CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761108Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Biologic license application
Application Number(s)	761108
Priority or Standard	Priority
Submit Date(s)	June 18, 2018
Received Date(s)	June 18, 2018
PDUFA Goal Date	February 18, 2019
Division/Office	Division of Hematology Products
Review Completion Date	December 20, 2018
Established Name	Ultomiris
Proper Name	Ravulizumab-cwvz
(Proposed) Trade Name	ULTOMIRIS
Pharmacologic Class	Selective Immunosuppressant/terminal complement inhibitor
Code name	ALXN1210
Applicant	Alexion Pharmaceuticals, Inc.
Formulation(s)	10 mg/mL formulation for IV administration
Dosing Regimen	Dosing is based on the patient's body weight. **Body Weight** / **Loading Dose (mg)** / **Maintenance Dose (mg)** ≥ 40 to < 60 kg / 2400 / 3000 ≥ 60 to < 100 kg / 2700 / 3300 ≥ 100 kg / 3000 / 3600 Maintenance doses should be administered once every 8-week interval, starting 2 weeks after loading dose administration.
Applicant Proposed Indication(s)/Population(s)	For the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

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OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology

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DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management

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Glossary

ADA	antidrug antibodies
ADME	absorption, distribution, metabolism, excretion
ADCC	antibody-dependent cell-mediated cytotoxicity
ADR	adverse drug reaction
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLA	biologics license application
BLOQ	below the limit of quantification
BTH	breakthrough hemolysis
C5	complement component 5
CDER	Center for Drug Evaluation and Research
CDP	clinical development program
CLIA	clinical laboratory improvement amendments
C_{max}	maximum observed serum concentration
C_{trough}	concentration at the end of the dosing
COA	clinical outcome assessment
CFR	Code of Federal Regulations
CSR	clinical study report
CV	coefficient of variation
DHOT	Division of Hematology Oncology Toxicology
ECG	electrocardiogram
ECL	electrochemiluminescence
eGFR	epidermal growth factor receptor
EOP2	End of Phase 2
EOI	end of infusion
FACIT	functional assessment of chronic illness therapy
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
GLP	good laboratory practice
HGB-S	stabilized hemoglobin
ICH	International Conference on Harmonization
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
I_{max}	maximal reduction of LDH synthesis
IV	intravenous
K_{out}	LDH first-order elimination rate constant
LD	loading dose
LDH	lactate dehydrogenase

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LDH-N	normalization of lactate dehydrogenase
LDH-PCHG	percent change in LDH
LLOQ	lower limit of quantification
mAb	monoclonal antibody
MAD	multiple-ascending dose
MAVE	major adverse vascular events
MedDRA	Medical Dictionary for Regulatory Activities
MD	maintenance dose
MG	macroglobulin
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NIM	noninferiority margin
NME	new molecular entity
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OR	odds ratio
PBRER	Periodic Benefit-Risk Evaluation Report
PBO	placebo
PD	pharmacodynamics
PI	prediction interval
PK	pharmacokinetics
PNH	paroxysmal nocturnal hemoglobinuria
PP	per protocol
PPI	patient package insert
PRO	patient reported outcome
pRBC	packed red blood cells
qXw	once every X week(s)
REMS	risk evaluation and mitigation strategy
RSE	relative standard error
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOC	standard-of-care
TA	transfusion avoidance
TEAE	treatment emergent adverse event
TMDD	target mediated drug disposition
T_{max}	time if maximum observed concentration
URTI	upper respiratory tract infection
ULN	upper limit of normal

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V_{ss}	volume of distribution at steady state
VPC	visual predictive check

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1 Executive Summary

1.1. Product Introduction

ULTOMIRIS (ravulizumab-cwvz) is recombinant humanized monoclonal antibody that binds to the human C5 complement protein and inhibits its cleavage to C5a and C5b, thereby preventing the generation of the terminal complement complex C5b9. Alexion (Applicant) submitted a biologics license application (BLA) for ULTOMIRIS for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). The Applicant's proposed indication for ULTOMIRIS is, "the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)."

The proposed dosing regimen for ULTOMIRIS in adult (≥ 18 years of age) patients with PNH consists of a loading dose followed by maintenance dosing, administered as an intravenous (IV) infusion. The dosing regimen for ULTOMIRIS is based on body weight as shown in the table below.

Table 1 ULTOMIRIS 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

Maintenance doses should be administered once every 8 weeks (q8w), starting 2 weeks after loading dose administration. For patients switching from eculizumab to ravulizumab-cwvz, the loading dose of ravulizumab-cwvz should be administered 2 weeks after the last eculizumab infusion, and then maintenance doses are administered q8w, starting 2 weeks after loading dose administration.

In this review document, ravulizumab refers to ravulizumab-cwvz because the suffix was not determined until late during the review cycle.

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1.2. Conclusions on the Substantial Evidence of Effectiveness

The review teams recommend regular approval of ULTOMIRIS (ravulizumab-cwvz) under 21 Code of Federal Regulations (CFR) 601 for the indication, "treatment of adult patients with paroxysmal nocturnal hemoglobinuria". The data submitted by the applicant provides for substantial review of effectiveness. The approval recommendation is supported by the results of two randomized, open-label, active-controlled, non-inferiority phase 3 studies (Study ALXN1210 PNH 301 and ALXN1210 PNH 302).

Study ALXN1210 PNH-301 enrolled 246 patients with complement inhibitor-naïve PNH with active hemolysis. Patients were randomized 1:1 to ravulizumab-cwvz or eculizumab. Efficacy was established based upon the transfusion avoidance and hemolysis as directly measured by normalization of LDH levels. Transfusion avoidance rate in the ULTOMIRIS arm was 73.6% compared to 66.1% in the eculizumab arm with a difference in rate of 6.8% (95% CI:, -4.66, 18.14) and LDH normalization of 53.6% in ULTOMIRIS arm compared to 49.4% in the eculizumab arm with odds ratio of 1.19 (95% CI: 0.80, 1.77). Supportive efficacy data included the percent change from baseline in LDH levels, the proportion of patients with breakthrough hemolysis defined as at least one new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥ 2 x upper limit of normal (ULN), after prior LDH reduction to < 1.5 x ULN on therapy and the proportion of patients with stabilized hemoglobin. Non-inferiority of ULTOMIRIS to eculizumab was demonstrated across the endpoints in the complement inhibitor naïve treatment population. Mean change in FACIT-fatigue total score from baseline to Day 183 was also evaluated and there was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared to baseline. The patient-reported fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment and are descriptive findings.

Study ALXN1210-PNH-302 enrolled patients with PNH who were clinically stable after receiving eculizumab for at least the past 6 months. In this study, 195 patients were randomized 1:1 to either continue eculizumab or to switch to ULTOMIRIS. Efficacy was established based on hemolysis as measured by LDH percent change from baseline to Day 183. The LDH percent change in the ULTOMIRIS arm was -0.82% compared to 8.4% with difference in percentage change from baseline of 9.2% (95% CI: -0.42, 18.8). Supportive efficacy data was transfusion avoidance [(87.6% in ravulizumab-cwvz arm and 82.7% in eculizumab arm with rate difference of 5.1 (95% CI: -8.9, 19.0)], proportion of patients with stabilized hemoglobin [(76.3% in ravulizumab-cwvz arm compared to 75.5% in eculizumab arm with rate difference of 1.4 (95% CI: -10.4, 13.3)] and the proportion of patients with breakthrough hemolysis through Day 183 [0% in the ravulizumab-cwvz arm, 5.1% in the eculizumab arm with rate difference of 5.1 (95% CI: -8.9, 19.0)]. Non-inferiority of ULTOMIRIS to eculizumab was demonstrated across endpoints in patients with PNH previously treated with eculizumab. Mean change in FACIT-fatigue total score from baseline to Day 183 was also evaluated and there was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared to baseline. The patient-reported

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fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment and are descriptive findings.

In summary, the results from studies ALXN1210 PNH 301 and ALXN1210 PNH 302 demonstrate the non-inferiority of ULTOMIRIS to eculizumab in patients with PNH. ULTOMIRIS appears to retain the efficacy of eculizumab in patients with PNH with a less frequent (8 weekly versus 2 weekly) dosing regimen which may be less burdensome to patients.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, progressive, and life-threatening disease characterized by uncontrolled complement activation leading to hemolytic anemia, thrombosis, bone marrow failure and systemic complications. Absence of the complement inhibitor proteins CD55 and CD59 on cell surfaces results in continuous activation of the alternative complement pathway. Chronic severe anemia frequently develops along with an increased risk of severe thromboembolism. Patients with PNH are at risk of substantial mortality and morbidity including pulmonary hypertension and end-organ damage of vital organs, such as the liver, kidneys, brain, and intestines. Eculizumab, a selective, humanized monoclonal antibody that specifically targets C5 of the terminal complement cascade, is currently the only approved drug for the treatment of PNH. Ravulizumab-cwvz is a derivative of eculizumab that binds with high affinity to C5, thereby inhibiting cleavage to C5a (proinflammatory anaphylatoxin) and C5b (initiating subunit of the terminal complex [C5b-9]) and prevents generation of terminal complement complex C5b9. The proposed indication for ULTOMIRIS is for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria.

The safety and efficacy of ULTOMIRIS in patients with PNH was assessed in two open-label, randomized, active-controlled, non-inferiority Phase 3 studies (ALXN1210 PNH 301 and ALXN1210 PNH 302). In both studies, ULTOMIRIS was dosed intravenously based on a weight-based dosing (4 infusions of ULTOMIRIS over 26 weeks). Eculizumab was administered on Days 1, 8, 15, and 22, followed by maintenance treatment with 900 mg of on Day 29 and every 2 weeks (q2w) thereafter for a total of 26 weeks of treatment, according to the approved dosing regimen of eculizumab which was the standard-of-care for PNH at the time of studies. Patients were vaccinated against meningococcal infections prior to or at the time of initiating treatment with ULTOMIRIS or eculizumab, or received prophylactic treatment with appropriate antibiotics until 2 weeks after vaccination.

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In ALXN1210 PNH 301, a total of 246 patients with documented PNH (at least 5% PNH cells) who were naïve to complement inhibitor treatment were randomized 1:1 to receive ULTOMIRIS (N = 125) or eculizumab (N = 121). Randomization was stratified by transfusion history (0, 1 to 14, or > 14 units) and screening lactate dehydrogenase (LDH) levels (1.5 to < 3 × upper limit of normal [ULN] or ≥ 3 × ULN). Major baseline characteristics were balanced between the two treatment groups (mean age 45.5, 54.5% male and mean pretreatment LDH of 1570). Efficacy was established based upon the transfusion avoidance and hemolysis as directly measured by normalization of LDH levels. Transfusion avoidance rate in the ravulizumab-cwvz arm was 73.6% compared to 66.1% in the eculizumab arm with a difference in rate of 6.8% (95% CI: -4.66, 18.14) and LDH normalization of 53.6% in ravulizumab-cwvz arm compared to 49.4% in the eculizumab arm with odds ratio of 1.19 (95% CI: 0.80, 1.77). Supportive efficacy data included the percent change from baseline in LDH levels [(-76.84% in ULTOMIRIS arm, -76.02 eculizumab arm with difference in chance from baseline of -0.83 (95% CI: -5.21,3.56)], the proportion of patients with breakthrough hemolysis defined as at least one new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥ 2 x upper limit of normal(ULN), after prior LDH reduction to < 1.5 x ULN on therapy [4.0% in ULTOMIRIS arm, 10.7% eculizumab arm with difference in rate of -6.7% (95% CI: -14.21, 0.18)] and the proportion of patients with stabilized hemoglobin [68% in ULTOMIRIS arm, 64.5% in eculizumab arm with rate difference of 2.9(95% CI: -8.80, 14.64)]. Non-inferiority of ULTOMIRIS to eculizumab was demonstrated across the endpoints in the complement inhibitor naïve treatment population

In Study ALXN1210-PNH-302, a total of 195 adult patients with PNH who were clinically stable after treatment with eculizumab for at least the previous 6 months continued treatment with eculizumab (n=98) or were switched to ULTOMIRIS (n=97) during the 26-week The major baseline characteristics were balanced between the two treatment groups (mean age 47.7 and 50.3% males). Efficacy was established based on hemolysis as measured by LDH percent change from baseline to Day 183. The LDH percent change in the ULTOMIRIS arm was -0.82% compared to 8.4% with difference in percentage change from baseline of 9.2%(95% CI: -0.42, 18.8). Supportive efficacy data was transfusion avoidance (87.6% in ULTOMIRIS arm and 82.7% in eculizumab arm with rate difference of 5.1 (95% CI: -8.9, 19.0), proportion of patients with stabilized hemoglobin (76.3% in ravulizumab-cwvz arm compared to 75.5% in eculizumab with rate difference of 1.4 (95% CI: -10.4, 13.3) and the proportion of patients with breakthrough hemolysis through Day 183 (0% in the ULTOMIRIS arm, 5.1% in the eculizumab arm with rate difference of 5.1 (95% CI: -8.9, 19.0). Non-inferiority of ULTOMIRIS to eculizumab was demonstrated across endpoints in patients with PNH previously treated with eculizumab.

In both studies, the mean change in FACIT-fatigue total score from baseline to Day 183 was also evaluated and there was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared to baseline. The patient-reported fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment and

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are descriptive findings.

In both phase 3 studies, the adverse event profile of ULTOMIRIS was similar to eculizumab. No new risks were identified. The incidence of TEAEs over 26 weeks of treatment was 87.8% and 87.2% for ULTOMIRIS and eculizumab, respectively in the pooled safety population (n=441 patients). Most AEs were Grade 1 or Grade 2 in severity. The most commonly reported TEAEs (> 10%) in ULTOMIRIS treated patients were upper respiratory tract infections (39%) and headache (32.0%). Serious adverse reactions were reported in 15 (6.8%) patients receiving ULTOMIRIS. The serious adverse reactions in patients treated with ULTOMIRIS included hyperthermia and pyrexia. No serious adverse reactions were reported in more than one patient treated with ULTOMIRIS. There was one case fatal case of sepsis identified in a patient treated with ULTOMIRIS. Longer exposure to ULTOMIRIS for up to 2 years (in Phase 1b and 2 studies) was not associated with an increase in the frequency or severity of AEs. There was a low incidence of immunogenicity in both complement inhibitor-naïve and eculizumab-experienced patients with PNH in the Phase 3 studies (0.5%). In the ULTOMIRIS clinical development program, a total of 3 patients with PNH (in the Phase 1b and 2 studies) experienced meningococcal infections/sepsis. No meningococcal infection/sepsis was reported in the Phase 3 studies.

The clinically significant adverse reactions associated with ULTOMIRIS include serious meningococcal infections, other infections, and infusion reactions. All patients should receive vaccination for meningococcal disease according to the most current Advisory Committee on Immunization Practice (ACIP) recommendations for patients with complement deficiencies. Patients without a history of meningococcal vaccinations should be vaccinated at least 2 weeks prior to receiving the first dose of ULTOMIRIS.

The most important risk associated with complement C5 inhibition is increased susceptibility to Neisseria meningitides infections. This risk has been well characterized with use of eculizumab. Due to the similar mechanism of action, ULTOMIRIS is expected to carry the same risk of meningococcal disease. To mitigate this risk, a Risk Evaluation and Mitigation Strategy (REMS) is recommended for ULTOMIRIS and the prescribing information will include a box warning for serious meningococcal infections. The benefit-risk profile for ULTOMIRIS in the target population of adult patients with PNH appears acceptable.

The intent of the non-inferiority studies was to demonstrate that the experimental treatment (ULTOMIRIS) is not substantially worse than a control treatment (eculizumab). Superiority studies were not feasible in this setting as ULTOMIRIS has similar mechanism of action compared to eculizumab and non-inferiority studies to placebo were not ethical or feasible as effective therapy as eculizumab is the existing standard of care for patients with PNH. In these studies, the efficacy of the active control was preserved thus a meaningful conclusion can be drawn regarding the non-inferiority of ULTOMIRIS to eculizumab.

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In summary, the results from studies ALXN1210 PNH 301 and ALXN1210 PNH 302 demonstrate the non-inferiority of ULTOMIRIS to eculizumab in patients with PNH. ULTOMIRIS appears to retain the efficacy of eculizumab in patients with PNH with a less frequent (8 weekly versus 2 weekly) dosing regimen which may be less burdensome to patients. To mitigate the risk of possible serious meningococcal infections, ULTOMIRIS will only be available through a REMS and under the Ultomiris REMS, providers must enroll in the program.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Paroxysmal nocturnal hemoglobinuria is a rare, progressive, and life-threatening disease characterized by uncontrolled complement activation leading to hemolytic anemia, thrombosis, bone marrow failure and systemic complications. The absence of complement inhibitor proteins CD55 and CD59 on cell surfaces results in continuous activation of the alternative complement pathway and chronic intravascular hemolysis. Patients with PNH are at risk of substantial morbidity including pulmonary hypertension and end-organ damage of vital organs, such as the liver, kidneys, brain, and intestines. The reported mortality in several cohorts of patients with PNH was approximately 35% at 5 years, with a median survival of 10 years after diagnosis. Thrombosis is the most common cause of mortality in PNH.	• PNH is a serious disease with increased morbidity and mortality. • PNH is a chronic disease that requires lifelong treatment.
Current Treatment Options	• Terminal complement inhibition and allogeneic bone marrow transplantation are the only widely effective therapies for patients with classical PNH. Corticosteroids may reduce hemolysis is some patients, but the long-term toxicity and limited efficacy limits its use. • Eculizumab, is a humanized monoclonal antibody that targets C5 of the terminal complement cascade, was approved in 2007 in the US for patients with PNH. The recommended dosing of eculizumab consists of weekly dosing	• There is a need for a therapy that completely suppresses hemolysis during the entire dosing interval in all patients with PNH. • A therapy that provides for similar efficacy but with reduced burden for patients with frequency of administration would be a benefit

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	for 4 weeks followed by maintenance dosing every 2 weeks. The majority of classical PNH patients respond to eculizumab; however, some patients treated with eculizumab have suboptimal C5 blockade, leaving them at potential risk of breakthrough hemolysis and return of the risk of thromboembolic events. The eculizumab dosing regimen may also impose a significant burden on patients, including missed days of work or school.	to patients.
Benefit	• In ALXN1210 PNH 301, a total of 246 patients with documented PNH (at least 5% PNH cells) who were naïve to complement inhibitor treatment were randomized 1:1 to receive ULTOMIRIS (N = 125) or eculizumab (N = 121). Major baseline characteristics were balanced between the two treatment groups (mean age 45.5, 54.5% male and mean pretreatment LDH of 1570). • Efficacy was established based upon the transfusion avoidance and hemolysis as directly measured by normalization of LDH levels. Transfusion avoidance rate in the ULTOMIRIS arm was 73.6% compared to 66.1% in the eculizumab arm with a difference in rate of 6.8% (95% CI: -4.66, 18.14) and LDH normalization of 53.6% in ravulizumab arm compared to 49.4% in the eculizumab arm with odds ratio of 1.19 (95% CI: 0.80, 1.77). • Supportive efficacy data included the percent change from baseline in LDH levels(-76.84% in ULTOMIRIS arm, -76.02 eculizumab arm with difference in chance from baseline of -0.83 (95% CI: -5.21,3.56), the proportion of patients with breakthrough hemolysis defined as at least one new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥ 2 x upper limit of normal(ULN), after prior LDH reduction to < 1.5 x ULN on therapy(4.0% in ULTOMIRIS arm, 10.7% eculizumab arm with difference in rate of -6.7% (95% CI: -14.21, 0.18) and the proportion of patients with stabilized hemoglobin(68% in ULTOMIRIS arm, 64.5% in eculizumab arm with rate difference of 2.9(95% CI: -8.80, 14.64). • Non-inferiority of ULTOMIRIS to eculizumab was demonstrated across the endpoints in the complement inhibitor naïve treatment population • In Study ALXN1210-PNH-302, a total of 195 adult patients with PNH who were clinically stable after treatment with eculizumab for at least the previous 6 months continued treatment with eculizumab (n=98) or were switched to	• Non-inferiority of ULTOMIRIS compared to eculizumab was established for both clinical and laboratory endpoints in patients who were naïve to complement inhibitor treatment. • Non-inferiority of ULTOMIRIS compared to eculizumab was established for both clinical and laboratory endpoints in patients who previously received a complement inhibitor treatment.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	ULTOMIRIS (n=97) during the 26-week The major baseline characteristics were balanced between the two treatment groups (mean age 47.7 and 50.3% males). • Efficacy was established based on hemolysis as measured by LDH percent change from baseline to Day 183. The LDH percent change in the ULTOMIRIS arm was -0.82% compared to 8.4% with difference in percentage change from baseline of 9.2%(95% CI: -0.42, 18.8). • Supportive efficacy data was transfusion avoidance (87.6% in ULTOMIRIS arm and 82.7% in eculizumab arm with rate difference of 5.1 (95% CI: -8.9, 19.0), proportion of patients with stabilized hemoglobin (76.3% in ULTOMIRIS arm compared to 75.5% in eculizumab with rate difference of 1.4 (95% CI: -10.4, 13.3) and the proportion of patients with breakthrough hemolysis through Day 183 (0% in the ULTOMIRIS arm, 5.1% in the eculizumab arm with rate difference of 5.1 (95% CI: -8.9, 19.0). • Non-inferiority of ULTOMIRIS to eculizumab was demonstrated across endpoints in patients with PNH previously treated with eculizumab. For both studies, mean change in FACIT-fatigue total score from baseline to Day 183 was also evaluated and there was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared to baseline. The patient-reported fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment and are descriptive findings.	
Risk and Risk Management	• The most important risk associated with complement C5 inhibition or deficiency is increased susceptibility to infections or caused by *Neisseria meningitidis* infections. This risk has been well characterized with use of eculizumab. Eculizumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) because of the risk of meningococcal infections. • ULTOMIRIS is a derivative of eculizumab. Due to its identical binding epitope on C5 and mechanism of action of near complete terminal complement inhibition, ravulizumab-cwvz is expected to carry the same risk of meningococcal disease as eculizumab. In the ravulizumab-cwvz clinical	• Overall, the risk of ULTOMIRIS appears acceptable for proposed indication, the biggest risk is serious meningococcal infections • To mitigate the risk of serious meningococcal infections Ultomiris will only be available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Under the ULTOMIRIS

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	development program, a total of 3 patients with PNH in the Phase 1b and 2 studies experienced meningococcal infections/sepsis. No case of meningococcal infection/sepsis was reported in the Phase 3 studies. • In the Phase 3 PNH studies, no deaths occurred during the Primary Evaluation Period. One death due to sepsis occurred on study day 496 in a ULTOMIRIS treated patient. • No patients discontinued from the Phase 3 PNH studies due to AEs through the 26-week Primary Evaluation Period. • In the Phase 3 studies, the incidence of TEAEs over 26 weeks of treatment was similar between the ULTOMIRIS and eculizumab groups (87.8% vs 87.2%). Most AEs were Grade 1 or Grade 2 in severity. The most commonly reported TEAEs (> 10%) in ULTOMIRIS treated patients were headache (32.0%) and upper respiratory tract infections (38.7%). • Overall, there were no significant differences in the safety profile of ULTOMIRIS across demographic subgroups. Demographic variables evaluated include: age, race, sex, body weight, and geographic region. • No notable differences in changes in clinical chemistry or hematology parameters across demographic groups were observed. • Longer exposure to ULTOMIRIS for up to 2 years in the Phase 1b and 2 studies was not associated with an increase in the frequency or severity of AEs.	REMS, prescribers must enroll in the program • Additional mitigation strategies for the risk of serious meningococcal infections, include a box warning in the prescribing information will include a box warning for serious meningococcal infections informing providers of the risk and mitigation strategies. • The Prescribing information will include information to immunize patients with meningococcal vaccines at least 2 weeks prior to administering the first dose of ULTOMIRIS. • Healthcare Professionals and patients should be educated regarding the increased risk of meningococcal infections, the early signs of invasive meningococcal infections, and the need for immediate medical evaluation of signs/symptoms consistent with possible meningococcal infections.

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

✓	The patient experience data that was submitted as part of the application, include: Patient-reported outcome (PRO) assessments in the two open-label, randomized, active-controlled, non-inferiority, phase,3 clinical trials (Studies ALXN1210 PNH 301 and ALXN1210 PNH 302) in adult patients with PNH.				
	✓	Clinical outcome assessment (COA) data, such as			
✓			✓	Patient reported outcome (PRO) The Applicant evaluated the effect of ULTOMIRIS treatment on the concepts of fatigue and General cancer symptoms and impacts as efficacy outcomes using 2 COA instruments: 1) the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue; PRO) and 2) European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core – 30 (EORTC QLQ C30; PRO). PROs used in Studies ALXN1210 PNH 301 and ALXN1210 PNH 302: **Instrument name** / **Concept(s)** / **Endpoint**[1] FACIT-Fatigue / Fatigue / Key Secondary EORTC QLQ C30 / General cancer symptoms and impacts; treatment symptoms / Secondary (b) (4) based on the improvements in the FACIT-Fatigue total score for Studies ALXN1210 PNH 301 and ALXN1210 PNH 302. FDA's review concluded that; • The open-label trial design of Studies ALXN1210 PNH 301 and ALXN1210 PNH 302 limit interpretability of the PRO data because patient's knowledge of treatment assignment may lead to systematic overestimation or underestimation of treatment effect of which is currently unknown. Studies ALXN1210 PNH 301 and ALXN1210 PNH 302 were also not enriched with patients who sufficiently experienced fatigue-	Section 8.1.1 and 8.1.3 - Study endpoints Discussed in Section 8.2.6

[1] Please see Section D 1.3 for a complete endpoint hierarchy.

