Normalization	Transfusion Avoidance
Power	80%	80%
Type I error	1-sided 0.025	1-sided 0.025
Noninferiority margin	0.39[a]	-0.20[b]
Allocation ratio	1:1	1:1
Mean eculizumab response	0.42[c]	0.57[d]
Standard deviation of eculizumab response	NA	NA
Assumed treatment difference	1	0
Estimated sample size	142	193
Adjusted sample size for 10% dropouts	158	214

Note: Analyzed using PASS 11 software (Hintze, 2011).
[a] Based on odds ratio.
[b] Based on difference in rates.
[c] Response rate from TRIUMPH study adjusted for baseline LDH.
[d] Response rate from Global PNH Registry adjusted for history of transfusion.
Abbreviations: LDH = lactate dehydrogenase; NA = not applicable; PNH = paroxysmal nocturnal hemoglobinuria
Source: Statistical Analysis Plan (Appendix 16.1.9)

Randomisation

Patients who met all criteria for enrolment were randomly assigned to treatment with ALXN1210 or eculizumab. Treatment group assignment was determined by a computer-generated random sequence using an interactive voice- or web-response system (IxRS). The randomization was a stratified randomization. Patients were stratified into 6 groups based on their transfusion history (0, 1 to 14, or > 14 units of pRBCs in the 1 year prior to first dose of study drug) and screening LDH levels (1.5 to < 3 or ≥ 3 × ULN). The patients within each of the 6 groups were then randomly assigned in a 1:1 ratio to receive ALXN1210 or eculizumab during the 26-week Primary Evaluation Period.

Blinding (masking)

The Phase 3 studies of ravulizumab in patients with PNH had an open-label design to allow for a comparison of the potential treatment differences of a q2w dose regimen versus a q8w dose regimen. Because ravulizumab has a prolonged elimination half-life compared to eculizumab and thus a longer dosing interval, the administration schedules of ravulizumab and eculizumab are markedly different.

The MAH has evaluated and has minimized as much as possible the potential impact and bias of not performing a double-blind study to ensure the adequacy of the clinical trial results. Specifically:

- Haemolysis as directly measured by LDH was assessed in the laboratory and was not affected by investigator/patient knowledge of treatment assignment. Because the trial was actively controlled, reduced haemolysis was anticipated in complement inhibitor-naïve patients in Study ALXN1210-PNH-301. Little or no change in haemolysis as measured by LDH was anticipated in the eculizumab-experienced patients in Study ALXN1210-PNH-302, as they were required to have stable LDH levels at study entry.
- Transfusion was guided by pre-specified protocol criteria consistent with medical practice (eg, laboratory and, if present, clinical evidence of anemia requiring transfusion). Patients who fulfilled the protocol-specified haemoglobin criteria for transfusion were considered as having received a transfusion regardless of whether a transfusion was administered by the investigator.

Statistical methods

In both studies the following efficacy analysis populations were considered:

Full Analysis Set (FAS): The FAS included all patients who received at least 1 dose of randomized treatment (ALXN1210 or eculizumab) and had at least 1 efficacy assessment after the first infusion of randomized treatment (the last statement on at least 1 efficacy assessment after the first infusion were not considered for ALXN1210-PNH-302 study). In the FAS, patients were compared for efficacy according to the treatment group to which they were randomized, regardless of which treatment they actually received.

Per Protocol Set (PP Set): The PP Set included all patients in the FAS who met the following criteria: Missed 0 doses of ALXN1210 or no more than 1 dose of eculizumab during the 26-week Primary Evaluation Period; Met inclusion criterion:

- Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation (Borowitz, 2010) of RBCs and white blood cells (WBCs), with granulocyte or monocyte clone size of ≥l5%.
- Presence of 1 or more of the following PNH-related signs or symptoms within 3 months of screening: fatigue, haemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (haemoglobin < 10 g/dL), history of a major adverse vascular event (MAVE, including thrombosis), dysphagia, or erectile dysfunction; or history of pRBC transfusion due to PNH.
- Lactate dehydrogenase level ≥ 1.5 × ULN at screening.

Did not meet exclusion criterion:

- Current or previous treatment with a complement inhibitor.
- Platelet count < 30,000/mm3 (30 × 109/L) at screening.
- Absolute neutrophil count (ANC) < 500/μL (0.5 × 109/L) at screening.

- History of bone marrow transplantation.

Non-inferiority Design

The ravulizumab Phase 3 studies used a non-inferiority design to compare results in patients treated with ravulizumab to those in patients treated with eculizumab.

Efficacy analyses were performed using the FAS, the primary efficacy population. The co-primary/primary efficacy endpoint analyses, as well as key secondary endpoint analyses, were repeated using the PP Set as a sensitivity analysis.

Co-primary efficacy analyses: For the co-primary endpoint of TA, a between-treatment difference in percentage of patients achieving TA was calculated along with a 95% CI for the difference using the stratified Newcombe CI method. This difference was computed using a weighted combination of the differences between treatment groups within the 6 stratification groups using Mantel-Haenszel weights. Patients who withdrew from the study due to lack of efficacy during the Primary Evaluation Period were considered as nonresponders and counted as requiring transfusions. For patients who withdrew for any other reason during this period, their data up to the time of withdrawal were used to assess TA.

For analysis of the co-primary endpoint of LDH-N, a generalized estimating equation approach was used to provide odds ratios and 95% CI. Day 29 through 183 (Week 26) LDH-N was used as the dependent variable and explanatory variables included an indicator variable for treatment; history of transfusion, which was a categorical variable based on the stratification factor level; and baseline LDH level, which was a continuous variable.

Key secondary efficacy analyses: Percent change in LDH and change in FACIT-Fatigue from baseline to Week 26 were analyzed using a mixed model for repeated measures (MMRM) with the fixed, categorical effects of treatment, the stratification randomization indicators of transfusion history and screening LDH levels, study visit and study visit by treatment group interaction as well as the continuous, fixed covariate of baseline FACIT-Fatigue (or LDH). For percent change in LDH, the baseline LDH level as a continuous variable was included. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. A difference between the ALXN1210 and eculizumab treatment groups along with a 2-sided 95% CI was calculated. For BTH and stabilized haemoglobin, the same approach used for TA was employed. These key secondary endpoints were tested in a hierarchical manner provided that noninferiority was declared for the co-primary endpoints.

When performing the analyses for the key secondary efficacy endpoints, a closed-testing procedure was used so that the lack of significance of a test precluded assessment of subsequent tests. Estimates and CIs were computed for all these key secondary efficacy endpoints irrespective of whether a lack of significance of a test precluded assessment of subsequent tests.

1. If the upper bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in the percentage change from Baseline to Week 26 in LDH is less than the noninferiority margin (NIM) of 20%, then ALXN1210 would be declared noninferior for this parameter and the next parameter would be tested.

2. If the lower bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in change from baseline in FACIT-Fatigue is greater than the NIM of -5, then ALXN1210 would be declared noninferior for this parameter and the next parameter would be tested.

3. If the upper bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in the proportion of patients with BTH is less than the NIM of 20%, then ALXN1210 would be declared noninferior for this parameter and the next parameter would be tested.

4. If the lower bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in the proportion of patients with stabilized haemoglobin is greater than the NIM of -20%, then ALXN1210 would be declared noninferior for this parameter.

If noninferiority was established for all key secondary endpoints, then superiority was assessed using a closed-testing procedure with the following order and using a 2-sided 0.05 test of significance for each parameter.

5. Proportion of patients with BTH through Day 183 (Week 26)

6. Percentage change from baseline to Day 183 (Week 26) in LDH

7. Haemolysis as directly measured by LDH-N from Day 29 through Day 183 (Week 26)

8. Change from baseline to Day 183 (Week 26) in FACIT-Fatigue

9. Proportion of patients with stabilized haemoglobin through Day 183 (Week 26)

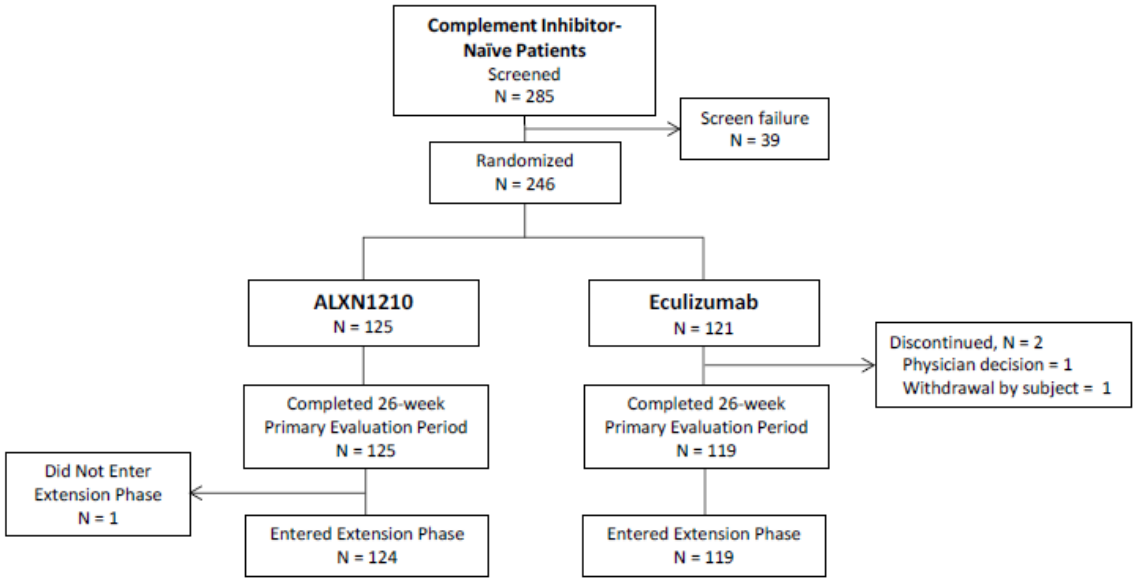
10. Transfusion avoidance

Due to the hierarchical testing order being pre-specified, no adjustment of the type I error was required. Other secondary efficacy analyses were summarized with only descriptive statistics.

Results

Participant flow - ALXN1210-PNH-301

Figure 8: Disposition of Patients – Primary Evaluation Period (All Randomized Patients)



All 246 treated patients (125 patients in the ALXN1210 group and 121 patients in the eculizumab group) were included in the FAS and Safety Set.

Two patients were excluded from the PP Set. One patient in the ALXN1210 group and 1 patient in the eculizumab group met the protocol-specified criteria for pRBC transfusion (haemoglobin ≤ 7 g/dL) but were not transfused at that time or at any other time during the Primary Evaluation Period. Although other

patients met the transfusion criteria at a particular visit but did not receive a transfusion, these patients were included in the PP Set because they received at least 1 transfusion according to the transfusion criteria.

Table 17: Analysis Data Sets (All Randomized Patients)

	ALXN1210 n (%)	Eculizumab n (%)	Total n (%)
Number of randomized patients	125 (100)	121 (100)	246 (100)
Number of patients in the FAS	125 (100)	121 (100)	246 (100)
Number of patients excluded from the FAS	0	0	0
Number of patients in the PP Set	124 (99.2)	120 (99.2)	244 (99.2)
Number of patients excluded from the PP Set	1 (0.8)	1 (0.8)	2 (0.8)
Number of patients in the Safety Set	125 (100)	121 (100)	246 (100)
Number of patients excluded from the Safety Set	0	0	0
Number of patients in the PK Analysis Set	125 (100)	121 (100)	246 (100)
Number of patients excluded from the PK Analysis Set	0	0	0

Abbreviations: FAS = Full Analysis Set; PK = pharmacokinetics; PP = Per Protocol
Source: Table 14.1.2.5.6

There were no differences in the actual stratification at the time of randomization compared to the observed stratification for the LDH groups (LDH 1.5 to < 3×ULN versus LDH ≥ 3×ULN). Of the 44 patients stratified to 0 unit of pRBCs, 1 patient was observed to have received 1 to 14 unit(s) of pRBCs. Of the 157 patients stratified to 1 to 14 unit(s) of pRBCs, 3 patients were observed to have received > 14 units of pRBCs. Of the 45 patients stratified to > 14 units unit of pRBCs, 1 patient was observed to have received 1 to 14 unit(s) of pRBCs.

Recruitment

- First patient treated: 20 Dec 2016
- Last patient completed Primary Evaluation Period: 25 Jan 2018
- Release date of report: 23 May 2018

246 patients were randomized, yielding n=125 for the ALXN1210 arm, and n=121 for the eculizumab arm. Two discontinuations were due to clinician's decision, and withdrawal of consent.

All but 1 patient entered the extension phase.

Conduct of the study

Protocol ALXN1210-PNH-301: Original Protocol 09 August 2016

Protocol amendments
From the original protocol (dated 09 Aug 2016, which was submitted to regulatory authorities), 6 country-specific and 3 global protocol amendments were made during the Primary Evaluation Period of the study.

Changes in Planned Analyses
The SAP (version 3.1) was finalized on 12 Dec 2017, prior to database lock for the Primary Evaluation Period.

Protocol deviations:

Table 18: Major Protocol Deviations (Full Analysis Set) ALXN1210-PNH-301

	ALXN1210 (N=125)	Eculizumab (N=121)	Total (N=246)
Patients with major deviations, n (%)	13 (10.4)	20 (16.5)	33 (13.4)
Type of major deviations			
Study procedures/tests	4 (3.2)	8 (6.6)	12 (4.9)
Informed consent	4 (3.2)	3 (2.5)	7 (2.8)
Safety reporting	3 (2.4)	3 (2.5)	6 (2.4)
Randomization	1 (0.8)	4 (3.3)	5 (2.0)
Investigational product	1 (0.8)	2 (1.7)	3 (1.2)
Eligibility and entry criteria	0	2 (1.7)	2 (0.8)

Baseline data

Table 19: Demographic and Other Baseline Characteristics Study ALXN1210-PNH-301

Variable	ALXN1210 (N = 125)	Eculizumab (N = 121)	Total (N = 246)
Sex, n (%)			
Male	65 (52.0)	69 (57.0)	134 (54.5)
Female	60 (48.0)	52 (43.0)	112 (45.5)
Ethnicity, n (%)			
Not Hispanic or Latino	116 (92.8)	102 (84.3)	218 (88.6)
Hispanic or Latino	5 (4.0)	13 (10.7)	18 (7.3)
Not reported	2 (1.6)	4 (3.3)	6 (2.4)
Missing/unknown	2 (1.6)	2 (1.7)	4 (1.6)
Race, n (%)			
Asian	72 (57.6)	57 (47.1)	129 (52.4)
Non-Japanese descent	53 (42.4)	42 (34.7)	95 (38.6)
Japanese descent	19 (15.2)	15 (12.4)	34 (13.8)
White	43 (34.4)	51 (42.1)	94 (38.2)
Other	4 (3.2)	4 (3.3)	8 (3.3)
Not reported	3 (2.4)	4 (3.3)	7 (2.8)
Black or African American	2 (1.6)	4 (3.3)	6 (2.4)
American Indian or Alaska Native	1 (0.8)	1 (0.8)	2 (0.8)
Age at first infusion (years)			
Mean (SD)	44.8 (15.16)	46.2 (16.24)	45.5 (15.69)
Median	43.0	45.0	44.0
Min, max	18, 83	18, 86	18, 86
Age at first infusion (years) category, n (%)			
18 to 65 years	111 (88.8)	103 (85.1)	214 (87.0)
> 65 years	14 (11.2)	18 (14.9)	32 (13.0)
Baseline weight (kg)			
Mean (SD)	68.2 (15.58)	69.2 (14.86)	68.7 (15.21)
Median	66.5	67.2	66.7
Min, max	40, 115	45, 113	40, 115
Baseline weight (kg) category, n (%)			
≥ 40 to < 60 kg	41 (32.8)	38 (31.4)	79 (32.1)
≥ 60 to < 100 kg	79 (63.2)	81 (66.9)	160 (65.0)
≥ 100 kg	5 (4.0)	2 (1.7)	7 (2.8)
Baseline BMI (kg/m^2)			
n	125	120	245
Mean (SD)	24.5 (4.70)	24.9 (4.26)	24.7 (4.48)
Median	23.9	24.2	24.0
Min, max	16, 41	16, 36	16, 41

Abbreviations: BMI = body mass index; max = maximum; min = minimum; SD = standard deviation

Table 20: Disease Characteristics (Full Analysis Set) Study ALXN1210-PNH-301

Variable Category	ALXN1210 (N = 125)	Eculizumab (N = 121)	Total (N = 246)
Age (years) at PNH diagnosis			
n	123	118	241
Mean (SD)	37.9 (14.90)	39.6 (16.65)	38.7 (15.77)
Median	34.0	36.5	35.0
Min, Max	15, 81	13, 82	13, 82
Years from diagnosis to informed consent			
n	123	118	241
Mean (SD)	6.7 (8.14)	6.4 (7.54)	6.6 (7.84)
Median	3.8	3.9	3.9
Min, max	0, 41	0, 34	0, 41
PNH clone size at baseline			
PNH RBC type II clone size (%)			
n	124	120	244
Mean (SD)	12.36 (20.539)	13.70 (17.672)	13.02 (19.155)
Median	4.00	6.15	5.00
Min, max	0.1, 99.5	0.1, 95.3	0.1, 99.5
PNH RBC type III clone size (%)			
n	124	120	244
Mean (SD)	26.29 (17.246)	25.21 (16.944)	25.76 (17.071)
Median	26.35	21.20	24.10
Min, max	0.1, 82.0	0.4, 75.6	0.1, 82.0
Total PNH RBC clone size (%)			
n	125	121	246
Mean (SD)	38.40 (23.748)	38.74 (23.194)	38.57 (23.430)
Median	33.60	34.20	33.75
Min, max	3.0, 99.6	2.2, 98.0	2.2, 99.6
Total PNH granulocyte clone size (%)			
n	125	121	246
Mean (SD)	84.22 (20.956)	85.28 (18.977)	84.74 (19.973)
Median	93.80	92.40	92.55
Min, max	4.2, 99.9	8.0, 100.0	4.2, 100.0
Total PNH monocyte clone size (%)			
n	125	121	246
Mean (SD)	86.86 (18.078)	89.15 (15.189)	87.99 (16.725)
Median	94.00	95.10	94.80
Min, max	8.5, 99.9	17.0, 99.9	8.5, 99.9

Note: Total RBC, granulocyte, monocyte clone size = sum type II and type III RBC, granulocyte, monocyte clone size, respectively. Baseline was defined as the last non-missing value prior to first dose of study drug.
Abbreviations: max = maximum; min = minimum; SD = standard deviation; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell

Enrolment into the 0 prior units of RBCs (ie, history of no transfusion) stratum was closed once the protocol-specified 20% cap on enrolment of patients with a history of no transfusions in the prior year was reached. Therefore, the majority of patients (82.5%) had a history of pRBC transfusions in the year prior to first dose of study drug. In the total population, a mean of 6.2 pRBC/whole blood transfusions were administered and a mean of 8.8 units were transfused during the 12 months prior to first dose.

Table 21: Study ALXN1210-PNH-301 Transfusion History: Red Blood Cell Transfusions Within 12 Months Prior to First Dose (Full Analysis Set)

Variable Category	Ravulizumab (N = 125)	Eculizumab (N = 121)	Total (N = 246)
Number of patients with pRBC/whole blood transfusions within 12 months prior to first dose, n (%)	103 (82.4)	100 (82.6)	203 (82.5)
pRBC/whole blood transfusions within 12 months prior to first dose			
Total	677	572	1249
Mean (SD)	6.6 (6.04)	5.7 (5.53)	6.2 (5.80)
Median	4.0	3.0	4.0
Min, max	1, 28	1, 28	1,28
Units of pRBC/whole blood transfused within 12 months prior to first dose			
Total	925	861	1786
Mean (SD)	9.0 (7.74)	8.6 (7.90)	8.8(7.81)
Median	6.0	6.0	6.0
Min, max	1, 44	1, 32	1,44

Abbreviations: max = maximum; min = minimum; pRBC = packed red blood cell; SD = standard deviation

In the total population, 98.0% of patients had documented PNH-associated conditions that were diagnosed prior to informed consent. The majority (84.6%) of patients had a prior diagnosis of anemia; 32.1% of patients had a history of aplastic anemia, 12.2% of patients had a history of renal failure, and 5.3% of patients had myelodysplastic syndrome.

Table 22: PNH-Associated Conditions Diagnosed at Any Time Prior to Informed Consent (Full Analysis Set)

PNH-Associated Condition, n (%)	Ravulizumab (N = 125)	Eculizumab (N = 121)	Total (N = 246)
Patients with any PNH conditions prior to informed consent	121 (96.8)	120 (99.2)	241 (98.0)
Anemia	103 (82.4)	105 (86.8)	208 (84.6)
Hematuria or haemoglobinuria	81 (64.8)	75 (62.0)	156 (63.4)
Aplastic anemia	41 (32.8)	38 (31.4)	79 (32.1)
Renal failure	19 (15.2)	11 (9.1)	30 (12.2)
Myelodysplastic syndrome	7 (5.6)	6 (5.0)	13 (5.3)
Pregnancy complication	3 (2.4)	4 (3.3)	7 (2.8)
Other[a]	27 (21.6)	13 (10.7)	40 (16.3)

Note: Conditions as documented in patient medical record. Patients could have been counted in more than one category.

[a] *"Other": as specified on case report from included thrombocytopenia, chronic kidney disease and pancytopenia, as well as number of other conditions.*

Abbreviations: CSR = clinical study report; PNH = paroxysmal nocturnal haemoglobinuria

Numbers analysed

Table 23: **Study ALXN1210-PNH-301 Efficacy Analysis Data Sets (All Randomized Patients)**

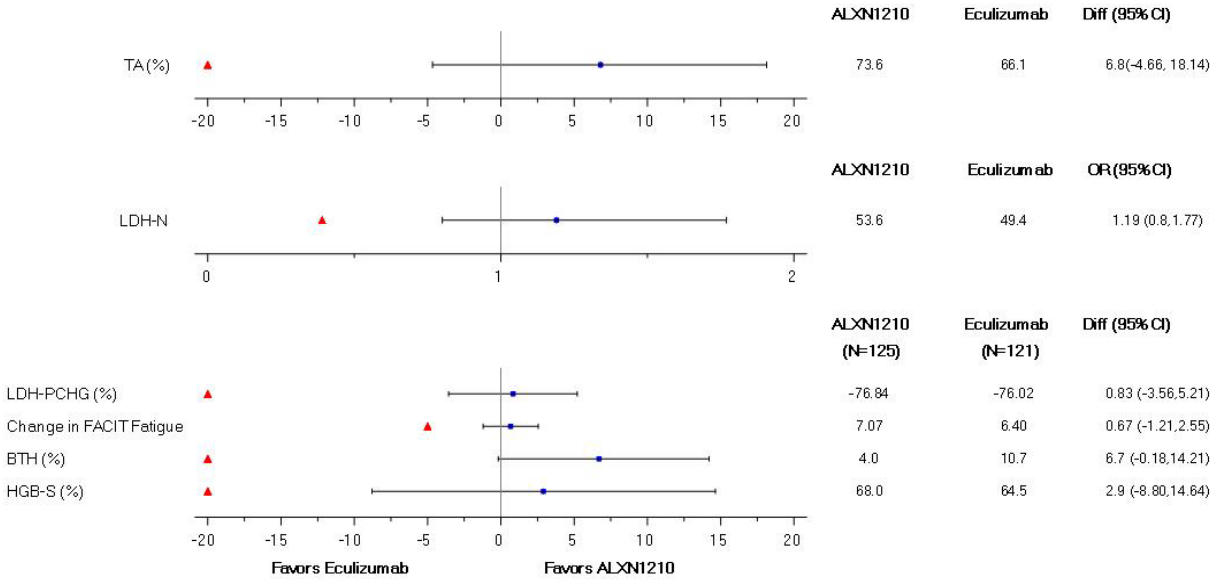
	Ravulizumab n (%)	Eculizumab n (%)	Total n (%)
Number of randomized patients	125 (100)	121 (100)	246 (100)
Number of patients in the FAS	125 (100)	121 (100)	246 (100)
Number of patients in the PP Set	124 (99.2)	120 (99.2)	244 (99.2)

Abbreviations: FAS = Full Analysis Set; PP = Per Protocol

Outcomes and estimation

Study ALXN1210-PNH-301: Complement Inhibitor-Naïve Patients

Figure 9: Study ALXN1210-PNH-301 Forest Plot of Co-primary and Key Secondary Endpoints – Primary Evaluation Period (Full Analysis Set)



Note: The red triangle indicates the noninferiority margin. For TA, Diff (95% CI) was based on estimated differences in percent with 95% CI. For endpoints LDH-PCHG, BTH, and HGB-S, Diff (95% CI) were based on estimated differences in percent with 95% CI. For LDH-N, adjusted prevalence within each treatment was displayed. To calculate the LDH-N odds ratio of ravulizumab relative to eculizumab from the displayed adjusted prevalence rates, divide the odds of LDH-N on ravulizumab (0.536/[1-0.536]) by the odds of LDH-N on eculizumab (0.494/[1-0.494]).
For FACIT-Fatigue, Diff (95% CI) were based on estimated differences in change from baseline with 95% CI. Treatment difference was estimated for ravulizumab - eculizumab except for LDH-PCHG and BTH where treatment difference is displayed as eculizumab - ravulizumab for consistency.
Abbreviations: ALXN1210 = ravulizumab; BTH = breakthrough haemolysis; CI = confidence interval; Diff = difference; LDH-N = lactate dehydrogenase normalization; OR = odds ratio; TA = transfusion avoidance

Co-primary Endpoints

Transfusion Avoidance Per Protocol Specified Guidelines (non-inferiority analysis)

In **Study ALXN1210-PNH-301**, 73.6% of patients in the ravulizumab group and 66.1% in the eculizumab group avoided pRBC transfusion. The difference between the ravulizumab and eculizumab treatment groups in the percentage of patients who avoided transfusion was 6.8% (95% CI: -4.66%, 18.14%). The lower bound of the 95% CI was greater than the protocol-specified NIM of -20%. Results from the primary analysis using the PP Set were consistent with those of the FAS, as were results from other sensitivity analyses.

Patients who fulfilled the protocol-specified transfusion criteria were analyzed as having received a transfusion, regardless of whether the patients had actually received a transfusion. This analysis includes 1 patient in the ravulizumab group and 1 patient in the eculizumab group who met the protocol-specified criteria for pRBC transfusion (haemoglobin ≤ 7 g/dL) but were not transfused at that time or at any other time during the Primary Evaluation Period.

Table 24: Study ALXN1210-PNH-301 - Number (%) of Patients Achieving Transfusion Avoidance Per Protocol Specified Guidelines During Primary Evaluation Period (Full Analysis Set)

Achieved Transfusion Avoidance	Ravulizumab (N = 125)	Eculizumab (N = 121)	Treatment Difference (Ravulizumab - Eculizumab)
n	92	80	
%	73.6	66.1	6.8
95% CI[b]	(65.87, 81.33)	(57.68, 74.55)	(-4.66, 18.14)

Note: Transfusion avoidance was defined as the proportion of patients who remained transfusion free and did not require a transfusion per protocol-specified guidelines through Day 183 (Week 26).