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			related symptoms at baseline. • Although ALXN1210 PNH 301 generated data that shows improvement in the FACIT-Fatigue total score, there were only select items within the FACIT-Fatigue scale that contributed more to the change observed in the total score upon review of item-level analyses. • The Applicant defined a clinically meaningful score change in the FACIT-Fatigue total score as 3-points, however there is insufficient data to support this threshold. The proposed PRO language for the label is: There was no observable difference in fatigue between ULTOMORIS and eculizumab after 26 weeks of treatment compared to baseline as measured by the FACIT-fatigue instrument. Patient-reported fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment.	
			□ Observer reported outcome (ObsRO)	
			□ Clinician reported outcome (ClinRO)	
			□ Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that was not submitted in the application, but was considered in this review.			

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X _____

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Rosanna Setse MD, PhD, Clinical Reviewer
Tanya Wroblewski MD, Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Paroxysmal nocturnal hemoglobinuria (PNH; ICD-10 classification: D59.5) is an ultra-rare, progressive, destructive, and life-threatening disease in which uncontrolled complement activation leads to systemic and potentially devastating complications, principally through intravascular hemolysis and thrombophilia (Brodsky, 2014; Brodsky, 2015). The median age at diagnosis is the early 30s (Schrezenmeier, 2014; Socie, 1996). The prevalence of PNH is estimated at 15.9 cases per million individuals worldwide (Hill, 2006). In Japan, the prevalence of PNH is estimated to be ~3.6 patients per 1 million inhabitants (Ohno, 2000).

The hallmark of PNH disease activity is complement-mediated hemolysis. Paroxysmal nocturnal hemoglobinuria 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 hemolysis. Intravascular hemolysis releases free hemoglobin, resulting in nitric oxide consumption and persistent smooth muscle cell contraction, along with an increased risk of severe thromboembolism. Chronic severe anemia also frequently develops. Exacerbations of the disease state may occur at any time either spontaneously or due to increased complement activation following infections, trauma, or physical exertion (Brodsky, 2017; Risitano, 2012; Sharma, 2015). The best direct measure of complement-mediated intravascular hemolysis is lactate dehydrogenase (LDH) (Canalejo, 2014; Dale, 1972; Hill, 2010; Parker, 2005).

Patients with PNH are at risk of substantial morbidity and mortality. Before the availability of eculizumab, the reported mortality in several cohorts of patients with PNH was approximately 35% at 5 years, with a median survival of 10 years after diagnosis (de Latour, 2008; Hillmen, 1995; Socie, 1996). 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 (Hill, 2013). Due to these adverse pathologic processes, patients with PNH have a decreased quality of life, which may include the inability to support themselves and social isolation due to debilitating fatigue, chronic pain, poor physical function, shortness of breath, abdominal pain, erectile dysfunction, frequent therapeutic interventions and hospitalization due to a need for anticoagulation, and the need for blood transfusions and/or dialysis (Hill, 2007; Hill, 2010).

The FDA's Assessment:

FDA agrees with the Applicant's position on the seriousness and rarity of PNH, the hallmarks of the disease, and the substantial morbidity and mortality risk for patients with this condition.

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2.2. Analysis of Current Treatment Options

The Applicant's Position:

Effective treatment of PNH requires immediate, complete, and sustained inhibition of terminal complement activity to block hemolysis and prevent thrombosis. The only approved drug for PNH, eculizumab (Soliris®), was approved in 2007 in the United States and subsequently in many countries globally.

Eculizumab is a selective, humanized monoclonal antibody (mAb) that specifically targets C5 of the terminal complement cascade (Rother, 2007), inhibiting its cleavage during complement activation into complement component 5a (C5a) and complement component 5b (C5b) (Matis, 1995). Eculizumab is highly effective in reducing hemolysis, improving quality of life and reducing the risk of thrombosis in patients with PNH.

Eculizumab transformed the treatment paradigm of patients with PNH and improved life expectancy; however, some patients treated with eculizumab have suboptimal C5 blockade, leaving them at potential risk of breakthrough hemolysis (Brodsky, 2017) and associated PNH morbidity which can be life threatening due to the return of the risk of thromboembolic events (Hill, 2013). There is a need for a therapy that completely suppresses hemolysis during the entire dosing interval in all patients with PNH.

Given that PNH is a chronic disease, and eculizumab treatment requires frequent (biweekly) infusions, the eculizumab dosing regimen may impose a significant burden on patients, including missed days of work or school and the need to carefully schedule travel and other life events to accommodate treatment.

Eculizumab also has the potential for suboptimal C5 blockade particularly at the end of biweekly dosing intervals resulting in the return of hemolysis. This "breakthrough hemolysis" (BTH), characterized by elevated LDH and symptoms consistent with intravascular hemolysis despite ongoing therapy, served as a compelling rationale for developing a longer-acting antibody that can address the medical needs for improvements in quality of life, treatment burden, and sustained efficacy throughout the dosing interval.

The FDA's Assessment:

Eculizumab (Soliris®) is currently the only approved drug for the treatment of PNH. Breakthrough hemolysis in some patients treated with eculizumab due to suboptimal C5 blockade can be life threatening due to the return of the risk of thromboembolic events. FDA agrees that there is the need for therapy that completely suppresses hemolysis during the entire dosing interval in all patients with PNH. Additionally, PNH is a chronic disease that requires life-long treatment. A therapy that provides for similar efficacy but with reduced burden for patients with frequency of administration would be a benefit to patients.

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3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Ravulizumab is a New Molecular Entity (NME) and is not currently marketed in any country.

The FDA's Assessment:

This submission is the first marketing application for ravulizumab, a NME. The proposed indication is for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria. The only approved drug for PNH, eculizumab (Soliris®), was approved in 2007.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

A clinical Type C meeting requested on 03 Feb 2016 (written response) confirmed the methodology for dose selection and endpoints for Phase 3 studies in PNH.

A Type B End of Phase 2 (EOP2) meeting was held on 18 Jul 2016 to discuss the Phase 3 development program for ravulizumab. During this meeting, agreement was reached on a common ravulizumab dosing regimen for the treatment of PNH (b) (4)), on the reliance on a single pivotal study to support approval (b) (4) indication, and on the coprimary endpoints of transfusion avoidance and LDH normalization to be used in the pivotal PNH study. Following the meeting, agreement was reached on the Phase 3 weight based dosing strategy through additional correspondence between Alexion and FDA.

A Written Response to a second Type C meeting request was received on 15 Dec 2016 to clarify elements of the Phase 3 design discussed with FDA during the EOP2 meeting, including the proposal to conduct a sensitivity analysis on transfusion history to evaluate the effect of treatment on transfusion avoidance. The FDA written responses highlighted that a noninferiority margin (NIM) of no more than 10% is expected to evaluate benefit risk in Study ALXN1210-PNH-301. FDA also recommended conduct of a study in an eculizumab-treated population to enlarge the pool of subjects studied as part of the Phase 3 program. FDA recommendations were broadly incorporated in Study ALXN1210-PNH-301, and a second Phase 3 study in eculizumab treated patients (Study ALXN1210-PNH-302) was initiated in 2017 as suggested.

A Type B (pre-BLA) meeting dedicated to Chemical Manufacturing and Control topics was held on 23 Jan 2018. A Type B (pre-BLA) meeting to discuss the format and content aspects for the proposed BLA was held on 12 Jun 2018.

The BLA was submitted to FDA on 18 Jun 2018.

The FDA's Assessment:

FDA agrees with the sponsors summary of significant pre-submission regulatory interactions and recommendations from the Agency.

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4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The FDA's Assessment:

Two clinical sites (Dr. Kulasekararaj, Site #223 and Dr. de Latour, Site #263) were selected for inspection in support of this Application. Alexion Pharmaceuticals, Inc. was also inspected.

Source documents for all enrolled subjects at the study sites were reviewed and verified against the case report forms and BLA subject line listings, in part, for primary efficacy endpoints, adverse events and serious adverse event reporting. OSI found no evidence of under-reporting of adverse events during this site audit. Both clinical sites were deemed to be in compliance with Good Clinical Practice. No Form FDA 483 (Inspectional Observations) was issued.

From the review by Dr. Anthony Orencia, "the preliminary regulatory classification of Dr. Kulasekararaj and Dr. de Latour is No Action Indicated. The final regulatory classification of Alexion Pharmaceuticals, Inc. is No Action Indicated".

Please refer to the Clinical Inspection Summary by Anthony Orencia M.D., Division of Clinical Compliance Evaluation, OSI.

4.2. Product Quality

The Applicant's Position regarding the above:

There are no significant issues related to product quality that would impact efficacy or safety.

The FDA's Assessment:

From the review by the CMC team, "The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of BLA 761108 for ULTOMIRIS (ravulizumab-cwvz) manufactured by Alexion Pharmaceuticals Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of ULTOMIRIS is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert" There are three recommended postmarketing commitments. Please refer to the CMC review by Quality Review Team(Application Team Lead Joslyn Brunelle Ph.D.)

4.3. Clinical Microbiology

Refer to CMC review and microbiology review by Bo Chi, PhD
Aimee Cunningham, PhD

4.4. Devices and Companion Diagnostic Issues

There are no devices or companion diagnostic issues pertaining to this Application.

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5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Ravulizumab (ALXN1210) is a recombinant monoclonal antibody (mAb) that binds to the human C5 (hC5) complement protein and inhibits its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]), thereby preventing the generation of the terminal complement complex C5b9. Ravulizumab is an amino-acid-substituted derivative of eculizumab, both of which are indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). The established pharmacologic class of ravulizumab is complement inhibitor.

The dissociation constant (K_D) of 0.5 nM was determined for ravulizumab binding to purified hC5 using surface plasmon resonance (SPR). Amino acid substitutions introduced in the first and second heavy chain variable regions have shown an increased K_D of ravulizumab for hC5, by approximately 17-fold at pH 7.4 and approximately 36-fold at pH 6.0, compared with eculizumab in vitro. Ravulizumab did not elicit effector function through FcγRs or C1q to mediate ADCC or CDC. In a comparative analysis of the pharmacokinetics and pharmacodynamics of ravulizumab and eculizumab in non-obese diabetic/severe combined immunodeficient (NOD-scid) mice, ravulizumab showed no antigen-mediated clearance through Day 28 and a greater than 3-fold longer half-life than eculizumab in the presence of C5. Ravulizumab retained significantly higher and prolonged inhibition of hemolysis compared to eculizumab. Ravulizumab had weaker or no detectable binding to recombinant C5 lacking key residues in the macroglobulin 7 (MG7) domain of human C5 that are important for binding (K879, K882, R885 and W917).

Ravulizumab did not exhibit detectable binding to any non-human species tested. A GLP-compliant 26-week repeat-dose toxicity study, and GLP-compliant reproductive and developmental toxicology studies, were performed in mice using a surrogate murine anti-mouse C5 mAb (BB5.1). BB5.1 binds to and prevents the cleavage of C5, thereby inhibiting generation of both C5a and C5b in the mouse. These studies were reviewed under BLA 125166 for SOLIRIS (eculizumab).

In the 26-week repeat-dose study, mice were administered once or twice weekly by intravenous (IV) injection resulting in doses of 30 or 60 mg/kg/week. Nine unscheduled deaths occurred (4/50 controls and 5/50 high dose animals). One high dose male died during injection and exhibited lung thrombosis, whereas one high dose female died after dosing. The cause of death for the others could not be determined. Adverse findings included, sores/scabs in the ear or cranial area, rough hair coat, and thin and hunched appearance, findings in the lung (congestion, thrombosis, and/or hemorrhage, neoplasia), skin (lesions), eyes (retrobulbar inflammation and hemorrhage), and the hematopoietic/lymphoid system (hyperplasia, neoplasia).

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Human IgGs are known to cross the human placental barrier, and thus ULTOMIRIS may potentially cause terminal complement inhibition in the fetal circulation. Animal reproduction studies were conducted in mice using doses of a murine anti-C5 antibody that approximated 1-2.2 times (loading dose) and 0.8-1.8 times (maintenance dose) the recommended human ULTOMIRIS dose, based on a body weight comparison.

In a fertility and early embryonic development study with the BB5.1 mAb, mice were administered IV doses at 0 (control), 30 or 60 mg/kg/week once weekly prior to mating and until termination (males) or through early gestation (females). Two unscheduled deaths occurred in high dose males. One mouse had a severely distended bladder and dark bright orange lungs upon necropsy, and the other mouse showed clinical signs of hypoactivity, being cold to the touch, with tremors prior to death. No decrease in fertility or reproductive performance was observed.

In a mouse embryofetal development study, BB5.1 was administered by IV injection at 0 (control), 30 and 60 mg/kg/week to pregnant mice during the period of organogenesis. Adverse findings included fetal malformations consisting of one umbilical hernia and two retinal dysplasia in the 60 mg/kg/week group among 230 offspring born to mothers exposed to the higher antibody dose. The exposure did not increase fetal loss or neonatal death.
In a study for effects on pre- and postnatal development, pre-mated female mice received IV doses of either 0 (vehicle control), 30 mg/kg/week or 60 mg/kg/week BB5.l from implantation through weaning. A higher number of male offspring became moribund or died; the dead/moribund animals included F0 generation females (1/25 each in control, low dose and high dose) and F1 generation males (1/25 in control, 2/25 in low-dose, and 5/25 in high dose). Surviving offspring had normal development and reproductive function.

There are no data on the presence of ravulizumab in human milk, the effect on the breastfed child, or the effect on milk production. Since many medicinal products and immunoglobulins are secreted into human milk, and because of the potential for serious adverse reactions in a nursing child, the Applicant proposed breastfeeding should be discontinued during treatment and up to 8 months after the final dose.

The nonclinical pharmacology and toxicology data submitted to this BLA are adequate to support the approval of ravulizumab for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no NDAs, BLAs, or DMFs referenced in this application.

Eculizumab, the comparator for studies ALXN1210-PNH-301 and ALXN1210-PNH-302, was approved in the United States under BLA 125166.

The FDA's Assessment:

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BLA 125166 is relevant to this application. There is a serious risk of meningococcal infections with eculizumab and there is an ongoing REMS program for eculizumab.

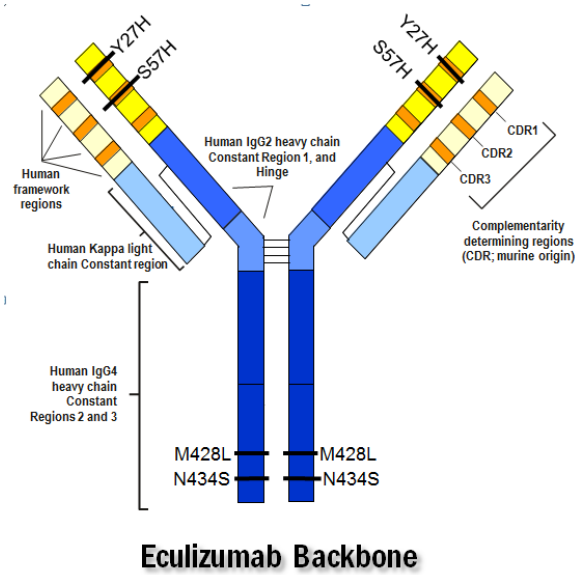
5.3. Pharmacology

Primary Pharmacology

The Applicant's Position:

Ravulizumab (ALXN1210), a derivative of eculizumab, is a humanized mAb that binds to human 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. ALXN1210 differs from eculizumab at 4 amino acid substitutions in the heavy chain, Tyrosine 27 to Histidine (Y27H), Serine 57 to Histidine (S57H), Methionine 428 to Leucine (M428L), and Asparagine 434 to Serine (N434S) (Figure 1).

Figure 1: Schematic Representation of ALXN1210 Recombinant Antibody



These substitutions are intended to enable an extended dosing interval by increasing the circulating half-life through 2 distinct mechanisms: reducing antibody clearance through antigen-mediated clearance and increasing the efficiency of neonatal Fc receptor (FcRn)-mediated antibody recycling. The 2 amino acid substitutions in the first and second complementarity-determining regions (CDRs) of the heavy chain variable region, Y27H and S57H, were introduced to destabilize binding to C5 in the acidified environment of the early endosome (~ pH 6.0) while maintaining enough binding affinity for C5 in the vascular compartment (pH 7.4) to ensure full antagonism of terminal complement pathway. Incorporation of these histidine substitutions was intended to significantly attenuate antigen-mediated clearance by increasing the percentage of dissociation of antibody-C5 complexes to free antibody in the acidified environment of the early endosome after pinocytosis (Figure 2).

Figure 2: Proposed Mechanism of Extended Duration of Action by ALXN1210

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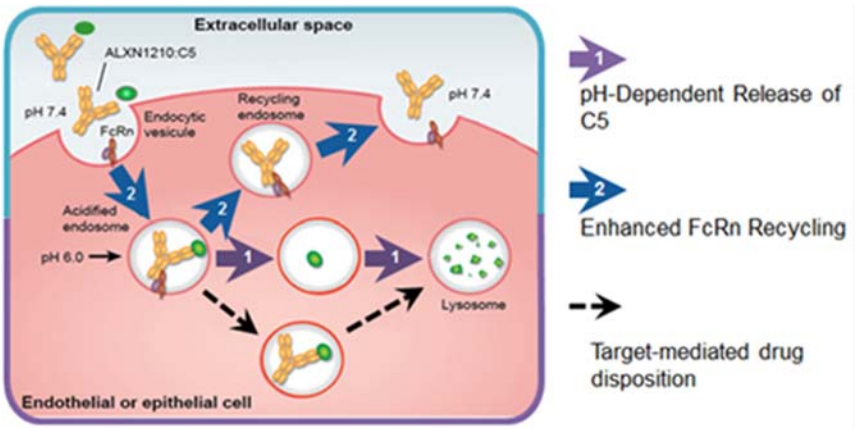

Similar to eculizumab, the mechanism of action of ALXN1210 is entirely through binding to C5. It functions to bind to C5 and block complement convertase-mediated cleavage to its active metabolites, C5a and C5b (to C5b-9). It is completely independent of any secondary pathways being induced or antagonized. 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. Neither ALXN1210 nor eculizumab exhibit detectable pharmacological activity against any non-human species tested, as was predicted by epitope mapping studies and sequence alignments of human and non-human C5 molecules, and confirmed by *in vitro* binding and activity studies. Similar to eculizumab, 4 residues in the macroglobulin 7 (MG7) domain of human C5 were identified to be important for ALXN1210 binding (K879, K882, R885 and W917); sequence alignments with C5 protein sequences from 10 different nonhuman primate species and 13 non-primate mammalian species show that out of the 4 critical residues identified, W917 was unique to human C5 (917 is a serine in nonhuman C5). Subsequently, *in vitro* binding studies and hemolytic activity assays were conducted using recombinant human C5 variants containing a serine substitution at W917. The data from the studies confirmed that ALXN1210 did not display any detectable specific binding to the recombinant C5 W917S variant, nor did ALXN1210 block *in vitro* hemolysis in reactions containing the W917S variant. Additional studies confirmed that ALXN1210 showed no pharmacologic inhibition of complement-mediated hemolysis in sera from 4 nonhuman primates and 5 non-primate species. The results also suggested that ALXN1210 binding to nonhuman C5 is insufficient to study the toxicology, pharmacokinetics (PK) and pharmacodynamics (PD) of ALXN1210 in preclinical settings.

The FDA's Assessment:

The kinetics of ALXN1210 (lot # ALXN1210G1201A MBR-0203) binding to purified C5 variants were determined using Biacore surface plasmon resonance (SPR) (Study # RTR-0006-v1.0). ALXN1210 bound native human C5 (hC5) and recombinant human C5 (RAA031) with dissociation constants (K_D) of 500 pM and 800 pM, respectively.

The kinetic parameters of pH-dependent binding showed the K_D of ALXN1210 for C5 was ~17-fold higher at pH 7.4 and ~36-fold higher at pH 6.0, compared to eculizumab, likely due to the 2 amino acid substitutions (Y27H and S57H) in the first and second CDRs of the heavy chain variable region, which resulted in reduced antibody clearance. The two mutations in the third CH3, (M428L and N434S), increase the affinity of ALXN1210 for FcRn by ~ 10-fold at pH 6.0

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compared to eculizumab and increased the efficiency of FcRn-mediated antibody recycling. These changes in binding to C5 and FcRn appear to aid the extended bioavailability of antibody for its activity.

Table 1: pH-dependent Binding Kinetics of ALXN1210 and Eculizumab to Purified Human C5

pH	Dissociation Constant: KD (M)
ALXN1210	2.13×10^{-10}
8.0	4.91×10^{-10}
7.4	9.11×10^{-10}
7.0	2.19×10^{-9}
6.5	2.18×10^{-8}
6.0	1.47×10^{-11}
Eculizumab	2.93×10^{-11}
8.0	7.15×10^{-11}
7.4	2.06×10^{-10}
7.0	6.06×10^{-10}
6.5	2.13×10^{-10}
6.0	4.91×10^{-10}

A comparative study of the PK and PD of single IV doses of ALXN1210 and eculizumab was performed in non-obese diabetic/severe combined immunodeficient (NOD-scid) mice in the presence or absence of antigen (human complement C5) to test whether 2 amino acid mutations in the heavy chain CDRs of ALXN1210 decrease antigen-mediated clearance over eculizumab (Study # RTR-0008v1.0). Mice were subcutaneously administered human C5 from Day 0 to Day 35 (250 µg/mouse loading dose at day - 1 followed by 50 µg dose twice daily). Mice received a single intravenous (IV) dose of 100 µg of ALXN1210 or eculizumab at Day 0. ELISAs were performed to determine the serum concentrations of ALXN1210 and eculizumab at specified time points post dose and ex vivo serum hemolytic activity was evaluated.

In the absence of C5, serum concentrations of ALXN1210 and eculizumab declined over the 35-day period and showed comparable PK profiles with similar half-lives. In the presence of C5, eculizumab serum concentrations declined to undetectable levels after Day 14, while serum concentration of ALXN1210 decayed slowly through Day 34. Hemolytic activity with ALXN1210 demonstrated extended exposure corresponded to extended duration of PD effect relative to eculizumab.

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Figure 5: PK and PD of ALXN1210 and Eculizumab in NOD-scid Mice

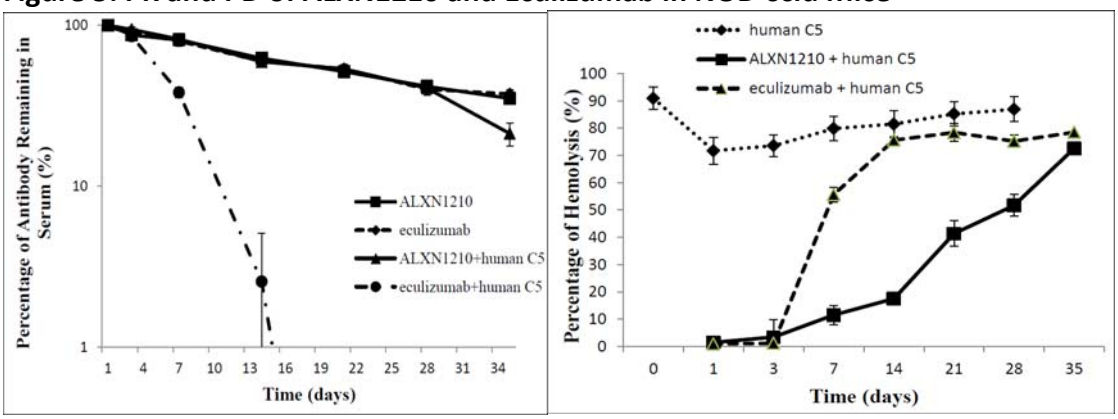

Table 2: Half-life of ALXN1210 and Eculizumab in the Absence and Presence of Human C5

Treatment Group	Half-life (days) (MEAN ±SE)
ALXN1210	25 ± 1
Eculizumab	28 ± 2
ALXN1210 +C5	13 ± 2
Eculizumab +C5	4 ± 0.5

Secondary Pharmacology

The Applicant's Position:

Similar to eculizumab, ALXN1210 contains a chimeric human IgG2-G4 Fc that combines the stable disulfide bond pairing of an IgG2 with the effector-less properties of an IgG4. To assess the potential effector function of ALXN1210, direct measurements of ALXN1210 or eculizumab binding to complement component C1q and Fc gamma receptors (FcγRs) were performed. ALXN1210 displayed no detectable binding to C1q, FcγRI, FcγRIIb/c, FcγRIIIa or FcγRIIIb, and a 4-fold weaker association with FcγRIIa than an IgG1 isotype control. Having both a soluble antigen and weak binding to effector molecules, ALXN1210 is unlikely to be capable of initiating complement-dependent cytotoxicity (CDC) or antibody-dependent cell-mediated cytotoxicity (ADCC) *in vivo.*

Table 3: 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	-	++	-	-	-	NA
SPR Steady state kinetics	3.75 µM	2.31 µM	8.09 µM	7.23 µM	3.33 µM	NA
Biolayer Interferometry						-
Eculizumab						
ELISA	-	++	-	-	-	NA
SPR Steady state kinetics	3.78 µM	2.58 µM	9.84 µM	6.78 µM	3.49 µM	NA
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	NA
Biolayer interferometry						+++

Abbreviations: ELISA = enzyme-linked immunosorbent assay, FcγRs = Fc-gamma receptors, K_D = dissociation constant, SPR = surface plasmon resonance
Source: Module 2.6.2

The FDA's Assessment:

The Agency agrees it is unlikely that ravulizumab is capable of initiating ADCC or CDC.

Safety Pharmacology

Applicant's Position:

As agreed with FDA at the EOP2 meeting on 18 Jul 2016, no safety pharmacology studies have been performed. As ALXN1210 is specific for human C5 and no other relevant toxicological species exist, *in vivo* safety pharmacology testing would not be predictive of human toxicity. In the toxicity studies performed in mice using the mouse surrogate anti-C5 antibody, there were no clinical signs or other findings indicative of central nervous system, cardiovascular, or respiratory adverse effects. Additionally, clinical experience with use of eculizumab and ravulizumab for long-term C5 blockade has not shown any increased risk for these effects.

The FDA's Assessment:

The Agency agrees that no safety pharmacology studies are needed with ALX1210.

5.4. ADME/PK

The Applicant's Position:

Reference ID: 4366451

Type of Study	Major Findings
Absorption	

Study 1727-009: **Single IV Dose PK Study in Cynomolgus Monkeys following 60 or 150 mg/kg ALXN1210**

60 and 150 mg/kg

Dose (N)	Statistic	C_{max} (mg/mL)	C_{max}/ Dose[a]	t_{max} (h)	AUC_{last} (h*mg/mL)	AUC_{∞} (h*mg/mL)	AUC_{∞}/ Dose[a]	V_{ss} (mL/kg)	CL (mL/h/kg)	$T_{1/2}$ (h)
60 mg/kg (N = 4; 2F, 2M)	**Mean**	**1.68**	**0.0280**	**2.00**	**579**	**597**	**9.95**	**64.3**	**0.103**	**537**
	SD	**0.269**	**0.00448**	**NA**	**97.0**	**113**	**1.89**	**7.53**	**0.0191**	**81.7**
	Median	**1.68**	**0.0279**	**2.00**	**572**	**585**	**9.74**	**64.2**	**0.103**	**513**
	CV%	**16.0**	**16.0**	**NA**	**16.8**	**19.0**	**19.0**	**11.7**	**18.5**	**15.2**
150 mg/kg (N = 4; 2F, 2M)	**Mean**	**4.30**	**0.0286**	**4.50**	**1110**	**1120**	**7.49**	**59.7**	**0.141**	**240**
	SD	**0.340**	**0.00227**	**NA**	**279**	**285**	**1.90**	**22.0**	**0.0377**	**346**
	Median	**4.44**	**0.0296**	**2.00**	**1100**	**1130**	**7.50**	**55.7**	**0.134**	**74.3**
	CV%	**7.91**	**7.91**	**NA**	**25.2**	**25.3**	**25.3**	**36.9**	**26.8**	**144**

[a] Units of C_{max}/Dose and AUC_{∞}/Dose = (mg/mL)/(mg/kg) and (h*mg/mL)/(mg/kg), respectively.
AUC_{last} = area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration (at 2664 hours); AUC_{∞} = AUC from time 0 to infinity; CL = total clearance; C_{max} = maximum observed plasma concentration; CV% = percent of coefficient variation; F = female; h = hour; IV = intravenous; M = male; NA = not applicable; SD = standard deviation; t_{max} = time to maximum observed concentration; V_{ss} = volume of distribution at steady state
The ALXN1210 plasma concentration was determined using validated test method SOP-(b) (4)-0082.01.
Source: Study report 1727-009 (Table 1 and Appendix D, Table 3-1 and Table 3-3)

- Absorption not applicable for IV route; mean C_{max} following IV infusion of ALXN1210 increased in a dose-proportional manner.
- The mean dose-normalized AUC_{∞} values were not dose-proportional between the studied dose groups due to treatment emergent cynomolgus anti-human antibody-mediated increase in clearance of ALXN1210 in the 150 mg/kg dose group.

Study 1727-050: **Single and Repeated SC Dose PK Study in Rabbits**

TK Parameters (Male and Female Combined) of ALXN1210 Following a Single SC Administration to Rabbits in the Recovery Arm of Phase A

Dose (mg/kg) (N)	Statistic	C_{max} (µg/mL)	C_{max} / Dose (µg/mL)/(mg/kg)	AUC_{0-24h} (µg*h/mL)	AUC_{0-24h} / Dose (µg*h/mL)/(mg/kg)	t_{max} (h)	AUC_{0-168h} (µg*h/mL)	AUC_{0-168h} / Dose (µg*h/mL)/(mg/kg)
30 (N = 12; 6F, 6M)	**Mean**	292	9.75	2300	76.7	NC	27600	922
	SD	54.4	1.81	392	13.1	NC	6730	224
	%CV	18.6	18.6	17.1	17.1	NC	24.3	24.3
	Median	292	9.75	2270	75.7	72	28200	941
60 (N = 12; 6F, 6M)	**Mean**	552	9.21	3370	56.1	NC	52500	875
	SD	48.6	0.810	625	10.4	NC	17700	295
	%CV	8.80	8.80	18.5	18.5	NC	33.8	33.8
	Median	551	9.18	3280	54.6	60	54700	912
100 (N = 12; 6F, 6M)	**Mean**	894	8.94	6880	68.8	NC	92500	925
	SD	127	1.27	1560	15.6	NC	20300	203
	%CV	14.3	14.3	22.7	22.7	NC	21.9	21.9
	Median	857	8.57	7090	70.9	48	99800	998

Reference ID: 4366451

Type of Study	Major Findings
	AUC_{0-24h} = area under the curve from time 0 to 24 hours; AUC_{0-168h} = area under the curve from time 0 to 168 hours C_{max} = maximum observed plasma concentration; CV% = percent of coefficient variation; NC = not calculated; SD = standard deviation; t_{max} = time of maximum observed concentration Source: Study Report 1727-050 Appendix K; Table 4-2 **TK Parameters (Male and Female Combined) of ALXN1210 Following Multiple SC Administration* to Rabbits in Phase B**

Dose (mg/kg) (N)	Statistic	C_{max} (µg/mL)	C_{max} / Dose (µg/mL)/(mg/kg)	t_{max} (h)	AUC_{0-168h} (µg*h/mL)	AUC_{0-168h} / Dose (µg*h/mL)/(mg/kg)
30 (N=12; 6F, 6M)	**Mean**	285	9.51	NC	29300	976
	SD	79.1	2.64	NC	9650	322
	CV%	27.7	27.7	NC	33.0	33.0
	Median	270	9.00	48	25900	865
60 (N=12; 6F, 6M)	**Mean**	638	10.6	NC	63300	1060
	SD	116	1.94	NC	14600	244
	CV%	18.2	18.2	NC	23.1	23.1
	Median	615	10.3	72	60900	1010
100 (N=12; 6F, 6M)	**Mean**	906	9.06	NC	104000	1040
	SD	240	2.40	NC	32100	321
	CV%	26.5	26.5	NC	30.8	30.8
	Median	824	8.24	72	97200	972

*Only 2 of planned 5 SC doses (Days 1 and 8) were administered due to observed toxicity.
AUC_{0-168h} = area under the curve from time 0 to 168 hours; C_{max} = maximum observed plasma concentration; CV% = percent of coefficient variation; NC = not calculated; SD = standard deviation; t_{max} = time of maximum observed concentration
Source: Study Report 1727-050 Appendix K; Table 4-3

Ravulizumab was immunogenic to rabbits with the incidence rate of developing ADA ranging from 83% to 100% across the doses studied.

Distribution	
N/A	No tissue distribution studies were conducted due to the absence of animal species that is pharmacologically responsive to ALXN1210 as a result of lack of binding of ALXN1210 to non-human C5.
Metabolism	
N/A	Consistent with guideline ICH S6, a designated nonclinical metabolism study was not performed for ALXN1210.

Reference ID: 4366451

Type of Study	Major Findings
Excretion	
N/A	The elimination of ALXN1210 is expected to be similar to that of endogenous IgG antibodies which involves fluid-phase endocytosis or receptor mediated endocytosis followed by intracellular lysosomal catabolism in endothelial cells or cells of the reticuloendothelial system (Lobo, 2004). The binding of ALXN1210 to C5 followed by intracellular uptake and catabolism is an important pathway of ALXN1210 elimination. ALXN1210 is designed to have minimal target mediated drug disposition (TMDD).
Drug Interaction Potential	
	Therapeutic proteins are not metabolized via oxidation or conjugation pathways common to small molecules. Therefore, ALXN1210 is unlikely to affect PK of co-administered small molecules. Similarly, co-administration of small molecules is unlikely to affect the PK of ALXN1210. ALXN1210 is neither a cytokine nor a ligand/modulator for a cytokine. Available safety data on ALXN1210 and long term safety data on another anti-C5 antibody, eculizumab, have not identified any drug-drug interaction-related concerns.

The FDA's Assessment:

FDA agrees with the results of the PK parameters provided above. No animal exposure data was collected for the surrogate murine antibody BB5.1 used in several toxicology studies.

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:
For the following studies in the toxicology package, the murine surrogate molecule BB5.1 was administered to mice due to lack of pharmacologic activity of ALXN1210 in mice.

ALXN1210 was used in the tissue cross reactivity studies in both normal human and normal non-human primate (cynomolgus) tissues, and in the rabbit subcutaneous local tolerance study.

Study 6709-108: Twenty-six Week Study in Mice With BB5.1 mAb

Key Study Findings

- Treatment did not affect any of the toxicity parameters examined
- The No Observed Adverse Effect Level (NOAEL) for BB5.1 mAb administered to CD-1 mice via IV injection twice weekly for 26 weeks was determined to be 60 mg/kg/week, the highest dose tested.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0, 30, 60 mg/kg/week, dosed once or twice weekly
Route of administration:	IV
Formulation/Vehicle:	20mM Tris-buffered saline
Species/Strain:	Male and female Crl:CD-1(ICR)BR mice
Number/Sex/Group:	25/sex/group in control and high dose, 15/sex/group for the low dose
Age:	~6 weeks old
Satellite groups/ unique design:	No
Deviation from study protocol affecting interpretation of results:	No

Reference ID: 4366451

Observations and Results:

Parameters	Major findings
Mortality	Nine unscheduled deaths occurred during the study (3 males and 1 female in the control group and 3 males and 2 females in the 60 mg/kg/week group); none were related to treatment.
Clinical Signs	There were no treatment-related clinical observations.
Body Weights	Treatment did not affect mean body weight changes.
Ophthalmoscopy	There were no treatment-related ophthalmic observations.
Hematology	There were no treatment-related clinical pathology findings.
Clinical Chemistry	There were no treatment-related clinical pathology findings.
Gross Pathology	There were no macroscopic or histomorphologic findings indicative of a treatment-related effect.
Organ Weights	There were no treatment-related organ weight changes.
Histopathology	There were no macroscopic or histomorphologic findings indicative of a treatment-related effect.

The FDA's Assessment:

This study was reviewed under BLA 125166 for eculizumab.

According to the nonclinical review of BLA 125166, adverse findings included: dose dependent sores/scabs in the ear or cranial area, rough hair coat, and thin and hunched appearance, findings in the lung (congestion, thrombosis, and/or hemorrhage, neoplasia), skin (lesions), eyes (retrobulbar inflammation and hemorrhage), and the hematopoietic/lymphoid system (hyperplasia, neoplasia).

The Applicant's Position:
There are no additional studies to report.

The FDA's Assessment:

A 4-week repeat-dose toxicology study was conducted with BB5.1 in mice. According to the nonclinical review of BLA 125166, there were no BB5.1-related toxicities, except for the PD effect of hemolytic inhibition at 60 and 90 mg/kg/week. Therefore, 60 mg/kg/week was selected as the maximum dose for subsequent studies.

5.5.2. Genetic Toxicology

The Applicant's Position:
In line with ICH S6 (R1), genotoxicity studies were not performed with ALXN1210.

Reference ID: 4366451

The FDA's Assessment:

The Agency agrees.

5.5.3. Carcinogenicity

The Applicant's Position:

No carcinogenicity studies were performed. The 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. Nonclinical studies utilizing the murine surrogate molecule of C5 blockade, BB5.1 were performed; in these studies no specific carcinogenicity risks were observed. Additionally, approximately 10 years of clinical use of eculizumab to effect long-term C5 blockade has not shown any increased risk of carcinogenicity.

The FDA's Assessment:
The carcinogenic potential of ALXN1210 in animals is unknown. However, in the 26-week repeat dose toxicology study in mice with BB5.1, multiple hematopoietic neoplasms (lymphoma/lung/salivary glands/thymus) occurred in 1 high dose female (60 mg/kg/week), lymphoid or lymphoreticular hyperplasia in mandibular lymph node and thymus occurred in another high dose female.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

The Applicant's Position:

Study 6709-104: Fertility and Early Embryonic Development in Mice (Segment I) with BB5.1 mAb

Key Study Findings

- 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
- There were no compound-related mortalities or clinical observations. Body weight, body weight gain, and food consumption were unaffected by BB5.1 mAb. There were no compound-related necropsy findings.
- BB5.1 mAb 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 cesarean section parameters indicating that BB5.1 mAb had no effect on implantation or embryo fetal viability.

Conducting laboratory and location	(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: Once weekly, prior to mating and until termination (males) or through early gestation (females).
The control group was dosed twice weekly with 20 mM Tris-buffered saline, while the high-dose group (Group 3) was dosed twice weekly with BB5.I at 30 mg/kg/dose. The low-dose group (Group 2) was dosed once weekly and received BB5.1 at 30 mg/kg/dose.

Route of administration: IV

Formulation/Vehicle: 20mM Tris-buffered saline

Species/Strain: Male and female Crl:CD-1® (ICR) BR mice, ~9 weeks of age

Number/Sex/Group: 25/sex/group

Study design:

	Number of Animals		Dose Levels			
Group	**Male**	**Female**	**mg/kg/dose**	**dose/ week**	**mg/kg/week**	**Concentration (mg/mL)**
1 (Control)	25	25	0	2	0	0
2 (Low)	25	25	30	1	30	3
3 (High)	25	25	30	2	60	3

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	**Major findings**
Mortality	There were no compound related mortalities.
Clinical Signs	There were no compound related clinical signs.
Body Weights	Body weights were unaffected by test compound.
Necropsy findings *[Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc]*	There were no compound-related necropsy findings.

The FDA's Assessment:

The Agency agrees with reproductive performance results described above. This study was reviewed under BLA 125166 for eculizumab. According to the nonclinical review of BLA 125166, adverse findings included two unscheduled deaths in the 60 mg/kg/week male group. Necropsy revealed a severely distended bladder and dark bright orange lungs in one mouse, and clinical signs of hypoactivity, cold to the touch, with tremors prior to death in the other mouse.

Embryo-Fetal Development

The Applicant's Position:

Study 6709-105: Mouse Developmental Toxicity Study with BB5.1

Key Study Findings

- No test-article related study mortality or clinical signs.
- BB5.1 in Tris-buffered saline and administered by intravenous injection to pregnant mice during the period of organogenesis determined the NOEL for maternal toxicity and embryo/fetal toxicity as ≥ 60 mg/kg/week, based on the lack of maternal and cesarean section findings at 60 mg/kg/week (i.e., the highest dose tested).
- Based on the observed fetal soft tissue malformations at 60 mg/kg/week, the NOEL for developmental toxicity was 30 mg/kg/week.
- Single incidence of umbilical hernia and 2 incidences of retinal dysplasia in high dose group deemed unlikely to be test-article related upon expert review.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	Premated female mice were assigned to 3 groups (25/group).The control and high-dose groups were dosed by IV injections with Tris-buffered saline (0 mg/kg/dose) or BB5.1 at 30 mg/kg/dose (Groups 1 and 3, respectively) on Gestation Days (GD) 6, 9, 12, and 15. The low dose group (Group 2) was dosed with BB5.1 at 30 mg/kg/dose on GD 6 and 12.
Route of administration:	IV
Formulation/Vehicle:	20 mM tris-buffered saline
Species/Strain:	female Crl:CD-1® (ICR) BR mice
Number/Sex/Group:	25 females/group, 12 weeks old, premated
Study design:	

	Number of Mice	Dose Levels			Concentration (mg/mL)	Dosing Schedule Gestation Day (GD)
Group	Female	mg/kg/dose	dose/week	mg/kg/week		
1 (Control)	25	0	2	0	0	GD 6, 9, 12, 15
2 (Low)	25	30	1	30	3	GD 6, 12
3 (High)	25	30	2	60	3	GD 6, 9, 12, 15

Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	There was no compound related mortality.
Clinical Signs	There were no compound related clinical signs.

Body Weights	Body weights were unaffected by test compound.
Necropsy findings Cesarean Section Data	LD: Necropsy findings unremarkable. HD: Single incidence of umbilical hernia and 2 fetal incidences of retinal dysplasia (1 fetus from 2 separate litters).

LD: low dose; MD: mid dose; HD: high dose

The FDA's Assessment:

This study was reviewed under BLA 125166 for eculizumab.
According to the nonclinical review of BLA 125166, adverse findings included: fetal malformations of one umbilical hernia and two retinal dysplasia in the 60 mg/kg/week group only (high dose).

Prenatal and Postnatal Development

The Applicant's Position:

Study 6709-107: Study for Effects on Pre-and Postnatal Development, Including Maternal Function, in Mice with BB5.1

Key Study Findings

- There were no compound-related mortalities or clinical observations. There were no compound-related necropsy findings.
- Natural deliver and litter data from F1 offspring were unremarkable. Exploratory activity and learning and memory of the F1 offspring were unaffected by BB5.1 treatment.
- The NOEL for maternal toxicity and F1 pup development and reproductive performance through to parturition of the F2 generation is ≥ 60mg/kg/week, the highest dose tested.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	Female mice were assigned to 3 groups. The control group received 20mM Tris-buffered saline, while the low and high-dose groups received BB5.1 at 30mg/kg/dose. Control and high dose groups (Groups 1 and 3, respectively) were dosed on Gestation Day 6, 9, 12, 15, and 18 and on Lactation Day 2, 6, 9, 12, 15, and 18. The low-dose group (Group 2) was dosed on Gestation day 6, 12, and 18 and Lactation Day 6, 12, and 18.
Route of administration:	IV
Formulation/Vehicle:	20 mM Tris-buffered saline
Species/Strain:	female Crl:CD-1® (ICR) BR mice
Number/Sex/Group:	37 females/group

Study design:

	Number of Animals[a]	Dose Levels				
Group	**Females**	**mg/kg/dose**	**Dose/ week**	**mg/kg/ week**	**Concentration (mg/mL)**	**Dosing Schedule Gestation-Lactation**
1 (Control)	37	0	2	0	0	GD 6, 9, 12, 15, and 18; LD 2, 6, 9, 12, 15, and 18
2 (Low)	37	30	1	30	3	GD 6, 12, and 18; LD 6, 12, and 18
3 (High)	37	30	2	60	3	GD 6, 9, 12, 15, and 18; LD 2, 6, 9, 12, 15, and 18

Abbreviations: GD = gestation day; LD = lactation day
[a] On 11 Oct 2001, 12 additional females were added (per group) to the study.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Generation	Major Findings
F0 Dams	No test-article related findings.
F1 Generation	No test-article related findings. BB5.1 had no effect on the overall reproductive performance of the F1 generation.
F2 Generation	No test-article related findings.

The FDA's Assessment:

The Agency agrees that exploratory activity and learning and memory of the F1 offspring were unaffected by BB5.1 treatment. This study was reviewed under BLA 125166 for SOLIRIS (eculizumab). According to the nonclinical review of BLA 125166, there were unscheduled deaths and moribund animals in the F0 and F1 generations. One 60 mg/kg/week F0 female died on Lactation Day 14 with necropsy revealing a pale liver. In addition, one female each were sacrificed in control and low dose groups of the F0 generation due to total litter death. Deaths or moribund F1 males numbered 1/25 controls, 2/25 low-dose, and 5/25 in the high dose group.

5.5.5. Other Toxicology Studies

The Applicant's Position:

Study 1727-050: Local Tolerance Study with Subcutaneous Formulation of ALXN1210: A Single and Repeat-Dose Subcutaneous Irritation Study in Rabbits

A GLP-compliant study was conducted to evaluate local irritation following acute and subchronic SC injections of a new formulation of ALXN1210 (b) (4)

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(b) (4). The test article was formulated at a higher concentration (100 mg/mL) with different excipients than the current IV formulation (10 mg/mL) being studied in human trials.

In summary, a single SC injection of ALXN1210 in rabbits was well tolerated, with no evidence of local reactogenicity. Repeated SC injection of ALXN1210 caused a severe immunological reaction in rabbits, indicative of a systemic, type III hypersensitivity response with an immune complex etiology. Immunological reactions are common in animals administered human proteins. A systemic immune response to human proteins in rabbits and other species is generally not considered to be relevant to immunogenicity risks in humans (Leach, 2014). For these reasons, the adverse findings from this study are not considered relevant to human safety of the ALXN1210.

Study 20039106: A Tissue Cross-Reactivity Study of Fluoresceinated ALXN1210 in Normal Human Tissues

The objective of this GLP-compliant study was to determine the potential cross-reactivity of fluoresceinated ALXN1210, a monoclonal antibody directed against human C5, with cryosections of human tissues. Staining with ALXN1210-FITC in the human tissue panel was observed in proteinaceous material in most human tissues, Cytoplasm and/or cytoplasmic granules in multiple tissues including mononuclear cells in the colon, esophagus, lymph node, parathyroid, spleen, and tonsil, platelets in blood smears and bone marrow, megakaryocytes in the bone marrow, epithelium in the fallopian tube, liver (hepatocytes), pancreatic ducts, and cervix, and mesothelium in the lung.

As C5 is a circulating serum protein, the staining of proteinaceous material was judged expected. Mononuclear cells, such as monocytes, macrophages, and dendritic cells, as well as platelets, have been reported to secrete C5; therefore, the staining of these cell types with ALXN1210-FITC was also judged as expected. Additionally, mesothelial cell lines have been shown to produce C5. However, no literature was available describing the expression of C5 by the epithelial cell types stained with ALXN1210-FITC in the current study or megakaryocytes, although platelets, which have been shown to produce C5, are derived from megakaryocytes. Therefore, the staining of epithelial cell types might represent either previously unrecognized sites of C5 expression or tissue cross-reactivity with a protein sequence or structure from a similar but unrelated protein or other constituent(s) of the tissue sections. However, with the exception of the staining of proteinaceous material, all staining observed in this study was cytoplasmic in nature, and it is unlikely that the cytoplasm and cytoplasmic structures would be accessible to the test article in vivo.

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

The objective of this GLP-compliant study was to determine the potential cross-reactivity of fluoresceinated ALXN1210, a monoclonal antibody directed against human C5, with cryosections of nonhuman primate (cynomolgus monkey) tissues. Staining with ALXN1210-FITC was observed in multiple cynomolgus monkey tissues, including proteinaceous material in most cynomolgus monkey tissues, cytoplasm and/or cytoplasmic granules in multiple tissues

including mononuclear cells in the lymph node, spleen, and tonsil and epithelium in the fallopian tube.

With the exception of the staining of proteinaceous material, the staining observed in this study was cytoplasmic in nature, and it is unlikely that the cytoplasm and cytoplasmic structures would be accessible to the test article in vivo. ALXN1210-FITC is specific to human C5 and should not recognize monkey C5. The ALXN1210-FITC staining pattern observed in the cynomolgus monkey tissue panel was overall less intense and less frequent than that observed in the human tissue panel in the companion human tissue cross-reactivity study (Study 20039106). Further, in the human tissue panel, staining of platelets, megakaryocytes, pancreatic ductal epithelium, cervical epithelium, hepatocytes, and mesothelium was observed, although these tissue elements were not stained in the cynomolgus monkey tissue panel. Since ALXN1210-FITC was not expected to bind to cynomolgus monkey C5, the observed staining in the current tissue cross-reactivity study might be demonstrating alterations in C5 induced by desiccation, exposure to fixative, or other artifact and/or the possibility that not all the observed staining in human and monkey tissue is due to C5 but included cross-reactive/FcR-mediated binding to proteinaceous material, mononuclear cells, and a few epithelial cells.

The FDA's Assessment:

In the local tolerance study, SC administration of ALXN1210 to rabbits on 2 occasions separated by a 1-week period, resulted in euthanasia of 7 animals in extremis due to the rapid progression and severity of the clinical signs (2 animals in the 30 mg/kg/week, 2 animals in the 60 mg/kg/week, and 4 animals in the 100 mg/kg/week groups). Animals euthanized in extremis had exhibited moderate to marked renal injury and inflammatory effects as indicated by increases in urea nitrogen, creatinine, phosphorus, fibrinogen, IL-6, MCP-1, IP10, and/or neutrophils. Other findings consisted of mild to moderate decreases in red cell mass with concurrent evidence of regeneration and associated alterations to erythrocyte morphology typical of membrane injury. Macroscopic findings included discoloration of varying severities in various tissues (ears, skin, subcutis, epididymides, and lung with bronchi). Vascular/perivascular inflammation, thrombi, with occasional necrosis and/or hemorrhage, were predominately in the skin, but occasionally on visceral organs.

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Ramadevi Gudi, PhD
Primary Reviewer

Christopher Sheth, PhD
Team Leader

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6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Applicant seeks approval of ravulizumab for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). The proposed ravulizumab dosing regimen is a loading dose followed by maintenance dosing intravenously every 8 weeks (Q8W), starting 2 weeks after loading dose administration, according to body weight as shown in the table below.

The Clinical Pharmacology section of the BLA is supported by single and repeat dose pharmacokinetics (PK) studies of ravulizumab in healthy subjects and in patients with PNH, immunogenicity assessment, and the following evaluations and analyses: population pharmacokinetics (PopPK) and exposure-response (ER) relationships, and potential QT/QTc prolongation. The covariates that were found to have no clinically significant differences in the pharmacokinetics of ravulizumab include sex, age (18 to 83 years), race (44% Asian, 43% White, 3% Black, 10% unknown), mild to severe hepatic impairment by NCI criteria, or mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2, estimated by MDRD). The effect of severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2, estimated by MDRD) on ravulizumab pharmacokinetics is unknown. Body weight was a significant covariate on the PK of ravulizumab.