Percentage and CI for the difference of percentages are calculated using stratified Newcombe confidence interval method. The stratification factors were observed stratification groups of pRBC/whole blood units transfused in the 1 year prior to first dose of study drug and screening LDH levels.
Abbreviations: CI = confidence interval; pRBC = packed red blood cell

Table 25: Study ALXN1210-PNH-301 - Sensitivity Analyses for Transfusion Avoidance

Analysis	Treatment Difference (95% CI)
Full Analysis Set	6.8% (-4.66%, 18.14%)
PP Set	7.2% (-4.27%, 18.51%)
pRBC categories: 0, 1 to 4, > 4 to 14 and > 14 units	7.5% (-4.14%, 18.93%)
Independent of protocol specified transfusion guidelines	6.9% (-4.55%, 18.09%)
Independent of randomization factors	7.5% (-3.95%, 18.70%)

Abbreviations: CI = confidence interval; PP = per protocol; pRBC = packed red blood cells
Source: Table 14.2.1.1.01.1, Table 14.2.1.1.01.3, Table 14.2.1.1.02.1, Table 14.2.1.1.03.1, and Table 14.2.1.1.04.1

LDH Normalization (non-inferiority analysis)

The adjusted prevalence of LDH-N (LDH levels ≤ 1 × ULN from Day 29 through Day 183) was 0.536 for the ravulizumab group and 0.494 for the eculizumab group. The adjusted odds ratio for the comparison of ravulizumab to eculizumab was 1.187 (95% confidence interval [CI]: 0.796, 1.769). The lower bound of the 95% CI was greater than the protocol-specified NIM of 0.39.

Results from the primary analysis using the PP Set were consistent with those of the FAS, as were results from other sensitivity analyses.

Table 26: Study ALXN1210-PNH-301 - LDH Normalization (Full Analysis Set)

Statistics	Ravulizumab (N = 125)	Eculizumab (N = 121)	Treatment Effect
Adjusted prevalence of LDH-N	0.536	0.494	
95% CI for adjusted prevalence of LDH-N	(0.459, 0.612)	(0.417, 0.570)	
Odds ratio			1.187
95% CI for odds ratio			(0.796, 1.769)

Note: The ULN for LDH is 246 U/L. LDH-N was LDH levels less than or equal to 1 × ULN, from Day 29 through Day 183. Estimation was based on a GEE approach. The model included the following terms: treatment group, history of transfusion (as a categorical variable based on the stratification factor levels), and baseline LDH level (as a continuous variable). Missing assessments of LDH for a particular patient at a particular visit was not imputed. An autoregressive (1) covariance structure was used.
Abbreviations: CI = confidence interval; GEE = generalized estimating equation; LDH-N = normalization of lactate dehydrogenase levels; ULN = upper limit of normal

Table 27: Study ALXN1210-PNH-301 - Sensitivity Analyses for LDH Normalization

Analysis	Treatment Effect (95% CI)
Full Analysis Set	1.187 (0.796, 1.769)
PP Set	1.230 (0.824, 1.835)
pRBC categories: 0, 1 to 4, > 4 to 14 and > 14 units	1.204 (0.808, 1.795)
Use of continuous transfusion history	1.202 (0.807, 1.791)
Independent of randomization factors	1.198 (0.804, 1.785)
Weighted GEE to handle dropouts	1.184 (0.794, 1.766)

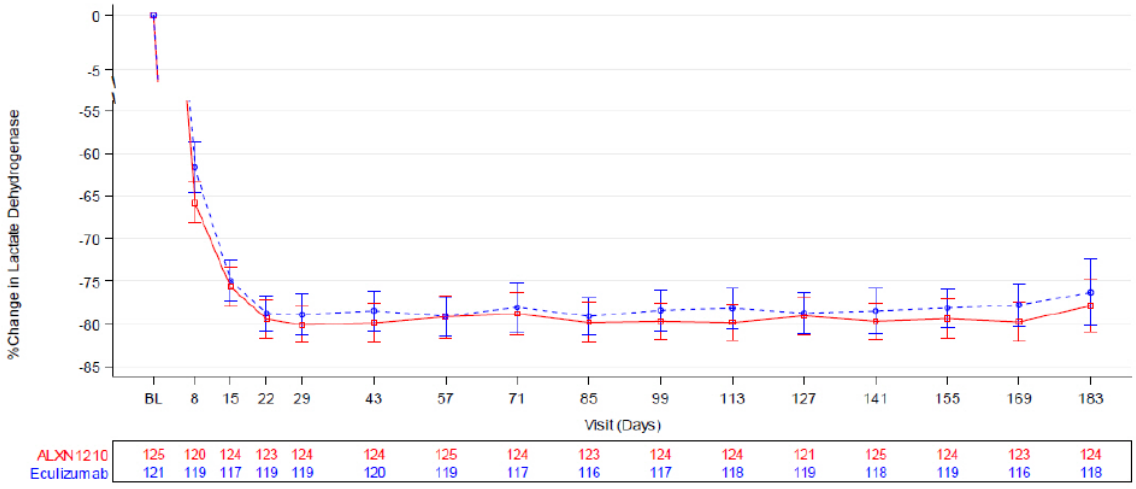
Abbreviations: CI = confidence interval; GEE = generalized estimating equation; LDH = lactate dehydrogenase; PP = per protocol; pRBC = packed red blood cell

Key Secondary Endpoints

Percent Change in LDH (non-inferiority analysis)

At baseline, mean (standard deviation [SD]) LDH values were 1633.53 (778.752) U/L and 1578.30 (727.061) U/L for ravulizumab and eculizumab, respectively. The least square (LS) mean (standard error of the mean [SEM]) percent change in LDH from baseline to Day 183 was –76.84% (1.582%) for the ravulizumab group and –76.02% (1.617%) for the eculizumab group. The LS mean difference between treatment groups was –0.83% (2.227%; 95% CI: –5.21%, 3.56%). The upper bound of the 95% CI was less than the protocol specified NIM of 20%.

Figure 10: Study ALXN1210-PNH-301 - Mean (95% CI) Percentage Change From Baseline in LDH (U/L) Over Time, by Treatment Group (Full Analysis Set)



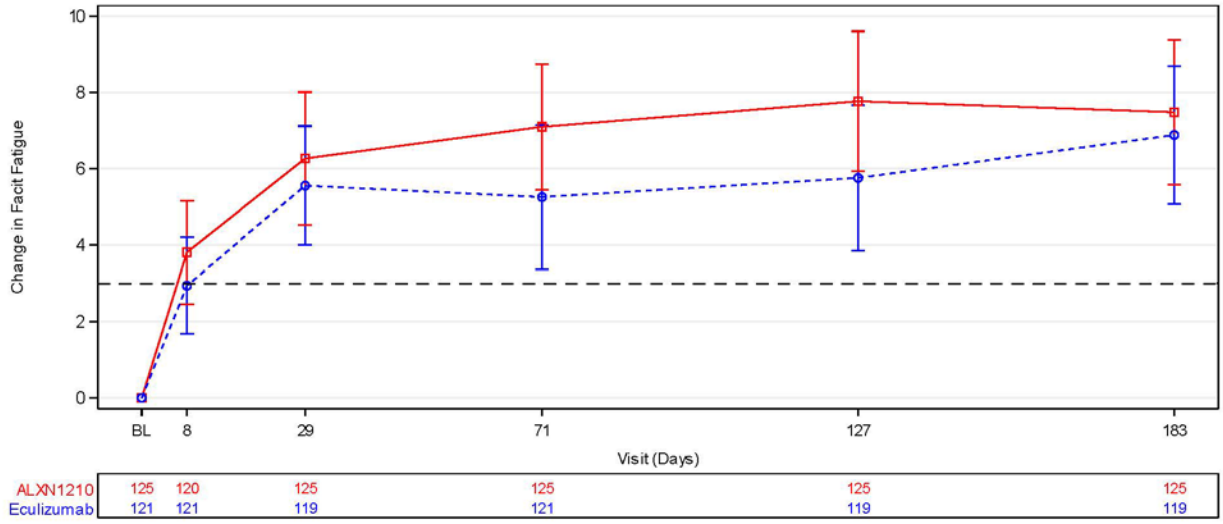
Note: Baseline was defined as the average of all available assessments from the central laboratory prior to first study drug dose.

Abbreviations: BL = baseline; CI = confidence interval; LDH = lactate dehydrogenase

FACIT-Fatigue (non-inferiority analysis)

At baseline, mean FACIT-Fatigue total scores were 36.66 for ravulizumab and 36.94 for eculizumab. At Day 183, the LS mean (SEM) change in FACIT Fatigue total score was 7.07 (0.773) for ravulizumab and 6.40 (0.789) for eculizumab. The LS mean difference between treatment groups was 0.67 (95% CI: –1.21, 2.55). The lower bound of the 95% CI was greater than the protocol specified NIM of –5.

Figure 11: Study ALXN1210-PNH-301 - Mean (95% CI) FACIT-Fatigue Over Time, by Treatment Group – Primary Evaluation Period (Full Analysis Set)



Note: FACIT score ranges from 0 to 52, with a higher score indicating less fatigue. Baseline was defined as the last non-missing assessment value prior to first study drug dose. Dashed horizontal line indicates threshold that delineates clinically meaningful improvement (> 3 points).
Abbreviation: ALXN1210 = ravulizumab; BL = baseline; CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy

An improvement of ≥ 3 points in FACIT-Fatigue score, considered to be a clinically meaningful improvement (Cella, 2002; Webster, 2003), was observed at Day 8 in 45.6% of ravulizumab-treated patients and 43.0% of eculizumab-treated patients. This improvement of ≥ 3 points in FACIT-Fatigue score was evident at all subsequent study time points and at Day 183 was observed in 61.6% of ravulizumab-treated patients and 58.7% of the eculizumab-treated patients.

Breakthrough Haemolysis (non-inferiority analysis)

The difference between treatment groups in the proportion of patients who experienced BTH was 6.7% (95% CI: –14.21%, 0.18%). The upper bound of the 95% CI was less than the protocol specified NIM of 20%. Fewer ravulizumab-treated patients (4.0%, n = 5) experienced BTH during the Primary Evaluation Period compared with eculizumab-treated patients (10.7%, n = 13), representing more than a 2-fold difference between treatment groups.

Table 28: Study ALXN1210-PNH-301 - Number (%) of Patients with Breakthrough Haemolysis Through Day 183 (Week 26) – Primary Evaluation Period (Full Analysis Set)

Experienced Breakthrough Haemolysis	**Ravulizumab (N = 125)**	**Eculizumab (N = 121)**	**Treatment Difference (Ravulizumab - Eculizumab)**
Number of patients (n) Percentage of patients (%) 95% CI	5 4.0 (0.56, 7.44)	13 10.7 (5.23, 16.26)	 -6.7 (-14.21, 0.18)

Note: Breakthrough haemolysis was defined as at least 1 new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [haemoglobin < 10 g/dL], major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy. The CI for the difference of percentages was calculated using stratified Newcombe CI method. The stratification factors were: observed stratification groups of pRBC units transfused in the 1 year prior to first dose of study drug and screening LDH levels. Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase; pRBC = packed red cell; ULN = upper limit of normal

Number (%) of Patients with Breakthrough Hemolysis Through Day 183 (Week 26)
Per Protocol Set

Variable	ALXN1210 (N=124)	Eculizumab (N=120)	Treatment Difference (ALXN1210-Eculizumab)
Experiencing Breakthrough Hemolysis Through Day 183 (Week 26)			
Number of Patients (n)	5	13	
Percentage (%)	4.0	10.8	-6.7
95% CI	(0.57, 7.49)	(5.27, 16.39)	(-14.33, 0.17)

Note: CI=Confidence Interval.
Note: Breakthrough hemolysis is defined as at least one new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2×ULN, after prior LDH reduction to < 1.5×ULN on therapy.
Note: Percentages are based on the total number of patients in each group.
Note: CI for the difference of percentages is calculated using stratified Newcombe confidence interval method. The stratification factors are: observed stratification groups of pRBC units transfused in the 1 year prior to first dose of study drug and screening LDH levels.
Source: ADaM.ADSL, ADaM.ADFA Based on data cutoff date of 06Mar2018
Run Date: 2018-05-10T03:59:11 FINAL
/alxn/a1210-pnh-301/a1210-pnh-301-csr/Files/tables/production/programs/t-pt-bh-dl83-pps.sas

Analysis of Patients Who Experienced Breakthrough Haemolysis

Each event of BTH was reviewed in an effort to evaluate the etiological factors involved, including time-matched PD parameters and/or presence of a potential infection or other complement amplifying condition (CAC), eg, trauma, surgery, or pregnancy (Brodsky, 2017; Risitano, 2012; Sharma, 2015). Breakthrough haemolysis associated with suboptimal PD was defined as free C5 ≥ 0.5 µg/mL. Adverse events temporally associated with the onset of BTH were also reviewed for each patient to evaluate for potential infections or other CAC.

In Study ALXN1210-PNH-301, 18 patients experienced BTH during the Primary Evaluation Period: 5 ravulizumab-treated patients experienced 1 event each and 13 eculizumab-treated patients had a total of 15 events. There was no clear pattern in the length of time elapsed from initiation of treatment to onset of BTH; the earliest BTH event occurred at Day 43 in the eculizumab group and at Day 71 in the ravulizumab group. None of the 5 BTH events in the ravulizumab group was associated with suboptimal C5 inhibition (free C5 ≥ 0.5 µg/mL), whereas 7 of the 15 BTH events in the eculizumab group were associated with suboptimal C5 inhibition. Infection was associated with 4 of the 5 BTH events in the ravulizumab group and 6 of the 15 BTH events in the eculizumab group (including 2 events also

associated with suboptimal C5 inhibition). Among these patients, no potential CAC other than infection was identified.

Table 29: Study ALXN1210-PNH-301 - Analysis of Breakthrough Haemolysis Cases in Phase 3 Studies (Full Analysis Set)

Breakthrough Haemolysis Events	**Ravulizumab (N = 125)**	**Eculizumab (N = 121)**
Total number of BTH events	5	15
Suboptimal PD[a]	0	7[b]
Infection/CAC	4	4
Undetermined[c]	1	4

Note: Breakthrough haemolysis was defined as at least 1 new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [haemoglobin < 10 g/dL], major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy.

[a] *Suboptimal PD was defined as free C5 ≥ 0.5 µg/mL.*

[b] *Two patients in the eculizumab group with suboptimal PD also had concomitant infection.*

[c] *Undetermined cases had neither suboptimal PD nor concomitant infection identified.*

Abbreviations: BTH = breakthrough haemolysis; CAC = complement amplifying condition; C5 = complement component 5; LDH = lactate dehydrogenase; PD = pharmacodynamics; ULN = upper limit of normal

Haemoglobin Stabilization (non-inferiority analysis)

The difference between treatment groups in the percentage of patients who experienced haemoglobin stabilization was 2.9% (95% CI: –8.80%, 14.64%). The lower bound of the 95% CI was greater than the protocol-specified NIM of –20%. The percentage of patients with haemoglobin stabilization was greater for the ravulizumab group (68%) compared with the eculizumab group (64.5%).

Table 30: Study ALXN1210-PNH-301 - Number (%) of Patients With Stabilized Haemoglobin Through Day 183 (Week 26) (Full Analysis Set)

Achieved Stabilized Haemoglobin	Ravulizumab (N = 125)	Eculizumab (N = 121)	Treatment Difference (Ravulizumab - Eculizumab)
Number of patients (n) Percentage (%) 95% CI	85 68.0 (59.82, 76.18)	78 64.5 (55.93, 72.99)	 2.9 (-8.80, 14.64)

Note: Stabilized haemoglobin was defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26). The CI for the difference of percentages was calculated using stratified Newcombe CI method. The stratification factors were observed stratification groups of pRBC units transfused in the 1 year prior to first dose of study drug and screening LDH levels.

Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase; pRBC = packed red blood cell

Number (%) of Patients with Stabilized Hemoglobin Through Day 183 (Week 26)
Per Protocol Set

Variable	ALXN1210 (N=124)	Eculizumab (N=120)	Treatment Difference (ALXN1210-Eculizumab)
Achieved Stabilized Hemoglobin Through Day 183 (Week 26)			
Number of Patients (n)	84	77	
Percentage (%)	67.7	64.2	3.3
95% CI	(59.51, 75.97)	(55.59, 72.75)	(-8.54, 15.03)

Note: CI=Confidence Interval.
Note: Stabilized Hemoglobin is defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26).
Note: Percentages are based on the total number of patients in each group.
Note: CI for the difference of percentages is calculated using stratified Newcombe confidence interval method. The stratification factors are: observed stratification groups of pRBC units transfused in the 1 year prior to first dose of study drug and screening LDH levels.
Source: ADaM.ADSL, ADaM.ADEFF Based on data cutoff date of 06Mar2018
Run Date: 2018-05-10T04:00:02 FINAL
/alxn/a1210-pnh-301/a1210-pnh-301-csr/Files/tables/production/programs/t-pt-stab-hgb-d183-pps.sas

Breakthrough haemolysis (superiority analysis)

Breakthrough haemolysis was the first endpoint to be tested for superiority. A trend in favor of ALXN1210 was observed for BTH (ALXN1210: 4.0% [95% CI: 0.6%, 7.4%]; eculizumab: 10.7% [95% CI: 5.2%, 16.3%]). In the assessment of the results for superiority, an approximate p-value was sought to understand how close the results were to meeting statistical significance. To calculate the p-value, the CI from the pre-specified analytic approach was inverted to solve for the type 1 error that would result in the observed CI that just excluded 0. This resulted in p = 0.0558. Since the difference did not reach statistical significance for superiority ($p < 0.05$), no further testing was conducted.

Table 31: Study ALXN1210-PNH-301 - Number (%) of Patients with Breakthrough Haemolysis Through Day 183 (Week 26) (FAS)

Variable	ALXN1210 (N=125)	Eculizumab (N=121)	Treatment Difference (ALXN1210-Eculizumab)
Experiencing Breakthrough Hemolysis Through Day 183 (Week 26)			
Number of Patients (n)	5	13	
Percentage (%)	4.0	10.7	-6.7
95% CI	(0.56, 7.44)	(5.23, 16.26)	(-14.21, 0.18)[1]

Note: CI=Confidence Interval.
Note: Breakthrough haemolysis is defined as at least one new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [haemoglobin < 10 g/dL], major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2×ULN, after prior LDH reduction to < 1.5×ULN on therapy.
Note: Percentages are based on the total number of patients in each group.
Note: CI for the difference of percentages is calculated using stratified Newcombe confidence interval method. The stratification factors are: observed stratification groups of pRBC units transfused in the 1 year prior to first dose of study drug and screening LDH levels.
[1] An approximate pvalue for superiority associated with the upper bound is 0.0558
Source: ADaM.ADSL, ADaM.ADFA Based on data cutoff date of 06Mar2018
Run Date: 2018-05-10T03:58:58 FINAL

Other Secondary Endpoints

EORTC QLQ-C30

An improvement of ≥ 10 points in the 3 subscales of the EORTC QLQ-C30 is considered to indicate a clinically meaningful improvement (King, 1996; Osoba, 1998). The mean EORTC QLQ-C30 Global Health Status subscale scores at baseline were 56.13% for the ravulizumab group and 57.51% for the eculizumab group. A higher percentage of patients in the ravulizumab group had at least a 10 point improvement in the Global Health Status, Physical Functioning, and Fatigue subscale scores at Day 29 and throughout the Primary Evaluation Period compared with the eculizumab group.

The mean Time to LDH Normalization; median time to first LDH-N was 24 days (95% CI: 22, 29) for the ravulizumab group and 29 days (95% CI: 24, 43) for the eculizumab group. The time to LDH-N was 5 days shorter for the ravulizumab group.

Total Number of pRBC Units Transfused; The majority of the complement inhibitor-naïve patients (82.5%) in Study ALXN1210 PNH 301 were transfusion dependent at study entry (ie, had received 1 or more transfusions in the year prior to study entry). During the Primary Evaluation Period, the total number of units transfused was lower in ravulizumab-treated patients compared with eculizumab-treated patients.

Table 32: pRBC Transfusions from First Dose of Study Drug to Day 183 (Week 26) (FAS)

Variable	**Ravulizumab (N = 125)**	**Eculizumab (N = 121)**
Number of patients who received any pRBC/whole blood transfusions from first dose of study drug to Day 183, n (%)	32 (25.6)	40 (33.1)
pRBC/whole blood transfusions from first dose of study drug to Day 183		
Total	107	144
Mean (SD)	3.3 (4.15)	3.6 (3.06)
Median	2.0	3.0
Min, max	1, 23	1, 14
Units of pRBC/whole blood transfused from first dose of study drug to Day 183		
Total	155	222
Mean (SD)	4.8 (5.06)	5.6 (5.93)
Median	2.5	3.0
Min, max	1, 24	1, 30

Abbreviations: min = minimum; max = maximum; pRBC = packed red blood cell; SD = standard deviation

Clinical Manifestations of PNH ;

Table 33: Shifts in Clinical Manifestations of PNH From Baseline to Day 183 (Full Analysis Set)

	ALXN1210					Eculizumab				
			Post-Baseline Time Point					Post-Baseline Time Point		
Parameter	Total N	Baseline	Yes n (%)	No n (%)	NA n (%)	Total N	Baseline	Yes n (%)	No n (%)	NA n (%)
Fatigue	125	Yes	30 (24.0)	50 (40.0)	--	119	Yes	31 (26.1)	45 (37.8)	--
		No	6 (4.8)	39 (31.2)	--		No	5 (4.2)	38 (31.9)	--
Abdominal pain	125	Yes	3 (2.4)	14 (11.2)	--	119	Yes	4 (3.4)	11 (9.2)	--
		No	3 (2.4)	105 (84.0)	--		No	2 (1.7)	102 (85.7)	--
Dyspnoea	125	Yes	14 (11.2)	28 (22.4)	--	119	Yes	11 (9.2)	27 (22.7)	--
		No	4 (3.2)	79 (63.2)	--		No	6 (5.0)	75 (63.0)	--
Dysphagia	125	Yes	1 (0.8)	12 (9.6)	--	119	Yes	1 (0.8)	15 (12.6)	--
		No	2 (1.6)	110 (88.0)	--		No	0	103 (86.6)	--
Chest pain	125	Yes	1 (0.8)	4 (3.2)	--	119	Yes	5 (4.2)	12 (10.1)	--
		No	2 (1.6)	118 (94.4)	--		No	2 (1.7)	100 (84.0)	--
Red/dark urine or hemoglobinuria	125	Yes	12 (9.6)	59 (47.2)	--	118	Yes	8 (6.8)	48 (40.7)	--
		No	1 (0.8)	53 (42.4)	--		No	3 (2.5)	59 (50.0)	--
Erectile dysfunction	125	Yes	6 (4.8)	10 (8.0)	0	119	Yes	3 (2.5)	18 (15.1)	0
		No	4 (3.2)	45 (36.0)	0		No	2 (1.7)	45 (37.8)	0
		NA	0	0	60 (48.0)		NA	0	0	51 (42.9)

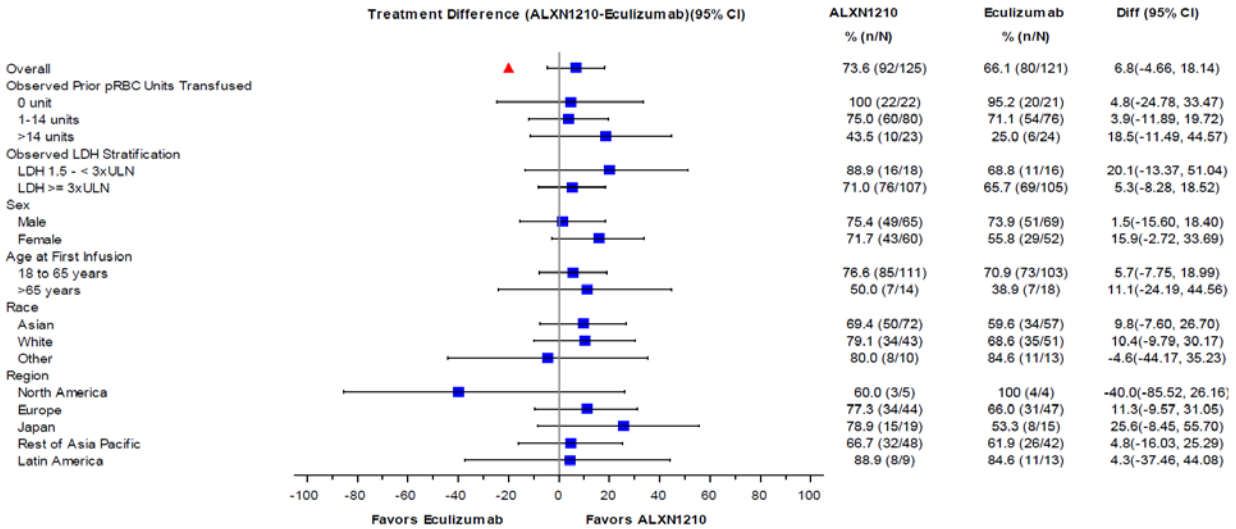
Note: Baseline was defined as the last non-missing value prior to first dose of study drug. Total N = Number of patients with both non-missing Baseline and the respective post-Baseline values for specified parameter. Percentages for each parameter are calculated using Total N as denominator.
Abbreviations: NA = not applicable; PNH = paroxysmal nocturnal hemoglobinuria

Major Adverse Vascular Events (MAVEs); 2 events occurred in the ravulizumab group and 1 event in the eculizumab group.

Ancillary analyses

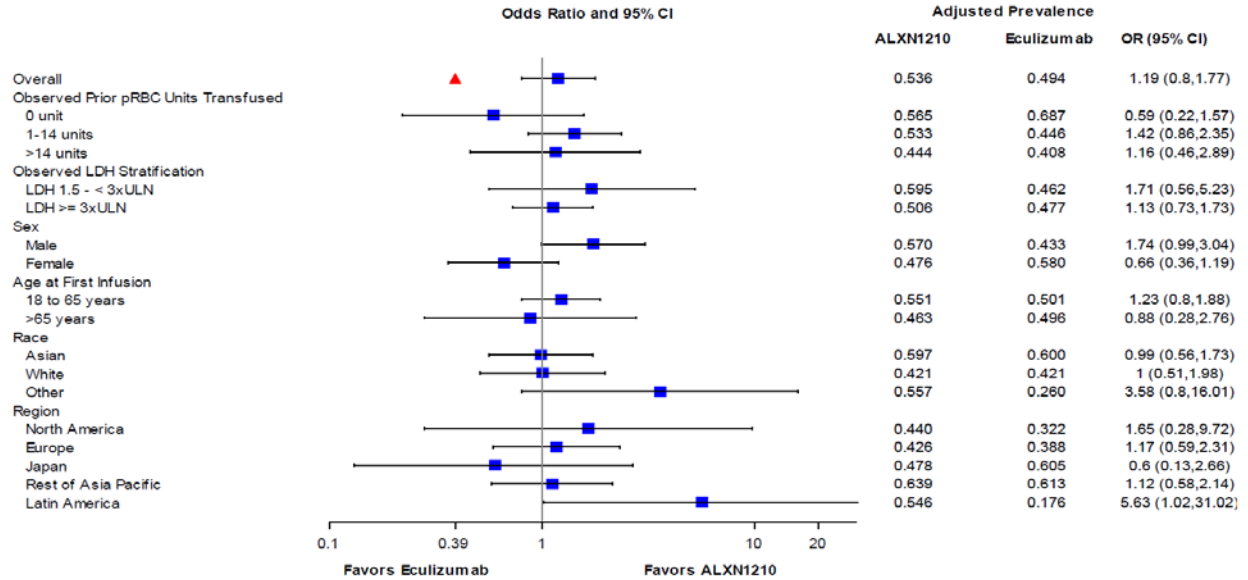
Subgroups analysis of primary and co-primary endpoints in Study ALXN1210-PNH-301

Figure 12: Forest Plot of Transfusion Avoidance Treatment Difference (Ravulizumab Eculizumab) During the Primary Evaluation Period, Overall and by Subgroup (FAS)



Note: Transfusion avoidance was defined as the proportion of patients who remained transfusion free and did not require a transfusion per protocol specified guidelines through Day 183 (Week 26). The red triangle indicates the noninferiority margin.Abbreviations: ALXN1210 = ravulizumab; CI = confidence interval; Diff = difference; LDH = lactate dehydrogenase; pRBC = packed red blood cell; ULN = upper limit of normal

Figure 13: Study ALXN1210 PNH 301 - Forest Plot of Patients Achieving LDH-N (Odds Ratio) During the Primary Evaluation Period, Overall and by Subgroup (Full Analysis Set)



Note: X-axis is presented on log scale. LDH-N is LDH levels less than or equal to 1 × ULN, from Day 29 through Day 183. The ULN for LDH is 246 U/L. The red triangle indicates the non-inferiority margin.
Abbreviations: ALXN1210 = ravulizumab; CI = confidence interval; OR = odds ratio; LDH-N = normalization of lactate dehydrogenase levels; pRBC = packed red blood cell; ULN = upper limit of normal

Study ALXN1210-PNH-302, a Phase 3, Randomized, Open-Label, Active-Controlled Study of ALXN1210 Versus Eculizumab in Adult Patients With Paroxysmal Nocturnal Haemoglobinuria (PNH) Currently Treated With Eculizumab

Methods

Study Participants

See table of Summary of inclusion and exclusion criteria under description of ALXN1210-PNH-301.