The key review question focuses on the appropriateness of the dosing regimen for the treatment of adult patients with PNH. The Applicant conducted pharmacokinetic/pharmacodynamic (PK/PD) simulations to inform an optimal phase 3 dosing regimen prior to initiation of the registration trials, Study 301 and 302. PopPK assessment indicated that body weight affected ravulizumab PK, resulting in higher exposure in lighter patients compared to heavier patients and therefore suggesting the need for weight-based dosing. PK/PD analysis suggested that achieving ravulizumab concentration above the target threshold (C_{trough} > 175 mcg/mL) would result in near maximal PD effect. Near normalization of LDH levels was observed at steady-state C_{trough} > 175 µg/mL. The minimum ravulizumab dose sufficient for maintaining the PK threshold was identified for each of 3 body weight categories. Following the proposed weight-based ravulizumab dosing regimen, complete inhibition of serum free C5 levels < 0.5 µg/mL (correlated with inhibition of intravascular hemolysis and LDH lowering) was observed by the end of the first dose and sustained throughout the entire 26-week treatment period in both complement inhibitor-naïve patients and patients previously treated with eculizumab. The Review team concludes that the Applicant's ER analysis appear to support their proposed dosing regimen.

Recommendations
The Office of Clinical Pharmacology has reviewed the information contained in BLA 761108. This BLA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized below:

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<table>
<tr><th>Review Issues</th><th>Recommendations and Comments</th></tr>
<tr><td>Evidence of effectiveness</td><td>In the 2 Phase 3 studies (ALXN1210-PNH-301 and ALXN1210-PNH-302), immediate and complete inhibition of serum complement protein (C5; terminal complement) was observed (as defined by free C5 serum concentrations of < 0.5 µg/mL) by the end of the first ravulizumab dose and sustained throughout the entire 26-week treatment period in all patients, both complement-inhibitor naïve and patients previously treated with eculizumab..</td></tr>
<tr><td>General Dosing instructions</td><td>The recommended dosing regimen for adult patients (≥ 18 years of age) with PNH consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. Administer the doses based on the patient's body weight, as shown in the table below. Starting 2 weeks after the loading dose administration, begin maintenance doses Q8W.

For patients switching from eculizumab to ravulizumab, administer the loading dose of ravulizumab 2 weeks after the last eculizumab infusion, and then administer maintenance doses Q8W at 2 weeks after loading dose administration.
<table>
<tr><th>Body Weight Range (kg)</th><th>Loading Dose (mg)</th><th>Maintenance Dose (mg)</th></tr>
<tr><td>≥ 40 to < 60</td><td>2400</td><td>3000</td></tr>
<tr><td>≥ 60 to < 100</td><td>2700</td><td>3300</td></tr>
<tr><td>≥ 100</td><td>3000</td><td>3600</td></tr>
</table></td></tr>
<tr><td>Dosing in patient subgroups (intrinsic and extrinsic factors)</td><td>No dose modification is needed for specific populations based on age, sex, race, hepatic impairment or mild to moderate renal impairment. The effect of severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2, estimated by MDRD) on ravulizumab PK is unknown. Body weight was a significant covariate on the PK of ravulizumab, supporting body weight-based dosing.</td></tr>
</table>

There is no Post-Marketing Requirement (PMR) or Post-Marketing Commitment (PMC) from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

<u>The Applicant's Position:</u>

Ravulizumab is a monoclonal antibody that specifically binds to the complement protein C5 with high affinity, inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]), thus preventing the generation of C5b-9. By binding specifically to C5, ravulizumab antagonizes terminal complement-mediated inflammation, cell activation, and cell lysis while preserving the early

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components of complement activation that are essential for opsonization of microorganisms and clearance of immune complexes.

Ravulizumab exhibited dose-linear and time-independent pharmacokinetics (PK) over the studied intravenous (IV) infusion dose range (200 to 5400 mg) and dosing schedule (up to once-every-12-week dosing). Ravulizumab C_{max} and C_{trough} parameters following the IV loading dose and the last (third) maintenance doses of the Phase 3 dosing regimen in patients with PNH were comparable between complement inhibitor-naïve and eculizumab-treated patients (Table 2).

Table 2: Mean ± SD (%CV) PK Parameters of Ravulizumab in Complement Inhibitor-Naïve and Eculizumab-Experienced Patients with PNH

		N	Complement Inhibitor-Naïve	N	Eculizumab-Experienced
C_{max} (mcg/mL)	LD	125	771 ± 166 (21.5)	95	843 ± 204 (24.1)
	MD[a]	124	1379 ± 276 (20.0)	95	1386 ± 268 (19.4)
C_{trough} (mcg/mL)	LD	125	391 ± 137 (35.0)	96	405 ± 121 (29.9)
	MD[a]	124	473 ± 158 (33.4)	95	501 ± 143 (28.6)

[a] Observed following the third maintenance dose.
Abbreviations: C_{max} = maximum observed serum concentration; C_{trough} = concentration at the end of the dosing interval; CV = coefficient of variation; LD = loading dose; MD = maintenance dose; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria; SD = standard deviation
Source: ALXN1210-PNH-301 CSR Table 14.2.5.1.1, Table 14.2.5.2.1; ALXN1210-PNH-302 CSR Table 14.2.6.1.1, Table 14.2.6.2.1

The FDA's Assessment:
FDA agrees with the Applicant's characterization of ravulizumab PK in complement-inhibitor naïve and patients previously treated with eculizumab.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

The recommended ravulizumab dosing regimen for adult (≥ 18 years of age) patients with PNH consists of a loading dose followed by maintenance dosing, administered as an IV infusion. The doses are based on the patient's body weight (Table 3). Maintenance doses should be administered once every 8 weeks (q8w), starting 2 weeks after loading dose administration. For patients switching from eculizumab to ravulizumab, the loading dose of ravulizumab should be administered 2 weeks after the last eculizumab infusion, and then maintenance doses are administered q8w, starting 2 weeks after loading dose administration.

Table 3: 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

Pharmacokinetic exposure versus pharmacodynamics (PD; free C5) and efficacy (LDH) endpoint relationships represent a biologically interdependent hierarchical continuum of endpoints

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starting from engagement of target to the downstream clinical benefits. These relationships provided a strong justification of clinical relevance for the threshold serum ravulizumab concentration identified. The optimal Phase 3 dosing regimen was characterized by conducting PK model-based simulations to target the clinically relevant threshold serum ravulizumab concentration in all patients with PNH to provide immediate and complete terminal complement inhibition, as defined as serum free C5 concentrations < 0.5 µg/mL, sustained throughout the entire 8-week maintenance dosing interval.

The FDA's Assessment:
FDA agrees with the Applicant's proposed dosing regimen, which was utilized in Studies ALXN1210-PNH-301 and ALXN1210-PNH-302 that assessed the safety and efficacy of ravulizumab and is supported by the exposure-response analyses.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

The results of the population-PK analysis support body weight-based dosing, as body weight was shown to impact both clearance and volume of distribution. No dose individualization is recommended based on sex, race, age, or hepatic or renal impairment. Dose individualization for extrinsic factors (e.g., food or drug interactions) is not applicable for IV ravulizumab.

The FDA's Assessment:
FDA agrees with the Applicant's position on body weight-based dosing and no therapeutic individualization due to intrinsic or extrinsic factors based on population PK analysis. The effect of severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2, estimated by MDRD) on ravulizumab pharmacokinetics is unknown.

6.2.2.3. Outstanding Issues

The FDA's Assessment:
There are no outstanding clinical pharmacology issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

Pharmacology	
Mechanism of Action	Ravulizumab is a mAb that specifically binds to the complement protein C5 with high affinity, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9, while preserving the early components of complement activation that are essential for the opsonization of microorganisms and clearance of immune complexes.
Pharmacodynamics	In the 2 controlled Phase 3 studies, serum free C5 versus time profiles were characterized by immediate and complete terminal complement inhibition, as defined by serum free C5 < 0.5 µg/mL, which was sustained throughout the 26-week treatment period in all ravulizumab-treated complement inhibitor-naïve and eculizumab-experienced patients with PNH.
QT Prolongation	No dedicated thorough QT study was conducted because it is irrelevant for a monoclonal antibody such as ravulizumab with a molecular weight of approximately 148 kDa.

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	Ravulizumab concentration versus QTc assessment confirmed the absence of an effect of ravulizumab on cardiac repolarization.
General Information	
Bioanalysis	In support of the ravulizumab clinical development program, bioanalytical assays were developed to measure total ravulizumab and eculizumab concentrations in human serum, serum free C5 concentration, serum total C5 concentrations, and *ex vivo* hemolysis as the functional activity of in vivo C5 inhibition. The measurement of serum LDH was performed as part of clinical central lab assessment using a standard Clinical Laboratory Improvement Amendments (CLIA) approved method. Assessment of immunogenicity to ravulizumab and eculizumab was performed via detection of antidrug antibody (ADA) incidence and titer, in all clinical studies. All ADA positive samples were further analyzed for neutralizing ADA (NAb). Two specific electrochemiluminescence (ECL) methods, 1 each for eculizumab and ravulizumab, have been used for analyzing serum free C5 concentrations in patients treated with eculizumab or ravulizumab during the ravulizumab development program. In vitro results suggested that serum free C5 values were comparable at concentrations > 0.5 µg/mL mainly due to the greater imprecision of the previous free C5 ECL assay of ravulizumab in measuring free C5 concentrations below 0.5 µg/mL. This did not allow for a direct comparison of free C5 concentrations between the 2 compounds in Phase 3 because the majority of free C5 measurements in Phase 3 studies were expected to be below 0.5 µg/mL. To resolve this issue, the ravulizumab free C5 assay method was changed from an ECL to a Gyros-based fluorescence assay for the support of Phase 3 studies. The Gyros assay methodology improved the accuracy and robustness of the ravulizumab free C5 assay results at free C5 levels < 0.5 µg/mL and enabled the direct comparison of the serum free C5 concentrations down to > 0.0274 µg/mL, the LLOQ of eculizumab free C5 ECL assay. The serum free C5 concentrations from the previous ECL assay for ravulizumab and the new Gyros assay for ravulizumab were not comparable at < 0.5 µg/mL and as a result a cross-validation over the serum free C5 concentration range of interest was not considered. The threshold of serum free C5 concentration of < 0.5 µg/mL has been established as representing complete inhibition of hemolysis (Soliris USPI).
Drug Exposure at Steady State Following the Therapeutic Dosing Regimen	Steady-state therapeutic concentrations were achieved following the first (loading) IV dose of ravulizumab in Phase 3 patients with PNH, with the following overall observed mean (SD) steady-state exposures: $C_{trough,ss}$: 497 (160) µg/mL $C_{max,ss}$: 1460 (283) µg/mL
Range of Effective Dose or Exposure	The proposed body weight-based IV infusion dosing regimen for adult patients ≥ 40 kg, where the LD is administered on Day 1, followed by q8w administration of the MD, starting on Day 15, is as follows: ≥ 40 to < 60 kg: 2400 mg LD / 3000 mg MD ≥ 60 to < 100 kg: 2700 mg LD / 3300 mg MD ≥ 100 kg: 3000 mg LD / 3600 mg MD
Maximally Tolerated Dose or Exposure	A maximally tolerated dose was not reached during clinical development. 5400 mg administered once every 12 weeks is the maximum dose tested with highest Cmax (Study ALXN1210-PNH-201, Cohort 4, N = 7) and was well tolerated in patients with PNH. 1800 mg administered once every 4 weeks is the dosing regimen with the highest systemic PK (AUC) exposure (Study ALXN1210-PNH-103, Cohort 2, N = 7). The exposures achieved following these Phase 2 doses were higher than the exposures achieved following the recommended dosing in the Phase 3 studies. All ravulizumab doses and regimens were well tolerated.

Dose Proportionality	Dose-proportional PK was noted across the studied range of ravulizumab doses (200 to 5400 mg) administered in the ravulizumab clinical development program in patients with PNH.
Accumulation	PK steady-state therapeutic concentrations were achieved after the first dose of ravulizumab.
Variability	Observed CV % for each of the exposure parameters is as follows: $C_{trough,ss}$: 32.2 % $C_{max,ss}$: 19.4 %
Absorption	
Bioavailability	Ravulizumab is administered IV as a solution for infusion and, as a result, 100% of the administered dose is bioavailable.
T_{max}	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 studies occurred either at, or within 3 hours of EOI.
Food effect (Fed/fasted)	Ravulizumab is administered intravenously. Food effect is not applicable.
Distribution	
Volume of Distribution	The mean (SD) volume of distribution at steady state for patients with PNH on the studied body weight-based dosing regimen was 5.35 (0.92) L.
Elimination	
Terminal Elimination Half-Life	The mean (SD) terminal elimination half-life in Phase 3 patients with PNH is 49.7 (8.9) days.
Immunogenicity	
Incidence	Ravulizumab exhibited a low incidence of immunogenicity in patients with PNH (both complement inhibitor-naïve and eculizumab-experienced) in Phase 3 (< 0.5%), with only 1 treatment-emergent antidrug antibody (ADA) observed with a low titer, no evidence of neutralization, and no apparent impact of immunogenicity on PK, PD, safety, or efficacy.
Dosing Considerations	
Special Population	No formal study assessing the effect of sex, race, age (geriatric), or hepatic or renal impairment on the PK of ravulizumab was conducted. However, based on population-PK assessment, sex, age, race, or hepatic (alanine aminotransferase [ALT] range, 8 to 152 U/L; aspartate aminotransferase [AST] range, 12 to 285 U/L) or renal (epidermal growth factor receptor [eGFR] range, 32 to 231 mL/min/1.73m^2) function has no impact on ravulizumab PK in the studied healthy adult subjects (N = 38) or patients with PNH (N = 261), and as a result no dosing adjustment is considered necessary.
Drug-Drug Interactions	No formal studies assessing the effect of other drugs on the pharmacokinetics of ravulizumab were conducted. It is not expected that other drugs will impact the pharmacokinetics of ravulizumab. The base population-PK model was used to evaluate the effects of concomitantly administered drugs on ravulizumab PK. The impact of concomitant medications from assorted drug classes (anabolic agents for systemic use, antithrombotic agents, antianemic preparations, antihypertensives, corticosteroids for systemic use, antibacterials for systemic use, antimycolitics for systemic use, and immunosuppressants) on subject-level variability parameters of ravulizumab were assessed. The assessment showed that the studied concomitant drugs do not impact ravulizumab PK. Ravulizumab does not bind to a cytokine and the available safety data (177 patient-years) have not shown a drug-induced cytokine modulation, indicating that the

	potential of drug-related cytokine based drug interaction is negligible. This is consistent with clinical and post-marketing eculizumab experience.

The FDA's Assessment:

FDA agrees with the Applicant's summary of the general pharmacology and pharmacokinetics of ravulizumab. The bioanalytical methods for PK and free C5 are summarized below.

Pharmacokinetic:

A total of 3 PK methods (BTM-0088, MTD052 and LCMSF 777) were developed and validated to quantitatively measure total ravulizumab (bound and free) in human serum from Phase 1, 2 and 3 clinical studies. Two methods (BTM-0088 and MTD052) employed an ECL method where biotinylated human C5 was used as capture reagent coated on streptavidin (SA) Meso Scale Discovery (MSD) plates, and ruthenium-conjugated murine anti-human IgG4 with MSD® SulfoTag (STAG) was used for detection. One method (LCMSF 777) utilized liquid chromatography with tandem mass spectrometry (LC-MS/MS) technology to quantify ravulizumab and eculizumab in human serum by measuring signature peptides. The LC-MS/MS method was applied in Phase 3 studies to both ravulizumab and eculizumab treatment arms. The assays were validated for precision, accuracy, dilutional linearity, selectivity, matrix interference, and stability.

Parameter	BTM-0088	MTD052	LCMSF 777	
			Ravulizumab	Eculizumab
Method Description	ECL	ECL	Immunoprecipitation and trypsin digestion with mass spectrometry detection	Immunoprecipitation and trypsin digestion with mass spectrometry detection
Lower Limit of Quantitation (LLOQ)	0.378 mcg/mL	0.378 mcg/mL	1.00 µg/mL	5.00 µg/mL
Upper Limit of Quantitation (ULOQ)	450 mcg/mL	450 mcg/mL	500 µg/mL	500 µg/mL
QC Accuracy, % RE, Range	4.4 to 19.6	0.2 to 9.3	-8.67 to 7.58	-1.06 to 12.1
QC Precision, %CV, Range	3.7 to 8.4	9.2 to 14.1	7.82 to 13.8	4.25 to 5.79
2-8°C Stability	Up to 4 hours	Up to 23 hours and 30 minutes	Up to 106 hours	Up to 106 hours
Freeze-thaw Stability (cycles)	Up to 3 cycles at -80 °C ± 10 °C	Up to 5 cycles at -80 °C ± 10 °C	5 cycles frozen at -20°C or -70°C and thawed on ice	5 cycles frozen at -20°C or -70°C and thawed on ice
Ambient room temperature Stability	Up to 4 hours at 25°C	Up to 5 hours and 30 minutes at 25°C	Up to 24 hours	Up to 24 hours
Long term Stability	Up to 9 months at -80 °C ± 10 °C	Up to 93 days at -20 °C ± 5 °C and 528 days at	Up to 234 days at -20°C and 708 days -70 °C	234 days at -20 °C and 708 days at -70

		-80 °C ± 10 °C		°C

(Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, page 7 to 13)

To ensure data comparability from ligand binding and LC-MS-based methods, a cross validation of the ligand binding PK method (MTD052, (b) (4) and LC-MS/MS PK method (LCMSF 777, (b) (4) was performed using QCs, pooled PNH study samples, and over 500 individual PNH study samples. The two analytical methods MTD052 and LCMSF 777 were shown to generate comparable results.

Free C5:

A free C5 method was developed and validated to quantitatively measure changes in serum free C5 levels in human samples from ravulizumab studies. The method relied on a surrogate matrix (C5-depleted serum) for quantitation of clinical samples. The reason for the change from an ECL immunoassay to a Gyros-based fluorescence assay was to improve accuracy, precision, robustness, and throughput of the method. The Gyros assay also utilized less human serum as compared to the ECL method.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

<u>The Applicant's Position:</u>

The ravulizumab clinical pharmacology program has provided robust supportive evidence of effectiveness. Ravulizumab' s comprehensive clinical development program includes 3 safety, tolerability, PK, and PD single-ascending dose (SAD) and multiple-ascending dose (MAD) trials in healthy adult subjects, 2 dose and regimen ranging PK, PD, safety, and efficacy clinical studies in patients with PNH, and 2 confirmatory PK, PD, safety, and efficacy clinical studies in patients with PNH. The clinical pharmacology assessment was integrated throughout the development program to characterize PK/PD attributes of ravulizumab; to understand PK-PD, PK-efficacy and PK-safety relationships; and to select the optimal dose (lowest dose with maximal benefit). The efficacy variables of interest characterize biologically interdependent hierarchical continuum of endpoints starting from engagement of target (measured by serum free C5 concentrations) to clinical benefits (serum LDH concentrations). The clinical pharmacology program identified significant and robust relationships between drug exposure and efficacy variables, demonstrating substantial evidence of proof-of-pharmacology and proof-of-efficacy. The following text describes the assessment of relationships between drug exposure and efficacy variables within the context of dose regimen characterization.

The Phase 3 body weight-based dosing regimen was determined based on modeling and simulation analyses of data at the end of Phase 2. A clinically relevant PK threshold was identified to achieve free C5 concentrations < 0.5 µg/mL and used for the dosing regimen selection, which was supported by the PK-LDH model by ensuring that the proposed Phase 3 dosing regimen would maintain serum drug concentrations above the therapeutic target

concentration in all patients at all times (i.e., lower bound of the 95% PI for C_{trough} for the proposed Phase 3 dose regimen > the therapeutic target concentration) and provide near-maximal LDH-normalization efficacy. This approach of selecting a Phase 3 dosing regimen was agreed upon with the regulatory agencies at the EOP2 meeting and in subsequent correspondence and ensured the selection of the lowest dose that was expected to provide immediate, complete, and sustained terminal complement inhibition in all patients with PNH throughout an 8-week dosing interval maximizing the LDH lowering benefit.

Resulting from the completed EOP2 modeling and simulation analyses, the proposed body weight-based dosing regimen, where the IV loading dose is administered on Day 1, followed by q8w IV administration of the maintenance dose, starting on Day 15, is presented in Table 3. This dosing regimen was administered in two Phase 3 studies (Study ALXN1210-PNH-301 and Study ALXN1210-PNH-302) and was expected to achieve:

- steady-state therapeutic serum concentrations immediately that would be sustained with q8w maintenance dosing throughout the 26-week treatment period and
- immediate, complete, and sustained terminal complement inhibition (free C5 < 0.5 µg/mL) in all patients over the entire treatment maximizing the LDH lowering benefit

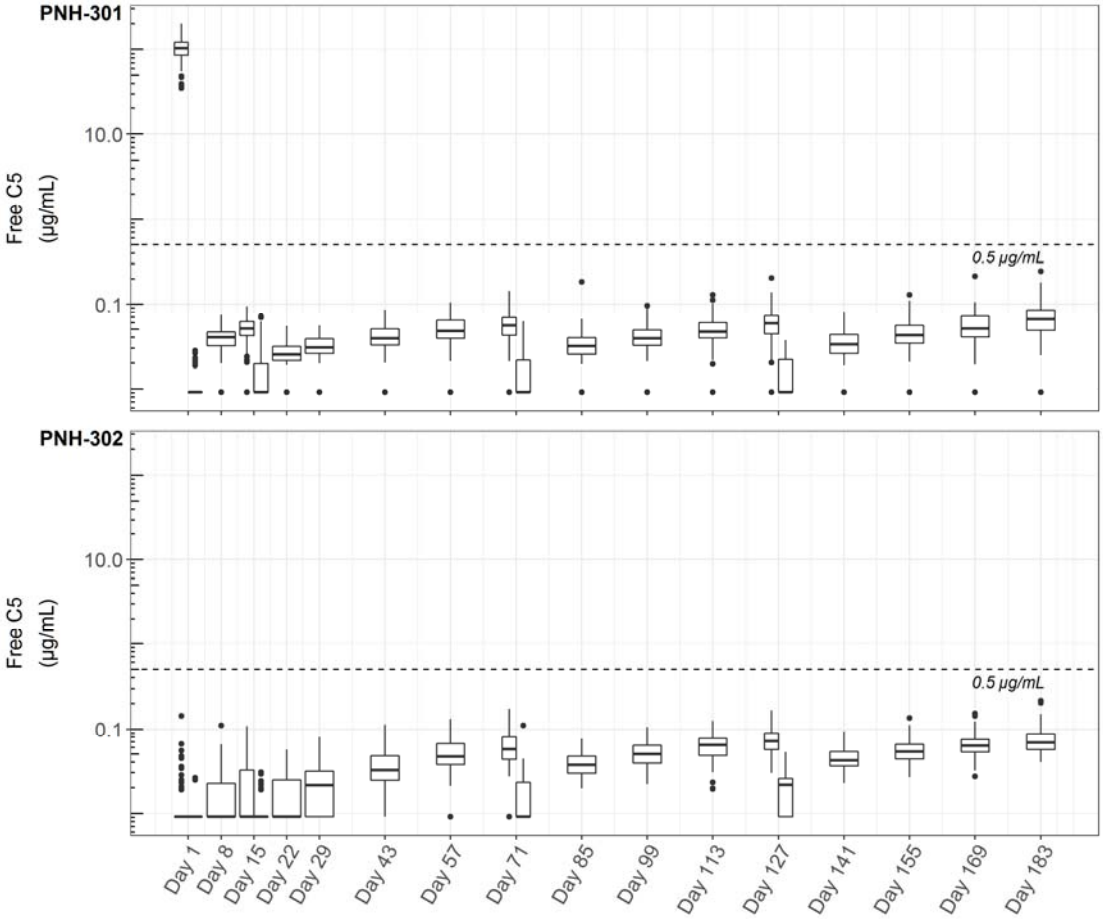
The appropriateness of the Phase 3 dosing regimen was established on the basis of efficacy and safety data generated in Phase 3. The Phase 3 results demonstrated immediate, complete, and sustained terminal complement inhibition in all patients over the entire treatment period, maximizing the LDH lowering benefit. The Phase 3 dosing regimen, which is the proposed labeled dosing regimen, has now been implemented in the Extension Periods of all ongoing studies in patients with PNH. The results of the integrated PK/PD analyses conducted on the pooled data from Phases 1, 2, and 3 are presented below.

PK/PD:

Following the body weight-based loading dose of ravulizumab, steady-state therapeutic serum concentrations were achieved immediately and were sustained with q8w maintenance dosing throughout the 26-week treatment period. In Studies ALXN1210-PNH-301 and ALXN1210-PNH-302, the ravulizumab C_{trough} was consistently maintained above the therapeutic target concentration at all time points in all patients.

Following the body weight-based ravulizumab dosing regimen studied in Phase 3, the serum free C5 versus time profiles were characterized by immediate and complete terminal complement inhibition, as defined by serum free C5 < 0.5 µg/mL, which was sustained throughout the 26-week treatment period in all patients (Figure 3).