Treatments

During the 26-week Primary Evaluation Period, the following treatments were administered via IV infusion:

• ALXN1210 treatment group: weight-based loading dose on Day 1 (2 weeks after the patient's last dose of eculizumab) followed by q8w weight-based maintenance doses on Days 15, 71, and 127

• Eculizumab treatment group: q2w 900 mg maintenance doses on Days 1, 15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169

ALXN1210 Dosages for the Primary Evaluation Period

Body Weight	ALXN1210 Loading Dose (Day 1)	ALXN1210 Maintenance Dose (Days 15, 71, 127)
≥ 40 to < 60 kg	2400 mg	3000 mg
≥ 60 to < 100 kg	2700 mg	3300 mg
≥ 100 kg	3000 mg	3600 mg

After completion of all assessments on Day 183 of the Primary Evaluation Period, all patients had the opportunity to enter an Extension Period and receive ALXN1210 until product registration or approval (in accordance with country-specific regulations) or for up to 2 years, whichever occurred first.

Objectives

Primary objective:

- to assess the **non-inferiority** of ALXN1210 compared to eculizumab in adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who were clinically stable after having been treated with eculizumab for at least the past 6 months.

Non-inferiority would be claimed if after 26 weeks of treatment the upper bound of the 95% confidence interval (CI) for the difference (ALXN1210 – eculizumab) in percent change in lactate dehydrogenase (LDH) level was less than 15%.

Secondary objective:

- To characterize the safety and tolerability of ALXN1210 in patients who switched from eculizumab to ALXN1210
- To evaluate the efficacy of ALXN1210 by additional efficacy measures
- To characterize the pharmacokinetics (PK)/ pharmacodynamics (PD) and immunogenicity of ALXN1210

- To evaluate the long-term safety and efficacy of ALXN1210

Outcomes/endpoints

Primary			
% Change in LDH	Difference in % change	15%[a]	89%
Key Secondary			
% Breakthrough Haemolysis	Difference in rate	20%[a,c]	51%
Change in FACIT-Fatigue	Difference in change	-3[c]	50%
% Transfusion Avoidance	Difference in rate	-20%[a]	60%
% Haemoglobin Stabilization	Difference in rate	-20%[a]	56%

Other Secondary endpoints

ALXN1210-PNH-302

• Total number of units of pRBC transfused from baseline to Day 183 (Week 26)

• Proportion of patients with LDH in the normal range (LDH-N) at Day 183 (Week 26)

• Change in the European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire-Core 30 scale (QLQ-C30), Version 3.0, from baseline to Day 183 (Week 26)

• Change in clinical manifestations of PNH (fatigue, haemoglobinuria, abdominal pain, shortness of breath, chest pain, dysphagia, and erectile dysfunction) from baseline to Day 183 (Week 26)

• Proportion of patients experiencing MAVEs from baseline to Day 183 (Week 26)

Sample size

Approximately 192 patients were planned to be randomly assigned in a 1:1 ratio to continue on eculizumab (N = 96) or switch to ALXN1210 (N = 96) to ensure at least 172 evaluable patients (assumes no more than a 10% dropout rate). The sample size estimation was based on a non-inferiority design comparing patients in the ALXN1210 group to patients in the eculizumab group. The primary endpoint of haemolysis as directly measured by percent change in LDH from baseline through Day 183 was used to assess non-inferiority.

For the primary endpoint of percent change in LDH from baseline to Day 183, using a non-inferiority margin (NIM) of 15% and a type I error of 1-sided 2.5%, and an SD of 30%, a minimum of 172 patients would be expected to provide 90% power to demonstrate non-inferiority of ALXN1210 to eculizumab. This margin was based on data from Alexion's PNH Registry. For patients who discontinued eculizumab, the mean percent change in LDH was +134% and represents the loss of benefit relative to patients who remained on eculizumab, whose change in LDH is expected to remain stable. Preserving 50% of the benefit would give a margin of 67%; however, the more conservative and clinically appropriate margin of 15% was selected to preserve a more substantial amount of treatment effect (89%).

Thus, adjusting for a possible 10% dropout rate, approximately 192 patients were planned to be enrolled in this study.

Summary of Parameters Used in Estimating Sample Size

Table 34:

Parameters	Percentage Change in LDH
Power	90%
Type I error	1-sided 0.025
Noninferiority margin	0.15
Allocation ratio	1:1
Standard deviation of eculizumab/ALXN1210 response[a]	0.30/0.30
Assumed treatment difference	0
Estimated sample size	172
Adjusted sample size for 10% dropouts	192

Note: Analyzed using PASS 11 software (Hintze, 2011).
[a] Standard deviation from TRIUMPH study on LDH PCHG from Week 8 to Week 26.
Abbreviations: LDH = lactate dehydrogenase; PCHG = percent change

Randomisation

Patients who met all criteria for enrolment were randomly assigned to treatment with ALXN1210 or eculizumab. Treatment group assignment was determined by a computer-generated random sequence using an interactive voice- or web-response system (IxRS). The randomization was stratified randomization. Patients were stratified into 2 groups based on their transfusion history (received a transfusion of pRBC within 12 months prior Day 1, yes or no). Patients within each of the 2 groups were then randomly assigned in a 1:1 ratio to either continue treatment with eculizumab or switch to ALXN1210 during the 26-week Primary Evaluation Period.

Blinding (masking)

This was an open-label design.

Statistical methods

In both studies the following efficacy analysis populations were considered:

Full Analysis Set (FAS): The FAS included all patients who received at least 1 dose of randomized treatment (ALXN1210 or eculizumab) and had at least 1 efficacy assessment after the first infusion of randomized treatment (the last statement on at least 1 efficacy assessment after the first infusion were not considered for ALXN1210-PNH-302 study). In the FAS, patients were compared for efficacy according to the treatment group to which they were randomized, regardless of which treatment they actually received.

Per Protocol Set (PP Set): The PP Set included all patients in the FAS who met the following criteria:

- Missed 0 doses of ALXN1210 or no more than 1 dose of eculizumab during the 26-week Primary Evaluation Period
- Met inclusion criterion: in ALXN1210-PNH-302
  - Treated with eculizumab according to the labelled dosing recommendation for PNH for at least 6 months prior to Day 1.
  - Lactate dehydrogenase (LDH) level recommendation for PNH for at least 6 months prior to Day 1 eculizumab dosing day prior to dose administration (ie, at trough eculizumab level) and analyzed by the central laboratory.

- Documented diagnosis of PNH, confirmed by high sensitivity flow cytometry evaluation (Borowitz, 2010) of RBCs and white blood cells (WBCs), with granulocyte or monocyte clone size of size o

- Did not meet exclusion criterion: in ALXN1210-PNH-302
  - LDH value > 2 × ULN in the 6 months prior to Day 1
  - Major adverse vascular event (MAVE) in the 6 months prior to Day 1
  - Platelet count < 30,000/mm3 (30 × 109/L) at screening
  - Absolute neutrophil count (ANC) < 500/µL (0.5 × 109/L) at screening
- Never received the wrong randomized treatment
- Followed the protocol-specified transfusion guidelines

Non-inferiority Design

The ravulizumab Phase 3 studies used a non-inferiority design to compare results in patients treated with ravulizumab to those in patients treated with eculizumab.

Efficacy analyses were performed using the FAS, the primary efficacy population. The co-primary/primary efficacy endpoint analyses, as well as key secondary endpoint analyses, were repeated using the PP Set as a sensitivity analysis.

Primary efficacy analysis: The primary efficacy endpoint was the percent change in LDH from baseline to Day 183. Baseline was defined as the average of all assessments analyzed by the central laboratory prior to first study drug administration.

The percent change in LDH was analyzed using a mixed-effect model for repeated measures (MMRM) with the fixed, categorical effects of treatment, study visit, and study visit by treatment group interaction as well as the continuous, fixed covariate of baseline LDH and the stratification randomization indicator of pRBC transfusion history (yes/no within 12 months prior to Day 1). A difference in percent change in LDH between the ALXN1210 and eculizumab treatment groups along with a 2-sided 95% CI was calculated.

Key secondary efficacy analyses: The key secondary endpoints of proportion of patients with BTH, change from baseline in FACIT-Fatigue, proportion of patients with transfusion avoidance, and proportion of patients with stabilized haemoglobin were summarized by treatment group. A difference in the percentage of patients with BTH in the 2 treatment groups was calculated, along with a 95% CI for the difference using the stratified Newcombe CI method. This difference was computed using a weighted combination of the differences between treatment groups within the stratification indicator of transfusion history using Mantel-Haenszel weights. If the stratified Newcombe method failed to provide estimates of CIs, the exact common risk difference method would be utilized in computing the CIs. The same approach was employed for TA and for stabilized haemoglobin. For change from baseline in FACIT-Fatigue, the same approach used for the primary endpoint was employed.

The key secondary endpoints were tested in a hierarchical manner provided that noninferiority was declared for the primary endpoint. When performing the analyses for the key secondary efficacy endpoints, a closed-testing procedure was used so that the lack of significance of a test precludes assessment of subsequent tests. Estimates and CIs were computed for all these key secondary efficacy endpoints irrespective of whether a lack of significance of a test precludes assessment of subsequent tests.

1. If the upper bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in the proportion of patients with BTH is less than the noninferiority margin (NIM) of 20%, then ALXN1210 would be declared noninferior for this parameter and the next parameter would be tested.

2. If the lower-bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in change from baseline in FACIT-Fatigue is greater than the NIM of -3, then ALXN1210 would be declared noninferior for this parameter and the next parameter would be tested.

3. If the lower bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups for TA is greater than the NIM of -20%, then ALXN1210 would be declared noninferior to eculizumab and the next parameter would be tested.

4. If the lower bound of the 95% CI for the difference between the ALXN1210 and eculizumab treatment groups in the proportion of patients with stabilized haemoglobin is greater than the NIM of -20%, then ALXN1210 would be declared noninferior for this parameter.

If noninferiority was established for all key secondary endpoints and a larger effect for ALXN1210 was observed, then superiority was assessed using a closed-testing procedure with the following order and using a 2-sided 0.05 test for each parameter:

5. Percent change in LDH from baseline to Day 183 (Week 26)

6. Change from baseline to Day 183 (Week 26) in FACIT-Fatigue

7. Proportion of patients with BTH through Day 183 (Week 26)

8. Proportion of patients with stabilized haemoglobin through Day 183 (Week 26)

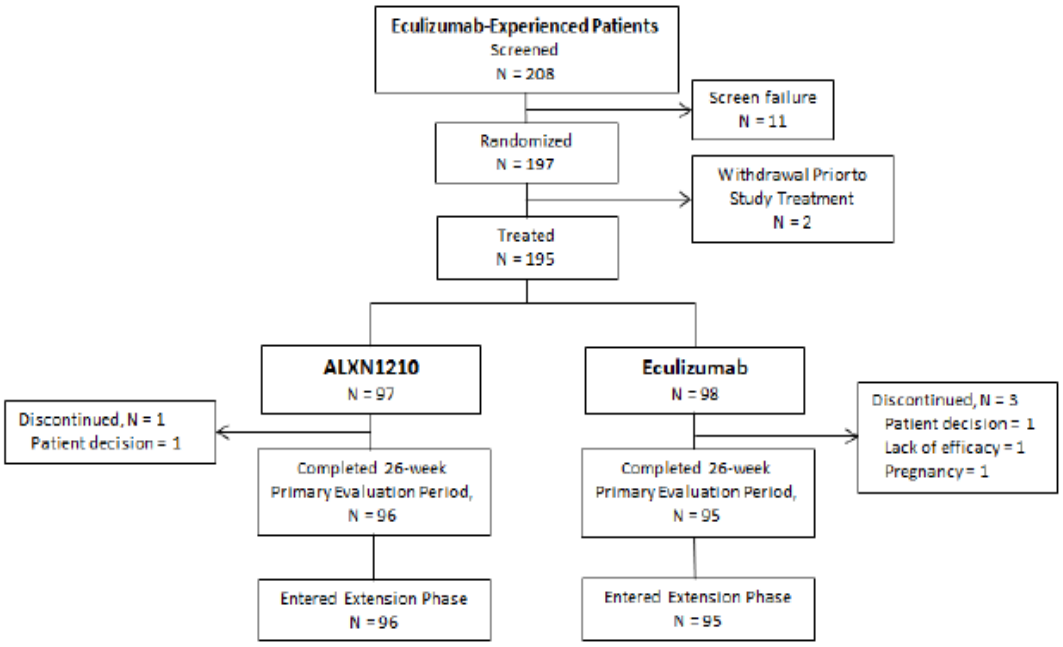
9. Transfusion avoidance

Due to the hierarchical testing order being pre-specified, no adjustment of the type I error was required. Other secondary efficacy analyses were summarized with only descriptive statistics.

Results

Participant flow

Figure 14: Disposition of Patients – Primary Evaluation Period (All Randomized Patients)



Of the 197 randomized patients, 195 treated patients (97 patients in the ALXN1210 group and 98 patients in the eculizumab group) were included in the FAS and Safety Set.

Table 35: Study ALXN1210-PNH-302 Efficacy Analysis Data Sets (All Randomized Patients)

	Ravulizumab n (%)	**Eculizumab n (%)**	**Total n (%)**
Number of randomized patients	98 (100)	99 (100)	197 (100)
Number of patients in the FAS	97 (99.0)	98 (99.0)	195 (99.0)
Number of patients in the PP Set	93 (94.9)	93 (93.9)	186 (94.4)

Abbreviations: FAS = Full Analysis Set; PP = Per Protocol

Three differences in the actual stratification at the time of randomization compared to the observed stratification for transfusion history occurred in this study. Of the 24 patients stratified to transfusion history “Yes”, 1 patient was determined to have no history of transfusion. Of the 173 patients stratified as transfusion history “No”, 2 patients had a history of transfusion.

In Study ALXN1210-PNH-302, 195 eculizumab-experienced patients were treated with ravulizumab or eculizumab; 191 completed the Primary Evaluation Period and 4 patients (1 in the ravulizumab group and 3 in the eculizumab group) prematurely discontinued study drug. All 191 patients who completed the Primary Evaluation Period entered the Extension Phase of the study.

Table 36: Major Protocol Deviations (Full Analysis Set)

	ALXN1210 (N = 97)	Eculizumab (N = 98)	Total (N = 195)
Patients with major deviations, n (%)	16 (16.5)	14 (14.3)	30 (15.4)
Type of major deviations			
Study procedures/criteria	8 (8.2)	6 (6.1)	14 (7.2)
Eligibility and entry criteria	5 (5.2)	2 (2.0)	7 (3.6)
Laboratory assessment criteria	2 (2.1)	2 (2.0)	4 (2.1)
Randomization	1 (1.0)	2 (2.0)	3 (1.5)
Informed consent	2 (2.1)	0 (0.0)	2 (1.0)
Safety reporting criteria	0 (0.0)	2 (2.0)	2 (1.0)

Note: Some patients had more than 1 major protocol deviation.
Source: Table 14.1.2.6.1.1

Recruitment

- First patient treated: 05 Jun 2017
- Last patient completed Primary Evaluation Period: 08 Mar 2018
- Release date of report: 30 May 2018

197 patients were randomized, yielding n=97 for the ALXN1210 arm, and n=98 for the eculizumab arm. 4 discontinuations were due to following reasons: patient's decision, pregnancy and lack of efficacy.

All but 1 patient entered the extension phase.

Conduct of the study

Protocol ALXN1210-PNH-302: Original Protocol 27 January 2017

Protocol amendments

From the original protocol (dated 27 Jan 2017), 1 global protocol amendment (dated 23 Oct 2017) was made during the Primary Evaluation Period of the study.

Changes in Planned Analyses

The SAP (version 2.1) was finalized on 12 Dec 2017, prior to database lock for the Primary Evaluation Period.

Protocol deviations:

Table 37: **Major Protocol Deviations (Full Analysis Set) ALXN1210-PNH-302**

	ALXN1210 (N = 97)	Eculizumab (N = 98)	Total (N = 195)
Patients with major deviations, n (%)	16 (16.5)	14 (14.3)	30 (15.4)
Type of major deviations			
Study procedures/criteria	8 (8.2)	6 (6.1)	14 (7.2)
Eligibility and entry criteria	5 (5.2)	2 (2.0)	7 (3.6)
Laboratory assessment criteria	2 (2.1)	2 (2.0)	4 (2.1)
Randomization	1 (1.0)	2 (2.0)	3 (1.5)
Informed consent	2 (2.1)	0 (0.0)	2 (1.0)
Safety reporting criteria	0 (0.0)	2 (2.0)	2 (1.0)

Note: Some patients had more than 1 major protocol deviation.

Baseline data

Table 38: Demographics Characteristics (Full Analysis Set) Study ALXN1210-PNH-302

Variable	ALXN1210 (N = 97)	Eculizumab (N = 98)	Total (N = 195)
Sex, n (%)			
Male	50 (51.5)	48 (49.0)	98 (50.3)
Female	47 (48.5)	50 (51.0)	97 (49.7)
Ethnicity, n (%)			
Not Hispanic or Latino	76 (78.4)	77 (78.6)	153 (78.5)
Not reported	15 (15.5)	17 (17.3)	32 (16.4)
Hispanic or Latino	3 (3.1)	4 (4.1)	7 (3.6)
Missing/unknown	3 (3.1)	0 (0.0)	3 (1.5)
Race, n (%)			
White	50 (51.5)	61 (62.2)	111 (56.9)
Asian	23 (23.7)	19 (19.4)	42 (21.5)
Non-Japanese descent	18 (18.6)	12 (12.2)	30 (15.4)
Japanese descent	5 (5.2)	7 (7.1)	12 (6.2)
Not reported	13 (13.4)	13 (13.3)	26 (13.3)
Black or African American	5 (5.2)	3 (3.1)	8 (4.1)
Unknown	3 (3.1)	1 (1.0)	4 (2.1)
Other	2 (2.1)	1 (1.0)	3 (1.5)
Multiple	1 (1.0)	0 (0.0)	1 (0.5)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Age at first infusion (years)			
n	97	98	195
Mean (SD)	46.6 (14.41)	48.8 (13.97)	47.7 (14.19)
Median	45.0	49.0	47.0
Min, max	18, 79	23, 77	18, 79
Age at first infusion (years) category, n (%)			
18 to 65 years	85 (87.6)	84 (85.7)	169 (86.7)
65 years	12 (12.4)	14 (14.3)	26 (13.3)
Baseline weight (kg)			
n	97	98	195
Mean (SD)	72.4 (16.84)	73.4 (14.60)	72.9 (15.73)
Median	71.7	72.5	72.4
Min, max	45, 129	44, 104	44, 129
Baseline weight (kg) category, n (%)			
≥ 40 to < 60 kg	27 (27.8)	22 (22.4)	49 (25.1)
≥ 60 to < 100 kg	62 (63.9)	74 (75.5)	136 (69.7)
≥ 100 kg	8 (8.2)	2 (2.0)	10 (5.1)
Baseline BMI (kg/m²)			
n	88	93	181
Mean (SD)	25.2 (4.71)	25.7 (4.17)	25.5 (4.44)
Median	24.7	25.9	25.0
Min, max	18, 41	18, 39	18, 41

Abbreviations: BMI = body mass index; max = maximum; min = minimum; SD = standard deviation
Source: Table 14.1.1.1.1

In the total population, mean age at PNH diagnosis was 35.5 years, with first (non-study) eculizumab infusion received at mean age 42 years. The mean time from PNH diagnosis to informed consent was 12.2 years (median = 9.8 years). On average, patients had 5.8 years of prior eculizumab therapy. Mean (SD) LDH value at baseline was 231.64 (49.222) U/L. All patients had PNH diagnosis confirmed by flow cytometry at Screening to quantify the percentage of PNH cells (clone size) in the peripheral blood. The mean total PNH RBC clone size was 60.05%, mean total PNH granulocyte clone size was 83.30%, and the mean total PNH monocyte clone size was 85.86%.

Table 39: **Disease Characteristics (Full Analysis Set) Study ALXN1210-PNH-302**

Variable Category	ALXN1210 (N = 97)	Eculizumab (N = 98)	Total (N = 195)
Age (years) at PNH diagnosis			
n	97	97	194
Mean (SD)	34.1 (14.41)	36.8 (14.14)	35.5 (14.30)
Median	32.0	35.0	33.0
Min, max	6, 73	11, 74	6, 74
Age (years) at first eculizumab infusion			
n	97	98	195
Mean (SD)	40.7 (14.30)	43.2 (13.93)	42.0 (14.14)
Median	40.0	43.0	41.0
Min, max	14, 74	17, 74	14, 74
Years on eculizumab prior to first in study transfusion			
n	97	98	195
Mean (SD)	6.0 (3.48)	5.6 (3.45)	5.8 (3.46)
Median	5.6	4.9	5.3
Min, max	1, 15	1, 15	1, 15
Years from diagnosis to informed consent			
n	97	97	194
Mean (SD)	12.4 (8.36)	11.9 (9.42)	12.2 (8.89)
Median	10.2	9.1	9.8
Min, max	1, 38	1, 47	1, 47
LDH (U/L) at baseline			
n	97	98	195
Mean (SD)	228.01 (48.712)	235.22 (49.710)	231.64 (49.222)
Median	224.00	234.00	229.00
Min, max	135.00, 383.5	100.0, 365.5	100.0, 383.5
PNH clone size at baseline			
PNH RBC type II clone size (%)			
n	89	87	176
Mean (SD)	14.90 (19.550)	16.33 (23.642)	15.61 (21.619)
Median	6.70	4.40	5.20
Min, max	0.1, 80.9	0.1, 91.9	0.1, 91.9
PNH RBC type III clone size (%)			
n	95	96	191
Mean (SD)	44.58 (30.520)	43.47 (29.713)	44.02 (30.043)
Median	42.50	36.95	40.50
Min, max	0.0, 98.8	0.9, 99.4	0.0, 99.4
Total PNH RBC clone size (%)			
n	90	89	179
Mean (SD)	60.63 (32.524)	59.47 (31.408)	60.05 (31.889)
Median	68.05	62.80	67.30
Min, max	0.1, 99.8	1.5, 99.6	0.1, 99.8
Total PNH granulocyte clone size (%)			
n	96	98	194
Mean (SD)	82.63 (23.602)	83.95 (21.377)	83.30 (22.456)
Median	93.75	93.90	93.80
Min, max	7.4, 99.9	3.3, 99.8	3.3, 99.9
Total PNH monocyte clone size (%)			
n	96	98	194
Mean (SD)	85.64 (20.450)	86.07 (19.737)	85.86 (20.042)
Median	95.80	95.20	95.50
Min, max	11.2, 99.9	12.1, 99.9	11.2, 99.9

Note: Total RBC, Granulocyte, Monocyte Clone Size = Sum Type II and Type III RBC, Granulocyte, Monocyte clone size, respectively.

Abbreviations: LDH = lactate dehydrogenase; max = maximum; min = minimum; SD = standard deviation; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell

Source: Table 14.1.3.1.1 and Listing 16.2.4.3.1.2

In this study population of patients with stable disease, 12.8% of patients had a history of pRBC transfusions in the year prior to first dose of study drug. The mean number of transfusions within 1 year prior to first dose was higher in the ALXN1210 group than in the eculizumab group, as was the mean

number of units transfused; this difference is attributable to 2 heavily transfusion-dependent patients in the ALXN1210 group (one patient 16 transfusions and another patient 17 transfusions).

Table 40: Red Blood Cell Transfusions Within 12 Months Prior to First Dose (Full Analysis Set)

Variable Category	ALXN1210 (N = 97)	Eculizumab (N = 98)	Total (N = 195)
Number of patients with pRBC/whole blood transfusions within 1 year prior to first dose, n (%)	13 (13.4)	12 (12.2)	25 (12.8)
pRBC/whole blood transfusions within 1 year prior to first dose			
Total	64	30	94
Mean (SD)	4.9 (5.51)	2.5 (2.32)	3.8 (4.38)
Median	3.0	1.5	2.0
Min, max	1, 17	1, 8	1, 17
Units of pRBC/whole blood transfused within 1 year prior to first dose			
Total	103	50	153
Mean (SD)	7.9 (8.78)	4.2 (3.83)	6.1 (7.00)
Median	4.0	2.5	3.0
Min, max	1, 32	2, 15	1, 32

Abbreviations: max = maximum; min = minimum; pRBC = packed red blood cells; SD = standard deviation
Source: Table 14.1.3.2.1

Based on available medical history, the majority (95.4%) of patients had documented PNH-associated conditions that were diagnosed at any time prior to informed consent. Of note, 37.4% of patients had a history of aplastic anemia, 9.2% of patients had a history of renal failure, and 4.6% of patients had myelodysplastic syndrome.