Figure 3: Longitudinal Concentration of Free C5 Following Administration of Ravulizumab



Note: Dashed horizontal line represents serum free C5 = 0.5 µg/mL.
Abbreviation: C5 = complement component 5; PNH-301 = Study ALXN1210-PNH-301; PNH-302 = Study ALXN1210-PNH-302
Source: Final Pop-PK-PD Report Figure 7

The PK-free C5 correlation assessment using data from Phase 3 confirmed that the resulting serum drug concentrations from the Phase 3 dosing regimen were at the plateau and provided complete terminal complement inhibition.

<u>Exposure-Response Analyses:</u>

Analysis of exposure-response data was performed on predefined efficacy endpoints, LDH, and BTH.

<u>Analysis of Efficacy Endpoints:</u>

<u>PK-LDH relationship:</u>

The PK-LDH response relationship was modeled using an indirect response PK-PD model using data from patients with PNH from Phase 2 and 3 studies. The indirect response PK-PD model assumes homeostasis of the response variable prior to drug treatment; governed by a

zero-order production and a first-order degradation process for the PD variable, i.e., serum LDH. In the indirect response model, the drug-induced serum LDH lowering effect was modeled by inhibiting production of response. Consistent with its good predictive performance at the end of Phase 2, the PK-LDH model continued to provide adequate description of the Phase 2 and 3 combined data (Table 4).

Table 4: Parameter Estimates for the Final Population PK-LDH Model

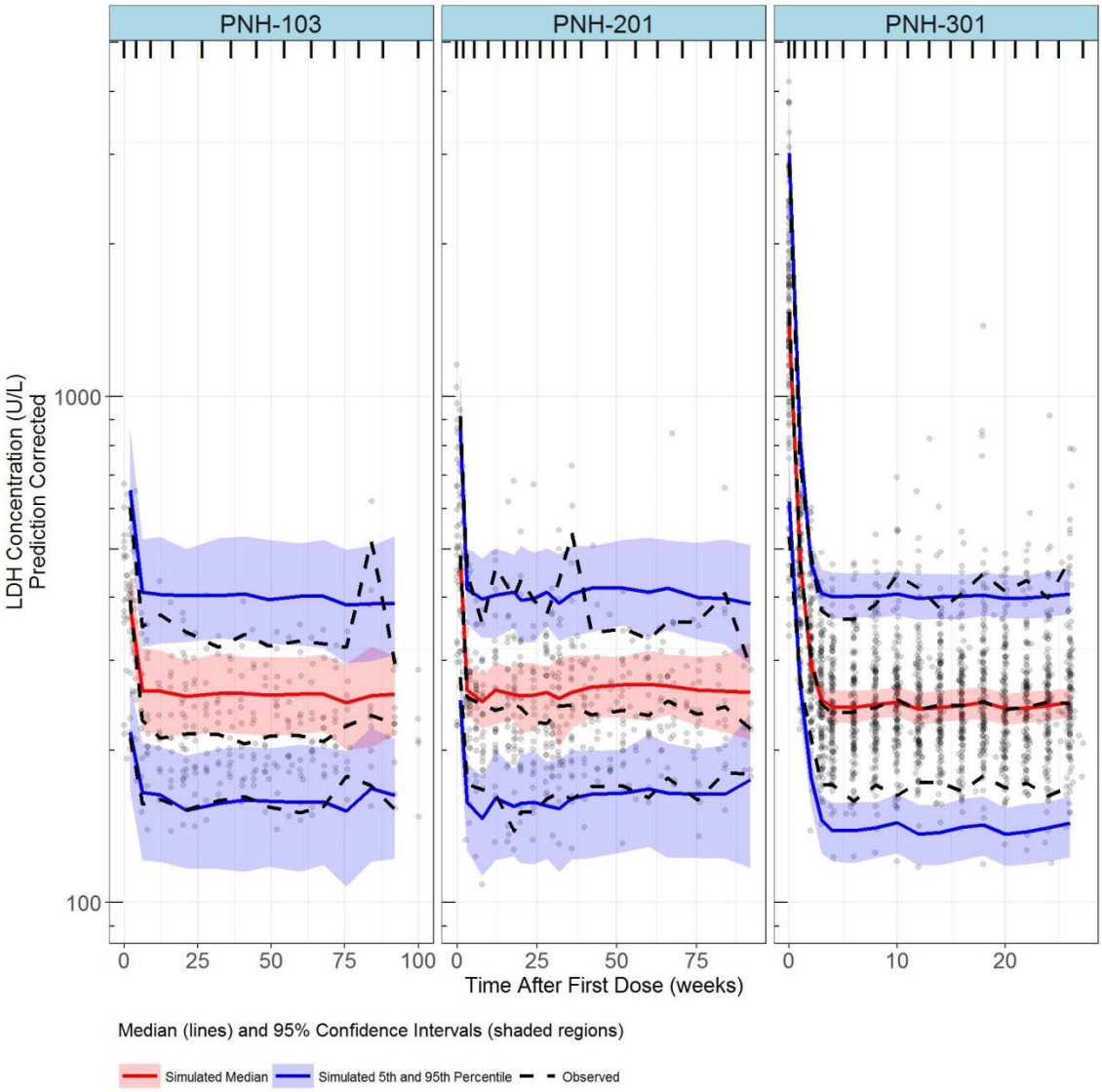
	Typical Values		Between-Subject Variability		
Parameters	**Estimate[a]**	**RSE (%)**	**Estimate**	**RSE (%)**	**Shrinkage (%)**
E_0 (U/L)	1404	3.87	0.447	6.96	6.84
I_{max} (fraction)	0.825	1.16	0.670	7.95	6.63
IC_{50}[b] (µg/mL)	21.0	NA	NA	NA	NA
IC_{95} (µg/mL)	146	13.4	NA	NA	NA
Hill Coefficient	1.52	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.
[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; PK = pharmacokinetic; RSE = relative standard error
Source: Final Pop-PK-PD Report Table 16

For the VPC, observed median, 5th and 95th percentiles of LDH measurements were contained within the model-predicted ranges (shaded areas) in Study ALXN1210-PNH-103, Study ALXN1210-PNH-201, and Study ALXN1210-PNH-301 (Figure 4).

Reference ID: 4366451

Figure 4: Final Population PK LDH Model of Ravulizumab: Prediction Corrected Visual Predictive Check for Induction/Loading and Maintenance Doses



Note: Prediction-corrected VPC figures retain the visual interpretation of traditional VPC figures while addressing the variability introduced with changes in independent variables (to address different dose cohorts used in Studies ALXN-PNH-103 and ALXN1210-PNH-201).
Initial dosing was referred to as induction dosing in Studies ALXN1210-PNH-103 and ALXN1210-PNH-201 and as loading dose in Study ALXN1210-PNH-301.
Abbreviations: LDH = lactate dehydrogenase; PK = pharmacokinetic; VPC = visual predictive check
Source: Final Pop-PK-PD Report Figure 11

PK-LDH Modeling Summary

- The IC_{95} (concentration to achieve 95% maximal effect) is 146 µg/mL, very close to the therapeutic target concentration (Table 4).

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- At the therapeutic target ravulizumab trough concentration, the expected LDH lowering effect is about 96% of maximal effect.
- Because more than 97.5% of the serum trough concentrations in Phase 3 studies are greater than the therapeutic target concentration, the maximal LDH lowering effect has been achieved using the Phase 3 dosing regimen.
- The Phase 3 dose regimen was selected with the aid of M&S at the EOP2, such that it would maintain serum drug concentrations optimally above the therapeutic target concentration. These results from the two Phase 3 studies confirm that the dose regimen studied in Phase 3 is the lowest dose with maximal benefit.

Correlation of Serum Free C5 to Breakthrough Hemolysis

One of the objectives of the ravulizumab clinical development program was to improve on the magnitude and consistency of terminal complement inhibition over the standard-of-care (SOC), eculizumab.

The comparison of serum free C5 concentrations over time between ravulizumab and eculizumab (Figure 5 for Study ALXN1210-PNH-301 and Figure 6 for Study ALXN1210-PNH-302) demonstrated the improvement of the magnitude and consistency of terminal complement inhibition by ravulizumab treatment; i.e., serum free C5 concentrations < 0.5 µg/mL have been achieved for all post dose measurements in all patients treated with ravulizumab, while multiple excursions of serum free C5 concentrations ≥ 0.5 µg/mL have been observed in some patients following SOC. Such an improvement in terminal complement inhibition by ravulizumab treatment over SOC has translated into a meaningful improvement in clinical benefit, i.e., consistent with sustained reduction in free C5, fewer BTH events occurred in patients with all serum free C5 concentrations < 0.5 µg/mL (Table 5).

- In both studies and across both treatment groups, the percentage of patients with all post baseline serum free C5 concentrations < 0.5 µg/mL who had at least 1 BTH event ranged from 0% to 6.6 %. The percentage of eculizumab-treated patients with at least 1 post baseline serum free C5 concentration ≥ 0.5 µg/mL who had at least 1 BTH event was 40% and 28.6% in Studies ALXN1210-PNH-301 and ALXN1210-PNH-302, respectively. There were no patients in the ravulizumab group in either study with free C5 excursions > 0.5 µg/mL.
- Combining data across treatment arms, these data illustrate that in patients with any excursions of serum free C5 concentrations ≥ 0.5 µg/mL, the risk of BTH increases by approximately 8-fold and 18-fold in complement inhibitor-naïve and in eculizumab-experienced patients with PNH, respectively, as compared with patients with no serum free C5 excursions ≥ 0.5 µg/mL.
- Across both studies, 81% (22 of 27) of BTH events occurred in eculizumab-treated patients (15 of 20 in Study ALXN1210-PNH-301 and 7 of 7 in Study ALXN1210-PNH-302) versus 19% (5 of 27) in ravulizumab-treated patients.

Ravulizumab improves free C5 control, reducing the overall risk of BTH by eliminating the risk of free C5 associated BTH.

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Table 5: Correlation Between Serum Free C5 Concentration and Patients With Breakthrough Hemolysis Events (Studies ALXN1210-PNH-301 and ALXN1210-PNH-302)

Study	Treatment	Number of Patients With BTH	% of Patients With All Free C5 < 0.5 µg/mL Experiencing BTH Events	% of Patient With Any Free C5 ≥ 0.5 µg/mL Experiencing BTH Events	Relative Risk[a]
ALXN1210-PNH-301	Ravulizumab (N = 125)	5	4 (5/125)	NA	
	Eculizumab (N = 121)	13	6.6 (7/106)	40 (6[b]/15[b])	
	Combined (N = 246)	18	5.2 (12/231)	40 (6/15)	7.7
ALXN1210-PNH-302	Ravulizumab (N = 97)	0	0 (0/97)	NA	
	Eculizumab (N = 98)	5	3.3 (3/91)	28.6 (2/7)	
	Combined (N = 195)	5	1.6 (3/188)	28.6 (2/7)	17.9

[a] Relative risk is calculated as the ratio of percentage of patients with any free C5 ≥ 0.5 µg/mL experiencing BTH over the ratio of percentage of patients with any free C5 < 0.5 µg/mL experiencing BTH.
[b] Excluded biologically implausible Day 1 EOI free C5 data: 3 patients from the ravulizumab group, 4 patients from the eculizumab group.
Abbreviations: BTH = breakthrough hemolysis; C5 = complement component 5; EOI = end of infusion; PNH = paroxysmal nocturnal hemoglobinuria; NA = not applicable as no ravulizumab patients experienced serum free C5 ≥ 0.5 µg/mL.
Source: Generated from Study ALXN1210-PNH-301 ADaM adlb and adfa datasets and Study ALXN1210-PNH-302 ADaM adlb and adfa datasets

Exposure-Response Conclusion

The PK-PD/LDH relationships were not influenced by intrinsic or extrinsic factors (race, sex, study, baseline age, baseline body weight, baseline BMI, baseline creatinine, baseline creatinine clearance, baseline eGFR, baseline AST, baseline ALP, baseline albumin, and baseline bilirubin).

In summary, the PK, PD and efficacy data collected during Phases 1 to 3 demonstrated significant and robust relationships between drug exposure and efficacy variables (PD: serum free C5 concentration, efficacy: serum LDH concentration, and clinical outcomes in PNH: BTH) demonstrating substantial evidence of proof-of-pharmacology and proof-of-efficacy. Therefore, the Clinical Development Program (CDP) and the Clinical Pharmacology data package have provided a strong evidence of ravulizumab effectiveness.

The FDA's Assessment:
FDA agrees with the Applicant's exposure-response analyses for efficacy (LDH levels) and pharmacodynamics (free C5 concentrations) to provide supportive evidence of effectiveness. There were no exposure-response relationships for safety. While the FDA agrees on the effect of ravulizumab and eculizumab on the free C5 concentrations, however the FDA considers this side-by-side comparison as qualitative (b) (4)

Reference ID: 4366451

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

The proposed dosing regimen is appropriate for the PNH patient population. The key rationale of establishing the ravulizumab dosing regimen in patients with PNH was as follows:

The PD endpoint serum free C5 concentration and the efficacy endpoint LDH measure the effectiveness of ravulizumab in patients with PNH at engagement of the target and the downstream clinical effect, respectively. Pharmacokinetic exposure versus PD and LDH endpoint relationships represent a biologically interdependent hierarchical continuum of endpoints starting from engagement of target to the downstream clinical benefits. These relationships provided a strong justification of clinical relevance for the threshold serum ravulizumab concentration identified. The optimal Phase 3 dosing regimen was identified at the EOP2 and characterized by conducting Pop-PK model-based simulations to target the clinically relevant threshold serum ravulizumab concentration in all patients with PNH to provide immediate, complete, and sustained terminal complement inhibition.

The selection of this Phase 3 dosing regimen was based on the principle of identifying the lowest dose with the maximum benefit across the patient population. The appropriateness of the ravulizumab Phase 3 dosing regimen was confirmed on the basis of the Phase 3 risk-benefit profile (safety and efficacy data); along with the demonstration of immediate, complete, and sustained terminal complement inhibition over the entire dosing interval and treatment period across all patients.

The Clinical Pharmacology module has provided a summary of the population PK-PD/LDH analyses used for Phase 3 dose characterization at EOP2, which was agreed with the FDA. The final PK/PD/LDH analyses conducted using all evaluable data from Phases 1, 2 and 3, have been provided in the Clinical Pharmacology module and had the following objectives:

- To quantitatively characterize the population PK of ravulizumab for patients with PNH and assess the impact of important covariates on PK.
- To explore the exposure-response (PK/PD) relationships for the inhibition of free C5.
- To quantitatively characterize the population exposure-response relationship and time course of the PK/PD relationship for LDH.
- To explore the exposure-response relationships across the ravulizumab treatment populations, for the safety endpoints (treatment-emergent adverse events) observed in Phase 3 studies.
- To integrate the PK and exposure response relationships to support the benefit-risk of ravulizumab as assessed by safety/efficacy data in Phase 3 and potential dose adjustment based on any identified influential intrinsic or extrinsic factors (covariates).

The Phase 3 dosing regimen selected based on the population-PK-PD analyses at the EOP2 and agreed upon with the FDA is presented in Table 3.

Reference ID: 4366451

Following the body weight-based ravulizumab dosing regimen studied in both Phase 3 studies, the serum free C5 versus time profiles were characterized by immediate and complete terminal complement inhibition, as defined by serum free C5 < 0.5 µg/mL, which was sustained throughout the 26-week treatment period in all patients.

The data following the ravulizumab body weight-based dosing regimen studied in Phase 3 showed the following:

- C_{trough} was optimally maintained above the target therapeutic PK threshold at essentially all time points in all patients. Serum free C5 versus time profiles were characterized by immediate and complete terminal complement inhibition, as defined by serum free C5 < 0.5 µg/mL, which was sustained throughout the 26-week treatment period in all patients (Figure 5 and Figure 6).
  - In patients with PNH with any excursions of serum free C5 concentrations ≥ 0.5 µg/mL, the risk of BTH increases by approximately 8-fold and 18-fold in complement inhibitor-naïve and in eculizumab-experienced patients with PNH, respectively, as compared with patients with no serum free C5 excursions ≥ 0.5 µg/mL (Section 6.3.2.1 and Table 5). Ravulizumab improves free C5 control relative to eculizumab (Figure 5 and Figure 6), reducing the overall risk of BTH by eliminating the risk of free C5-associated BTH.
- C_{trough} was maintained above the IC_{95} concentration characterized in the exposure-response (PK-LDH) relationship at all time points in all patients, demonstrating that the studied Phase 3 dosing regimen maximizes the LDH lowering benefit. See Section 6.3.2.1 for further information regarding population exposure-response relationship for efficacy (serum LDH concentration).
- No trends were observed between ravulizumab exposure and safety endpoints of interest.

Therefore, the objective of lowest dose with maximal LDH lowering benefit has been achieved at the studied Phase 3 dosing regimen.

In summary, based on the totality of PK, PD, ADA, efficacy, and safety data obtained from the ravulizumab development program, the current body weight-based dosing regimen for adult patients with PNH is well supported by quantitative model-based analyses of exposure-response relationships, which further confirmed that ravulizumab dose adjustments are unnecessary in special populations to maintain a favorable benefit-risk in adult patients with PNH, in both the naïve and switch populations.

The FDA's Assessment:
FDA agrees that the Applicant's proposed dosing regimen is appropriate for the indicated patient population based on analysis conducted and is supported by the results from Studies ALXN1210-PNH-301 and ALXN1210-PNH-302 that assessed the safety and efficacy of ravulizumab and exposure-response analyses.

Reference ID: 4366451

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

An alternative ravulizumab dosing regimen and/or management strategy is not required for subpopulations based on intrinsic factors. Of the covariates tested (age; body weight; body mass index; disease-specific covariates of healthy adult subjects vs patients with PNH, baseline LDH, baseline serum free C5, baseline total C5, hematocrit, hemoglobin, albumin, bilirubin, eGFR, creatinine clearance, and liver enzymes [AST, ALT, and alkaline phosphatase]; sex; race; and immunogenicity), only body weight had any impact on ravulizumab exposure. The recommended dosing regimen is body weight adjusted to ensure similar ravulizumab exposures across the weight range in patients with PNH. The available clinical data in patients with PNH demonstrated that ravulizumab has a wide therapeutic window.

The FDA's Assessment:

FDA agrees with the Applicant's position on no alternative ravulizumab dosing regimen or management strategy based on intrinsic factors. The effect of severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2, estimated by MDRD) on ravulizumab PK is unknown.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

An alternative dosing regimen and/or management strategy is not required for subpopulations based on extrinsic factors. None of the investigated concomitant medication classes or formulation factors (Process A vs Process B) had any clinically meaningful impact on ravulizumab parameter estimates.

Potential for Drug Interactions:

Because ravulizumab is a monoclonal antibody, clinically meaningful drug-drug PK interactions with small molecule drugs or other biologics are generally not expected (In Vitro Metabolism and Transporter Mediated Drug-Drug Interaction Studies; FDA Draft Guidance, 2017). The clearance pathways of therapeutic proteins differ from those of small molecules. The latter are usually metabolized by oxidation via cytochrome P450s and/or conjugation (EMEA Guideline on the Investigation of Drug Interactions, 2013). In addition, ravulizumab does not bind to a cytokine and the available safety data (177 patient-years) have not shown a drug-induced cytokine modulation, indicating that the potential of drug-related cytokine based drug interaction is negligible. This is consistent with clinical and post-marketing eculizumab experience.

The base Pop-PK model was used to evaluate the effects of concomitantly administered drugs on ravulizumab PK. The impact of concomitant medications from assorted drug classes (anabolic agents for systemic use, antithrombotic agents, antianemic preparations, antihypertensives, corticosteroids for systemic use, antibacterials for systemic use, antimycolitics for systemic use, and immunosuppressants) on subject-level variability

parameters of ravulizumab were assessed. The assessment showed that the studied concomitant drugs do not impact ravulizumab PK.

The FDA's Assessment:

FDA agrees that there are no clinically relevant food-drug or drug-drug interactions for ravulizumab.

X X

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X X

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:

Table 6 lists the clinical studies used in the BLA submission and the sources of the safety and efficacy populations in the application. The primary evidence to support clinical efficacy of ravulizumab in patients with PNH is from 2 separate Phase 3 studies (ALXN1210-PNH-301 and ALXN1210-PNH-302).

The primary data used to characterize the safety profile safety of ravulizumab in patients with PNH is derived from 4 clinical studies with a total of 480 patients with PNH who were enrolled and treated, 261 of whom received ravulizumab.

Reference ID: 4366451

Reference ID: 4366451

Table 6: Listing of Clinical Studies Relevant to this BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients planned/ analyzed	Study Population
Controlled Studies to Support Efficacy and Safety							
ALXN1210-PNH-301	NCT 02946463	Phase 3, randomized (1:1), open-label, multicenter, active-controlled, non-inferiority study in patients with PNH who were naïve to complement inhibitor treatment	**Primary Evaluation Period:** Ravulizumab IV weight-based loading[a] dose on Day 1 and maintenance[b] dose on Day 15 and q8w Eculizumab IV 600 mg q1w for 4 doses, then 900 mg q2w	Coprimary Efficacy: • Transfusion avoidance • Hemolysis as directly measured by LDH-N Key Secondary Efficacy: • Percentage change in LDH • Change in QoL assessed via the FACIT-Fatigue Scale • Proportion of patients with breakthrough hemolysis • Proportion of patients with stabilized hemoglobin PK/PD Safety	26-week Primary Evaluation Period followed by extension period of up to 2 years	214/246 Ravulizumab 107/125 Eculizumab 107/121	Adult patients with PNH who were naïve to complement inhibitor treatment
		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					
ALXN1210-PNH-302	NCT 03056040	Phase 3, randomized (1:1), open-label, multicenter, active-controlled, non-inferiority study in patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months	**Primary Evaluation Period:** Ravulizumab IV weight-based loading[a] dose on Day 1 and maintenance[b] dose on Day 15 and q8w thereafter Eculizumab IV 900 mg q2w	Primary Efficacy: • Hemolysis as directly measured by percent change in LDH Key Secondary Efficacy: • Proportion of patients with breakthrough hemolysis • Change in QoL assessed via the FACIT-Fatigue Scale • Transfusion avoidance • Proportion of patients with stabilized hemoglobin PK/PD Safety	26-week Primary Evaluation Period followed by extension period of up to 2 years	192/195 Ravulizumab 96/97 Eculizumab 96/98	Adult patients with PNH who had been previously treated with eculizumab
		49 sites in 11 countries: Australia, Canada, France, Germany, Italy, Japan, Netherlands, Republic of Korea, Spain, United Kingdom, and United States					

Reference ID: 4366451

Table 6: Listing of Clinical Studies Relevant to this BLA (Continued)

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
ALXN1210-PNH-103	NCT 02598583	Phase 1b, open-label, uncontrolled, multiple-dose, multicenter, intra- and interpatient dose escalation in sequential cohorts of patients with PNH who were naïve to complement inhibitor treatment	**Primary Evaluation Period:** Ravulizumab IV *Cohort 1a*: 400 mg on Day 1 and Day 8, 600 mg on Day 15, 900 mg on Day 29 and q4w *Cohort 1b*: 600 mg on Day 1 and Day 15, 900 mg on Day 29 and q4w *Cohort 2*: 600 mg on Day 1, 900 mg on Day 15, 1800 mg on Day 29 and q4w	Primary Efficacy: • Change in LDH levels Secondary Efficacy • Changes in hemolysis-related hematologic parameters: free hemoglobin, haptoglobin, reticulocyte count, PNH red blood cell clone, and D-dimer • Changes in clinical manifestations of PNH PK/PD Immunogenicity Safety	169-day Primary Evaluation Period followed by extension period of up to 3 years	12/13 Ravulizumab *Cohort 1a*: 2/2 *Cohort 1b*: 4/4 *Cohort 2*: 6/7	Adult patients with PNH
		10 centers in 2 countries: Australia and Republic of Korea					
ALXN1210-PNH-201	NCT 02605993	Phase 2, open-label, uncontrolled, multicenter, multiple ascending dose study in sequential cohorts of patients with PNH who were naïve to complement inhibitor treatment	**Primary Evaluation Period:** Ravulizumab IV *Cohort 1:* 1400 mg on Day 1, 1000 mg on Day 15 and Day 29 and q4w *Cohort 2:* 2000 mg on Day 1, 1600 mg on Day 22 and Day 43 and q6w *Cohort 3:* 1600 mg on Day 1 and Day 15, 2400 mg on Day 29 and q8w *Cohort 4:* 3000 mg on Day 1, 5400 mg on Day 29 and q12w	Primary Efficacy • Change in LDH levels Secondary Efficacy • Changes in hemolysis-related hematologic parameters: free hemoglobin, haptoglobin, reticulocyte count, PNH red blood cell clone, and D-dimer • Changes in clinical manifestations of PNH Immunogenicity PK/PD Safety	253-day (Cohorts 1-3) or 281-day (Cohort 4) Primary Evaluation Period followed by extension period of up to 3 years	26/26 Ravulizumab *Cohort 1*: 6 *Cohort 2*: 6 *Cohort 3*: 7 *Cohort 4*: 7	Male and female patients ≥ 18 years of age with PNH confirmed by documented high-sensitivity flow cytometry, who were required to have mean LDH value ≥ 3 × ULN
		15 centers in 7 countries: Canada, France, Germany, South Korea, Spain, Taiwan, and United Kingdom					

Reference ID: 4366451

Table 6: Listing of Clinical Studies Relevant to this BLA (Continued)

Abbreviations: FACIT = Functional Assessment of Chronic Illness Therapy; IV = intravenous; LDH = lactate dehydrogenase; LDH-N = normalization of LDH levels; NCT = National Clinical Trial; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria; qXw = once every X week(s); QoL = quality of life; ULN = upper limit of normal

[a] Ravulizumab loading dose: 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 mg for patients weighing ≥ 100 kg

[b] Ravulizumab maintenance dose: 3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 10

The FDA's Assessment:

FDA agrees with the summary of ALXN1210-PNH-301 and ALXN1210-PNH-302 study designs as displayed in Table 6.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The FDA's Position:

The efficacy of ravulizumab (ALXN1210) in patients with PNH was assessed in two open-label, randomized, active-controlled, non-inferiority phase 3 studies: ALXN1210-PNH-301 and ALXN1210-PNH-302, thereafter refer to as 301 and 302, respectively. Study 301 enrolled patients with PNH who were complement inhibitor naïve and had active hemolysis. Study 302 enrolled patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months.

Data sources include Clinical Study Report (CSR), protocol and amendments, SAP and amendments, data sets, literature referenced, as well as electronic data sets and SAS programs under original submission date 06/18/2018 are shown in the following link: \\CDSESUB1\evsprod\BLA761108\0001

During the review process, we sent an information request (IR) to the sponsor to request simple readable programs without calling too many macros in order to verify the primary and secondary efficacy results. Sponsor's responses to our IRs are located at:

\\CDSESUB1\evsprod\BLA761108\0005,
under submission date 07/19/2018 and

\\CDSESUB1\evsprod\BLA761108\0008,
under submission date 08/03/2018.

8.1.1. ALXN1210-PNH-301

The Applicant's Position:

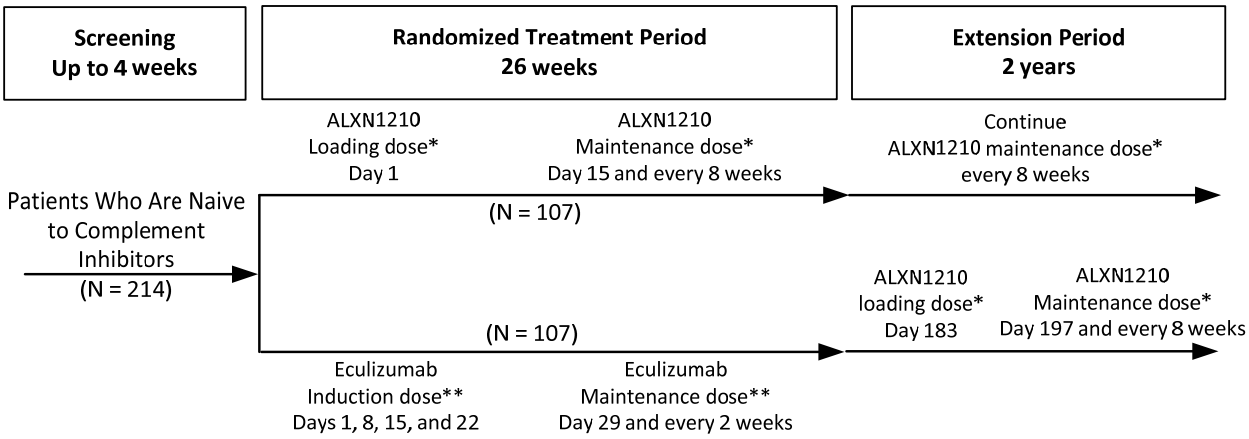
Trial Design

The ravulizumab clinical development program was designed to assess whether ravulizumab retains the efficacy and safety of eculizumab with a less frequent (q8w versus q2w) dosing regimen and a reduced risk of breakthrough hemolysis associated with inadequate C5 inhibition in patients with PNH.

Study ALXN1210-PNH-301 is a Phase 3, open-label, randomized, active-controlled, multicenter global study to evaluate the safety and efficacy of ravulizumab versus eculizumab administered by IV infusion to adult patients with PNH who were naïve to complement inhibitor treatment. The study population selected represented patients likely to receive ravulizumab in clinical practice following initial diagnosis of PNH. This study consists of a 4-week Screening Period, a 26-week Randomized Treatment Period, and an Extension Period of up to 2 years. Data through the end of the 26-week Randomized Treatment Period, referred to as the Primary Evaluation Period, form the basis for submission. A study schematic for ALXN1210-PNH-301 is presented in Figure 7.

Reference ID: 4366451

Figure 7: Study Schematic for ALXN1210-PNH-301



* ALXN1210 dosage: loading dose = 2400 mg for patients weighing ≥ 40 to < 60 kg, 2700 mg for patients weighing ≥ 60 to < 100 kg, 3000 for patients weighing ≥ 100 kg; maintenance dose = 3000 mg for patients weighing ≥ 40 to < 60 kg, 3300 mg for patients weighing ≥ 60 to < 100 kg, 3600 mg for patients weighing ≥ 100 kg

** Eculizumab dosage: induction dose = 600 mg; maintenance dose = 900 mg

Source: ALXN1210-PNH-301 CSR, Figure 1

Patients were randomly assigned using an interactive voice- or web-response response system (IxRS was used to generate subject randomization list) to treatment with ravulizumab or eculizumab. Randomization was stratified by:

- transfusion history (0, 1 to 14, or > 14 units of packed red blood cells [pRBCs] in the 1 year prior to first dose of study drug)
- screening lactate dehydrogenase (LDH) levels (1.5 to < 3 × upper limit of normal [ULN] or ≥ 3 × ULN)

The patients within each of the 6 stratification groups were then randomly assigned in a 1:1 ratio, using permuted block randomization procedure with a fixed block size, to receive ravulizumab or eculizumab. Enrollment of patients without a history of transfusion in the prior year was capped at 20%. The randomization codes and treatments assigned are provided in ALX1210-PNH-301, Appendix 16.1.7.

Patients randomly assigned to the ravulizumab treatment group received a loading dose of ravulizumab on Day 1, followed by maintenance doses of ravulizumab on Day 15 and every 8 weeks (q8w) thereafter for a total of 26 weeks. Loading and maintenance doses were based on body weight (Table 7). Patients randomly assigned to the eculizumab treatment group received an induction dose of 600 mg of eculizumab on Days 1, 8, 15, and 22, followed by a maintenance dose of 900 mg of eculizumab on Day 29 and every 2 weeks (q2w) thereafter for a total of 26 weeks of treatment. All doses for both treatments were administered as IV infusions. The weight-based dosages of ravulizumab administered in this study were premised on PK/PD

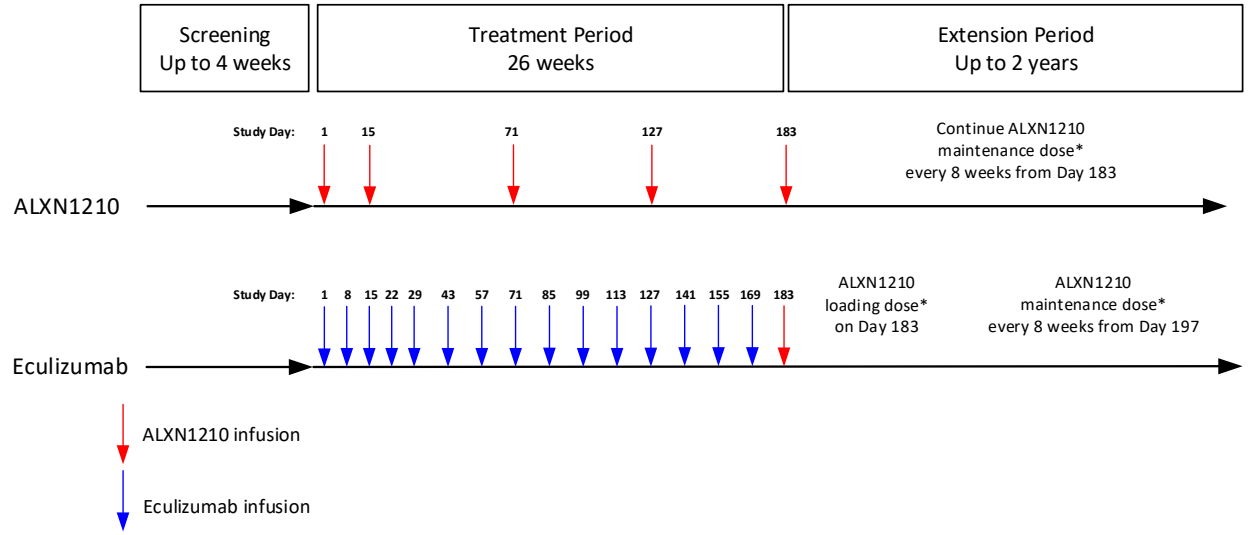
data from early development studies in healthy adult volunteers as well as the available data from patients with PNH in the ongoing Phase 1b dose finding study (ALXN1210-PNH-103) and the ongoing Phase 2 study (ALXN1210-PNH-201). The selection of ravulizumab dose regimen was based on targeting immediate, complete, and sustained inhibition of terminal complement in patients with PNH over an 8-week dose interval. Eculizumab is the only approved treatment for PNH that blocks terminal complement activity and was therefore selected as the active comparator in this study.

Table 7: Ravulizumab Dosages for the Randomized Treatment Period

Body Weight	Ravulizumab Loading Dose (Day 1)	Ravulizumab 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

The primary objective of this study was to assess the non-inferiority of ravulizumab compared to eculizumab in adult patients with PNH who were naïve to treatment with a complement inhibitor. The comparator, eculizumab, the only approved treatment for PNH, has been shown to be superior to placebo (Soliris USPI). Given that this was an active-controlled study of 2 treatments with different dosing regimens, the open-label design facilitated proper dosing of patients in each treatment group and minimized the number of study drug infusions any given patient was required to receive (Figure 8).

Figure 8: Study ALXN1210-PNH-301 Dosing Schematic



Source: ALXN1210-PNH-301 CSR, Figure 2

Eligibility Criteria

Study entry criteria were carefully selected to reflect an adult patient population consistent with the population likely to be treated with ravulizumab in clinical practice.

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Inclusion/exclusion criteria were aligned with those of the historical eculizumab studies that established the efficacy of eculizumab relative to placebo and supported regulatory approval (Brodsky, 2008; Hillmen, 2006). Key inclusion/exclusion criteria for Study ALXN1210-PNH-301 in complement inhibitor-naïve patients are summarized below:

- ≥ 18 years of age
- Documented diagnosis of PNH confirmed by high-sensitivity flow cytometry
- Presence of 1 or more PNH-related signs or symptoms within 3 months of screening
- LDH value ≥ 1.5 × ULN at screening
- No current or previous treatment with a complement inhibitor
- To reduce the risk of meningococcal infection, all patients must have been vaccinated against *Neisseria meningitides.* All patients were required to have been vaccinated against meningococcal infection 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

Patients were not permitted to use complement inhibitors other than the assigned study treatment. An independent Data Monitoring Committee was in place to monitor for meningococcal infection cases.

A schedule of events is provided in Table 8.

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Table 8: Study ALXN1210-PNH-301 Schedule of Events – Primary Evaluation Period

Period	**Screening**	**Primary Evaluation Period**															
Study Day	**–28 to –1**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183 or ET**
Window, days	**NA**		**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
Informed consent	X																
Confirmation or administration of meningococcal vaccination[a]	X	X															
Medical history and demographics	X																
HIV testing	X																
PNH clone size[b]	X	X							X								X
Height	X																
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[c]	X	X		X					X				X				X
Record transfusions and transfusion parameters[d]	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PNH symptomatology[f,g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FACIT-Fatigue[g]	X	X	X			X			X				X				X
EORTC QLQ-C30[g]	X	X	X			X			X				X				X
Physical examination	X																
Abbreviated physical examination[h]		X							X								X
Vital signs[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety 12-lead ECG[j]	X							X									X
Chemistry including LDH[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology including free hemoglobin and coagulation[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis and urine chemistry[k]	X	X		X		X			X				X				X
PK/PD sampling		X[l]	X[m]	X[l]	X[m]	X[m]	X[m]	X[m]	X[l]	X[m]	X[m]	X[m]	X[l]	X[m]	X[m]	X[m]	X[l]
Immunogenicity (ADA)[n]		X							X				X				X
Review safety card		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Breakthrough hemolysis[o]		←Monitor continuously→															

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Table 8: Study ALXN1210-PNH-301 Schedule of Events – Primary Evaluation Period (Continued)

Period:	**Screening**	**Randomized Treatment Period**															
Study Day:	**–28 to –1**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183 or ET**
Window, days:	**N/A**		**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**
Concomitant medications	X	←Monitor continuously→															
Adverse events	X	←Monitor continuously→															
Randomization[p]		X															
Ravulizumab administration[q]		X		X					X				X				--[r]
Eculizumab administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[a] All patients had been vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug treatment. Patients who initiated study drug treatment less than 2 weeks after receiving a meningococcal vaccine received treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination.

[b] White blood cell (granulocyte and monocyte) and RBC clone size were measured by high-sensitivity flow cytometry at the Screening and on Day 1 Visits; RBC clone size only was measured on Day 71 and Day 183.

[c] Female patients of childbearing potential only had a serum pregnancy test at the Screening and Day 183 Visits and a urine pregnancy test at all other required time points. A negative urine test result was required prior to administering ravulizumab or eculizumab to female patients of childbearing potential at the indicated visits.

[d] Transfusions given during and between visits were recorded.

[e] Prior to randomization and within 5 days prior to study drug administration on Day 1, each patient's hemoglobin was evaluated by either the central or local laboratory. If at that time the patient's hemoglobin value met protocol-specified transfusion guidelines, the patient was transfused with pRBCs to a hemoglobin level above the protocol-specified transfusion threshold in order to be eligible for randomization. The patient's post-transfusion hemoglobin value was confirmed by central or local laboratory to be above the protocol-specified transfusion threshold.

[f] Investigator or designee assessed the following events: fatigue, hemoglobinuria, abdominal pain, dyspnea, dysphagia, chest pain, and erectile dysfunction.

[g] Physician- and patient-reported assessments were performed prior to study drug administration.

[h] Abbreviated physical examination consisted of a body system relevant examination based upon Investigator (or qualified designee) judgment and patient symptoms. At least 1 body system was checked for an abbreviated physical examination.

[i] Vital sign measurements were taken after the patient had been resting for at least 5 minutes and include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. On dosing days, vital signs were taken before study drug administration.

[j] Single 12-lead ECG was collected at screening and predose on Day 57 and Day 183. Patients were supine for approximately 5 to 10 minutes before ECG collection and were to remain supine, but awake, during ECG collection.

[k] Clinical laboratory measurements were collected predose on dosing days and not from a heparinized line. Follicle stimulating hormone levels were measured in female patients only during screening only in order to confirm postmenopausal status.

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Table 8: Study ALXN1210-PNH-301 Schedule of Events – Primary Evaluation Period (Continued)

[l] Serum samples for PK/PD analyses were collected predose (within 0.5 hours prior to the start of infusion) and at end-of-infusion (within 0.5 hours after the end of infusion). The predose PK/PD sample was drawn through the venous access created for the dose infusion, prior to administration of the dose. End-of-infusion PK/PD samples were drawn from the patient's opposite, noninfused arm. Note that the Day 183 end-of-infusion sample was considered an Extension Period assessment. All collection times were recorded in the eCRF. In the event of BTH, a serum sample for PK/PD analysis was collected.

[m] Serum samples for PK/PD analyses were collected predose (within 0.5 hours prior to the start of infusion) for eculizumab-treated patients and at any time for ALXN1210-treated patients. All collection times were recorded in the eCRF. In the event of BTH, a serum sample for PK/PD analysis was collected.

[n] Samples for ADA were collected predose or at any time when a dose of study drug was not administered.

[o] If a suspected event of BTH occurred, LDH, PK, and PD parameters were analyzed at the central laboratory. If the suspected event of BTH did not occur at a scheduled visit, an unscheduled visit should have occurred for evaluation of the patient and collection of the required LDH, PK, and PD parameters.

[p] Patients were randomly assigned to treatment based on screening LDH result and history of blood transfusions through an IxRS.

[q] The dose of ALXN1210 was based on the patient's last recorded study visit body weight.

[r] The primary efficacy endpoint assessment was before dosing on Day 183. Dosing on Day 183 was the start of the Extension Period.

Abbreviations: ADA = antidrug antibody; eCRF = electronic case report form; ECG = electrocardiogram; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30 Scale; ET = early termination; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; HIV = human immunodeficiency virus; IxRS = interactive voice- or web-response system; LDH = lactate dehydrogenase; NA = not applicable; PD = pharmacodynamics; PK = pharmacokinetics; PNH = paroxysmal nocturnal hemoglobinuria; pRBC = packed red blood cell; RBC = red blood cell

Source: ALXN1210-PNH-301 Table 6

Study Endpoints

The efficacy endpoints in the ravulizumab studies were chosen to represent the continuum of inter-related endpoints that reflect the pathophysiology of PNH and collectively assess the multiple clinically important disease parameters relevant to the functional well-being of patients with PNH. The endpoint continuum begins with the biochemical effect (reduction in free C5) to downstream hemolytic parameters (LDH and cRBC hemolysis), which are central to all aspects of the pathophysiology of PNH. Evaluation of critical clinical outcomes (transfusions, BTH, hemoglobin stabilization, PNH symptoms, major adverse vascular event [MAVEs]), and related quality of life measures (FACIT-Fatigue, EORTC-QLQ-C30) follows.

The breakthrough hemolysis endpoint assessed cases of return of complement-mediated hemolysis in patients with PNH who are being treated with a complement inhibitor. Breakthrough hemolysis is recognized in the literature as a phenomenon of loss of disease control in eculizumab-treated patients and is characterized by laboratory evidence of intravascular hemolysis (increased LDH) as well as signs and symptoms of intravascular hemolysis (de Latour, 2015; Hillmen, 2013; Nakayama, 2016).

See Section 3, Regulatory Background.

<u>Coprimary Efficacy Endpoints</u>

- Transfusion avoidance (TA), 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)
- Hemolysis as directly measured by LDH-normalization (LDH-N), defined as LDH levels less than or equal to 1 x ULN (246 U/L), from Day 29 (first scheduled evaluation status post initiation of maintenance dosing) through Day 183 (Week 26)

Given its clinical relevance and precedence as a clinical study endpoint in the eculizumab TRIUMPH, SHEPHERD, and AEGIS studies in patients with PNH (Brodsky, 2008; Hillmen, 2006; Kanakura, 2011), TA was chosen as a coprimary endpoint for Study ALXN1210-PNH-301.

Per Sponsor-Agency agreement, LDH-N was chosen as a coprimary efficacy measure in Study ALXN1210-PNH-301 as it provides robust evidence of disease control and return of the key pathophysiologic marker of hemolysis to the normal range. Although LDH-N is a more stringent threshold than the more traditional cutoff of 1.5 × ULN, its clinical relevance as indicated by inhibition of hemolysis to normal levels makes it a more robust endpoint for the ravulizumab clinical program.

<u>Key Secondary (tested in a hierarchical manner)</u>

If non-inferiority was met for both coprimary endpoints, key secondary endpoints were tested for non-inferiority using a closed testing procedure in the following order so that the lack of significance of a test precluded assessment of subsequent tests:

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

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2. 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)
3. Proportion of patients with breakthrough hemolysis (BTH), defined as at least 1 new or worsening symptom or sign of intravascular hemolysis (fatigue, hemoglobinuria, abdominal pain, shortness of breath [dyspnea], anemia [hemoglobin < 10 g/dL], 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
4. Proportion of patients with stabilized hemoglobin, defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26)

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

5. Proportion of patients with breakthrough hemolysis through Day 183 (Week 26)
6. Percentage Change from Baseline to Day 183 (Week 26) in LDH
7. Hemolysis as directly measured by LDH-N from Day 29 through Day183 (Week 26)
8. Change from Baseline to Day 183 (Week 26) in FACIT-Fatigue
9. Proportion of patients with stabilized hemoglobin through Day 183 (Week 26)
10. Transfusion avoidance

It is important to include all of the primary and key secondary endpoints in labeling, in order to give physicians a full and broad understanding of the effect of ravulizumab on PNH disease. The primary and key secondary endpoints measure different aspects of PNH disease that are important to the evaluation of efficacy. LDH is a direct measure of hemolysis, the central pathophysiological feature of PNH disease. Transfusions and hemoglobin levels are clinically meaningful results of this hemolysis. Quality of life and breakthrough hemolysis are additional key measures of efficacy for a complement inhibitor that blocks C5 and therefore the consequences of PNH diseases.

FDA Position
Inclusion of primary and secondary endpoints in the USPI is based upon robustness of results and considerations of the trial design. Given the open-label nature of trial design, interpretation of the patient reported outcome measures (FACIT-fatigue) will be limited and likely considered descriptive findings. The demonstration of both laboratory findings and clinical meaningful outcomes such as transfusion avoidance or stabilization of hemoglobin is paramount in assessing the efficacy of ravulizumab for the treatment of PNH.

Statistical Analysis Plan and Amendments

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

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Sample Size Determination

Approximately 214 patients with documented PNH who were naïve to treatment with complement inhibitor were planned to be randomly assigned in a 1:1 ratio to receive ravulizumab (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 ravulizumab-treated patients with eculizumab-treated patients. Coprimary endpoints of hemolysis 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 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 ravulizumab to eculizumab (Table 9). 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 coprimary 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. This margin was based on data from Alexion's PNH Registry for eculizumab treated patients enrolling into the registry in 2012 or later (data on file).

Endpoints and NIMs for the Phase 3 studies are presented in Table 9. The factors used to estimate sample size and determine NIMs are detailed in the statistical analysis plan appended to the clinical study report (ALXN1210-PNH-301 CSR Appendix 16.1.9).

Table 9: Study ALXN1210-PNH-301 Primary and Key Secondary Endpoints

Endpoint	Statistic for Treatment Comparison	NIM	Eculizumab Effect Preserved
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 Hemolysis	Difference in rate	20%[c,d]	70%
% Hemoglobin Stabilization	Difference in rate	-20%[c]	50%

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 NIM.

[b] An NIM of 0.39 on the odds ratio scale which was derived from TRIUMPH clinical study 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 hemoglobinuria; SAP = statistical

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analysis plan
Source: Module 2.7.3, Table 9

Analysis Population

Efficacy analyses were performed using the Full Analysis Set (FAS), the primary efficacy population. The FAS included all patients who received at least 1 dose of randomized treatment (ravulizumab or eculizumab) and had at least 1 efficacy assessment after the first infusion of randomized treatment.
The coprimary efficacy endpoint analyses, as well as key secondary endpoint analyses, were repeated using the Per Protocol Set (PP Set) as a sensitivity analysis. The PP Set was used for analyses of the coprimary and key secondary efficacy endpoints. The PP Set included all patients in the FAS who met the following criteria:

- Missed 0 doses of ravulizumab or no more than 1 dose of eculizumab during the 26-week Primary Evaluation Period
- Met inclusion criterion #2, 3, and 4 (ALXN1210-PNH-301 CSR Section 9.3.1)
- Did not meet exclusion criterion #1, 2, 3, or 4 (ALXN1210-PNH-301 CSR Section 9.3.2)
- Never received the wrong randomized treatment
- Followed the protocol specified transfusion guidelines

Analysis Methods

For the coprimary 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 coprimary 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.

In designing these Phase 3 studies, particular consideration was given to the assessment of assay sensitivity, as outlined in the CDER 2016 Guidance for Industry on Non-inferiority Clinical Trials to Establish Effectiveness. The primary endpoints were chosen for their clinical relevance in PNH and ability to reflect pathophysiologic changes that are a direct consequence of treatment. Use of these endpoints as the basis for clinically relevant NIMs meets the FDA requirement for demonstrating “Historical Evidence of Drug Sensitivity.” The constancy assumption was met through a rigorous selection of historical data from the eculizumab clinical

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program, data from the PNH disease registry (Study M07-001), and results from the ravulizumab Phase 1b and Phase 2 studies.

Sensitivity Analyses

The coprimary efficacy endpoint analyses, as well as key secondary endpoint analyses, were repeated using the PP Set as a sensitivity analysis. Sensitivity analyses for the coprimary analyses are described in the SAP (Appendix 16.1.9, Section 7.2.1.7).

Subgroup Analyses

Summaries of TA and LDH-N were produced for the subgroups of the randomization stratification variables. Summaries of the coprimary endpoints of TA and LDH-N and for the key secondary endpoints also were produced for subgroups based on sex, race, region, and age at first study drug infusion (18 to 65 and > 65 years).

Protocol Amendments

The original protocol (dated 09 Aug 2016) was globally amended 3 times during the Primary Evaluation Period of the study. Significant changes at each protocol amendment are provided below. None of the protocol modifications had an impact on the integrity of the study or the interpretation of the results.

First global amendment (dated 28 Sep 2016):

- Modified the weight-based dosing for ravulizumab. The initial dosing regimen was designed to achieve complete inhibition of terminal complement activity over the entire dosing interval in all patients. After discussion with FDA, it was determined that these slightly lower dosing levels also met the initially established trough exposure levels to ensure complete inhibition of C5 activity in all patients.

Second global amendment (dated 25 Jan 2017):

- Modified the use of concomitant medications described in exclusion criterion #15 to allow for global differences in standard of care
- Revised exclusion criterion #16 to encompass hypersensitivity to any ingredient contained in the study drug globally
- Added text to ensure independent review of meningococcal infection cases.

Third global amendment (dated 23 Oct 2017):

- Revised the statistical analysis description regarding control of Type I error when testing the primary and secondary endpoints for non-inferiority and superiority
- To reduce the patient data collection burden, removed the exploratory endpoints of Patient-Reported PNH Symptoms and Healthcare Resource Utilization

Changes in Planned Analyses

There were no significant modifications to the planned analyses in the SAP.