Table 41: PNH-Associated Conditions Diagnosed at Any Time Prior to Informed Consent (Full Analysis Set)

PNH-Associated Conditions, n (%)	ALXN1210 (N = 97)	Eculizumab (N = 98)	Total (N = 195)
Patients with any PNH conditions prior to informed consent	90 (92.8)	96 (98.0)	186 (95.4)
Anemia	64 (66.0)	67 (68.4)	131 (67.2)
Hematuria or hemoglobinuria	47 (48.5)	48 (49.0)	95 (48.7)
Aplastic anemia	34 (35.1)	39 (39.8)	73 (37.4)
Renal failure	11 (11.3)	7 (7.1)	18 (9.2)
Pregnancy complication	4 (4.1)	9 (9.2)	13 (6.7)
Myelodysplastic syndrome	3 (3.1)	6 (6.1)	9 (4.6)
Other[a]	14 (14.4)	14 (14.3)	28 (14.4)

Note: Conditions as documented in patient medical record. Patients could have been counted in more than one category.
[a] "Other" category included neutropenia (n = 3), proteinuria (n = 1), renal dysfunction (n = 3), lymphoid hyperplasia (n = 1), pancytopenia (n = 2), thrombopenia (n = 3), iron deficiency (n = 2), non-severe aplasia (n = 1), splenomegaly (n = 1), hepatic cytolysis Grade 1 (n = 2), hemolytic anemia, haptoglobin collapse, pulmonary hypertension, monosomy 7, mildly hypocellular marrow, reduced trilineage hematopoiesis, medullar hypoplasia, haptoglobin deficiency and hyper reticulocytosis, leucopenia, dysgranulopoiesis, dyserythropoiesis, dysplasia dyserythropoiesis, relapse of idiopathic medullary aplasia, thrombocytosis, thrombocytopenia, leukocytosis, muscle aches and pains, and gallstones (each n = 1).
Abbreviation: PNH = paroxysmal nocturnal hemoglobinuria

Numbers analysed

Table 42: Study ALXN1210-PNH-302 Efficacy Analysis Data Sets (All Randomized Patients)

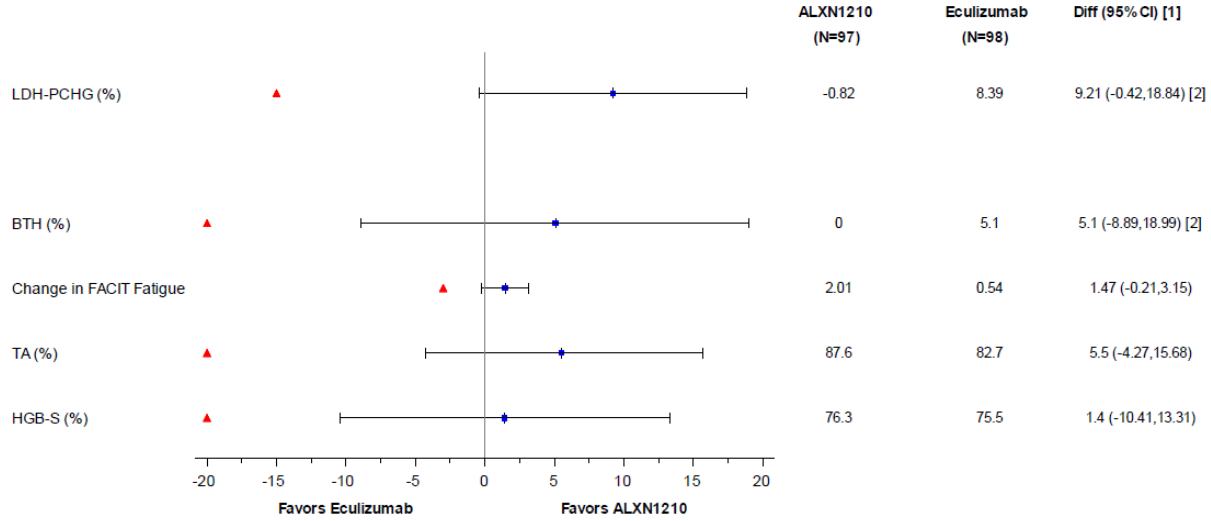
	Ravulizumab n (%)	Eculizumab n (%)	Total n (%)
Number of randomized patients	98 (100)	99 (100)	197 (100)
Number of patients in the FAS	97 (99.0)	98 (99.0)	195 (99.0)
Number of patients in the PP Set	93 (94.9)	93 (93.9)	186 (94.4)

Abbreviations: FAS = Full Analysis Set; PP = Per Protocol
Source: ALXN1210-PNH-302 CSR Table 14.1.2.5.6

Outcomes and estimation

Study ALXN1210 PNH 302 (Phase 3): Eculizumab-Experienced Patients

Figure 15: Study ALXN1210-PNH-302 - Forest Plot of Primary and Key Secondary Endpoint – Primary Evaluation Period (Full Analysis Set)



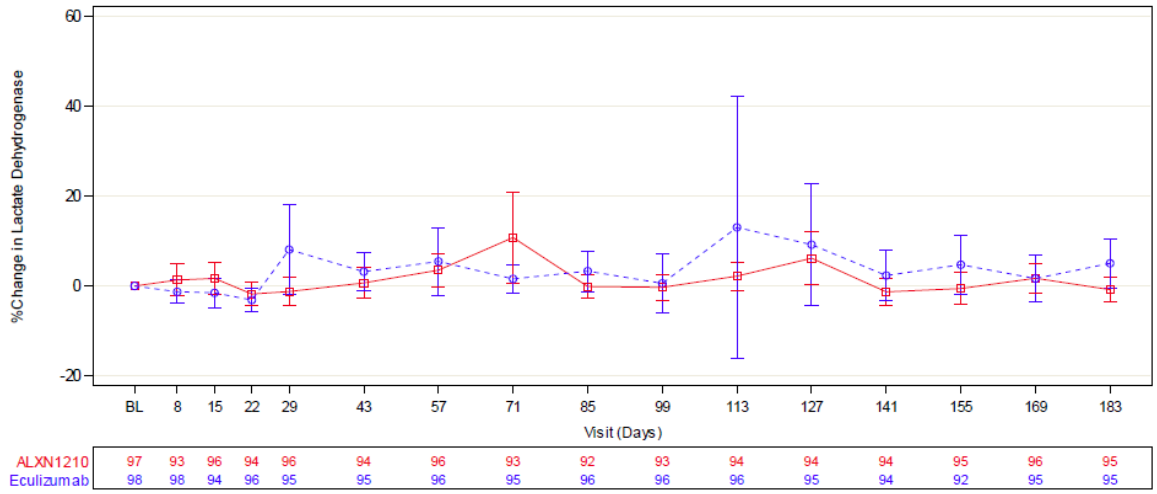
Note: The red triangle indicates the non-inferiority margin.
[1] For endpoints TA, BTH, and HGB-S, Diff (95% CI) were based on estimated differences in percent with 95% CI. For FACIT-Fatigue, Diff (95% CI) was based on estimated difference in change from baseline with 95% CI.
[2] Treatment difference was estimated for ravulizumab - eculizumab except for LDH-PCHG and BTH where treatment difference was based on eculizumab - ravulizumab.
Abbreviations: ALXN1210 = ravulizumab; BTH = breakthrough haemolysis; CI = confidence interval; Diff = difference; FACIT = Functional Assessment of Chronic Illness Therapy; HGB-S = haemoglobin stabilization; LDH = lactate dehydrogenase; LDH-PCHG = percent change in LDH; TA = transfusion avoidance

Primary endpoint

<u>% Change of LDH (Non-inferiority analysis)</u>

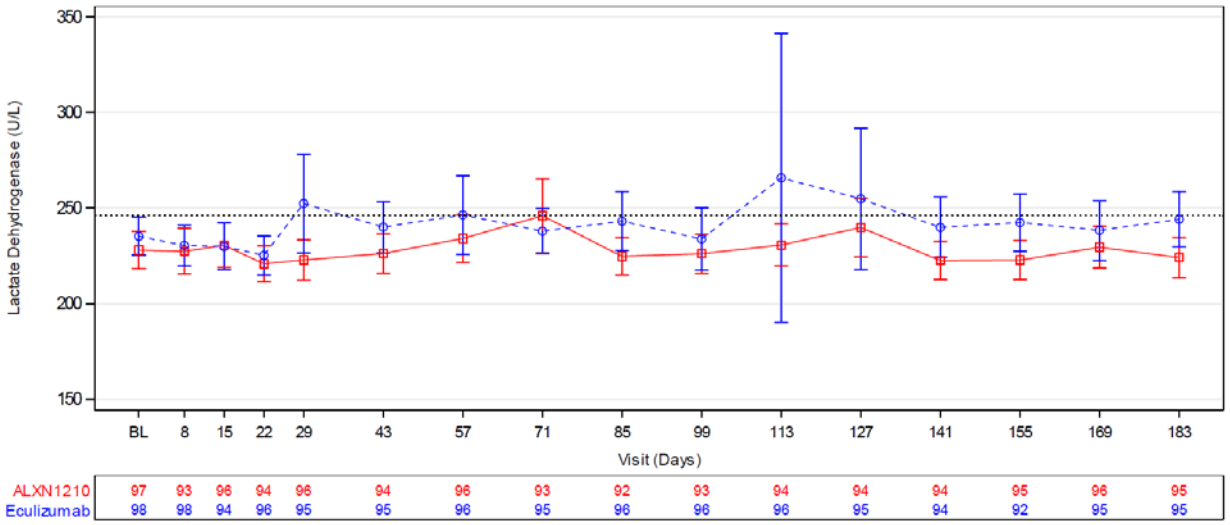
At baseline, mean LDH values in these previously eculizumab-treated patients were within normal range at 228.01 U/L and 235.22 U/L for the ravulizumab and eculizumab groups, respectively. The LS estimate of the mean percent change in LDH showed a decrease of less than 1% (-0.82% [SEM = 3.033%]) for the ravulizumab group and an increase of greater than 8% (8.39% [SEM = 3.041%]) for the eculizumab group with a treatment difference (ravulizumab - eculizumab) of -9.21% (95% CI: -18.84%, 0.42%). The upper bound of the 95% CI of 0.42% was less than the protocol-specified NIM of 15%.

Figure 16: Study ALXN1210-PNH-302 - Mean Percentage Change (95% CI) in LDH Over Time, by Treatment Group (Full Analysis Set)



Note: Baseline was defined as the average of all available assessments from the central laboratory prior to first study drug dose. At Day 113, 1 eculizumab patient (0615-404) had an event of BTH with LDH = 3846 U/L; this patient withdrew from the study due to lack of efficacy (Listing 16.2.6.4.1.1).
Abbreviations: BL = baseline; BTH = breakthrough hemolysis; CI = confidence interval; LDH = lactate dehydrogenase
Source: Figure 14.2.1.1.1

Figure 17: Study ALXN1210-PNH-302 - Mean (95% CI) LDH Over Time, by Treatment Group – Primary Evaluation Period (Full Analysis Set)



Note: Baseline was defined as the average of all available assessments from the central laboratory prior to first study drug dose. Dotted horizontal lines indicate upper normal value of 246 U/L. At Day 113, 1 eculizumab patient had an event of BTH event with LDH = 3846 U/L; this patient withdrew from the study due to lack of efficacy.
Abbreviations: ALXN1210 = ravulizumab; BL = baseline; BTH = breakthrough haemolysis; CI = confidence interval; LDH = lactate dehydrogenase.

Table 43: Study ALXN1210-PNH-302 - Sensitivity Analyses for Mean Percent Change (95% CI) in LDH

Analysis	Treatment Difference (95% CI)
Full Analysis Set	-9.21 (-18.84, 0.42)
Per Protocol Set	-9.58 (-20.23, 1.06)
Excluding observed transfusion history and baseline LDH level	-8.68 (-18.48, 1.12)

Note: Because the patient dropout rate was < 5%, additional analyses were not conducted for the primary endpoint of LDH percent change with consideration of the "missing not at random" assumption.
Abbreviations: CI = confidence interval; LDH = lactate dehydrogenase
Source: Table 14.2.1.1.1, Table 14.2.1.1.3, and Table 14.2.1.2.01.1

Key Secondary Endpoints

Breakthrough Haemolysis (Non-inferiority analysis)

None of the patients in the ravulizumab group experienced BTH during the Primary Evaluation Period compared with 5 (5.1%) patients in the eculizumab group. The difference between treatment groups in the proportion of patients who experienced BTH was -5.1% (95% CI: - 18.99%, 8.89%).

Table 44: Study ALXN1210-PNH-302 - Number (%) of Patients With Breakthrough Haemolysis Through Day 183 (Week 26) – Primary Evaluation Period (Full Analysis Set)

Variable	Ravulizumab (N = 97)	Eculizumab (N = 98)	Treatment Difference (Ravulizumab - Eculizumab)
Experiencing BTH through Day 183 (Week 26)			
Number of patients (n)	0	5	
Percentage (%)	0.0	5.1	-5.1
95% CI	(0.00, 3.73)	(1.68, 11.51)	(-18.99, 8.89)

Note: Breakthrough haemolysis was defined as at least 1 new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [haemoglobin < 10 g/dL], major adverse vascular event [MAVE, including thrombosis], dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN. Exact unconditional approach was used for calculating the CIs for the treatment difference.

Abbreviations: BTH = breakthrough haemolysis; CI = confidence interval; LDH = lactate dehydrogenase; ULN = upper limit of normal

Analysis of Patients Who Experienced Breakthrough Haemolysis

In Study ALXN1210-PNH-302, 5 patients in the eculizumab group had events of BTH during the Primary Evaluation Period; 4 patients had 1 BTH event each, and 1 patient had 3 BTH events and discontinued from the study due to lack of efficacy after the third event of BTH caused hospitalization. There was no clear pattern in the length of time elapsed from initiation of treatment to onset of BTH.

Four of the 7 BTH events in the eculizumab group were associated with suboptimal C5 inhibition (free C5 ≥ 0.5 µg/mL) indicating immediate, complete, and sustained C5 inhibition had not been achieved. Infection was associated with 3 of the 7 BTH events in the eculizumab group (including 1 event also

associated with free C5 > 0.05 µg/mL). Among these patients, no potential complement amplifying condition (CAC) other than infection was identified.

Table 45: Study ALXN1210-PNH-302 - Analysis of Breakthrough Haemolysis Cases in Phase 3 Studies (Full Analysis Set)

Primary Cause of Breakthrough Haemolysis Events	Ravulizumab (N = 97)	Eculizumab (N = 98)
Total number of BTH events	0	7
Suboptimal PD[a]	0	4[b]
Infection/CAC	0	2
Undetermined[c]	0	1

[a] Suboptimal PD was defined as free C5 ≥ 0.5 µg/mL.

[b] One patient in the eculizumab group with suboptimal PD also had concomitant infection.

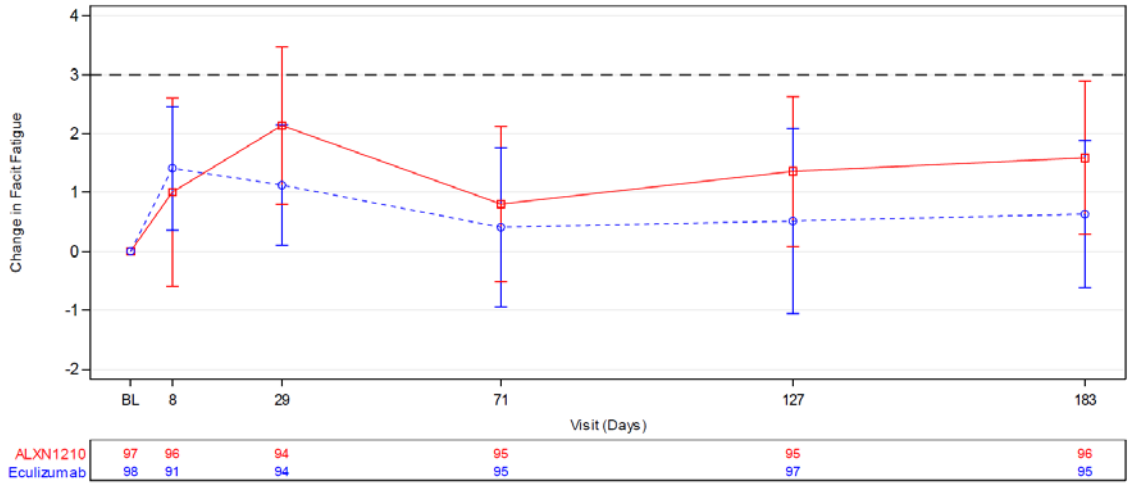
[c] Undetermined cases had neither suboptimal PD nor concomitant infection identified.

Abbreviations: BTH = breakthrough haemolysis; CAC = complement amplifying condition; PD = pharmacodynamics

FACIT-Fatigue (Non-inferiority analysis)

At baseline, mean FACIT-Fatigue total scores were 42.54 for ravulizumab and 40.69 for eculizumab. Both treatment groups showed improvement in FACIT-Fatigue over time, with less fatigue in the ravulizumab group compared to the eculizumab group at all-time points following Day 8. At Day 183, the LS mean (SEM) change in FACIT-Fatigue total score was 2.01 (0.697) for ravulizumab and 0.54 (0.704) for eculizumab. The LS mean difference between treatment groups was 1.47 (95% CI: -0.21, 3.15). The lower bound of the 95% CI was greater than the protocol specified NIM of -3.

Figure 18: Study ALXN1210-PNH-302 - Mean (95% CI) From Baseline in FACIT-Fatigue Over Time, by Treatment Group – Primary Evaluation Period (Full Analysis Set)



Note: FACIT score ranges from 0 to 52, with a higher score indicating less fatigue. Baseline was defined as the last non-missing assessment value prior to first study drug dose. Dashed horizontal line indicates threshold that delineates clinically meaningful improvement (> 3 points).

Abbreviations: ALXN1210 = ravulizumab; BL = baseline; CI = confidence interval; FACIT = Functional Assessment of Chronic Illness Therapy

Transfusion Avoidance Per Protocol Specified Guidelines (Non-inferiority analysis)

Patients who fulfilled the protocol-specified transfusion criteria were analyzed as having received a transfusion, regardless of whether the patients had actually received a transfusion. This analysis includes 2 patients in the ravulizumab group and 3 patients in the eculizumab group who met the protocol-specified criteria for pRBC transfusion (haemoglobin ≤ 7 g/dL) but were not transfused at that time or at any other time during the Primary Evaluation Period.

During the Primary Evaluation Period, 87.6% of patients in the ravulizumab group and 82.7% in the eculizumab group avoided pRBC transfusion. The difference between the ravulizumab and eculizumab treatment groups in the percentage of patients who avoided transfusion was 5.5% (95% CI: - 4.27%, 15.68%). The lower bound of the 95% CI was greater than the protocol specified NIM of 20%. The treatment difference was consistent when TA was analyzed independent of protocol-specified transfusion guidelines. Results using the PP Set were consistent with those of the FAS.

Table 46: Study ALXN1210-PNH-302 - Number (%) of Patients Achieving Transfusion Avoidance Per Protocol Specified Guidelines During Primary Evaluation Period (Full Analysis Set)

Variable	Ravulizumab (N = 97)	Eculizumab (N = 98)	Treatment Difference (Ravulizumab - Eculizumab)
Number of patients (n)	85	81	
Percentage (%)	87.6	82.7	5.5
95% CI	(81.08, 94.18)	(75.16, 90.15)	(-4.27, 15.68)

Note: Transfusion avoidance was defined as the proportion of patients who remained transfusion free and did not require a transfusion per protocol-specified guidelines through Day 183 (Week 26). Patients who withdrew from the study during Primary Evaluation Period due to lack of efficacy were considered as nonresponders and counted in the group requiring transfusions.

[a] Percentage and CI for the difference of percentages was calculated using stratified Newcombe CI interval method. The stratification factor was observed stratification factor of transfusion history (yes/no) within 1 year prior to first dose of study drug.

Abbreviation: CI = confidence interval

Haemoglobin Stabilization (Non-inferiority analysis)

Table 47: Study ALXN1210-PNH-302 - Number (%) of Patients With Stabilized Haemoglobin Through Day 183 (Week 26) (Full Analysis Set)

Variable	Ravulizumab (N = 97)	Eculizumab (N = 98)	Treatment Difference (Ravulizumab - Eculizumab)

Variable	Ravulizumab (N = 97)	Eculizumab (N = 98)	Treatment Difference (Ravulizumab - Eculizumab)
Achieved stabilized haemoglobin through Day 183 (Week 26)			
Number of patients (n)	74	74	
Percentage (%)	76.3	75.5	1.4
95% CI	(67.82, 84.75)	(67.00, 84.02)	(-10.41, 13.31)

Note: Stabilized haemoglobin was defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26). The CI for the difference of was calculated using stratified Newcombe CI method. The stratification factor was the observed stratification factor of transfusion history (yes/no) within 1 year prior to first dose of study drug.

Abbreviation: CI = confidence interval

Percent change from baseline in LDH (Superiority analysis)

Because statistically significant noninferiority was achieved for the primary endpoint and all 4 key secondary endpoints, the pre-specified hierarchical order continued with superiority testing of percent change from baseline in LDH. The assessment of the treatment difference for superiority resulted in p-value = 0.0583 which did not reach the pre-specified significance threshold for superiority ($p < 0.05$) and therefore no additional superiority testing was conducted.

Table 48: Study ALXN1210-PNH-302 - Percentage Change from Baseline to Day 183 (Week 26) in LDH: Mixed Model Repeated Measures (MMRM) Full Analysis Set

Statistics	Variable	ALXN1210 (N=97)	Eculizumab (N=98)	Difference (ALXN1210-Eculizumab)
From Baseline to	LS Mean (SEM)	-0.82 (3.033)	8.39 (3.041)	-9.21 (4.112)
Day 183 in LDH (%)	95% CI for LS MEAN	(-7.75, 6.11)	(1.47, 15.32)	(-18.84, 0.42) [1]

Other Secondary Endpoints

Total Number of pRBC Units Transfused

Table 49: **Study ALXN1210-PNH-302 - pRBC Transfusions From First Dose of Study Drug to Day 183 (Week 26) (Full Analysis Set)**

Variable	Ravulizumab (N = 97)	Eculizumab (N = 98)
Number of patients who received any pRBC/whole blood transfusions from first dose of study drug to Day 183, n (%)	10 (10.3)	14 (14.3)
pRBC/whole blood transfusions from first dose of study drug to Day 183		
Total	27	26
Mean (SD)	2.7 (2.75)	2.0 (1.29)

Variable	Ravulizumab (N = 97)	Eculizumab (N = 98)
Median	1.0	1.0
Min, max	1, 9	1, 5
Units of pRBC/whole blood transfused from first dose of study drug to Day 183		
Total	43	44
Mean (SD)	4.3 (4.76)	3.4 (3.01)
Median	2.0	3.0
Min, max	1, 16	1, 12

Abbreviations: min = minimum; max = maximum; pRBC = packed red blood cell; SD = standard deviation

LDH Normalization

In Study ALXN1210 PNH 302, LDH-N was achieved at Day 183 by 64 of 97 (66.0%) patients treated with ravulizumab and 58 of 98 (59.2%) patients treated with eculizumab.

The adjusted odds ratio from the generalized estimating equation model excluding baseline LDH as an explanatory variable for the comparison of ravulizumab to eculizumab was 1.179 (95% CI: 0.737, 1.887) indicating a patient switching to ravulizumab has a nearly 18% increased probability of achieving LDH-N compared to a patient who remains on eculizumab. The adjusted rate of LDH-N post first study drug infusion through Day 183 for ravulizumab was 0.608 (95% CI: 0.508, 0.700) and for eculizumab was 0.568 (95% CI: 0.467, 0.664).

EORTC QLQ-C30

In Study ALXN1210 PNH 302, mean EORTC QLQ-C30 subscale scores at baseline for both treatment groups reflected a patient population with stable disease: Global Health Status and Physical Functioning subscale scores were ranging from 69% to 88% across treatment groups, and Fatigue subscale scores were ranging from 25% to 26%. Changes in scores during the study were not notable in either treatment group. Similar percentages of patients in the ravulizumab group had at least a 10 point improvement in the Global Health Status, Physical Functioning, and Fatigue subscale scores at each assessment during the Primary Evaluation Period compared with the eculizumab group.

Clinical Manifestations of PNH

Table 50: Shifts in Clinical Manifestations of PNH From Baseline to Day 183 (Full Analysis Set)

Parameter	ALXN1210					Eculizumab				
	Total N	Baseline	Post-Baseline Time Point			Total N	Baseline	Post-Baseline Time Point		
			Yes n (%)	No n (%)	NA n (%)			Yes n (%)	No n (%)	NA n (%)
Fatigue	96	Yes	22 (22.9)	7 (7.3)	--	95	Yes	28 (29.5)	10 (10.5)	--
		No	20 (20.8)	47 (49.0)	--		No	8 (8.4)	49 (51.6)	--
Abdominal pain	96	Yes	2 (2.1)	3 (3.1)	--	95	Yes	4 (4.2)	2 (2.1)	--
		No	3 (3.1)	88 (91.7)	--		No	8 (8.4)	81 (85.3)	--
Dyspnoea	96	Yes	3 (3.1)	3 (3.1)	--	95	Yes	8 (8.4)	2 (2.1)	--
		No	3 (3.1)	87 (90.6)	--		No	9 (9.5)	76 (80.0)	--
Dysphagia	96	Yes	2 (2.1)	0	--	95	Yes	2 (2.1)	0	--
		No	3 (3.1)	91 (94.8)	--		No	3 (3.2)	90 (94.7)	--
Chest pain	96	Yes	0	0	--	95	Yes	1 (1.1)	0 (0.0)	--
		No	2 (2.1)	94 (97.9)	--		No	4 (4.2)	90 (94.7)	--
Red/dark urine or hemoglobinuria	96	Yes	4 (4.2)	0	--	95	Yes	1 (1.1)	6 (6.3)	--
		No	4 (4.2)	88 (91.7)	--		No	8 (8.4)	80 (84.2)	--
Erectile dysfunction	96	Yes	3 (3.1)	2 (2.1)	0	95	Yes	5 (5.3)	2 (2.1)	0
		No	3 (2.1)	42 (43.8)	0		No	1 (1.1)	39 (41.1)	0
		NA	0	0	47 (49.0)		NA	0	0	48 (50.5)

Note: Baseline was defined as the last non-missing value prior to first dose of study drug. Total N = Number of patients with both non-missing baseline and the respective post-baseline values for specified parameter. Percentages for each parameter are calculated using Total N as denominator.
Abbreviations: NA = not applicable; PNH = paroxysmal nocturnal hemoglobinuria

Major Adverse Vascular Events

In Study ALXN1210-PNH-302, no patients experienced a MAVE during the Primary Evaluation Period.

Major Adverse Vascular Events

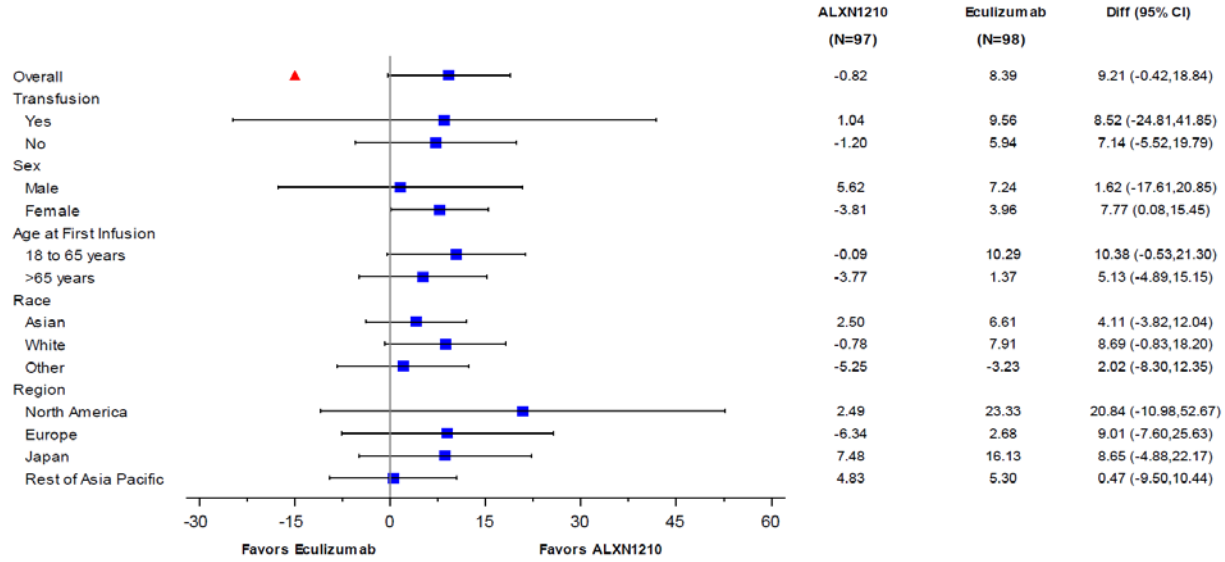
In Study ALXN1210-PNH-302, no patients experienced a MAVE during the Primary Evaluation Period.