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The FDA's Assessment:

The trial design, study endpoints, and protocol amendments described above by the Applicant are acceptable. Additional details regarding the SAP are presented below.

SAP Amendments

SAP version 3 (dated 26October 2017):

- The choice of covariance structure to be utilized in the mixed model repeated measures (MMRM) analysis has been updated to use an unstructured covariance structure to model the within patient errors, and if that fails to converge, to use a pre-specified list of appropriate structures. The covariance structure converging to the best fit, as determined by Akaike's information criterion, would then be used in the analysis.

SAP version 3 (dated 26October 2017):

- The analysis of breakthrough hemolysis was updated to be consistent with the PNH-302 study. The change included utilizing exact methods if the stratified Newcombe method fails to provide estimates of confidence intervals due to small cell sizes.

Non-inferiority Margin Derivation:

Unless otherwise stated, the NIMs were determined based on a randomized placebo-controlled study (TRIUMPH study, Hillmen 2006).

Normalization of lactate dehydrogenase levels (LDH-N)

The NIM determination was based on several factors. As baseline LDH is a predictor of the rate of normalization, in order to preserve the constancy assumption, the rate of LDH-N was calculated adjusted to the observed baseline LDH of the current ALXN1210 Phase 1b and 2 data. This was done by including patients from the TRIUMPH study whose baseline LDH was<2400. The estimate of LDH-N for eculizumab was then calculated to be a weighted average of the proportions of LDH-N from Day 29 to Day 183 to be consistent with the proposed analysis plan for this study. As the proportion of LDH-N for placebo treated patients was 0% at all visits, the upper bound of the 95% CI was used in order to be able to calculate an odds ratio. The final estimate of benefit was based on a LDH-N proportion of 42% for eculizumab-treated patients and 10% for placebo for an odds ratio of 6.5. The applicant chose to preserve 50% of benefit. The NIM is calculated using the following formula.

$$\begin{aligned} \text{Margin} &= 1/\{OR^{0.5}\} \\ &= 1/\{[0.42/(1-0.42)]/[0.1/(1-0.1)]\}^{0.5} \\ &= 0.39 \end{aligned}$$

where OR represents the odds ratio of eculizumab compared to placebo and 0.5 is the fraction of benefit to be preserved.

The non-inferiority margin for LDH-N was based on the point estimate of the effect of eculizumab. The applicant stated that more conservative approach of using the lower bound of

the 95% CI for eculizumab would make the study operationally infeasible in light of the rarity of PNH and the paucity of eculizumab-naïve patients.

If we assume LDH-N proportion of 31% for eculizumab treated patients and 10% for placebo, a more conservative NIM would be 0.50 using the above formula.

Transfusion Avoidance Rate

The NIM was determined based on the global PNH Registry for eculizumab-treated patients enrolling into the registry in 2012 or later (Soliris Type II Variation Procedure No. MEA/H/C/000791/II/66). Patients treated with eculizumab (TA rate of 57.1%) showed a benefit over untreated patients (TA rate of 18.6%) with a difference of approximately 40% (38.5%) after adjustment for history of transfusions 12 months prior to enrollment. The applicant chose margin of -20% to preserve about 50% of the eculizumab effect of treatment. Again, the non-inferiority margin was based on the point estimate of the effect of eculizumab due to the feasibility of the trial sample size.

Percent of patients with stabilized hemoglobin:

The TRIUMPH study showed a benefit of eculizumab over placebo with a difference of 39.5% in proportion of patients with stabilized hemoglobin as defined in this protocol after 26 weeks of treatment. The applicant chose margin of -20% to preserve about 50% of the eculizumab effect of treatment. Again, the non-inferiority margin was based on the point estimate of the effect of eculizumab due to the feasibility of the trial sample size.

Percent of patients with breakthrough hemolysis:

The TRIUMPH study showed a benefit of eculizumab over placebo with a difference of -81.4% with a 95% confidence interval of -69.8% to -92.96% in breakthrough hemolysis. Using the lower bound of -69.8% as a conservative estimate of benefit, a traditional choice of NIM is one with ≤ 50% loss of benefit resulting in a NIM of approximately 35%. However, a more conservative and clinically appropriate choice is a NIM of 20%.

Percentage change in LDH:

The TRIUMPH study showed a benefit of eculizumab over placebo with a difference in LDH percent change from baseline to Week 26 of -101% with a 95% confidence interval of -114% to -88%. Using the upper bound of -88% as a conservative estimate of benefit, a traditional choice of NIM is one with ≤ 50% loss of benefit resulting in a NIM of approximately 44%. However, because the benefit of eculizumab over placebo is so great, a more conservative and clinically appropriate choice is a NIM with ≤ 25% loss of benefit, which results in an NIM of 22% and rounded to 20%.

Change in FACIT-Fatigue:

The TRIUMPH study showed a benefit of eculizumab over placebo with a difference in FACIT-Fatigue change from baseline to Week 26 of 10.4. A traditional choice of NIM is one with ≤50% loss of benefit. This would result in a NIM of -5. Again, the non-inferiority margin was based on the point estimate of the effect of eculizumab due to the feasibility of the trial sample size.

Statistical Reviewer's comment:

- Non-inferiority margins for primary and secondary efficacy endpoints were never agreed in the IND meetings or correspondence between the applicant and FDA.
- When deriving the non-inferiority margins, FDA's guidance recommends a non-inferiority margin derived by statistical methods based on the bound of the confidence interval to account for the variability of the estimate from placebo-controlled trials.
- In the Written Response of the Type C Guidance meeting sent to the Applicant on December 15, 2016, FDA reiterated that "a NIM of 20% for both co-primary endpoints is greater than the largest clinically acceptable difference and that we will accept a non-inferiority margin of no more than 10% given the established importance of the efficacy of eculizumab for the treatment of PNH."

In summary, due to the clinical important of preserving treatment effect, we conducted an analysis of NIMs of 0.50 to compare odds ratio of ALXN1210 versus eculizumab for the coprimary endpoint of LDH-N and 10% for coprimary endpoint of Transfusion Avoidance Rate (TA), and other secondary endpoints including Proportion of patients with stabilized hemoglobin, Proportion of patients with breakthrough hemolysis, and Percentage change in LDH in this review to establish the efficacy.

FDA Clinical Reviewer's Comments:

The study population, trial design and study endpoints described above by the Applicant are acceptable. The efficacy endpoints of transfusion avoidance and hemolysis adequately represent the pathophysiology of PNH and the clinically important disease parameters relevant to patients with PNH and were agreed to by the Agency prior to study conduct.

The sample size estimate was based on a non-inferiority design comparing ravulizumab-treated patients with eculizumab-treated patients. To demonstrate non-inferiority, both coprimary endpoints individually needed to be met. Although FDA recommended a NIM of 10% for the TA endpoint, the Applicant used a NIM of 20% in Study ALXN1210-PNH-301 based data from the global PNH Registry for eculizumab-which showed patients treated with eculizumab had a TA rate of 57.1% compared with the TA rate of 18.6% in un-treated patients (difference of approximately 40% after adjustment for history of transfusions 12 months prior to enrollment). The NIM of 20% was selected by the Applicant to account for ≤ 50% loss of benefit.

FDA acknowledges the Applicant's explanation that use of the more conservative 10% NIM recommended by the Agency would have required a larger sample size which may have been

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difficult to obtain given the rarity of PNH and the paucity of eculizumab-naïve patients. Sensitivity analyses using the 10% NIM were conducted by the FDA. The results are discussing in Section 8.1.2 below.

Analysis for Key Secondary Efficacy Endpoints:

Change in FACIT-Fatigue score and percent change in LDH from baseline to Day 183 (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 (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), study visit and study visit by treatment group interaction as well as the continuous fixed covariates of baseline FACIT-Fatigue or LDH.

For percent change in LDH, the baseline LDH level as a continuous variable was included. An unstructured covariance matrix was used to model the within-patient errors. If this analysis failed to converge, the following structures were tested and the final covariance structure was determined by Akaike's information criterion, first order autoregressive, compound symmetry and Toeplitz method. The Kenward-Roger approximation was used to estimate denominator degrees of freedom A difference between the ravulizumab and eculizumab treatment groups along with a 2-sided 95% CI was calculated. Missing LDH or FACIT-Fatigue values for a patient at a particular visit were not imputed.

The same approach using the stratified Newcombe CI method as described for the primary analysis of TA was employed for the key secondary endpoints of BTH and stabilized hemoglobin. Patients who withdrew from the study due to lack of efficacy during the Primary Evaluation Period were considered as non-responders and were counted as having BTH and as not meeting the stabilized hemoglobin definition.

FDA Clinical Reviewer Comments

(b) (4)

The Division requested Clinical Outcomes Assessment (COA)Staff input on the adequacy of the FACIT-Fatigue scale (b) (4) The review concluded that, the open-label trial design limits interpretability of the PRO data because patient's knowledge of treatment assignment may lead to systematic overestimation or underestimation of treatment effect of which is currently unknown. Studies 301 and 302 were also not enriched with patients with sufficiently severe fatigue-related symptoms and impacts at baseline as noted by floor effects in several items across the study. Additional concerns included that while Study 301 generates data that shows improvement in the FACIT-Fatigue total score, there are only select items within the FACIT-Fatigue scale that contribute more to the change observed in the total score based upon review of item-level analyses. Additionally, the Applicant defined a clinically meaningful score change in the FACIT-Fatigue total score as 3-points, however there is insufficient data to support this threshold. While one anchor-based empirical cumulative distribution function (eCDF) curve potentially supports a threshold for within-patient meaningful change of 3-points (on a 0-52 scale) if anchored to "A little" response category on

the EORTC QLQ-C30 item 12 ("Have you felt weak?"), the other anchor-based eCDF curves suggests that thresholds for within-patient meaningful change range from 5-7 points (on a 0-52 scale) based on "A little" to "Not at all" anchor response categories in EORTC QLQ-C30 item 18 ("Were you tired?") and item 12, respectively. However, the anchor-based eCDF curves should be interpreted cautiously as change is not observed in all FACIT-Fatigue items; further the anchors are not the typical anchors recommended for these types of analyses but were the only items administered in Studies 301 and 302 that could serve as anchors.

Therefore, the PRO analyses for this application was considered exploratory. Please refer to COA review by Julia Ju, PharmD, PhD and Selena Daniels, Pharm D, Ph.D. for additional details.

8.1.2. Study Results

The Applicant's Position:

Compliance with Good Clinical Practices

Study ALXN1210-PNH-301 was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council for Harmonization (ICH) E6 Guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements. Ethics Committees and Institutional Review Boards reviewed and approved the protocol, protocol amendments, and patient informed consent forms. All patients or their legal representatives voluntarily consented prior to study enrollment.

Financial Disclosure

Disclosure information is presented in Section 19.2. Given the distribution of patients across multiple investigative sites, the randomized study design, and the objective nature of the primary and most key secondary endpoints, it is unlikely for any 1 investigator to influence overall outcomes.

Data Quality and Integrity

The data submitted in this BLA were of high quality and should facilitate an adequate efficacy review. There were no concerns regarding the integrity of data in this submission.

A prospective program was put in place during protocol development to identify Critical to Quality factors. Triggers and thresholds were set to enable the identification of systemic issues that could impact the reliability of the study results or subject safety. The Critical to Quality factors were routinely assessed throughout the study.

To ensure the integrity of the clinical data and investigational site personnel compliance with governing regulations, 27 sites were audited as part of the GCP audit program for this program.

The FDA's Assessment:

The Agency agrees with the Applicants comment on compliance with good clinical practice and

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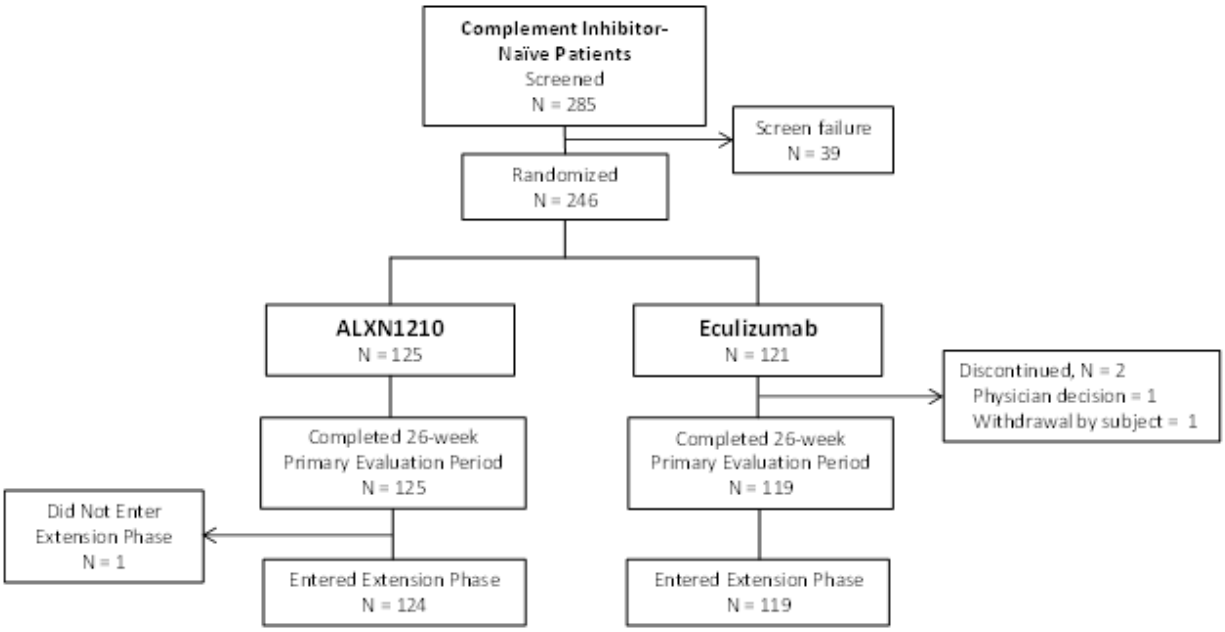
financial disclosures. The quality of the original data submission is adequate to evaluate and review the submission in general. Refer to appendix 19.2 for financial disclosure information.

Patient Disposition

A total of 246 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). Of the 246, 244 patients completed the Primary Evaluation Period; 2 patients in the eculizumab group prematurely discontinued study drug (Figure 9).

Figure 9: Study ALXN1210-PNH-301 Patient Disposition – Primary Evaluation Period



Source: ALXN1210-PNH-301 CSR, Figure 3

All 246 treated patients (125 patients in the ravulizumab 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 ravulizumab group and 1 patient in the eculizumab group met the protocol-specified criteria for pRBC transfusion (hemoglobin ≤ 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.

Protocol Violations/Deviations

Any departure from the approved protocol was considered a protocol deviation. Major deviations were those that could potentially impact the rights, welfare, or safety of the patient

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and/or the integrity of study data; all others were considered minor. A total of 33 patients had major protocol deviations in the Primary Evaluation Period. None of these protocol deviations were considered to impact the safety of the patients or the interpretation of efficacy and safety results from this study.

The FDA's Assessment:

The FDA agrees with the results presented in this section. Major protocol deviations by treatment is presented below.

Table 10: Study ALXN1210-PNH-301 Major Protocol Deviations (Full Analysis Set)

	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)

Source: ALXN1210-PNH-301 CSR, Table 9

Demographic Characteristics

Study entry criteria were carefully selected to reflect an adult patient population consistent with the population likely to be treated with ravulizumab in clinical practice. Patients enrolled in ALXN1210-PNH-301 had active hemolysis as evidenced by the laboratory parameter of LDH ≥ 1.5 × ULN plus the presence of a clinical sign or symptom of active intravascular hemolysis: fatigue, hemoglobinuria, abdominal pain, shortness of breath (dyspnea), anemia (hemoglobin < 10 g/L), major adverse vascular event (including thrombosis), dysphagia, or erectile dysfunction. A majority (> 80%) of patients were transfusion-dependent at baseline. Special attention was given to meeting the constancy requirement (CHMP 2005 and CDER 2016 Guidance) such that the patient population from earlier Phase 3 studies in eculizumab, used to establish the non-inferiority margins (NIMs) for the key efficacy endpoints, would be similar to the expected complement inhibitor-naïve patient population in Study ALXN1210-PNH-301.

There were no noteworthy differences in the demographic characteristics between the ravulizumab and eculizumab treatment groups (Table 11).

Table 11: Study ALXN1210-PNH-301 Demographic Characteristics

Characteristic	ALXN1210-PNH-301 (Complement Inhibitor-Naïve)		
	Ravulizumab (N = 125)	Eculizumab (N = 121)	Total (N = 246)
Age (years) at first infusion in study			
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
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)
Body 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
Body weight (kg) category, n (%)			
≥ 40 to < 60	41 (32.8)	38 (31.4)	79 (32.1)
≥ 60 to < 100	79 (63.2)	81 (66.9)	160 (65.0)
≥ 100	5 (4.0)	2 (1.7)	7 (2.8)

Abbreviations: max = maximum; min = minimum; SD = standard deviation
Source: Module 2.7.3, Table 13

Other Baseline Disease Characteristics

Baseline disease characteristics were similar between ravulizumab and eculizumab treatment groups (Table 12). The large PNH granulocyte and monocyte clone sizes at baseline indicate substantial burden of disease, and the comparatively lower PNH RBC clone size indicates uncontrolled hemolysis in these complement inhibitor-naïve patients.

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Table 12: Study ALXN1210-PNH-301 Baseline Disease Characteristics

Parameter	Statistics	Ravulizumab (N = 125)	Eculizumab (N = 121)
Pre-treatment LDH levels	Mean (SD) Median	1633.5 (778.75) 1513.5	1578.3 (727.06) 1445.0
Number of patients with pRBC/whole blood Transfusions within 12 months prior to first dose	n (%)	103 (82.4)	100 (82.6)
pRBC/whole blood Transfusions within 12 months prior to first dose	Total Mean (SD) Median	677 6.6 (6.04) 4.0	572 5.7 (5.53) 3.0
Units of pRBC/whole blood transfused within 12 months prior to first dose	Total Mean (SD) Median	925 9.0 (7.74) 6.0	861 8.6 (7.90) 6.0
Patients with any PNH conditions prior to informed consent	n (%)	121 (96.8)	120 (99.2)
Anemia		103 (82.4)	105 (86.8)
Hematuria or hemoglobinuria		81 (64.8)	75 (62.0)
Aplastic anemia		41 (32.8)	38 (31.4)
Renal failure		19 (15.2)	11 (9.1)
Myelodysplastic syndrome		7 (5.6)	6 (5.0)
Pregnancy complication		3 (2.4)	4 (3.3)
Other[a]		27 (21.6)	13 (10.7)

a "Other" as specified on case report form included thrombocytopenia, chronic kidney disease, and pancytopenia, as well as a number of other conditions.
Abbreviations: SD = standard deviation; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell
Source: Study ALXN1210-PNH-301 CSR, Section 2.1.2.4

The FDA's Assessment:

The FDA agrees with the results presented in this section. Demographic characteristics and baseline disease characteristics were similar between ravulizumab and eculizumab treatment groups. Randomization was stratified by transfusion history (0, 1 to 14, or > 14 units) and screening lactate dehydrogenase (LDH) levels (1.5 to < 3 × upper limit of normal [ULN] or ≥ 3 × ULN).Observed stratification factors are summarized in Table 13. There are seems to have some imbalance among treatment arms regarding the pRBC stratification factor. There were higher percent of 0 unit of pRBC (92.8%) in ravulizumab arm than the eculizumab arm (84.3%). These led to imbalance in overall stratification groupings: 57.6% of patients with pRBC = 0 unit and LDH = 1.5 to < 3×ULN in ravulizumab arm compared to 47.1% of patients in eculizumab arm.

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Table 13: Study ALXN1210-PNH-301 Stratification Factor by Treatment (FAS)

Variable	ALXN1210-PNH-301 (Complement Inhibitor-Naïve)		
	Ravulizumab (N = 125)	Eculizumab (N = 121)	Total (N = 246)
LDH stratification groups, n (%)			
1.5 to < 3×ULN	43.0	45.0	44.0
≥ 3×ULN	18, 83	18, 86	18, 86
pRBC stratification groups, n (%)			
0 unit	116 (92.8)	102 (84.3)	218 (88.6)
1 to14 units	5 (4.0)	13 (10.7)	18 (7.3)
> 14 units	2 (1.6)	4 (3.3)	6 (2.4)
Overall stratification groupings, n (%)			
pRBC = 0 unit and LDH = 1.5 to < 3×ULN	72 (57.6)	57 (47.1)	129 (52.4)
pRBC = 1 to14 units and LDH = 1.5 to < 3×ULN	53 (42.4)	42 (34.7)	95 (38.6)
pRBC > 14 units and LDH = 1.5 to < 3×ULN	19 (15.2)	15 (12.4)	34 (13.8)
pRBC = 0 unit and LDH ≥ 3×ULN	43 (34.4)	51 (42.1)	94 (38.2)
pRBC = 1 to 14 units and LDH ≥ 3×ULN	4 (3.2)	4 (3.3)	8 (3.3)
pRBC > 14 units and LDH ≥ 3×ULN	3 (2.4)	4 (3.3)	7 (2.8)

Source: Study ALXN1210-PNH-301 CSR, Table 11.

Treatment Compliance and Concomitant Medications

Treatment compliance was high. All patients in the ravulizumab group received all of the planned infusions during the Primary Evaluation Period; 1 patient in the eculizumab group missed a planned infusion (99.2% compliance). Four patients (ravulizumab: 3; eculizumab = 1) each had 1 infusion in which they did not receive the full dose.

Overall, 95.9% of patients (98.4% in the ravulizumab group and 93.4% in the eculizumab group) took at least 1 concomitant medication. The prior and concomitant medications used were consistent with a PNH patient population.

The FDA's Assessment:

The FDA agrees with the results in this section.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Ravulizumab met the primary objective of statistically significant non-inferiority compared to eculizumab on both coprimary endpoints, avoidance of pRBC transfusion per protocol-specified guidelines and LDH-N, from Day 29 to Day 183 (Figure 10). Results favored ravulizumab over eculizumab for both endpoints.

- Transfusion avoidance through Day 183 was achieved by 73.6% of patients in the ravulizumab group compared to 66.1% in the eculizumab group. The lower bound of the 95% CI of the 6.8% treatment difference (95% CI: -4.66%, 18.14%) was greater than the

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protocol-specified NIM of -20%. Total number of units transfused was also lower for the ravulizumab group (155 units) than for the eculizumab group (222 units).

- The adjusted prevalence of LDH normalization (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% CI: 0.796, 1.769). The lower bound of the 95% CI was greater than the protocol-specified NIM of 0.39. The median time to first LDH normalization was 24 days for ravulizumab and 29 days for eculizumab.

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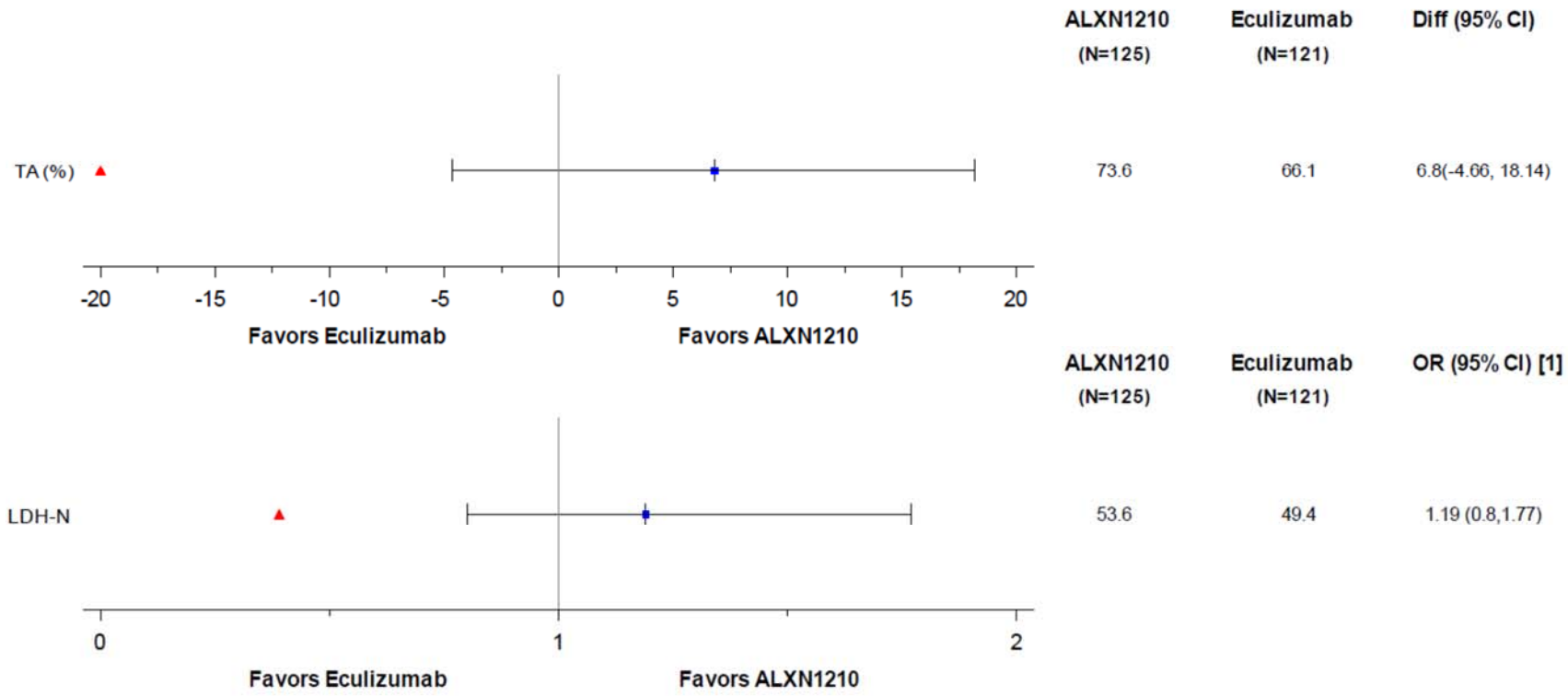
Figure 10: Study ALXN1210-PNH-301 Forest Plot of Coprimary Endpoints – Primary Evaluation Period (Full Analysis Set)



Note: The red triangle indicates the non-inferiority margin. For TA, Diff (95% CI) was based on estimated differences in percent with 95% CI. For LDH-N, adjusted prevalence within each treatment is displayed. Treatment difference was estimated for ravulizumab - eculizumab.