Ancillary analyses

Subgroups analysis of primary and co-primary endpoints

Study ALXN1210 PNH 302 (Phase 3): Eculizumab-Experienced Patients

Figure 19: Forest Plot of Percent Change to Day 183 (Week 26) in LDH Treatment Difference During the Primary Evaluation Period, Overall and by Subgroup (FAS)



Note: The red triangle indicates the non-inferiority margin. Treatment difference was estimated for eculizumab - ravulizumab.
Abbreviations: ALXN1210 = ravulizumab; CI = confidence interval; Diff = difference; LDH = lactate dehydrogenase

Summary of main studies

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

Table 51: Summary of Efficacy for trial ALXN1210-PNH-301

Title: **ALXN1210-PNH-301 A PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY OF ALXN1210 VERSUS ECULIZUMAB IN COMPLEMENT INHIBITOR-NAÏVE ADULT PATIENTS WITH PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA (PNH)**		
Study identifier	ALXN1210-PNH-301	
Design	Phase 3, Randomized, Multicentre, Open-Label, Active-Controlled Study Patients were enrolled at 123 sites in 25 countries (Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Estonia, France, Germany, Italy, Japan, Malaysia, Mexico, Poland, Republic of Korea, Russia, Singapore, Spain, Sweden, Taiwan, Thailand, Turkey, United Kingdom, and United States).	
	Duration of main phase / Run-in phase: 26-week Ramdomized treatment period Duration of Extension phase: 2 years	Date first patient treated: 20 Dec 2016 Date last patient completed the Primary Evaluation Period: 25 Jan 2018 Release date of report: 23 May 2018
Hypothesis	**Non-inferiority** of ALXN1210 compared to eculizumab in adult patients with PNH who had never been treated with a complement inhibitor	

Treatments groups	RAVULIZUMAB (ALXN1210)		ALXN1210 treatment group: weight-based loading dose on Day 1 followed by weight-based maintenance doses on Days 15, 71, and 127 Primary Evaluation Period: 26 weeks (183 days) Number randomized: - Planned: 107 patients per treatment group - Primary efficacy evaluation: 125 in the ALXN1210 treatment group
	ECULIZUMAB		Eculizumab treatment group: 600-mg induction doses on Days 1, 8, 15, and 22 followed by 900-mg maintenance doses on Days 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169 Primary Evaluation Period: 26 weeks (183 days) Number randomized: - Planned: 107 patients per treatment group - Primary efficacy evaluation: 121 in the eculizumab treatment group
Endpoints and definitions	Co- Primary endpoint	-Transfusion avoidance	– **<u>Transfusion avoidance</u>**, defined as the proportion of patients who remain transfusion-free and do not require a transfusion per protocol-specified guidelines through Day 183 (Week 26)
		-Haemolysis	– **<u>Haemolysis</u>** as directly measured by LDH-N from Day 29 (first scheduled evaluation status post initiation of maintenance dosing) through Day 183 (Week 26)
	Key Secondary (tested in a hierarchical manner)	-Percentage change in LDH from baseline	– **Percentage change in LDH** from baseline to Day 183 (Week 26) – **Change in quality of life**

		-Change in quality of life	(QoL) assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, Version 4, from baseline to Day 183 (Week 26)
		- Proportion of patients with breakthrough haemolysis	– **Proportion of patients with breakthrough haemolysis** (BTH), defined as at least one new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [haemoglobin < 10 g/dL], major adverse vascular event [MAVE] including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy
		-Proportion of patients with stabilized haemoglobin	– **Proportion of patients with stabilized haemoglobin**, defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26)
	Other Secondary	–Change in the EORTC)-QoL (QLQ-C30)	–Change in the **European Organisation for Research and Treatment of Cancer** (EORTC) **QoL Questionnaire-Core 30 Scale** (QLQ-C30), Version 3.0, from baseline through Day 183 (Week 26)
		– Time to first occurrence of LDH-N	– Time to **first occurrence of LDH-N**
		– Total number of units of pRBCs transfused through Day 183 (Week 26)	– **Total number of units of pRBCs transfused** through Day 183 (Week 26)
		– Change in clinical manifestations of PNH	– **Change in clinical manifestations of PNH** (fatigue, haemoglobinuria, abdominal pain, shortness of breath, chest pain, dysphagia, and erectile dysfunction) from

		– Proportion of patients experiencing MAVEs	baseline through Day 183 (Week 26) – Proportion of patients experiencing **MAVEs** from baseline through Day 183 (Week 26)
Database lock	25 January 2018		

Results and Analysis

ALXN1210 met the primary objective of statistically significant non-inferiority compared to eculizumab on both co-primary endpoints, avoidance of pRBC transfusion per protocol-specified guidelines and LDH-N, from Day 29 to Day 183.

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full Analysis Set (FAS)			
Descriptive statistics and estimate variability:	Treatment group	ALXN1210	Eculizumab	Treatment Difference (ALXN1210 - Eculizumab)
	Number of subject	N = 125	N = 121	
Co-primary endpoints	Patients Achieving **Transfusion Avoidance** Per Protocol (n) Percentage (%) 95% CI	92 73.6 (65.87;81.33)	80 66.1 (57.68;74.55)	6.8 (-4.66;18.14)
	LDH Normalization (Adjusted prevalence of LDH-N) 95% CI for adjusted prevalence of LDH-N Odds ratio (OR) 95% CI for OR	0.536 (0.459, 0.612)	0.494 (0.417, 0.570)	Treatment effect 1.187 (0.796, 1.769)
	Percentage change from baseline in **LDH levels** (day 183) LS Mean (SEM) 95% CI for LS MEAN	-76.84 (1.582) (-79.96, -73.73)	-76.02 (1.617) (-79.20, -72.83)	Difference (ALXN1210-Eculizumab) -0.83 (2.227) (-5.21, 3.56)

Key Secondary Endpoints	Change from baseline in **QoL** as assessed by the FACIT-Fatigue scale (%)(day 183) LS Mean (SEM) 95% CI for LS MEAN	7.07 (07.773) (5.55, 8.60)	6.40 (0.789) (4.85, 7.96)	0.67 (0.955) (-1.21, 2.55)
	Proportion of patients with **BTH** (day 183) Number of patients (n) Percent. of patients (%) 95% CI	5 4 (0.56,7.44)	13 10.7 (5.23, 13.26)	Treatment Difference (ALXN1210 - Eculizumab) -6.7 (-14.21, 0.18)
	Proportion of patients with **stabilized haemoglobin levels** (day 183) Number of patients (n) Percentage of patients (%) 95% CI	85 68.0 (59.82, 76.18)	78 64.5 (55.93, 72.99)	2.9 (-8.80, 14.64)
Notes	Statistically significant non-inferiority was achieved for both co-primary and all 4 key secondary endpoints. Both co-primary and all 4 key secondary endpoints had point estimates which favored ravulizumab over eculizumab. Superiority testing was assessed following a prespecified hierarchical order that began with breakthrough haemolysis endpoint. The treatment difference for breakthrough haemolysis (p = 0.0558 favouring ravulizumab) did not reach the prespecified threshold for superiority (p < 0.05), and no further superiority testing of other endpoints was conducted.			
CONCLUSION	For both coprimary endpoints and all 4 key secondary efficacy endpoints, ALXN1210 achieved statistically significant noninferiority compared to eculizumab, with treatment differences favouring ALXN1210. Compared to eculizumab, ALXN1210 provided better disease control as evidenced by immediate, complete, and sustained inhibition of terminal complement throughout the entire 26-week treatment period.			

Table 52: Summary of efficacy for trial ALXN1210-PNH-302

Title: **ALXN121 0-PNH -302** **A PHASE 3, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY OF ALXN1210 VERSUS ECULIZUMAB IN ADULT PATIENTS WITH PAROXYSMAL NOCTURNAL HAEMOGLOBINURIA (PNH) CURRENTLY TREATED WITH ECULIZUMAB**			
Study identifier	ALXN121 0-PNH -302		
Design	A PHASE 3, RANDOMIZED, OPEN-LABEL, MULTICENTRIC ACTIVE-CONTROLLED STUDY Study centers: 70 sites were initiated, of which 52 sites in 12 countries screened patients. Patients were enrolled at 49 sites in 11 countries (Australia, Canada, France, Germany, Italy, Japan, Netherlands, Republic of Korea, Spain, United Kingdom, and United States).		
	Duration of main phase / Run-in phase: – 26-week ramdomized treatment period Duration of Extension phase: – 2 years		First patient treated: 05 Jun 2017 Last patient completed Primary Evaluation Period: 08 Mar 2018 Release date of report: 30 May 2018
Hypothesis	**Non-inferiority** of ALXN1210 compared to eculizumab in adult patients with PNH who had been treated with a complement inhibitor		
Treatments groups	RAVULIZUMAB (ALXN1210)		ALXN1210 treatment group: weight-based loading dose on Day 1 followed by weight-based maintenance doses on Days 15, 71, and 127 Primary Evaluation Period: 26 weeks (183 days) Number randomized: - Planned: 96 patients per treatment group - Primary efficacy evaluation: 97 in the ALXN1210 treatment group
	ECULIZUMAB		Eculizumab treatment group: 900-mg maintenance doses on Days 1,15, 29, 43, 57, 71, 85, 99, 113, 127, 141, 155, and 169 Primary Evaluation Period: 26 weeks (183 days) Number randomized: - Planned: 96 patients per treatment group - Primary efficacy evaluation: 98 in the eculizumab treatment group
Endpoints and definitions	Primary endpoint	– Haemolysis	Haemolysis as directly measured by percent change in LDH from baseline to Day 183 (Week 26)
	Key Secondary	– Proportion of patients with	– Proportion of patients with breakthrough haemolysis, defined as at least one new or

	Endpoints (tested in a hierarchical manner)	breakthrough haemolysis	worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [haemoglobin < 10 g/dL], major adverse vascular event [MAVE] including thrombosis, dysphagia, or erectile dysfunction) in the presence of elevated LDH ≥ 2 × upper limit of normal (ULN)
		– Change in quality of life (QoL)	– Change in quality of life (QoL) assessed via the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, Version 4, from baseline to Day 183 (Week 26)
		– Transfusion avoidance (TA)	– Transfusion avoidance (TA), defined as the proportion of patients who remained transfusion-free and did not require a transfusion as per protocol-specified guidelines from baseline to Day 183 (Week 26)
		– Proportion of patients with stabilized haemoglobin	– Proportion of patients with stabilized haemoglobin, defined as avoidance of a ≥ 2 g/dL decrease in haemoglobin level from baseline in the absence of transfusion measured from baseline to Day 183 (Week 26)
	Other Secondary:	– Total number of units of pRBC transfused	– Total number of units of pRBC transfused from baseline to Day 183 (Week 26)
		– Proportion of patients with LDH in the normal range (LDH-N)	– Proportion of patients with LDH in the normal range (LDH-N) at Day 183 (Week 26)
		–QoL	– Change in the European Organisation for Research and Treatment of Cancer (EORTC) QoL Questionnaire-Core 30 scale (QLQ-C30), Version 3.0, from baseline to Day 183 (Week 26)
		– Clinical manifestations of PNH	– Change in clinical manifestations of PNH (fatigue, haemoglobinuria, abdominal pain, shortness of breath, chest pain, dysphagia, and erectile dysfunction) from baseline to Day 183 (Week 26)
		– Proportion of patients experiencing MAVEs	– Proportion of patients experiencing MAVEs from baseline to Day 183 (Week 26)}
Database lock	30 May 2018		
Results and Analysis The primary efficacy endpoint was the percent change in LDH from baseline to Day 183. Baseline was defined as the average of all assessments analyzed by the central laboratory prior to first study drug administration. The percent change in LDH was analyzed using a mixed-effect model for repeated measures (MMRM) with the fixed, categorical effects of treatment, study visit, and study visit by treatment group interaction as well as the continuous, fixed covariate of baseline LDH and the stratification randomization indicator of pRBC transfusion history (yes/no within 12 months prior to Day 1). A difference in percent change in LDH between the ALXN1210 and eculizumab treatment groups along with a 2-sided 95% CI was calculated.			
Analysis description	**Primary Analysis**		

Analysis population and time point description	In total, 195 eculizumab-experienced patients with PNH were enrolled and treated with ALXN1210 (N = 97) or eculizumab (N = 98); 191 patients completed the Primary Evaluation Period. One patient in the ALXN1210 group did not complete the Primary Evaluation Period due to patient decision to withdraw from the study, and 3 patients in the eculizumab group did not complete due to patient decision to withdraw, lack of efficacy, and pregnancy (1 patient each). All patients in both treatment groups received all planned infusions. This clinical study report presents results from the Primary Evaluation Period (through Day 183).			
Descriptive statistics and estimate variability	Treatment group	ALXN1210	Eculizumab	Treatment Difference (ALXN1210 – Eculizumab)
	Number of subject	N = 97	N = 98	N =195
Primary endpoint	Percentage change from baseline in **LDH levels** (day 183)			Difference (ALXN1210-Eculizumab)
	LS Mean (SEM) 95% CI for LS MEAN	-0.82 (3.033) (-7.75, 6.11)	8.39 (3.041) (1.47, 15.32)	-9.21 (4.112) (-18.84, 0.42)
Key Secondary Endpoints	Proportion of patients with **BTH** (day 183)			
	Number of patients (n) Percentage (%) 95% CI	0 0.0 (0.00, 3.73)	5 5.1 (1.68, 11.51)	-5.1 (-18.99, 8.89)
	Change from baseline in quality of life as assessed by the **FACIT-Fatigue scale** (%) (day 183)	2.01 (0.697) (0.64, 3,39)		
	LS Mean (SEM) 95% CI for LS MEAN		0.54 (0.704) (-0.84, 1.93)	1.47 (0.853) (-0.21, 3.15)
	Proportion of patients with **transfusion avoidance** (day 183)	85 87.6 (81.08, 94.18)		
	Number of patients (n) Percentage (%) 95% CI		81 82.7 (75.16, 90.15)	5.5 (-4.27, 15.68)
	Proportion of patients with **stabilized haemoglobin levels** (day 183)	74 76.3 (67.82, 84.75)		
	Number of patients		74 75.5	1.4

	(n) Percentage (%) 95% CI		(67.00, 84.02)	(-10.41, 13.31)
Notes	Statistically significant non-inferiority was achieved for both the primary and all 4 key secondary endpoints. Both the primary and all 4 key secondary endpoints had point estimates which favoured ravulizumab over eculizumab. Superiority testing was assessed following a prespecified hierarchical order that began with percent change from baseline in LDH. The assessment of the treatment difference for superiority resulted in a p-value = 0.0583 favouring ravulizumab. The prespecified threshold for superiority ($p < 0.05$) for percent change from baseline in LDH was not reached, and no further superiority testing was conducted.			
Analysis description	Subgroup analyses were performed for the observed stratification variable of transfusion history and for sex, race, region, and age for the primary endpoint and key secondary endpoints. No sensitive subgroups were identified in these analyses. The point estimates for all subgroups favoured ALXN1210**.**			
CONCLUSION	For the primary endpoint and all 4 key secondary efficacy endpoints, ALXN1210 achieved statistically significant non-inferiority compared to eculizumab, with treatment differences consistently favouring ALXN1210. Compared to eculizumab, ALXN1210 provided better disease control as evidenced by complete and sustained inhibition of terminal complement throughout the entire 26-week treatment period with no events of BTH.			

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

There were no pooled or integrated analyses performed since the two Phase 3 studies enrolled different patient populations (naïve vs pre-treated patients).

Clinical studies in special populations

	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	48	15	1

Supportive study(ies)

Early phase clinical trials, ALXN1210-HV-101, ALXN1210-HV-102, ALXN1210-PNH-103 ALXN1210-HV-104 and ALXN1210-PNH-201 have been run to proof safety, tolerability and immunogenicity in healthy subjects and lastly, in adult patients with PNH for also evaluate efficacy. A summary of the most relevant above-mentioned studies have been included in the dose finding section. PK and PD results of studies on healthy subjects have been assessed in pharmacology section.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Four Phase I studies were conducted in healthy volunteer to collect data on safety, tolerability, immunogenicity, PK and PD. A Phase 1b and a Phase 2 dose escalation studies were conducted for dose

selection in patients with PNH who were naïve to complement inhibitor treatment. Phase 1 and Phase 2 study designs (ALXN1210-PNH-103 and ALXN1210-PNH-201) were acceptable to provide the necessary additional data to understand the drug and to design the confirmatory trials. Size, number and range of studied doses seem correct for the best starting choice for phase 3 studies. Results of those studies suggest that ALXN1210 was well tolerated and resulted in a rapid and sustained reduction of plasma LDH levels together with an improvement on LDH, free haemoglobin and QoL. However, efficacy and safety data from only those studies are quite limited to properly justify dose selection. Therefore, dose selection is mainly based on modelling and simulation methods that utilized the Phase 1 and Phase 2 PK, PD, and LDH data over a wide range of doses and regimens in healthy volunteers and patients with PNH (see Pharmacology section).

No modification of this dosing regimen was proposed for any special populations or demographic subgroups. According to the applicant it is expected ravulizumab is metabolized as any endogenous IgG (degraded into small peptides and amino acids via catabolic pathways), with a similar elimination, thus no dose adjustment is deemed necessary in patients with renal impairment. Regarding hepatic impairment, a statement that *safety and efficacy of Ultomiris have not been studied in patients with hepatic impairment* has been included in section 4.2 of the SmPC. It should be also highlighted that according to the SmPC, ravulizumab dosing schedule is allowed to occasionally vary by ± 7 days of the scheduled infusion day (except for the first maintenance dose of ravulizumab) but the subsequent dose should be administered according to the original schedule. The delay in ≤7 days from the targeted dosing day seems not relevant for the outcome of the patient. However, there are very limited data on a longer delay; any further information available will be provided once the maintenance period is concluded (see RMP). The MAH will submit data once the studies are completed [ALXN1210-PNH-301 (estimated Dec 2023) and ALXN1210-PNH-302 (Dec 2021)] (see RMP).

Two multicenter, open-label, randomised, active-controlled, Phase 3 studies — ALXN1210-PNH-301 and ALXN1210-PNH-302— were conducted as pivotal studies. Open-label design seems reasonable due to marked differences in IV infusion schedules and high number of sham IV infusion required as consequence for a blinded trial.

One study was conducted in patients with PNH who were naïve to complement inhibitor treatment (ALXN1210-PNH-301) and other in patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months (ALXN1210-PNH-302). ALXN1210 has been planned as a possible fist line treatment as an alternative to eculizumab, as a continuation therapy after eculizumab or as a maintenance therapy due to the 2 years of continuation treatment.

These populations represent the patients who could benefit from receiving ravulizumab in clinical practice. The populations were characterized differently in so far as naïve patients have active haemolytic disease and the patients on eculizumab have stable disease. Therefore, inclusion and exclusion criteria and efficacy endpoints were slightly different in both studies.

The proposed inclusion and exclusion criteria are considered acceptable in both studies. It should be noted that patients who have been treated with eculizumab and who do not achieve stable disease are excluded from both trials. No option has been given for patients with active disease after eculizumab or non-responding patients. So those patients who have not responded to eculizumab may not be potential candidates to receive ravulizumab as rescue therapy, unless complementary studies or a long follow-up of the pre-treated population indicate otherwise.

For Study ALXN1210 PNH 301, the co-primary endpoints of transfusion avoidance and LDH normalization allowed optimal characterization of the magnitude of effect in patients who were complement inhibitor-naïve and had active PNH disease. In contrast, for Study ALXN1210 PNH-302, the primary endpoint of change in LDH allowed optimal characterization of the maintenance of the high degree of

disease control that patients had already achieved at baseline after a minimum of 6 months of eculizumab treatment.

Apart from breakthrough haemolysis, all of the proposed primary and secondary endpoints were in line with endpoints used in the eculizumab studies (TRIUMPH and SHEPHERD studies).

Thrombosis has been well-recognized as the leading cause of death in PNH. Major vascular events, including thrombosis, have been discussed in safety section.

For all above, the proposed primary/co-primary endpoints and secondary endpoints are considered acceptable since they have been properly justified by the applicant. Both studies consists of a 4-week Screening Period, a 26-week Randomized Treatment Period, and an Extension Period of up to 2 years. The 26-weeks treatment duration is considered acceptable since is in line with eculizumab clinical development and 6 months seems to be sufficient to characterize the comparison between ravulizumab and eculizumab. However, it should be kept in mind that only the loading dose and 3 dose of maintenance can be properly assessed. The 3rd maintenance dose will be administered on week 18 and the 4th maintenance dose will be administered on week 26 without time for follow-up. Applicant´s proposal to provide the final results from the extension periods as a post-approval commitment is acceptable. Nevertheless, the applicant was requested to provide any additional data available (PD, efficacy and safety). Data up to week 52 (data cut-off date 04 Sep 2018), –showed that although most of the cases adequately maintain the response, there is an escape of LDH values in certain subjects over time, which does not correlate with C5 levels, and which should be confirmed in terms of clinical relevance with a longer follow-up.

PNH has a high risk for significant morbidity and mortality in untreated patients, so that placebo controls were not considered acceptable for use as a comparator in the ravulizumab PNH clinical studies. Patients in the Phase 3 studies were randomly assigned to active treatment, either ravulizumab or eculizumab (since 2007, the PNH standard of care). Eculizumab has been administered in both studies according to the SmPC. The choice of comparator for both target population and doses used seem to be adequate.

In both studies randomization has been 1:1. The stratified factors (transfusion history and/or screening LDH levels) are reasonable since they are considered relevant prognostic factors. . Regarding sensitivity analysis (splitting the 1-14 level into two levels [1-4 and 4-14]), the level 4 to 14 units includes a group of patients with extremely heterogeneous transfusion dependence. However, it does not seem to be clinically relevant to continue to pursue this discussion.

The two Phase 3 studies used a non-inferiority design to compare results in patients treated with ravulizumab to those in patients treated with eculizumab. The endpoints were tested in hierarchical order for non-inferiority. Additional testing order for superiority is also pre-specified if non-inferiority was established for all key secondary endpoints.

Efficacy analyses were performed using the FAS as the primary efficacy population. The co-primary/primary efficacy endpoint analyses, as well as key secondary endpoint analyses, were repeated using the PP Set as a sensitivity analysis. However, it should be noted that in non-inferiority studies PP set is preferred as primary efficacy population. In this case, in both studies FAS and PP set are quite similar [ALXN1210-PNH-301: FAS (ALXN1210 n= 125; Eculizumab n=121); PP (ALXN1210 n= 124; Eculizumab n=120) and ALXN1210-PNH-302: FAS (ALXN1210 n= 97; Eculizumab n=98); PP (ALXN1210 n= 93; Eculizumab n=93)] and results in both population are in line. Thus, this issue is not further pursued.

In ALXN1210-PNH-301, NIMs for co-primary endpoint % transfusion avoidance is based on data from Alexion's PNH Registry. According to that registry, the mean eculizumab response was 57%. The NIM was established as -20% which represents a preservation of 65% of effect. It should be noted that a different approach was submitted in the CHMP scientific advice (EMA/CHMP/SAWP/403560/2016). In that case

NIM was based on the eculizumab TRIUMPH study, in which a difference of 51% in the proportion of patients with TA after 26 weeks of treatment of eculizumab over placebo was observed and a traditional choice of NIM of ≤50% loss of benefit was considered. With this approach NIM resulted in 25%, although was highlighted by the CHMP that this NIM was not based on the lower bound of the 95% CI for the treatment difference (95%CI: 0.367 to 0.654). Using the lower bound of the 95% CI, a more conservative NIM resulted (18.3%). As this is not far from 20% considered with the new approach, this issue is not further pursued.

NIM for co-primary endpoint LDH normalization is based on eculizumab TRIUMPH study. According to this study mean eculizumab response was 0.42. The NIM was established in 0.39. It should be noted this approach was not discussed in the scientific advice since in this one a different co-primary endpoint was proposed, change of LDH from baseline. The applicant has provided an explanation for the choice of the NIM. Even a more conservative NIM should have been chosen, taking into account the outcomes of the study, this discussion is no longer needed.

In ALXN1210-PNH-302, NIM is based on data from Alexion's PNH Registry for patients who discontinued eculizumab relative to patients who remained on eculizumab, whose change in LDH is expected to remain stable (the mean percent change in LDH was +134%) The NIM was established in 15% which represent a preservation of 89% of effect. The approach is accepted as the preservation of effect (89%) is conservative. However, it has to be kept in mind that the fact that is based only on data from a registry is a relevant limitation.

Considering the established NIMs for %TA in ALXN1210-PNH-301 and % Change in LDH in ALXN1210-PNH-302, the sample size has been considered acceptable, although sample size in ALXN1210-PNH-301 was calculated to provide 80% power, which is minimum acceptable level of power. As the sample size estimate based on LDH-N was smaller than that based on TA, the final sample size estimate selected for ALXN1210-PNH-301 study was based on the TA endpoint.

Efficacy data and additional analyses

The results of the conducted Phase 3 studies provide evidence of data from both studies without relevant differences between treatment groups in demographic characteristics, with an acceptable treatment compliance and absence of key protocol deviations that impacted interpretation of efficacy results. Diagnostic criteria, adherence to intent to treat principles, inclusion of stratification factors, and the selection of endpoints apparently have been well applied for reducing the potential for bias.

Although no protocol deviations that impacted on interpretation of efficacy results were observed, in the ALXN1210-301, five patients (ALXN1210: n= 1, eculizumab: n= 4) were inadvertently assigned to the incorrect stratification group. Moreover, in the ALXN1210-302 study, 3 patients (ALXN1210: n=1, eculizumab: n=2) were also stratified to the wrong group. However, no relevant implications were observed.

In study ALXN1210-301 (Complement Inhibitor-Naïve Patients), ALXN1210 met the primary objective of statistically significant non-inferiority compared to eculizumab on both co-primary endpoints, avoidance of pRBC transfusion per protocol-specified guidelines *[Difference between treatment: 6.8% (95% CI: -4.66%, 18.14%) with a lower bound of the 95% CI greater than the protocol-specified NIM of -20%]* and LDH-N *[Adjusted odds ratio for the comparison of treatment: 1.187 (95% confidence interval [CI]: 0.796, 1.769) with lower bound of the 95% CI greater than the protocol-specified NIM of 0.39]*, from Day 29 to Day 183. ALXN1210 also achieved statistically significant non-inferiority compared to eculizumab on all 4 key secondary endpoints according to a pre-specified hierarchical testing order (1 Percentage change from baseline in LDH levels, 2 Change from baseline in QoL as assessed by the FACIT-Fatigue scale, 3 Proportion of patients with BTH and 4 Proportion of patients with stabilized haemoglobin levels). As statistically significant non-inferiority was achieved for both co-primary and all 4 key secondary

endpoints, superiority was assessed using a pre-specified hierarchical testing order. However, the assessment of the treatment difference for superiority in Breakthrough haemolysis resulted in p-value = 0.0558 which did not reach the pre-specified significance threshold for superiority ($p < 0.05$) and therefore no additional superiority testing was conducted.

In study ALXN1210-302 (Eculizumab-Experienced Patients), ALXN1210 achieved statistically significant non-inferiority compared to eculizumab for the primary endpoint, percent change in LDH from baseline to Day 183, with a treatment difference (ALXN1210 - eculizumab) of -9.21% (95% CI: -18.84%, 0.42%. The upper bound of the 95% CI was less than the pre-specified NIM of 15%. ALXN1210 also achieved statistically significant non-inferiority compared to eculizumab on all 4 key secondary endpoints according to a pre-specified hierarchical testing order for non-inferiority (1 Proportion of patients with BTH, 2 Change from baseline in quality of life as assessed by the FACIT-Fatigue scale, 3 Proportion of patients with transfusion avoidance and 4 Proportion of patients with stabilized haemoglobin levels). As statistically significant non-inferiority was achieved for the primary endpoint and all 4 key secondary endpoints, the pre-specified hierarchical order continued with superiority testing of percent change from baseline in LDH. However, the assessment of the treatment difference for superiority resulted in p-value = 0.0583 which did not reach the pre-specified significance threshold for superiority ($p < 0.05$) and therefore no additional superiority testing was conducted.

The first endpoint to be tested for superiority in both studies did not reach statistical significance and no other superiority test was performed. So even when results apparently show a favourable trend for ravulizumab for all primary and key secondary efficacy endpoints in both studies, superiority has not been achieved. Consequently, no other conclusion apart from similarity between both treatments can be considered.

In the study ALXN1210-PNH-301 BTH events where described in 5/125 patients in ravulizumab arm (none with suboptimal PD) and 15/121 patients in the eculizumab arm (7/121 with suboptimal PD). In the eculizumab arm there were 15 patients with suboptimal PD response (none in the ravulizumab group), of whom 6 (40%) experienced BTH. A careful medical review of these patients with free C5 excursions > 0.5 µg/mL revealed that several of these patients did have symptoms of BTH or elevated LDH that taken together did not meet the protocol-specified definition. Overall, these observations seem to suggest that free C5 excursions > 0.5 µg/mL may be associated with symptoms and signs of intravascular haemolysis that do not meet the more robust definition of breakthrough haemolysis defined in the protocols of both Phase 3 studies and it should be further observed if it comes with a worsened quality of life during the extension phase of the studies (see RMP). In this context, raises the possibility that a complete inhibition or blocking of C5 may not be —from a given threshold— so important for the control of the disease.

In study ALXN1210 PNH 301, TA subgroups analysis is quite in line with overall analysis. There are slightly deviations in several subgroups (0 prior pRBC units transfused, >65 years, North America Region) but they seem to be led by small number of patients included in those subgroups. Variability on LDH-N subgroups analysis is higher than for TA. The same slightly deviation were observed in those subgroups with lower patients (0 prior pRBC units transfused, >65 years, North America and Japan Regions). Pointing out the results of female, whose OR (95%CI) was 0.66 (0.36, 1.19) while OR (95%CI) in male was 1.74 (0.99, 3.04). The applicant argues there is no plausible biologic explanation for an effect of gender on ravulizumab efficacy: The most relevant finding among male vs female baseline population characteristics, was the distribution of Asian subjects; the number of Japanese's descendants was higher in the male group than in the female group, what is not consistent with what is observed in the Forest plot and that supports the explanation that basal characteristics data do not clearly identify any prognostic factors that could explain the observed gender-based difference in LDH-N, what leads to assume that it could be a random result. In study ALXN1210 PNH 302, Percent Change in LDH subgroups analysis did not show relevant different results for any group. Although it is suppressive the wide 95 CI observed in males, because number of patients included in this subgroups is quite similar to the subgroup of females.

In study ALXN1210-302, it has been described that a patient with stable disease but suboptimal response changing to ravulizumab has a nearly 18% increased probability of reaching LDH-N compared to a patient who remains with eculizumab; therefore eculizumab could be a good option for treating the first line (induction) and that it could be changed to ravulizumab in case of suboptimal response. Patients under eculizumab treatment with good control of the disease could decide on continuing with eculizumab or change to ravulizumab only because of more convenient dosing of the latter, where there would be a real benefit in the maintenance period allowing a better quality of life. Nevertheless, no data have been provided to confirm this statement, thus there is no evidence regarding an increased probability of reaching LDH-N with ravulizumab compared to a patient who remains with eculizumab. Moreover, according to the applicant, this statement is based on an exploratory analysis and as such cannot be supported.

Across both phase 3 studies, ravulizumab showed statistically significant non-inferiority compared to eculizumab, reducing and maintaining control of haemolysis in patients with PNH and suggesting that complement inhibitor-naïve and eculizumab-experienced patients with PNH both respond to ravulizumab treatment.

The benefit/risk of continuous versus intermittent disease-driven treatment with ravulizumab would be of interest, given the fact that PNH is a chronic disease. In this context data about ravulizumab discontinuation and outcome of these patients who discontinued ravulizumab in the long term follow up should be submitted once the trials have been completed (See RMP).

2.5.4. Conclusions on the clinical efficacy

The results presented show the non-inferiority of ravulizumab versus eculizumab in complement inhibitor-naïve and eculizumab-experienced PNH patients, for primary endpoints and for all endpoints of key secondary efficacy in both Phase 3 studies.

- The CHMP considers the following measures necessary to address issues related to efficacy:

Final Clinical Study Report for Studies ALXN1210-PNH-301 and ALXN1210-PNH-302 should be submitted when available.

2.6. Clinical safety

The safety profile of ravulizumab (ALXN1210) administered intravenously (IV) for the treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH) is based on 4 clinical studies:

- Two Phase 3 studies in patients with PNH: Study ALXN1210-PNH-301 and Study ALXN1210-PNH-302. In Study ALXN1210-PNH-301, 246 patients were randomized (ravulizumab, N = 125; eculizumab, N = 121) and in Study ALXN1210-PNH-302, 197 patients were randomized (ravulizumab, N = 97; eculizumab, N = 98).
- One Phase 1b and One Phase 2 study in patients with PNH: Study ALXN1210-PNH-103 and Study ALXN1210-PNH-201 A total of 39 patients received ravulizumab in the Primary Evaluation Period of these 2 studies (13 in Study ALXN1210-PNH-103 and 26 in Study ALXN1210-PNH-201). All 39 patients entered the Extension Periods to continue ravulizumab treatment.

Patient exposure

Phase 3 PNH population

The Phase 3 PNH Population comprises pooled data from all patients who received at least 1 dose of study drug in Study ALXN1210-PNH-301 or Study ALXN1210-PNH-302. In the pooled analysis, data are included up to the end of the 26-week Primary Evaluation Period of the 2 studies.

Table 53: Patient disposition (Phase 3 PNH Population)

Variable	PNH-301 (Eculizumab Naïve)		PNH-302 (Eculizumab Experienced)		All Ravulizumab (N = 222)	All Eculizumab (N = 219)	Total (N = 441)
	Ravulizumab (N = 125)	Eculizumab (N = 121)	Ravulizumab (N = 97)	Eculizumab (N = 98)			
Treated	125	121	97	98	222	219	441
Completed Primary Evaluation Period	125 (100.0)	119 (98.3)	96 (99.0)	95 (96.9)	221 (99.5)	214 (97.7)	435 (98.6)
Planned to continue to Extension Period	124 (99.2)	119 (98.3)	96 (99.0)	95 (96.9)	220 (99.1)	214 (97.7)	434 (98.4)
Did not complete Primary Evaluation Period	0	2 (1.7)	1 (1.0)	3 (3.1)	1 (0.5)	5 (2.3)	6 (1.4)
Physician decision	0	1 (0.8)	0	0	0	1 (0.5)	1 (0.2)
Pregnancy	0	0	0	1 (1.0)	0	1 (0.5)	1 (0.2)
Withdrawal by patient	0	1 (0.8)	1 (1.0)	1 (1.0)	1 (0.5)	2 (0.9)	3 (0.7)
Lack of efficacy	0	0	0	1 (1.0)	0	1 (0.5)	1 (0.2)

Notes: Phase 3 PNH Population = ALXN1210-PNH-301 and ALXN1210-PNH-302.
The data cut-off dates were the end of randomized treatment period for ALXN1210-PNH-301 and ALXN1210-PNH-302.
Abbreviations: PNH = paroxysmal nocturnal hemoglobinuria

Table 54: Exposure by Treatment within Study (Phase 3 PNH Population)

Variable	PNH-301 (Eculizumab Naïve)		PNH-302 (Eculizumab Experienced)	
	Ravulizumab (N = 125)	Eculizumab (N = 121)	Ravulizumab (N = 97)	Eculizumab (N = 98)
Treatment duration from Day 1 to Day 183 (days)[a]				
N	125	121	97	98
Mean (SD)	181.9 (1.83)	179.6 (18.63)	180.3 (18.32)	178.8 (19.72)
Median	182.0	182.0	182.0	182.0
Min, Max	175, 191	10, 186	2, 187	9, 185
Total patient years of exposure (years)	62.3	59.5	47.9	48.0
Treatment duration category, n (%)[a]				
1 day – < 13 weeks	0	2 (1.7)	1 (1.0)	1 (1.0)
13 – < 26 weeks[b]	33 (26.4)	31 (25.6)	15 (15.5)	23 (23.5)
≥ 26 weeks	92 (73.6)	88 (72.7)	81 (83.5)	74 (75.5)
Number of infusions from Day 1 to Day 183[a]				
N	125	121	97	98
Mean (SD)	4.0 (0.00)	14.8 (1.38)	4.0 (0.30)	12.8 (1.37)
Median	4.0	15.0	4.0	13.0
Min, Max	4, 4	2, 15	1, 4	1, 14
Number of patients with an infusion interruption from Day 1 to Day 183, n (%)[a]	10 (8.0)	12 (9.9)	1 (1.0)	5 (5.1)
Number of infusions interrupted from Day 1 to Day 183[a]				
Total	12	14	1	7
Mean (SD)	1.2 (0.63)	1.2 (0.39)	1.0 (NA)	1.4 (0.89)
Median	1.0	1.0	1.0	1.0
Min, Max	1, 3	1, 2	1, 1	1, 3
Number of infusions interrupted due to adverse event from Day 1 to Day 183[a]				
Total	4	1	0	4
Mean (SD)	2.0 (1.41)	1.0 (NA)	NA	2.0 (1.41)
Median	2.0	1.0	NA	2.0
Min, Max	1, 3	1, 1	NA	1, 3
Drug compliance from Day 1 to Day 183, n (%)[a]				
≥ 100%	125 (100.0)	120 (99.2)	97 (100.0)	98 (100.0)
≥ 80% to < 100%	0	1 (0.8)	0	0

Notes: Phase 3 PNH Population = ALXN1210-PNH-301 and ALXN1210-PNH-302.
The data cut-off dates were the end of randomized treatment period for ALXN1210-PNH-301 and ALXN1210-PNH-302.

Percent compliance = Total number of infusions taken from Day 1 to end of randomized treatment period (excluding Day 183 infusion)/Total number of expected infusions to end of randomized treatment period (excluding Day 183 infusion)

[a] Treatment duration = Day 183 visit date - first study drug infusion date or discontinuation date - first study drug infusion date + 1. Dosing on Day 183 represents the start of the extension period and is not considered as a dose of the randomized treatment period. Dosing on Day 183 represents the start of the Extension Period and was not included in these calculations.

[b] Patients who received their Day 183 dose earlier than the actual Day 183 visit were counted in the category 13 - <26 weeks

Abbreviations: Min = minimum; Max = maximum; PNH = paroxysmal nocturnal hemoglobinuria

PNH extension population

The PNH Extension Population includes those patients from Study ALXN1210-PNH-103 and Study ALXN1210-PNH-201 who completed the last visit of the Primary Evaluation Period and entered into the

Extension Period of the respective studies, and had at least 1 safety observation beyond the last visit day of the Primary Evaluation Period.

Table 55: Exposure to Ravulizumab (PNH Extension Population)

Variable	Ravulizumab (N = 39)
Treatment duration from Day 1 to data cut-off (days)[a]	
n	39
Mean (SD)	625.6 (64.00)
Median	634.0
Min, Max	478, 727
Total patient years of exposure (years)	66.8
Treatment duration category, n (%)[a]	
0 to 6 months	0
> 6 to 12 months	0
> 12 to 18 months	7 (17.9)
> 18 months	32 (82.1)
Drug compliance from Day 1 to data cut-off, n (%)[a]	
≥ 100%	39 (100.0)

Notes: PNH Extension Population = patients from ALXN1210-PNH-103 and ALXN1210-PNH-201 who entered into Extension Period.
The data cut-off dates were 07 Nov 2017 for ALXN1210-PNH-103 and 24 Nov 2017 for ALXN1210-PNH-201.
Percent compliance = Total number of infusions taken from Day 1 to data cut-off date/Total number of expected infusions to data cut-off date.
[a] Treatment duration = data cut-off date or discontinuation date - first study drug infusion date + 1. Dosing on the date of the data cut-off was included in these calculations.
Abbreviations: Min = minimum; Max = maximum

Table 56: Study Duration, Treatment Duration, Compliance and Exposure up to Data Cut-off among Patients Who Entered into Extension Period PNH Extension Population

Variable	ALXN1210 (N=39)
Number of Infusions from Day 1 to Data Cut-off [2]	
n	39
Mean (SD)	17.1 (5.98)
Median	17.0
Min, Max	7, 24
Number of patients with an Infusion Interruption from Day 1 to Data Cut-off, n(%)[2]	2 (5.1)
Number of Infusions Interrupted from Day 1 to Data Cut-off [2]	
Total	2
Mean (SD)	1.0 (0.00)
Median	1.0
Min, Max	1, 1
Number of Infusions Interrupted due to Adverse Event from Day 1 to Data Cut-off [2]	
Total	0
Mean (SD)	
Median	
Min, Max	

Note: Percentages are based on the number of patients in the PNH Extension Population in each column. PNH Extension Population = patients from ALXN1210-PNH-103 and ALXN1210-PNH-201 who entered into extension period.

[1] Study duration = date of data cut-off or discontinuation - date of informed consent + 1.

[2] Treatment duration = data cut-off date or discontinuation date - first study drug infusion date + 1. Dosing on the date of the data cut-off will be included in these calculations. Percent compliance = total number of infusions taken from Day 1 to data cut-off date / total number of expected infusions to data cut-off date. The data cut-off dates are 2017-11-07 for ALXN1210 PNH-103, 2017-11-24 for ALXN1210 PNH-201.

Adverse events

Table 57: Overview of All Treatment-Emergent Adverse Events and Serious Adverse Events by Pooled Treatment Groups (Phase 3 PNH Population)

Variable	All Ravulizumab (N = 222)		All Eculizumab (N = 219)	
	n (%)	E	n (%)	E
Any TEAE	195 (87.8)	932	191 (87.2)	922
Related TEAE	75 (33.8)	179	64 (29.2)	148
Unrelated TEAE	185 (83.3)	753	187 (85.4)	774
Grade 1	172 (77.5)	651	169 (77.2)	644
Grade 2	117 (52.7)	228	106 (48.4)	218
Grade 3	28 (12.6)	44	33 (15.1)	57
Grade 4	7 (3.2)	9	2 (0.9)	2
Grade 5	0	0	1 (0.5)	1
TEAE leading to study drug interruption	2 (0.9)	4	3 (1.4)	5
TEAE leading to study drug discontinuation	0	0	1 (0.5)[a]	1
TEAE considered as a MAVE	2 (0.9)	2	1 (0.5)	1
TEAE of special interest	27 (12.2)	33	18 (8.2)	20
Any Serious TEAE (SAE)	15 (6.8)	22	17 (7.8)	21
Related SAE	5 (2.3)	8	2 (0.9)	2
Unrelated SAE	10 (4.5)	14	15 (6.8)	19
SAE leading to study drug interruption	0	0	0	0
SAE leading to study drug discontinuation	0	0	1 (0.5)	1
SAE considered as a MAVE	1 (0.5)	1	0	0
TEAE leading to death	0	0	1 (0.5)[a]	0

Notes: Phase 3 PNH Population = ALXN1210-PNH-301 and ALXN1210-PNH-302.
The data cut-off dates were the end of randomized treatment period for ALXN1210-PNH-301 and ALXN1210-PNH-302.
[a] Patient ALXN1210-PNH-301-0694-304 received all study drug infusions during the randomized period. Study drug withdrawal and death occurred in the extension.
Treatment emergent AEs are AEs with a start date and start time on or after the date and time of the first infusion of study drug.
Related AEs are defined as AEs that are possibly, probably, or definitely related to study drug. Not related AEs are defined as AEs that are unlikely or not related to study drug.
Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = Fatal.
AEs are coded using MedDRA 20.1.
Abbreviations: AE = adverse event; E = number of events; MAVE = Major Adverse Vascular Events; SAE = serious adverse events; TEAE = treatment-emergent adverse events.

Table 58: Overview of All Treatment-Emergent Adverse Events and Serious Adverse Events by treatment within study (Phase 3 PNH Population)

	PNH-301 (Eculizumab Naïve)				PNH-302 (Eculizumab Experienced)			
	ALXN1210 (N=125)		Eculizumab (N=121)		ALXN1210 (N=97)		Eculizumab (N=98)	
Variables	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Any Treatment-Emergent Adverse Event (TEAE)	110 (88.0)	566	105 (86.8)	556	85 (87.6)	366	86 (87.8)	366
Related TEAE	51 (40.8)	118	50 (41.3)	117	24 (24.7)	61	14 (14.3)	31
Unrelated TEAE	103 (82.4)	448	101 (83.5)	439	82 (84.5)	305	86 (87.8)	335
Grade 1	98 (78.4)	379	94 (77.7)	388	74 (76.3)	272	75 (76.5)	256
Grade 2	65 (52.0)	149	56 (46.3)	130	52 (53.6)	79	50 (51.0)	88
Grade 3	21 (16.8)	33	19 (15.7)	35	7 (7.2)	11	14 (14.3)	22
Grade 4	5 (4.0)	5	2 (1.7)	2	2 (2.1)	4	0 (0.0)	0
Grade 5	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
TEAE Leading to Study Drug Interruption	2 (1.6)	4	1 (0.8)	1	0 (0.0)	0	2 (2.0)	4
TEAE Leading to Study Drug Discontinuation	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
TEAE Considered as a MAVE	2 (1.6)	2	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
TEAE of Special Interest	17 (13.6)	20	13 (10.7)	15	10 (10.3)	13	5 (5.1)	5
Any Serious Treatment-Emergent Adverse Events (SAE)	11 (8.8)	15	9 (7.4)	13	4 (4.1)	7	8 (8.2)	8
Related SAE	4 (3.2)	5	1 (0.8)	1	1 (1.0)	3	1 (1.0)	1
Unrelated SAE	7 (5.6)	10	8 (6.6)	12	3 (3.1)	4	7 (7.1)	7
SAE Leading to Study Drug Interruption	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
SAE Leading to Study Drug Discontinuation	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
SAE Considered as a MAVE	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Death	0 (0.0)		1 (0.8)		0 (0.0)		0 (0.0)	

Note: Phase 3 PNH population = ALXN1210-PNH-301 and ALXN1210-PNH-302.
Percentages are based on the number of patients in the Phase 3 PNH population in each column, i.e., % = n/N*100. E=number of events; MAVE=Major Adverse Vascular Events.
Treatment emergent AEs are AEs with a start date and start time on or after the date and time of the first infusion of study drug.
Related AEs are defined as AEs that are possibly, probably, or definitely related to study drug. Not related AEs are defined as AEs that are unlikely or not related to study drug.
Grade 1=mild; Grade 2=moderate; Grade 3=severe; Grade 4=life-threatening; Grade 5=Fatal
Aes are coded using MedDRA 20.1. Patient 0694-304 received all study drug infusions during the randomised period. Study drug withdrawal and death occurred in the extension.
The data cut-off dates are the end of randomized treatment period for ALXN1210 PNH-301 and ALXN1210 PNH-302.

Table 59: Overview of All Treatment-Emergent Adverse Events and Serious Adverse Events (PNH Extension Population)

Variable	Total Ravulizumab (N = 39)	
	n (%)	E
Any TEAE	39 (100.0)	405
Related TEAE	16 (41.0)	37
Unrelated TEAE	39 (100.0)	368
Grade 1	36 (92.3)	222
Grade 2	25 (64.1)	140
Grade 3	19 (48.7)	35
Grade 4	6 (15.4)	8
Grade 5	0	0
TEAE leading to study drug interruption	0	0
TEAE leading to study drug discontinuation	0	0
TEAE considered as a MAVE	1 (2.6)	1
TEAE of special interest	11 (28.2)	14
Any SAE	11 (28.2)	18
Related SAE	4 (10.3)	4
Unrelated SAE	11 (28.2)	14
SAE leading to study drug interruption	0	0
SAE leading to study drug discontinuation	0	0
SAE considered as a MAVE	0	0
Death	0	

Notes: PNH Extension Population = patients from ALXN1210-PNH-103 and ALXN1210-PNH-201 who entered into Extension Period.
The data cut-off dates were 07 Nov 2017 for ALXN1210-PNH-103 and 24 Nov 2017 for ALXN1210-PNH-201.
Treatment emergent AEs are AEs with a start date and start time on or after the date and time of the first infusion of study drug.
Related AEs are defined as AEs that are possibly, probably, or definitely related to study drug. Not related AEs are defined as AEs that are unlikely or not related to study drug.
E = number of events and rate = rate of AE adjusted by patient-years of exposure, defined as (number of events)/100 patient years

Common adverse events

Table 60: Treatment-Emergent Adverse Events Reported by ≥ 5% of Patients by Pooled Treatment Groups (Phase 3 PNH Population)

System Organ Class Preferred Term	All Ravulizumab (N = 222)		All Eculizumab (N = 219)	
	n (%)	E	n (%)	E
Gastrointestinal disorders	79 (35.6)	131	75 (34.2)	128
Diarrhoea	19 (8.6)	22	12 (5.5)	14
Nausea	19 (8.6)	23	19 (8.7)	23
Abdominal pain	13 (5.9)	16	16 (7.3)	16
General disorders and administration site conditions	55 (24.8)	87	58 (26.5)	91
Pyrexia	15 (6.8)	18	18 (8.2)	23
Chest pain	5 (2.3)	9	14 (6.4)	19
Infections and infestations	108 (48.6)	164	109 (49.8)	155
Nasopharyngitis	32 (14.4)	40	38 (17.4)	41
Upper respiratory tract infection	31 (14.0)	37	17 (7.8)	20
Musculoskeletal and connective tissue disorders	56 (25.2)	99	58 (26.5)	88
Pain in extremity	14 (6.3)	15	11 (5.0)	14
Arthralgia	11 (5.0)	15	12 (5.5)	13
Myalgia	9 (4.1)	10	13 (5.9)	16
Nervous system disorders	86 (38.7)	133	72 (32.9)	132
Headache	71 (32.0)	101	57 (26.0)	98
Dizziness	12 (5.4)	12	14 (6.4)	18
Respiratory, thoracic and mediastinal disorders	44 (19.8)	60	47 (21.5)	73
Oropharyngeal pain	12 (5.4)	14	15 (6.8)	15
Cough	9 (4.1)	9	18 (8.2)	22

Notes: Phase 3 PNH Population = ALXN1210-PNH-301 and ALXN1210-PNH-302.

The data cut-off dates were the end of randomized treatment period for ALXN1210-PNH-301 and ALXN1210-PNH-302.

AEs are coded using MedDRA 20.1.

Abbreviations: AE = adverse event; E = number of events; SOC = System Organ Class; TEAE = treatment-emergent adverse event.

Table 61: Treatment-Emergent Adverse Events Occurring in >=5% of Patients during Randomized Treatment Period by MedDRA System Organ Class and Preferred Term, by Treatment within Study (Phase 3 PNH Population)

	PNH-301 (Eculizumab Naïve)				PNH-302 (Eculizumab Experienced)			
	ALXN1210 (N=125)		Eculizumab (N=121)		ALXN1210 (N=97)		Eculizumab (N=98)	
System Organ Class Preferred term	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Patients with at least one Treatment-Emergent Adverse Event (TEAE)	86 (68.8)	243	86 (71.1)	255	70 (72.2)	200	76 (77.6)	202
Blood and lymphatic system disorders								
Anaemia	3 (2.4)	3	5 (4.1)	8	6 (6.2)	7	3 (3.1)	4
Gastrointestinal disorders								
Nausea	11 (8.8)	14	10 (8.3)	14	8 (8.2)	9	9 (9.2)	9
Diarrhoea	10 (8.0)	12	5 (4.1)	7	9 (9.3)	10	7 (7.1)	7
Abdominal pain	7 (5.6)	7	7 (5.8)	7	6 (6.2)	9	9 (9.2)	9
Vomiting	5 (4.0)	5	4 (3.3)	5	6 (6.2)	6	4 (4.1)	4
Constipation	1 (0.8)	1	3 (2.5)	4	7 (7.2)	7	5 (5.1)	6
General disorders and administration site conditions								
Pyrexia	6 (4.8)	7	13 (10.7)	16	9 (9.3)	11	5 (5.1)	7
Fatigue	5 (4.0)	6	4 (3.3)	6	6 (6.2)	8	6 (6.1)	8
Influenza like illness	3 (2.4)	3	1 (0.8)	1	7 (7.2)	8	8 (8.2)	10
Chest pain	2 (1.6)	4	5 (4.1)	7	3 (3.1)	5	9 (9.2)	12
Infections and infestations								
Upper respiratory tract infection	13 (10.4)	15	7 (5.8)	7	18 (18.6)	22	10 (10.2)	13
Nasopharyngitis	11 (8.8)	14	18 (14.9)	20	21 (21.6)	26	20 (20.4)	21
Viral upper respiratory tract infection	9 (7.2)	10	10 (8.3)	12	1 (1.0)	3	0 (0.0)	0
Rhinitis	2 (1.6)	2	3 (2.5)	3	5 (5.2)	7	4 (4.1)	5
Musculoskeletal and connective tissue disorders								
Pain in extremity	9 (7.2)	10	7 (5.8)	8	5 (5.2)	5	4 (4.1)	6
Arthralgia	8 (6.4)	12	8 (6.6)	9	3 (3.1)	3	4 (4.1)	4
Back pain	7 (5.6)	9	6 (5.0)	6	4 (4.1)	7	4 (4.1)	6
Myalgia	7 (5.6)	8	9 (7.4)	12	2 (2.1)	2	4 (4.1)	4
Musculoskeletal pain	4 (3.2)	4	2 (1.7)	2	2 (2.1)	2	5 (5.1)	5
Nervous system disorders								
Headache	45 (36.0)	70	40 (33.1)	72	26 (26.8)	31	17 (17.3)	26
Dizziness	9 (7.2)	9	7 (5.8)	10	3 (3.1)	3	7 (7.1)	8
Respiratory, thoracic and mediastinal disorders								
Oropharyngeal pain	8 (6.4)	10	6 (5.0)	6	4 (4.1)	4	9 (9.2)	9
Cough	4 (3.2)	4	8 (6.6)	11	5 (5.2)	5	10 (10.2)	11
Dyspnoea	3 (2.4)	4	2 (1.7)	2	0 (0.0)	0	6 (6.1)	8

Note: Phase 3 PNH population = ALXN1210-PNH-301 and ALXN1210-PNH-302.
Percentages are based on the number of patients in the Phase 3 PNH population in each column, i.e., % = n/N*100. E=number of events.
Treatment emergent AEs are AEs with a start date and start time on or after the date and time of the first infusion of study drug.
Under patient count columns, n(%), if a patient had more than one event for a particular SOC, the patient is counted only once for that SOC under n(%).
If a patient had more than one event for a particular PT, the patient is counted only once for that PT.
AEs are coded using MedDRA 20.1
The data cut-off dates are the end of randomized treatment period for ALXN1210 PNH-301 and ALXN1210 PNH-302.

Adverse events of special interest (AEOSIs)

Table 62: Summary of Adverse Events of Special Interest by Pooled Treatment Groups (Phase 3 PNH Population)

Adverse Events of Interest Preferred Term	All Ravulizumab (N = 222)		All Eculizumab (N = 219)	
	n (%)	E	n (%)	E
Patients with at least one AESI	**27 (12.2)**	**33**	**18 (8.2)**	**20**
Angioedema	4 (1.8)	5	0	0
Urticaria	3 (1.4)	4	0	0
Gingival swelling	1 (0.5)	1	0	0
Cardiac Disorder	2 (0.9)	2	1 (0.5)	1
Left ventricular failure	1 (0.5)	1	0	0
Myocardial ischaemia	1 (0.5)	1	0	0
Palpitations	0	0	1 (0.5)	1
Infusion reaction	19 (8.6)	22	13 (5.9)	13
Rash	5 (2.3)	5	4 (1.8)	4
Rhinitis allergic	5 (2.3)	6	1 (0.5)	1
Infusion related reaction	4 (1.8)	5	1 (0.5)	1
Eczema	2 (0.9)	2	0	0
Rash pruritic	2 (0.9)	2	1 (0.5)	1
Dermatitis	1 (0.5)	1	0	0
Dermatitis allergic	1 (0.5)	1	0	0
Dermatitis atopic	0	0	1 (0.5)	1
Hypersensitivity	0	0	3 (1.4)	3
Rash erythematous	0	0	1 (0.5)	1
Rash maculo-papular	0	0	1 (0.5)	1
Other serious infection	4 (1.8)	4	5 (2.3)	6
Influenza	1 (0.5)	1	0	0
Leptospirosis	1 (0.5)	1	0	0
Lower respiratory tract infection	1 (0.5)	1	0	0
Systemic infection	1 (0.5)	1	0	0
Abscess limb	0	0	1 (0.5)	1
Cellulitis	0	0	1 (0.5)	1
Infection	0	0	1 (0.5)	1
Pneumonia	0	0	1 (0.5)	1
Pyelonephritis acute	0	0	1 (0.5)	1
Viral upper respiratory tract infection	0	0	1 (0.5)	1

Notes: Phase 3 PNH Population = ALXN1210-PNH-301 and ALXN1210-PNH-302.
The data cut-off dates were the end of randomized treatment period for ALXN1210-PNH-301 and ALXN1210-PNH-302.
Under patient count columns, n (%), if a patient had more than one event for a particular SOC, the patient is counted only once for that SOC under n (%). If a patient had more than one event for a particular PT, the patient is counted only once for that PT.
AEs are coded using MedDRA 20.1.
Abbreviations: AE = adverse event; E = number of events; MedDRA = Medical Dictionary for Regulatory Activities; PNH = paroxysmal nocturnal hemoglobinuria; PT = Preferred Term; SOC = System Organ Class

Table 63: Treatment-Emergent Adverse Events of Special Interest during Randomized Treatment Period by Treatment within Study (Phase 3 PNH population)

	PNH-301 (Eculizumab Naïve)				PNH-302 (Eculizumab Experienced)			
	ALXN1210 (N=125)		Eculizumab (N=121)		ALXN1210 (N=97)		Eculizumab (N=98)	
Adverse Events of Interest Preferred term	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Patients with at least one Treatment-Emergent Adverse Event (TEAE)	17 (13.6)	20	13 (10.7)	15	10 (10.3)	13	5 (5.1)	5
Angioedema	3 (2.4)	4	0 (0.0)	0	1 (1.0)	1	0 (0.0)	0
Urticaria	2 (1.6)	3	0 (0.0)	0	1 (1.0)	1	0 (0.0)	0
Gingival swelling	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Cardiac Disorder	2 (1.6)	2	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1
Left ventricular failure	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Myocardial ischaemia	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Palpitations	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1
Infusion Reaction	11 (8.8)	12	10 (8.3)	10	8 (8.2)	10	3 (3.1)	3
Rhinitis allergic	4 (3.2)	5	1 (0.8)	1	1 (1.0)	1	0 (0.0)	0
Rash	2 (1.6)	2	3 (2.5)	3	3 (3.1)	3	1 (1.0)	1
Rash pruritic	2 (1.6)	2	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1
Dermatitis	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Dermatitis allergic	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Infusion related reaction	1 (0.8)	1	0 (0.0)	0	3 (3.1)	4	1 (1.0)	1
Dermatitis atopic	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Eczema	0 (0.0)	0	0 (0.0)	0	2 (2.1)	2	0 (0.0)	0
Hypersensitivity	0 (0.0)	0	3 (2.5)	3	0 (0.0)	0	0 (0.0)	0
Rash erythematous	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Rash maculo-papular	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Other Serious Infection	2 (1.6)	2	4 (3.3)	5	2 (2.1)	2	1 (1.0)	1
Leptospirosis	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Systemic infection	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Abscess limb	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Cellulitis	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Infection	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Influenza	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1	0 (0.0)	0
Lower respiratory tract infection	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1	0 (0.0)	0
Pneumonia	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Pyelonephritis acute	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1
Viral upper respiratory tract infection	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0

Note: Phase 3 PNH population = ALXN1210-PNH-301 and ALXN1210-PNH-302.

Percentages are based on the number of patients in the Phase 3 PNH population in each column, i.e., % = n/N*100. E=number of events.

Treatment emergent AEs are AEs with a start date and start time on or after the date and time of the first infusion of study drug.

Under patient count columns, n(%), if a patient had more than one event for a particular AE Special Interest category, the patient is counted only once for that AESI category under n(%). If a patient had more than one event for a particular PT, the patient is counted only once for that PT.

AEs are coded using MedDRA 20.1

The data cut-off dates are the end of randomized treatment period for ALXN1210 PNH-301 and ALXN1210 PNH-302.

Major adverse vascular events

In the Phase 3 PNH Population, three patients experienced a MAVE:

• Pooled ravulizumab (n = 2): DVT, thrombosis (verbatim: thrombosis lower leg right side)

• Pooled eculizumab (n = 1): thrombosis (verbatim: intravascular thrombosis)

In PNH Extension Population, one patient experienced DVT on Day 442 that resolved by Day 531 while continuing treatment.

Serious adverse event / deaths / other significant events

Serious adverse events (SAEs)

Table 64: Summary of Serious Adverse Events by Pooled Treatment Groups (Phase 3 PNH Population)

System Organ Class Preferred Term	All Ravulizumab (N = 222)		All Eculizumab (N = 219)	
	n (%)	E	n (%)	E
Patients with at least one TEAE	15 (6.8)	22	17 (7.8)	21
Blood and lymphatic system disorders	4 (1.8)	5	2 (0.9)	2
Anaemia	1 (0.5)	1	0	0
Aplastic anaemia	1 (0.5)	1	0	0
Neutropenia	1 (0.5)	2	0	0
Thrombocytopenia	1 (0.5)	1	0	0
Haemolysis	0	0	2 (0.9)	2
Cardiac disorders	2 (0.9)	2	1 (0.5)	1
Left ventricular failure	1 (0.5)	1	0	0
Myocardial ischaemia	1 (0.5)	1	0	0
Palpitations	0	0	1 (0.5)	1
Gastrointestinal disorders	1 (0.5)	2	2 (0.9)	3
Colitis	1 (0.5)	2	0	0
Ileus	0	0	1 (0.5)	1
Neutropenic colitis	0	0	1 (0.5)	2
General disorders and administration site conditions	2 (0.9)	2	5 (2.3)	5
Hyperthermia	1 (0.5)	1	0	0
Pyrexia	1 (0.5)	1	5 (2.3)	5
Hepatobiliary disorders	0	0	1 (0.5)	1
Cholelithiasis	0	0	1 (0.5)	1
Infections and infestations	4 (1.8)	4	5 (2.3)	6
Influenza	1 (0.5)	1	0	0
Leptospirosis	1 (0.5)	1	0	0
Lower respiratory tract infection	1 (0.5)	1	0	0
Systemic infection	1 (0.5)	1	0	0
Abscess limb	0	0	1 (0.5)	1
Cellulitis	0	0	1 (0.5)	1
Infection	0	0	1 (0.5)	1
Pneumonia	0	0	1 (0.5)	1
Pyelonephritis acute	0	0	1 (0.5)	1
Viral upper respiratory tract infection	0	0	1 (0.5)	1
Injury, poisoning and procedural complications	1 (0.5)	1	0	0
Laceration	1 (0.5)	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5)	2	2 (0.9)	2
Uterine leiomyoma	1 (0.5)	2	0	0
Adenocarcinoma of colon	0	0	1 (0.5)	1
Lung adenocarcinoma	0	0	1 (0.5)	1
Nervous system disorders	1 (0.5)	1	0	0
Epilepsy	1 (0.5)	1	0	0
Renal and urinary disorders	1 (0.5)	1	1 (0.5)	1
Renal colic	1 (0.5)	1	0	0
Paroxysmal nocturnal haemoglobinuria	0	0	1 (0.5)	1
Respiratory, thoracic and mediastinal disorders	1 (0.5)	1	0	0
Respiratory failure	1 (0.5)	1	0	0
Vascular disorders	1 (0.5)	1	0	0
Deep vein thrombosis	1 (0.5)	1	0	0

Notes: Phase 3 PNH Population = ALXN1210-PNH-301 and ALXN1210-PNH-302.
The data cut-off dates were the end of randomized treatment period for ALXN1210-PNH-301 and ALXN1210-PNH-302.
AEs are coded using MedDRA 20.1.
Abbreviations: AE = adverse events; E = number of events; SOC = System Organ Class; TEAE = treatment-emergent adverse events.

Table 65: Serious Treatment-Emergent Adverse Events during Randomized Treatment Period by MedDRA System Organ Class and Preferred Term, by Treatment within Study (Phase 3 PNH Population)

	PNH-301 (Eculizumab Naïve)				PNH-302 (Eculizumab Experienced)			
	ALXN1210 (N=125)		Eculizumab (N=121)		ALXN1210 (N=97)		Eculizumab (N=98)	
System Organ Class Preferred term	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Patients with at least one Treatment-Emergent Adverse Event (TEAE)	11 (8.8)	15	9 (7.4)	13	4 (4.1)	7	8 (8.2)	8
Blood and lymphatic system disorders	4 (3.2)	5	0 (0.0)	0	0 (0.0)	0	2 (2.0)	2
Anaemia	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Aplastic anaemia	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Neutropenia	1 (0.8)	2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Thrombocytopenia	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Haemolysis	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	2 (2.0)	2
Cardiac disorders	2 (1.6)	2	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1
Left ventricular failure	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Myocardial ischaemia	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Palpitations	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1
Gastrointestinal disorders	0 (0.0)	0	2 (1.7)	3	1 (1.0)	2	0 (0.0)	0
Colitis	0 (0.0)	0	0 (0.0)	0	1 (1.0)	2	0 (0.0)	0
Ileus	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Neutropenic colitis	0 (0.0)	0	1 (0.8)	2	0 (0.0)	0	0 (0.0)	0
General disorders and administration site conditions	1 (0.8)	1	2 (1.7)	2	1 (1.0)	1	3 (3.1)	3
Pyrexia	1 (0.8)	1	2 (1.7)	2	0 (0.0)	0	3 (3.1)	3
Hyperthermia	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1	0 (0.0)	0
Hepatobiliary disorders	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1
Cholelithiasis	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1
Infections and infestations	2 (1.6)	2	4 (3.3)	5	2 (2.1)	2	1 (1.0)	1
Leptospirosis	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Systemic infection	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Abscess limb	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Cellulitis	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Infection	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Influenza	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1	0 (0.0)	0
Lower respiratory tract infection	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1	0 (0.0)	0
Pneumonia	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Pyelonephritis acute	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1
Viral upper respiratory tract infection	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Injury, poisoning and procedural complications	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Laceration	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.8)	2	2 (1.7)	2	0 (0.0)	0	0 (0.0)	0
Uterine leiomyoma	1 (0.8)	2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Adenocarcinoma of colon	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Lung adenocarcinoma	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Nervous system disorders	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1	0 (0.0)	0
Epilepsy	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1	0 (0.0)	0
Renal and urinary disorders	1 (0.8)	1	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Renal colic	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Paroxysmal nocturnal haemoglobinuria	0 (0.0)	0	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1	0 (0.0)	0
Respiratory failure	0 (0.0)	0	0 (0.0)	0	1 (1.0)	1	0 (0.0)	0
Vascular disorders	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Deep vein thrombosis	1 (0.8)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

Note: Phase 3 PNH population = ALXN1210-PNH-301 and ALXN1210-PNH-302.
Percentages are based on the number of patients in the Phase 3 PNH population in each column, i.e., % = n/N*100. E=number of events.
Treatment emergent AEs are AEs with a start date and start time on or after the date and time of the first infusion of study drug.
Under patient count columns, n(%), if a patient had more than one event for a particular SOC, the patient is counted only once for that SOC under n(%).
If a patient had more than one event for a particular PT, the patient is counted only once for that PT.
AEs are coded using MedDRA 20.1
The data cut-off dates are the end of randomized treatment period for ALXN1210 PNH-301 and ALXN1210 PNH-302.

PNH Extension Population

Table 66: Serious Adverse Events, by Time Interval (PNH Extension Population)

System Organ Class Preferred Term	Ravulizumab							
	0 to 6 months (N = 39)		>6 to 12 months (N = 39)		>12 months (N = 39)		Total up to Data Cut-off (N = 39)	
	n (%)	E (rate)	n (%)	E (rate)	n (%)	E (rate)	n (%)	E (rate)
Total patient-years of exposure (years)		**19.4**		**19.5**		**27.8**		**66.8**
Patients with at least one TEAE	**6 (15.4)**	**7 (36.0)**	**5 (12.8)**	**5 (25.6)**	**5 (12.8)**	**6 (21.6)**	**11 (28.2)**	**18 (26.9)**
Blood and lymphatic system disorders	1 (2.6)	1 (5.1)	2 (5.1)	2 (10.2)	1 (2.6)	1 (3.6)	4 (10.3)	4 (6.0)
Febrile neutropenia	1 (2.6)	1 (5.1)	0	0	0	0	1 (2.6)	1 (1.5)
Anaemia	0	0	1 (2.6)	1 (5.1)	1 (2.6)	1 (3.6)	2 (5.1)	2 (3.0)
Haemolysis	0	0	1 (2.6)	1 (5.1)	0	0	1 (2.6)	1 (1.5)
Gastrointestinal disorders	1 (2.6)	1 (5.1)	0	0	0	0	1 (2.6)	1 (1.5)
Nausea	1 (2.6)	1 (5.1)	0	0	0	0	1 (2.6)	1 (1.5)
General disorders and administration site conditions	1 (2.6)	1 (5.1)	0	0	0	0	1 (2.6)	1 (1.5)
Pyrexia	1 (2.6)	1 (5.1)	0	0	0	0	1 (2.6)	1 (1.5)
Hepatobiliary disorders	0	0	0	0	2 (5.1)	2 (7.2)	2 (5.1)	2 (3.0)
Cholecystitis acute	0	0	0	0	1 (2.6)	1 (3.6)	1 (2.6)	1 (1.5)
Hyperbilirubinaemia	0	0	0	0	1 (2.6)	1 (3.6)	1 (2.6)	1 (1.5)
Infections and infestations	2 (5.1)	2 (10.3)	1 (2.6)	1 (5.1)	3 (7.7)	3 (10.8)	6 (15.4)	6 (9.0)
Meningococcal infection	1 (2.6)	1 (5.1)	0	0	1 (2.6)	1 (3.6)	2 (5.1)	2 (3.0)
Urinary tract infection	1 (2.6)	1 (5.1)	0	0	0	0	1 (2.6)	1 (1.5)
Meningococcal sepsis	0	0	1 (2.6)	1 (5.1)	0	0	1 (2.6)	1 (1.5)
Pneumonia	0	0	0	0	1 (2.6)	1 (3.6)	1 (2.6)	1 (1.5)
Upper respiratory tract infection	0	0	0	0	1 (2.6)	1 (3.6)	1 (2.6)	1 (1.5)
Injury, poisoning and procedural complications	0	0	1 (2.6)	1 (5.1)	0	0	1 (2.6)	1 (1.5)
Post procedural complication	0	0	1 (2.6)	1 (5.1)	0	0	1 (2.6)	1 (1.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (2.6)	1 (5.1)	0	0	1 (2.6)	1 (1.5)
Papillary thyroid cancer	0	0	1 (2.6)	1 (5.1)	0	0	1 (2.6)	1 (1.5)
Nervous system disorders	1 (2.6)	1 (5.1)	0	0	0	0	1 (2.6)	1 (1.5)
Headache	1 (2.6)	1 (5.1)	0	0	0	0	1 (2.6)	1 (1.5)
Skin and subcutaneous tissue disorders	1 (2.6)	1 (5.1)	0	0	0	0	1 (2.6)	1 (1.5)
Rash maculo-papular	1 (2.6)	1 (5.1)	0	0	0	0	1 (2.6)	1 (1.5)

Notes: PNH Extension Population = patients from ALXN1210-PNH-103 and ALXN1210-PNH-201 who entered into Extension Period.
The data cut-off dates were 07 Nov 2017 for ALXN1210-PNH-103 and 24 Nov 2017 for ALXN1210-PNH-201.
E = number of events and rate = rate of AE adjusted by patient-years of exposure, defined as (number of events)/100 patient years.
AEs are coded using MedDRA 20.1.

Deaths

No deaths were reported up to the end of the 26-week Primary Evaluation Period for the Phase 3 PNH Population.

One patient in the pooled eculizumab group died during the Extension Period following an AE (lung adenocarcinoma) that began during the Primary Evaluation Period. The patient developed symptoms of lung cancer (blood-tinged sputum, cough, and wheezing) during the Primary Evaluation Period and was diagnosed with lung adenocarcinoma after entering the Extension Period. Study drug was discontinued, and the patient started palliative -chaemotherapy. Subsequently, the patient died due to lung adenocarcinoma. The investigator assessed the event to be not related to study drug.

No deaths occurred in the PNH Extension Population up to the data cut-off.

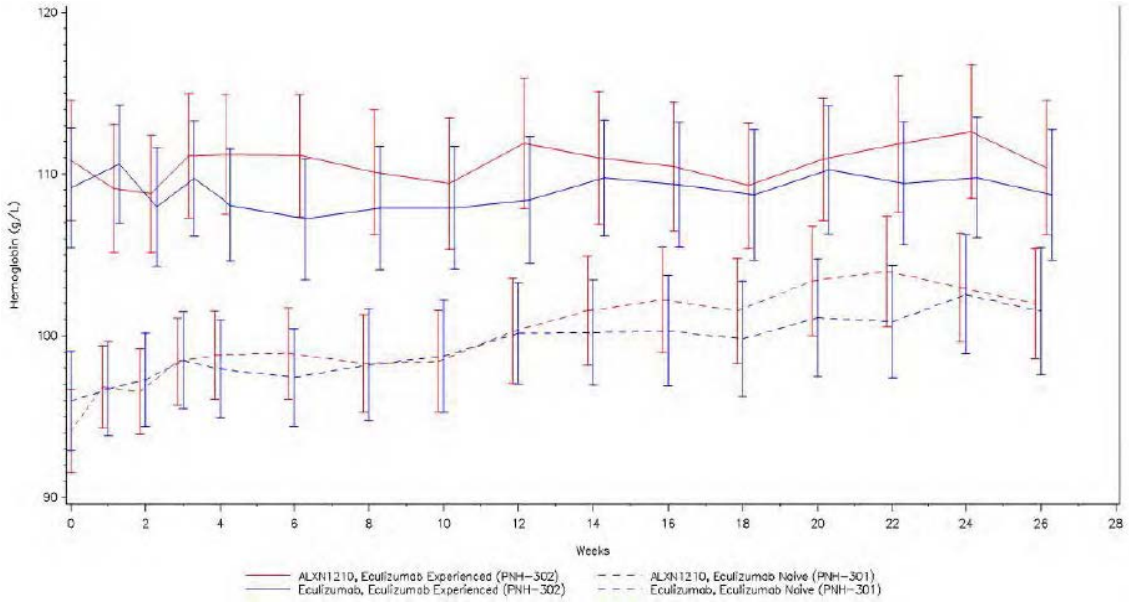
Laboratory findings

Hematology

Mean values for hematology parameters at baseline were generally similar between the ravulizumab and eculizumab groups in Studies ALXN1210-PNH-301 and ALXN1210-PNH-302.

Mean haemoglobin values showed improvement or remained stable from baseline through the 26-week Primary Evaluation Period in both treatment groups (Figure **19**). Mean platelet counts and mean neutrophil counts were either stable or showed small fluctuations which remained above the upper limit of normal (130 × 109/L and 1.8 × 109/L, respectively) in both treatment groups at all post-baseline study visits.

Figure 20: Mean (± SD) Values over Time for Haemoglobin During the Primary Evaluation Period (Phase 3 PNH Population)



Safety in special populations

Table 67: **Ravulizumab Safety Characteristics in Elderly Subgroups**

MedDRA Preferred Terms	Age Subgroups (years)			
	< 65 (N = 194)	65 to < 75 (N = 23)	75 to < 85 (N = 5)	> 85 (N = 0)
Total AEs	172 (88.7)	18 (78.3)	5 (100.0)	-
Serious AEs – total	13 (6.7)	2 (8.7)	0	-
Fatal	0	0	0	-
Hospitalization/prolong existing hospitalization	11 (5.7)	2 (8.7)	0	-
Life-threatening	1 (0.5)	1 (4.3)	0	-
Disability/incapacity	0	0	0	-
Other (medically significant)	2 (1.0)	0	0	-
AE leading to drop-out	0	0	0	-
Psychiatric disorders	9 (4.6)	1 (4.3)	0	-
Nervous system disorders	80 (41.2)	5 (21.7)	1 (20.0)	-
Accidents and injuries	14 (7.2)	1 (4.3)	0	-
Cardiac disorders	8 (4.1)	1 (4.3)	0	-
Vascular disorders	11 (5.7)	0	0	-
Cerebrovascular disorders	0	0	0	-
Infections and infestations	98 (50.5)	8 (34.8)	2 (40.0)	-
Anticholinergic syndrome	0	0	0	-
Quality of life decreased	0	0	0	-
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	14 (7.2)	3 (13.0)	0	-
Other AE appearing more frequently in older patients				
Anemia	5 (2.6)	3 (13.0)	1 (20.0)	-
Abdominal pain	9 (4.6)	3 (13.0)	1 (20.0)	-
Upper respiratory tract infection	27 (13.9)	4 (17.4)	0	-
Neutropenia	3 (1.5)	3 (13.0)	0	-
Dizziness	9 (4.6)	3 (13.0)	0	-

Immunological events

Study ALXN1210-PNH-301

Table 68: Anti-Drug Antibodies During the Randomized Treatment Period Safety Set

Visit	ALXN1210 (N=125)	Eculizumab (N=121)
Day 1, Predose		
Negative	113 (90.4)	115 (95.0)
Positive	12 (9.6)	6 (5.0)
Indeterminate	0 (0.0)	0 (0.0)
Day 71, Predose		
Negative	125 (100)	116 (95.9)
Positive	0 (0.0)	2 (1.7)
Indeterminate	0 (0.0)	0 (0.0)
Day 127, Predose		
Negative	123 (98.4)	117 (96.7)
Positive	1 (0.8)	0 (0.0)
Indeterminate	0 (0.0)	0 (0.0)
Day 183, Predose		
Negative	124 (99.2)	118 (97.5)
Positive	1 (0.8)	0 (0.0)
Indeterminate	0 (0.0)	0 (0.0)

Table 69: Anti-Drug Neutralizing Antibodies During the Randomized Treatment Period Safety Set

Visit	ALXN1210 (N=125)	Eculizumab (N=121)
Day 1, Predose		
Negative	12 (9.6)	4 (3.3)
Positive	0 (0.0)	1 (0.8)
Indeterminate	0 (0.0)	1 (0.8)
Day 71, Predose		
Negative	0 (0.0)	2 (1.7)
Positive	0 (0.0)	0 (0.0)
Indeterminate	0 (0.0)	0 (0.0)
Day 127, Predose		
Negative	1 (0.8)	0 (0.0)
Positive	0 (0.0)	0 (0.0)
Indeterminate	0 (0.0)	0 (0.0)
Day 183, Predose		
Negative	1 (0.8)	0 (0.0)
Positive	0 (0.0)	0 (0.0)
Indeterminate	0 (0.0)	0 (0.0)

Table 70: Anti-Drug Cross-Reactivity to Eculizumab During the Randomized Treatment Period Safety Set

Visit	ALXN1210 (N=125)
Day 1, Predose	
Negative	10 (8.0)
Positive	1 (0.8)
Indeterminate	1 (0.8)
Day 127, Predose	
Negative	0 (0.0)
Positive	0 (0.0)
Indeterminate	1 (0.8)
Day 183, Predose	
Negative	1 (0.8)
Positive	0 (0.0)
Indeterminate	0 (0.0)

Study ALXN1210-PNH-302

Table 71: Anti-Drug Antibodies During the Randomized Treatment Period - Safety Set

Visit	ALXN1210 (N=97)	Eculizumab (N=98)
Day 1, Predose		
Negative	93 (95.9)	98 (100)
Positive	4 (4.1)	0 (0.0)
Indeterminate	0 (0.0)	0 (0.0)
Day 71, Predose		
Negative	94 (96.9)	95 (96.9)
Positive	2 (2.1)	0 (0.0)
Indeterminate	0 (0.0)	0 (0.0)
Day 127, Predose		
Negative	94 (96.9)	94 (95.9)
Positive	2 (2.1)	1 (1.0)
Indeterminate	0 (0.0)	0 (0.0)
Day 183, Predose		
Negative	95 (97.9)	94 (95.9)
Positive	0 (0.0)	0 (0.0)
Indeterminate	0 (0.0)	0 (0.0)

Table 72: Anti-Drug Neutralizing Antibodies During the Randomized Treatment Period Safety Set

Visit	ALXN1210 (N=97)	Eculizumab (N=98)
Day 1, Predose		
Negative	4 (4.1)	0 (0.0)
Positive	0 (0.0)	0 (0.0)
Indeterminate	0 (0.0)	0 (0.0)
Day 71, Predose		
Negative	2 (2.1)	0 (0.0)
Positive	0 (0.0)	0 (0.0)
Indeterminate	0 (0.0)	0 (0.0)
Day 127, Predose		
Negative	2 (2.1)	1 (1.0)
Positive	0 (0.0)	0 (0.0)
Indeterminate	0 (0.0)	0 (0.0)

Table 73: Anti-Drug Cross-Reactivity to Eculizumab During the Randomized Treatment Period Safety Set

Visit	ALXN1210 (N=97)
Day 1, Predose	
Negative	4 (4.1)
Positive	0 (0.0)
Indeterminate	0 (0.0)
Day 71, Predose	
Negative	2 (2.1)
Positive	0 (0.0)
Indeterminate	0 (0.0)
Day 127, Predose	
Negative	1 (1.0)
Positive	1 (1.0)
Indeterminate	0 (0.0)

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been conducted with ravulizumab. Because ravulizumab, is a monoclonal antibody, clinically meaningful drug-drug PK interactions with small molecule drugs or other biologics are generally not expected.

Discontinuation due to adverse events

No AEs led to treatment discontinuation during the 26-week Primary Evaluation Period in the

Phase 3 PNH Population. In one patient from the pooled eculizumab group, lung adenocarcinoma led to death during the Extension Period (a patient was diagnosed with lung adenocarcinoma in the Extension Period and study drug was discontinued). The event was assessed by the Investigator to be not related to study drug.

In phase 3 PNH population, five patients had temporary interruptions due to AEs. In the pooled ravulizumab group (n = 2) 1 patient had infusion-related reaction with no recurrence at subsequent infusions and 1 patient had muscle spasms with each infusion. In the pooled eculizumab group (n = 3), 1 patient had headache (recurrence following a reduction in the rate of infusion at subsequent dosing visits), and 1 each, experienced back pain and flank pain.

Infusion interruptions due to these AEs were temporary, and all infusions were ultimately completed.

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

The safety profile of ravulizumab in the treatment of patients with PNH is based mainly on two phase 3 clinical trials in which ravulizumab was compared to eculizumab in complement inhibitor-naïve patients (Study PNH-301; n=246) and in patients who were clinically stable on eculizumab treatment (Study PNH-302; n=195). In total, 222 patients were treated with ravulizumab in these phase 3 clinical trials and

this population is considered the main safety database. Additionally, data on 39 patients from studies PNH-103 (a phase 1b study) and PNH-201 (a phase 2 study) have been provided, although in these studies ravulizumab was administered at different doses.

Patients were treated with either ravulizumab or eculizumab for 26 weeks, with a median of infusions received of 4 (range: 1; 4) and 15 (range: 1; 15), in the ravulizumab and eculizumab groups, respectively. The majority of patients completed the 26 weeks period and only 6 patients (1 in the ravulizumab group and 5 in the eculizumab group) discontinued study treatment, although none of discontinuations were due to adverse events. Infusion interruptions were reported in 11 (5%) patients in the pooled ravulizumab group and 17 (7.8%) patients in the pooled eculizumab group. Adverse events were the leading cause of infusion interruption in 2 patients treated with ravulizumab (1 infusion-related reaction and 1 muscle spam) and 3 patients treated with eculizumab (1 headache, 1 back pain and 1 flank pain). Nevertheless, all infusion interruptions were temporary and were finally completed.

Regarding baseline characteristics (demographic/disease) treatment groups were in general well-balanced, except for some imbalances in the proportion of White (41.9% pooled ravulizumab vs. 51.1% pooled eculizumab) and Asian (42.8% pooled ravulizumab vs. 34.7% pooled eculizumab) patients. Median age at first infusion in the pooled ravulizumab group was 43.5 years (range: 18; 83) and only 26 patients (11.7%) were older than 65 years. Data on the use of ravulizumab in elderly patients are considered limited, especially in patients ≥ 75 years. There are no data on the use of ravulizumab in paediatric patients (study ALXN1210-PNH-304 in children is ongoing) nor in pregnant/lactating women. This information has been properly reflected in the SmPC. The overall incidence of AEs was similar between treatment groups (87.8% pooled ravulizumab vs. 87.2% pooled eculizumab). The most commonly reported AEs (≥ 10%) were headache (32% pooled ravulizumab vs. 26.0% pooled eculizumab), nasopharyngitis (14.4% vs. 17.4%) and upper respiratory tract infection (14.0% vs. 7.8%). Of the total number of AEs, 33.8% and 29.2% in both ravulizumab and eculizumab groups were considered by the investigator to be related to study drug. Among these, headache was the most commonly reported AE in both groups (16.7% ravulizumab vs. 14.6% eculizumab). The majority of AEs were of grade 1 or grade 2 and a similar rate of grade 3 AEs was reported in both treatment arms (12.6% ravulizumab and 15.1% eculizumab). There were 7 (3.2%) patients in the ravulizumab group and 2 (0.9%) patients in the eculizumab group that reported AEs of grade 4. The majority of events were related to haematology values altered and were considered by the investigator not related or unlikely related to study drug. In the ravulizumab group events were resolved in 3 of the 7 patients. Only one AE of grade 5 was reported in the eculizumab group (a patient diagnosed with lung adenocarcinoma).

No deaths were reported in the 26-week period in either treatment group. Two patients died in the eculizumab group during the extension study period, one of them due to a lung adenocarcinoma and the other one due to a pulmonary sepsis. None of these fatal AEs was considered treatment-related. Regarding SAEs, the incidence was similar between treatment groups (15 [6.8%] pooled ravulizumab vs. 17 [7.8%] pooled eculizumab), although a slightly higher number of SAEs were considered related to study drug in the ravulizumab arm (5 [2.3%] vs. 2 [0.9%]). Overall, the most frequent SAEs, reported in at least 2 patients, were pyrexia (1 [0.5%] pooled ravulizumab and 5 [2.3%] eculizumab) and haemolysis (2 [0.9%] in the eculizumab group). Most of the events resolved, except a DVT event reported in the ravulizumab group and lung adenocarcinoma in the eculizumab group. SAEs considered by the investigator as possibly related to ravulizumab treatment include: leptospirosis, pyrexia, anaemia and left ventricular failure, systemic infection and SAEs of hyperthermia, epilepsy and respiratory failure reported in one patient in study PNH-302.

Adverse events of special interest (AESIs) with ravulizumab were defined according to the important identified risk in the eculizumab RMP, and include: infections (meningococcal infections, Aspergillus infections, sepsis and other serious infections), infusion reactions, serious cutaneous adverse reactions, cardiac disorders and angioedema.

The frequency of AESIs was similar in the ravulizumab and eculizumab pooled groups (12.2% vs. 8.2%, respectively), with infusion reaction as the most commonly reported AE (8.6% vs. 5.9%).

Infections have been the most commonly reported AEs in both treatment arms. Meningococcal infection is an identified risk of eculizumab, which can be life-threatening and which is related to its mode of action. In the phase 3 studies no events of meningococcal infections/sepsis were reported; however, 3 events of meningococcal infection were reported in studies PNH-201 (2 events) and PNH-103 (1 event) among patients treated with ravulizumab. One of the events occurred at day 57, (approximately one month after the last infusion), while the other two events occurred during the extension study period (Day 222, 24 days after the last dose, and Day 615, approximately 28 days after the last dose) and all of them resolved. The 3 patients had been properly vaccinated. All patients had received vaccines against serogroups A, C, Y, W 135 and B. Meningococcal infections were caused by *Neisseria meningitidis* serotype Y in all cases and additionally serotype W 135 in one of the patients the. Meningococcal infection is described in sections 4.4 and 4.8 of the SmPC and has been included as a safety concern in the RMP. Infections by *Neisseria sp*. others than *Neisseria meningitides* were not mentioned as AEs in the submitted clinical safety documentation. According to the Applicant, no other *Neisseria sp.* infections were reported from ravulizumab clinical studies. Nevertheless, cases of serious infections with Neisseria species other than *Neisseria meningitidis*, including disseminated gonococcal infections, have been reported with eculizumab.

Angioedema was more common in the ravulizumab arm than in the eculizumab arm (4 [1.8%] vs. 0%, respectively). However, the number of subjects was very low and AEs reported within this category were gingival swelling after tooth extraction (n = 1) and urticaria (n = 3). .

Major adverse vascular events were also assessed as part of the safety evaluation. Among patients treated with ravulizumab, 2 events of DVT (1 in study PNH-301 and 1 in study PNH-201) and 1 event of thrombosis (study PNH-301) were reported. In the eculizumab group 1 event of thrombosis was also reported.

Immunogenicity profile of ravulizumab appears low and comparable to eculizumab. A higher number of patients were ADA-positive at baseline in the ravulizumab arm compared to eculizumab arm, mainly in study PNH-301 (eculizumab – naïve). In the ravulizumab pooled group, treatment-emergent ADA positive were observed in 1 patient (study PNH-301) compared to 2 patients in eculizumab group (one in each phase 3 study). None of ADAs were neutralizing and none showed cross-reactivity to eculizumab.

The safety profile of ravulizumab in specific subgroups appears in general comparable to the overall population with no major differences in terms of AEs (all grades) and SAEs according to sex and age. Regarding elderly patients (> 65 years), a higher frequency of anaemia (15.4% vs. 3.1%) and neutropenia (11.5% vs. 3.1%) were observed with ravulizumab compared to eculizumab. Moreover, headache was more commonly reported in female patients treated with ravulizumab (36.4% ravulizumab vs. 29.4% eculizumab). Since body weigh affect ravulizumab PK, a body weight-based regimen has been used in the pivotal clinical trials. However, despite weight adjustment, exposure to ravulizumab was approximately 20% higher in patients with a lower weight (≥ 40 to < 60 kg) compared to patients with a medium weight (≥ 60 to < 100 kg) whereas in the highest weight patients (≥ 100 kg), exposure was approximately 20% lower than in patients with a medium weight (See PK). Overall, no major differences have been observed in terms of efficacy and safety by body weight.

Regarding race, although within the White and the Asian race AE profile of ravulizumab and eculizumab by SOC was not remarkably different, some imbalances can be experienced between these two races within the ravulizumab-treated patient population. However, these differences do not seem relevant and do not suggest a different safety profile of ravulizumab between Asian and White patients.

Safety data of the 39 patients who were treated with ravulizumab in the extension period of studies PNH-103 and PNH-201, with a median of treatment duration of almost 2 years, provide additional information of the safety profile of ravulizumab in the long-term. In this population a higher rate of grade 3 and grade 4 TEAEs, AEs of special interest, as well as SAEs (related and not-related) were reported, compared to the phase 3 studies, with the higher incidence reported during the first six months. However, taking into account the low number of subjects, the absence of a comparator as well as that in these studies ravulizumab was used at different doses, no firm conclusions can be drawn.

Overall, the safety profile of ravulizumab appears comparable to that of eculizumab in patients with PNH with no major differences observed, neither in quantitative nor qualitative terms. However, considering the limited number of infusions received by patients in the ravulizumab group, additional data in the long term are deemed necessary. Additional safety data of the extension study period, up to week 52 (data cut-off date 04 Sep 2018), from both studies (PNH-301 and PNH-302) were submitted during the procedure.

In the study PNH-301, of the 125 patients randomized to ravulizumab group, 124 patients entered the extension study period. In general, incidence of AEs appears to decrease over time. In the study PNH-302, of the 97 patients randomized to ravulizumab group, 96 patients entered the extension study period. In this study, while overall incidence of AEs decreased over time, an increase in the number of Grade 3 AEs was observed (7.2% Period 1 [26 weeks Primary evaluation period] and 13.5% Period 2 (0 to 6 months of the extension study period). Haematocrit values seem to remain stable during long term (52 weeks) ravulizumab treatment. The applicant should provide final results of both studies as a Post-Authorisation Measure (PAM).

With regard to the two populations included in pivotal clinical trials, that is, patients complement inhibitor naïve (n=246) and patients already on treatment with eculizumab (n=195), no major differences were observed in the safety profile of ravulizumab with data available so far. Overall incidence of AEs was comparable between studies. However, in study PNH-302, AEs related to study drug were more frequent in the ravulizumab arm than in the eculizumab arm (24.7% vs. 14.3%), mainly driven by the higher incidence of headache in patients treated with ravulizumab (12.4% vs. 4.1%). Nevertheless, the incidence was still lower than in the PNH-301 study (40.8% ravulizumab vs. 41.3% eculizumab). On the contrary, SAEs and AEs grade 3 were lower in patients treated with ravulizumab in study PNH-302. Regarding AESIs, in study PNH-302 the proportion was higher in the ravulizumab arm than in the eculizumab arm (10.3% vs. 5.1%), mainly due to infusion reactions (8.2% vs. 3.1%, respectively), although the incidence was comparable with that reported in the study PNH-301. Among the most commonly reported AEs, in the study PNH-302 the incidence of headache was higher in patients treated with ravulizumab than with eculizumab, but lower than in the PNH-301 study.

Ravulizumab PK profile, allows a more comfortable posology for the patient. However, from a safety point of view, the longer half-life of ravulizumab could make difficult to manage toxicity in case it appears.

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

2.6.2. Conclusions on the clinical safety

Overall, the safety profile of ravulizumab appears similar to that of eculizumab in patients with PNH, both in patients complement inhibitor naïve and in patients already on treatment with eculizumab. The most commonly reported adverse events with ravulizumab were headache, upper respiratory tract infections and nasopharyngitis. Meningococcal infection is an important risk of ravulizumab related to its mode of action. In ravulizumab clinical trials, three cases of meningococcal infection were reported.

Safety data are limited. Final results of both studies will be submitted as a category 3 measure (see RMP) in the post authorisation phase to better characterize the safety profile of ravulizumab.

- The CHMP considers the following measures necessary to address issues related to safety:

PNH Registry study: 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.

PNH extension safety study ALXN1210-PNH-301; the Final Clinical Study Report for Study ALXN1210-PNH-301 should be submitted when available.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Meningococcal infections
Important potential risks	Serious haemolysis after drug discontinuation in PNH patients Immunogenicity Serious infections Malignancies & Haematologial abnormalities
Missing information	Use in pregnant and breast-feeding women

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				
PNH extension safety study ALXN1210-PNH-301 Ongoing	To evaluate the safety and efficacy of ALXN1210 versus eculizumab 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 • Immunogenicity • Serious infections • Malignancies and haematologic abnormalities • Use in pregnant and breast-feeding women	Final CSR	October 2023
PNH extension safety study ALXN1210-PNH-302	To evaluate the safety and efficacy of ALXN1210 versus eculizumab administered by intravenous (IV) infusion to	• Meningococcal infection • Serious haemolysis after drug	Final CSR	September 2021

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	adult patients with PNH who have been treated with eculizumab for at least the past 6 months. 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	discontinuation in PNH • Immunogenicity • Serious infections • Malignancies and haematologic abnormalities • Use in pregnant and breast-feeding women		
M07-001 "PNH REGISTRY" Ongoing	To collect and evaluate safety data specific to the use of SOLIRIS / Ultomiris and to collect data to characterise the progression of PNH as well as clinical outcomes, mortality and morbidity in SOLIRIS / Ultomiris and non-SOLIRIS / Ultomiris treated patients.	• Meningococcal Infection • Serious haemolysis after drug discontinuation in PNH • Immunogenicity • Serious infections • Malignancies and haematologic abnormalities • Use in pregnant and breast-feeding women	Interim data analysis	Every 2 years interim data analysis report

Risk minimisation measures

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	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: Study ALXN1210-PNH-301 Study ALXN1210-PNH-302 PNH registry (M07-001)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	– PNH Physician's guide – PNH Patient's information brochure – Patient safety card Controlled distribution Revaccination reminder	
Serious haemolysis after drug discontinuation in PNH patients	Routine risk minimisation measures – SmPC section 4.4 – PL section 3 Monitoring of patients who discontinued Ultomiris recommended in SmPC section 4.4 and PL section 3 Additional risk minimisation measures Educational materials – PNH Physician's guide – PNH Patient's information brochure	Additional pharmacovigilance activities: Study ALXN1210-PNH-301 Study ALXN1210-PNH-302 PNH registry (M07-001)
Immunogenicity	Routine risk minimisation measures – SmPC section 4.4 Additional risk minimisation measures Educational materials – PNH Physician's guide – PNH Patient's information brochure	Additional pharmacovigilance activities: Study ALXN1210-PNH-301 Study ALXN1210-PNH-302 PNH registry (M07-001)
Serious infections	Routine risk minimisation measures – SmPC sections 4.4 and 4.8 – PL sections 2 and 4 Additional risk minimisation measures Educational materials – PNH Physician's guide – PNH Patient's information brochure	Additional pharmacovigilance activities: Study ALXN1210-PNH-301 Study ALXN1210-PNH-302 PNH registry (M07-001)
Malignancies and haematologic abnormalities	Routine risk minimisation measures – SmPC section 4.2 Additional risk minimisation measures Educational materials	Additional pharmacovigilance activities: Study ALXN1210-PNH-301 Study ALXN1210-PNH-302 PNH registry (M07-001)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	– PNH Physician's guide – PNH Patient's information brochure	
Use in pregnant and breastfeeding 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 Physician's guide – PNH 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 Study ALXN1210-PNH-302 PNH registry (M07-001)

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 01.01.2019.

2.9. New Active Substance

The applicant declared that ravulizumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers ravulizumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.*

2.10.2. 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

Paroxysmal nocturnal haemoglobinuria is a very rare and life threatening acquired haemolytic disorder. The hallmark of PNH disease activity is complement-mediated haemolysis.

3.1.2. Available therapies and unmet medical need

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.

Ravulizumab is a humanized monoclonal antibody (mAb) that binds to complement component 5 (C5) and blocks its activation by complement pathway convertases.

3.1.3. Main clinical studies

Two non-inferiority, Phase 3, Randomized, Multicentre, Open-Label, Active-Controlled studies of ravulizumab versus eculizumab were conducted in 2 distinct and complementary populations with PNH: a complement inhibitor naïve population of patients with active haemolysis to establish the efficacy response with ravulizumab (Study ALXN1210-PNH-301; N=246), and a population of patients on eculizumab therapy for at least the past 6 months with stable disease to assess maintenance of response with ravulizumab (Study ALXN1210-PNH-302; N=195).

For Study ALXN1210 PNH 301, the co-primary endpoints of transfusion avoidance and LDH normalization allowed optimal characterization of the magnitude of effect in patients who were complement inhibitor-naïve and had active PNH disease. In contrast, for Study ALXN1210 PNH-302, the primary endpoint of change in LDH allowed optimal characterization of the maintenance of the high degree of disease control that patients had already achieved at baseline after a minimum of 6 months of eculizumab treatment.

3.2. Favourable effects

In both phase 3 studies ravulizumab achieved statistically significant non-inferiority compared to eculizumab, with lower bound of the 95% confidence interval (CI) being greater than the pre-specified NIMs, reducing and maintaining control of haemolysis in patients with PNH.

- Study ALXN1210-PNH-301 (Eculizumab naïve patients)

73.6% of patients in the ravulizumab group and 66.1% in the eculizumab group avoided pRBC transfusion. The difference between the ravulizumab and eculizumab treatment groups in the percentage of patients who avoided transfusion was 6.8% (95% CI: -4.66%, 18.14%; NIM 20%).

The adjusted prevalence of LDH-N (LDH levels $\leq 1 \times$ ULN from Day 29 through Day 183) was 0.536 for the ravulizumab group and 0.494 for the eculizumab group. The adjusted odds ratio for the comparison of ravulizumab to eculizumab was 1.187 (95% confidence interval [CI]: 0.796, 1.769; NIM 0.39). Results from the primary analysis using the PP Set were consistent with those of the FAS, as were results from other sensitivity analyses

Ravulizumab also achieved statistically significant non-inferiority compared to eculizumab on all 4 key secondary endpoints according to a pre-specified hierarchical testing order (1 Percentage change from baseline in LDH levels, 2 Change from baseline in QoL as assessed by the FACIT-Fatigue scale, 3 Proportion of patients with BTH and 4 Proportion of patients with stabilized haemoglobin levels).

- Study ALXN1210 PNH 302 (Phase 3): Eculizumab-Experienced Patients

The LS estimate of the mean percent change in LDH showed a decrease of less than 1% (0.82% [SEM = 3.033%]) for the ravulizumab group and an increase of greater than 8% (8.39% [SEM = 3.041%]) for the eculizumab group with a treatment difference (ravulizumab eculizumab) of 9.21% (95% CI: 18.84%, 0.42%; NIM 15%).

Ravulizumab also achieved statistically significant non-inferiority compared to eculizumab on all 4 key secondary endpoints according to a pre-specified hierarchical testing order for non-inferiority (1 Proportion of patients with BTH, 2 Change from baseline in quality of life as assessed by the FACIT-Fatigue scale, 3 Proportion of patients with transfusion avoidance and 4 Proportion of patients with stabilized haemoglobin levels)

The potential advantage of ravulizumab is the dosage and schedule of administration (q8w) in a chronic disease that could affect patients at different ages and conditions (old patients and young adults with/without other comorbidities).

Comparison of efficacy results from the two Phase 3 studies shows that complement inhibitor-naïve and eculizumab-experienced patients with PNH both respond to ravulizumab treatment.

3.3. Uncertainties and limitations about favourable effects

Final results for Studies ALXN1210-PNH-301 and ALXN1210-PNH-302 will be submitted when available to confirm durability of response and safety profile. In order to avoid confusion due to potential change of treatment, a subset efficacy and safety analysis should be provided for patients from ALXN1210 arm.

3.4. Unfavourable effects

The safety profile of ravulizumab in the treatment of patients with PNH is based mainly on two phase 3 clinical trials; one in complement inhibitor-naïve patients (Study PNH-301; n=246) and the other in patients who were clinically stable on eculizumab treatment (Study PNH-302; n=195). In total, 222 patients were treated with ravulizumab in these phase 3 clinical trials and this population is considered the main safety database.

Patients were treated with either ravulizumab or eculizumab for 26 weeks, with a median of infusions received of 4 (range: 1; 4) in the ravulizumab group and 15 (range: 1; 15) in the eculizumab group.

The overall incidence of AEs was 87.8% in the pooled ravulizumab group vs. 87.2% in the pooled eculizumab group. The most commonly reported AEs (≥ 10%) were headache (32% pooled ravulizumab vs. 26.0% pooled eculizumab), nasopharyngitis (14.4% vs. 17.4%) and upper respiratory tract infection (14.0% vs. 7.8%).

Grade 3 AEs were reported in 12.6% of patients treated with ravulizumab and 15.1% of patients treated with eculizumab. There were 7 (3.2%) patients in the ravulizumab group and 2 (0.9%) patients in the eculizumab group that reported AEs of grade 4. The majority of events were related to haematology values altered and were considered by the investigator not related or unlikely related to study drug.

SAEs were reported in 6.8% of patients in the pooled ravulizumab group vs. 7.8% in the pooled eculizumab group (5 [2.3%] vs. 2 [0.9%], considered related to study drug, respectively). Overall, the most frequent SAEs, reported in at least 2 patients, were pyrexia (1 [0.5%] pooled ravulizumab and 5 [2.3%] eculizumab) and haemolysis (2 [0.9%] in the eculizumab group).

Adverse events of special interest (AESIs) with ravulizumab include: infections (meningococcal infections, Aspergillus infections, sepsis and other serious infections), infusion reactions, serious cutaneous adverse reactions, cardiac disorders and angioedema. The incidence of AESIs in the ravulizumab group was 12.2% vs. 8.2% in the eculizumab group.

Three events of meningococcal infection were reported in studies PNH-201 (2 events) and PNH-103 (1 event) among patients treated with ravulizumab. This is a well-known safety risk with Soliris due to the mechanism of action of these monoclonal antibodies and is manged with risk minimisation measures (see RMP).

3.5. Uncertainties and limitations about unfavourable effects

One of the main limitations is the absence of comparative long-term safety data, especially in the setting of a chronic indication. Patients were treated with either ravulizumab or eculizumab for 26 weeks, with a median of only 4 ravulizumab infusions received.

Only 26 patients (11.7%) were older than 65 years among patients treated with ravulizumab in pivotal clinical trials. Thus, data on the use of ravulizumab in elderly patients are considered limited, especially in patients ≥ 75 years.

Further safety data will be obtained from the final Clinical Study Report for Studies ALXN1210-PNH-301 and ALXN1210-PNH-302 a registry study.

3.6. Effects Table

Table 74: Effects Table for Ravulizumab as treatment of adult patients with paroxysmal nocturnal haemoglobinuria.

Effect	Short Description	Unit	Ravulizumab	Eculizumab	Diff. (95% CI)	Uncertainties/ Strength of evidence
Favourable Effects- Study ALXN1210-PNH-301 (Eculizumab naïve patients)						
TA	Transfusion avoidance	%	73.6	66.1	6.8 (-4.66, 18.14)	The lower bound of the 95% CI was greater than the protocol-specified NIM of -20%, indicating that ravulizumab was statistically non-inferior to eculizumab

Effect	Short Description	Unit	Ravulizumab	Eculizumab	Diff. (95% CI)	Uncertainties/ Strength of evidence
LDH-N	Lactate dehydrogenase normalization	%	53.6	49.4	1.19 (0.8, 1.77)	adjusted odds ratio for comparison was 1.187 (95% CI: 0.796, 1.769), indicating that a patient initiating treatment on ravulizumab has a nearly 19% increased probability of achieving LDH-N compared to a patient initiating treatment on eculizumab.
LDH-PCHG	Percent change in LDH	%	-76.84	-76.02	0.83 (-3.56,5.21)	statistically significant non-inferiority
Change in FACIT Fatigue	Functional Assessment of Chronic Illness Therapy		7.07	6.40	0.67 (-1.21, 2.55)	Both treatment groups showed improvement in FACIT Fatigue over time.
BTH	Breakthrough haemolysis	%	4.0	10.7	6.7 (-0.18,14.21)	statistically significantly non- BTH events where described in 5/125 patients in ravulizumab arm (none with suboptimal PD) and 15/121 patients in the eculizumab arm (7/121 with suboptimal PD).
HGB-S	Haemoglobin stabilization	%	68.0	64.5	2.9 (-8.80, 14.64)	statistically significant non-inferiority
Favourable Effects- Study ALXN1210-PNH-301 (Eculizumab experienced patients)						
LDH-PCHG	Percent change in LDH	%	-0.82	8.39	9.21 (-0.42,18.84)	statistically significant non-inferiority
Change in FACIT Fatigue	Functional Assessment of Chronic Illness Therapy		2.01	0.54	1.47 (-0.21, 3.15)	
BTH	Breakthrough haemolysis	%	0	5.1	5.1 (-8.89,18.99)	
Change in FACIT Fatigue	Functional Assessment of Chronic Illness Therapy		2.01	0.54	1.47 (-0.21, 3.15)	statistically significant non-inferiority
TA	Transfusion avoidance	%	87.6	82.7	5.5 (-4.27, 15.68)	statistically significantly non-inferior
HGB-S	Haemoglobin stabilization	%	76.3	75.5	1.4 (-10.41, 13.31)	statistically significant non-inferiority
Unfavourable Effects						
AEs	Adverse events	%	87.8	87.2	Percentages calculated on the basis of	Phase 3 PNH population (Study

Effect	Short Description	Unit	Ravulizumab	Eculizumab	Diff. (95% CI)	Uncertainties/ Strength of evidence
Related AEs	Adverse events related to study drug	%	33.8	29.2	available data from 222 patients on ravulizumab and 219 patients on eculizumab.	ALX1210-PNH-301 and Study ALX1210-PNH-302 Combined safety analysis)
Grade 3 AEs	Adverse events of grade 3	%	12.6	15.1		
Grade 4 AEs	Adverse events of grade 4	%	3.2	0.9		
SAEs	Serious adverse events	%	6.8	7.8		
Headache	Common adverse event	%	32.0	26.0		
Upper respiratory tract infection	Common adverse event	%	14.0	7.8		
Nasopharyngitis	Common adverse event	%	14.4	17.4		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In both phase 3 studies ravulizumab achieved statistically significant non-inferiority compared to eculizumab, with lower bound of the 95% confidence interval (CI) being greater than the pre-specified NIMs, reducing and maintaining control of haemolysis in patients with PNH. The evidence of non-inferiority was considered statistically convincing and there is good concordance among efficacy endpoints. Considering those results and non-inferiority design, and the indication being in line with eculizumab, ravulizumab offers an option to patients with a very rare disease with the added potential advantage of a more convenient treatment schedule as per the q8w dose.

From a safety point of view, while no major differences have been observed in the safety profile of ravulizumab compared to eculizumab, data are still rather limited, thus, additional data in the long term will be obtained from post authorisation studies to better characterize the safety profile of ravulizumab.

3.7.2. Balance of benefits and risks

Non-inferiority of ravulizumab to eculizumab has been demonstrated in phase 3 trials for naïve and eculizumab-pretreated patients, in a consistent manner across subgroups studied. The safety profile is in line with the already known for eculizumab. The efficacy outweighs the risks associated with the treatment which can be managed with risk minimisation measures (see SmPC, Annex II and RMP).

3.8. Conclusions

The overall Benefit/Risk of Ultomiris 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

is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus decision is of the opinion that Ultomiris is similar to Soliris within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Derogation(s) from market exclusivity

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

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

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ultomiris is favourable in the following indication:

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 hare clinically stable after having been treated with eculizumab for at least the past 6 months.

The CHMP therefore recommends the granting of the marketing authorisation 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).

Other 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

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

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

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

- Physician educational material
- Patient information pack

The physician educational material should contain:

  - The Summary of Product Characteristics
  - Guide for healthcare professionals

- **The Guide for healthcare professionals** shall contain the following key elements:
  - To address the risks of meningococcal infection, serious haemolysis after drug discontinuation in PNH patients, immunogenicity, serious infections, malignancies and haematological abnormalities, use in pregnant and breast-feeding women.
  - Treatment with ravulizumab increases the risk of *N. meningitidis* infections.
  - All patients must be monitored for signs of meningitidis.
  - The need for patients to be vaccinated against *N. meningitidis* two weeks prior to receiving ravulizumab and/or to receive antibiotic prophylaxis.
  - The risk of immunogenicity and advice on post-infusion monitoring.
  - The risk of developing antibodies to ravulizumab.

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

The patient information pack should contain:

- Package leaflet
- A patient guide
- A patient alert card

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

- Potential risks of severe, non-neisserial infections and malignancies and haematologic abnormalities in PNH patients treated with ravulizumab.
- Enrolment in the PNH registry.

- **The patient alert 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

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.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that ravulizumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union has not been authorised previously in the European Union.