[1] To calculate the OR 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]).

Abbreviations: ALXN1210 = ravulizumab; CI = confidence interval; Diff = difference; LDH-N = normalization of lactate dehydrogenase levels; OR = odds ratio; TA = transfusion avoidance

Source: Module 2.7.3 Figure 2

Efficacy Results – Secondary and other relevant endpoints

Statistically significant non-inferiority was achieved for all 4 key secondary endpoints (Figure 11). Results for all 4 key secondary endpoints consistently favored ravulizumab.

- Mean percent change in LDH from baseline to Day 183 was -76.84% for the ravulizumab group and -76.02% for the eculizumab group. The LS mean difference between treatment groups was -0.83% (95% CI: -5.21%, 3.56%).
- Mean change in FACIT-Fatigue total score from baseline to Day 183 was 7.07 for the ravulizumab group and 6.40 for the eculizumab group, with a 3-point improvement from baseline on this scale considered a clinically meaningful improvement. The mean difference between treatment groups was 0.67 (95% CI: -1.21, 2.55). Both treatment groups showed improvement in fatigue as measured by FACIT-Fatigue overtime, with ravulizumab better than eculizumab at all time points for the FACIT Fatigue.
- Breakthrough hemolysis was experienced by 4.0% of patients in the ravulizumab group and 10.7% of patients in the eculizumab group. The difference between treatment groups was -6.7% (95% CI: -14.21%, 0.18%). The incidence of breakthrough hemolysis was more than 2-fold higher in the eculizumab group (13 patients with 15 events) than in the ravulizumab group (5 patients with 5 events). Of the 15 breakthrough hemolysis events observed in the eculizumab group, 7 were associated with elevated free C5 above 0.5 µg/mL. No patients in the ravulizumab group had elevations of free C5 levels above 0.5 µg/mL.
- Hemoglobin stabilization through Day 183 was achieved by 68.0% of patients in the ravulizumab group and 64.5% of patients in the eculizumab group. The difference between treatment groups was 2.9% (95% CI: -8.80%, 14.64%).

Because statistically significant non-inferiority was achieved for both coprimary and all 4 key secondary endpoints, superiority was assessed following the prespecified hierarchical testing order that began with BTH. The treatment difference for BTH ($p = 0.0558$ favoring ravulizumab) did not reach the prespecified threshold for superiority ($p < 0.05$), and no further superiority testing was conducted.

FDA Assessment

Although the patient reported outcome (FACIT-fatigue) did achieve non-inferiority as a secondary endpoint, there are several concerns with the interpretation of the PRO data. Refer to the COA review in Section 8.1.5.

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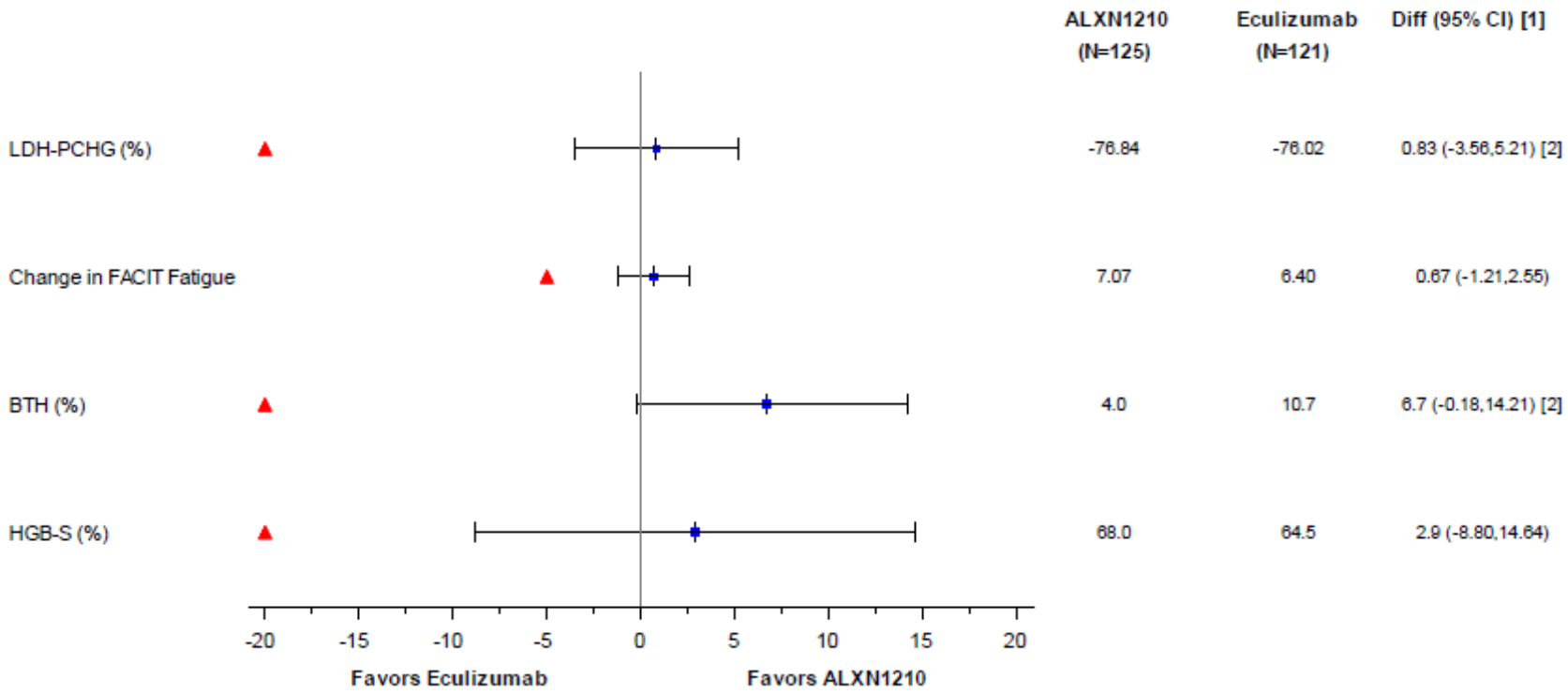
Figure 11: Study ALXN1210-PNH-301 Forest Plot of Key Secondary Endpoints – Primary Evaluation Period (Full Analysis Set)



Note: The red triangle indicates the non-inferiority margin.

[1] For endpoints LDH-PCHG, 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 differences 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. This was done for presentation purposes only so results may be interpreted on a consistent scale where point estimates on the right side of the x axis = 0 represent differences favoring ravulizumab and on the left side favoring eculizumab.

Abbreviations: ALXN1210 = ravulizumab; BTH = breakthrough hemolysis; CI = confidence interval; Diff = difference; FACIT = Functional Assessment of Chronic Illness Therapy; HGB-S = stabilized hemoglobin; LDH = lactate dehydrogenase; LDH-PCHG = percent change in LDH

Source: Module 2.7.3 Figure 3

The FDA's Assessment:

Efficacy was assessed based upon transfusion avoidance and hemolysis as directly measured by normalization of LDH levels. Supportive efficacy data included the percent change from baseline in LDH levels, the proportion of patients with breakthrough hemolysis defined as at least one new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥ 2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy and the proportion of patients with stabilized hemoglobin. As presented in Table 14, non-inferiority of ravulizumab compared to eculizumab was demonstrated across all efficacy endpoints in the complement inhibitor naïve treatment population using both sponsor's and FDA recommended NIMs.

(b) (4)

Table 14: Efficacy Results in Study ALXN1210-PNH-301 (Full Analysis Set)

	Ravulizumab (N=125) n (%)	Eculizumab (N=121) n (%)	Ravulizumab vs. Eculizumab Difference (95% CI)
Transfusion Avoidance (%)	92 (73.6)	80 (66.1)	6.8 (-4.7, 18.1)
Hemoglobin Stabilization (%)	85 (68.0)	78 (64.5)	2.9 (-8.8, 14.6)
Breakthrough Hemolysis (%)	5 (4.0)	13 (10.7)	-6.7 (-14.2, 0.18)
LDH Normalization (%) [1]	61 (53.6)	54 (49.4)	1.19 (0.80, 1.77) OR (95% CI) [2]
LDH Percent Change [3]	LS Mean (SEM) -76.8 (1.6)	LS Mean (SEM) -76.0 (1.6)	Difference (95% CI) -0.8 (-5.2, 3.6)

Note: LDH-N = lactate dehydrogenase normalization; CI = confidence interval; OR = odds ratio; LS=Least square; SEM=Standard error of the mean; MMRM=Mixed Model for Repeated Measures;
[1] Adjusted prevalence of LDH-N based on a GEE approach.
[2] OR of Ultomiris relative to Soliris® was calculated by dividing the odds of LDH-N on Ultomiris (0.536/[1-0.536]) by the odds of LDH-N on Soliris® (0.494/[1-0.494]).
[3]: Estimates are based on MMRM that includes treatment group, history of transfusion (as a categorical variable based on the stratification factor levels) and baseline LDH level (as a continuous variable), study visit and study visit by treatment group interaction. An unstructured covariance structure was used.
Source: FDA's Analyses

FDA Additional Analysis

Sensitivity Analysis for LDH-N

The Agency conducted additional sensitivity analysis using the stratified Newcombe CI method as described for the primary analysis of TA because the results from OR is hard to interpret. Patients who withdrew from the study due to lack of efficacy during the Primary Evaluation Period were considered as non-responders. As showed in Table 15, 48.8% of patients in the ravulizumab group and 44.6% in the eculizumab group achieve LDH Normalization at Day 183.

The difference between the ravulizumab and eculizumab treatment groups was 4.4% (95% CI: -8.04%, 16.69%) with the lower bound of the 95% CI greater than NIM of -10%.

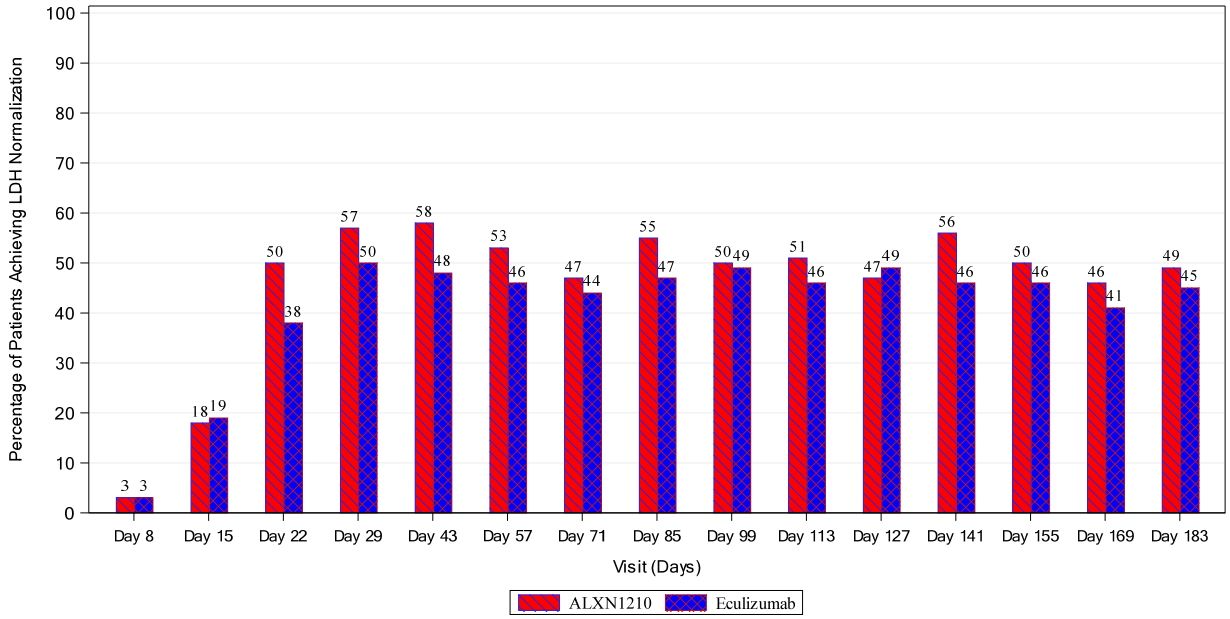
Table 15: Number (%) of Patients Achieving LDH Normalization (Full Analysis Set)

Variables	Ravulizumab	Eculizumab	Treatment Difference (Ravulizumab -Eculizumab)
Overall			
Number of Patients (n)	125	121	
Percentage (%)	48.8	44.6	4.4
95% CI	(39.8, 57.9)	(35.6, 53.9)	(-8.04, 16.69)

Source: FDA's Analyses

The percentage of patients achieving LDH normalization by visit is presented in Figure 12. At Day 22, about 50% patients in ravulizumab (ALXN1210) group and 38% in the eculizumab group achieved LDH Normalization. The percent of patients who achieved LDH Normalization are quite stable over time starting Day 22 for ravulizumab group and Day 29 for eculizumab group. Ravulizumab group is consistently outperforming eculizumab group.

Figure 12: Percentage of Patients Achieving LDH Normalization by Visit (Full Analysis Set)



Source: FDA's Analyses

Other Secondary Endpoint: Time to LDH Normalization

For patients with PNH who were naïve to complement inhibitor treatment, time to LDH normalization was analyzed. Patients who did not achieve LDH-N by the end of the Primary Evaluation Period or who were lost to follow-up were censored at the date of Day 183 or date of last contact. The median time to first LDH normalization was 24 days (95% CI: 22, 29) for the

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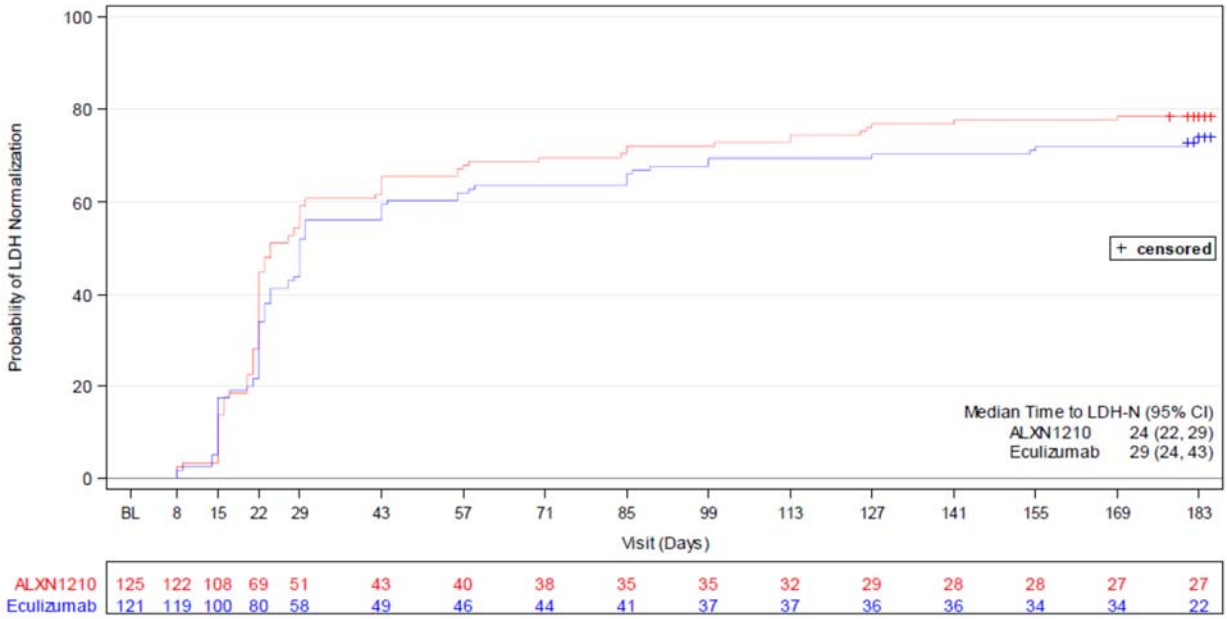
ravulizumab (ALXN1210) group and 29 days (95% CI: 24, 43) for the eculizumab group (**Figure 13**).

Figure 13: KM Plot of Time (Days) to First Occurrence of LDH-N Since First Dose of Study Drug During the Primary Evaluation Period (Full Analysis Set)



BL = baseline; CI = confidence interval; LDH-N = lactate dehydrogenase normalization

Source: CSR Figure 12

Subgroup Analyses

Subgroup analyses were performed for the randomization stratification variables of transfusion history and screening LDH levels and for sex, race, region, and age for the coprimary and key secondary endpoints. No sensitive subgroups were identified. The point estimates for subgroup analyses were generally consistent with the primary analysis: most favored ALXN1210. Results for subgroup analyses in Study ALXN1210-PNH-301 are presented graphically for TA (Figure 14) and LDH-N (Figure 15).

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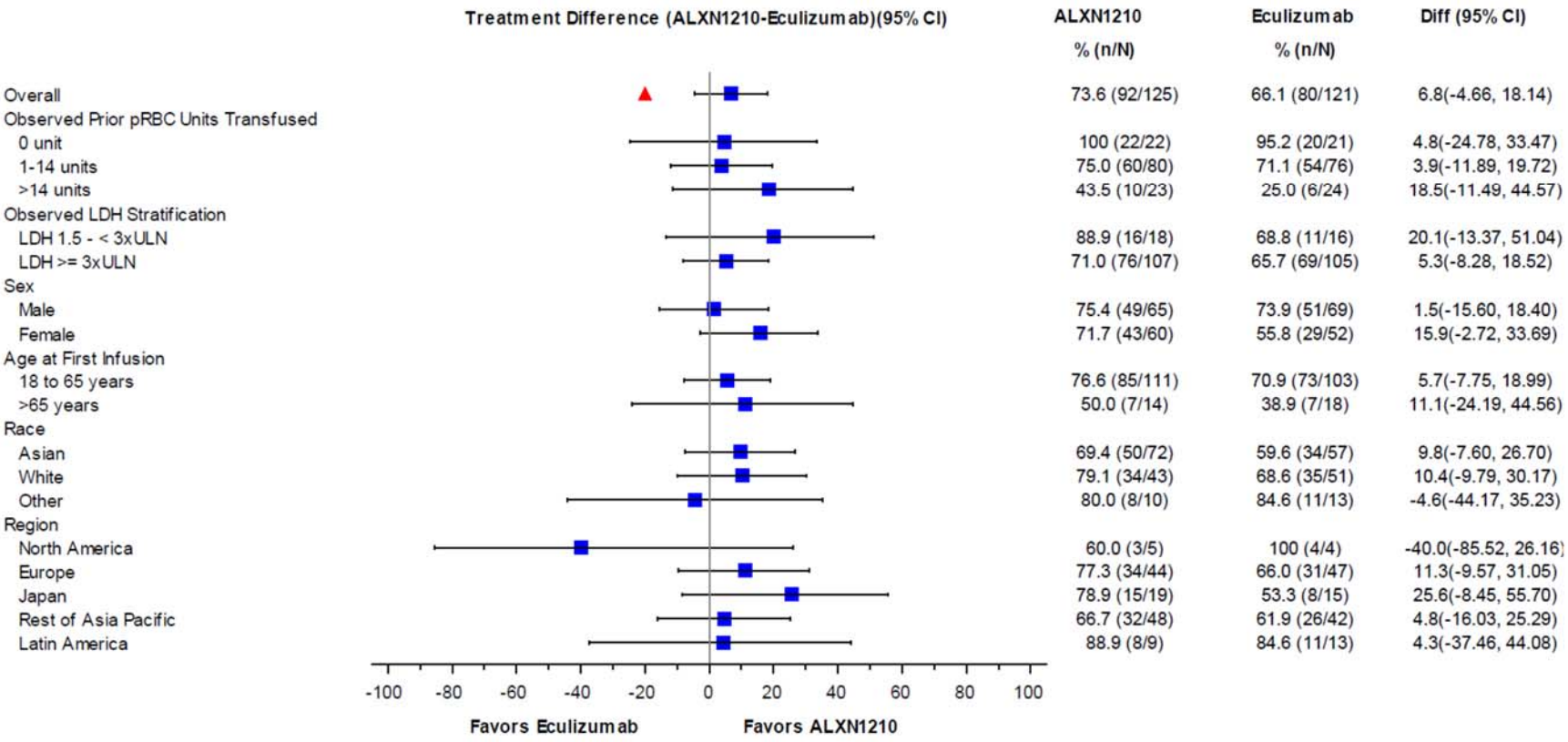
Figure 14: Study ALXN1210-PNH-301 Forest Plot of Transfusion Avoidance Treatment Difference (Ravulizumab - Eculizumab) During the Primary Evaluation Period, Overall and by Subgroup (Full Analysis Set)



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 non-inferiority margin.

Abbreviations: ALXN1210 = ravulizumab; CI = confidence interval; Diff = difference; LDH = lactate dehydrogenase; pRBC = packed red blood cell; ULN = upper limit of normal

Source: Module 2.7.3 Figure 10

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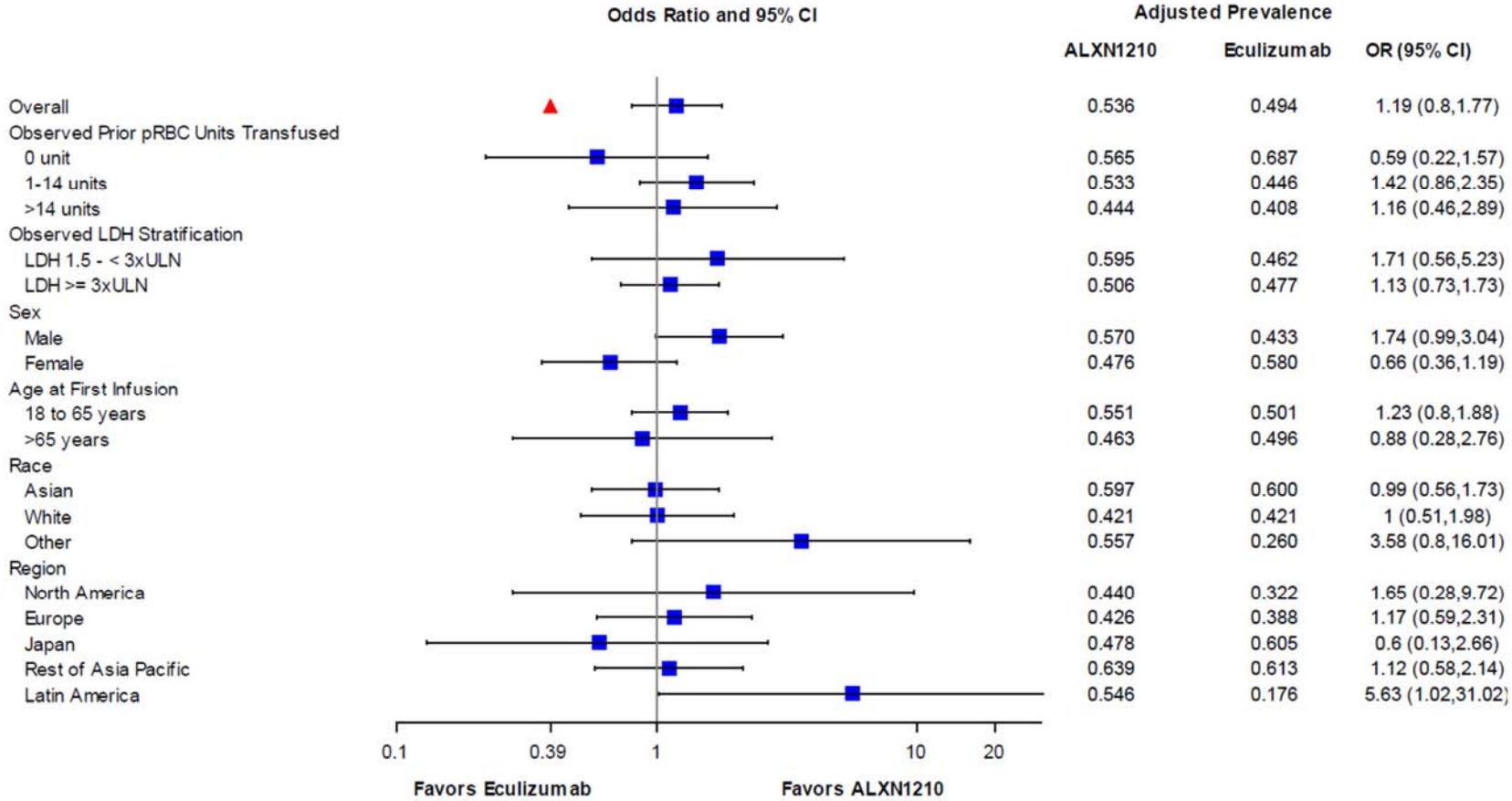
Figure 15: Study ALXN1210-PNH-301 Forest Plot of Patients Achieving LDH-N (Odds Ratio) During the Primary Evaluation Period, Overall and by Subgroup (Full Analysis Set)



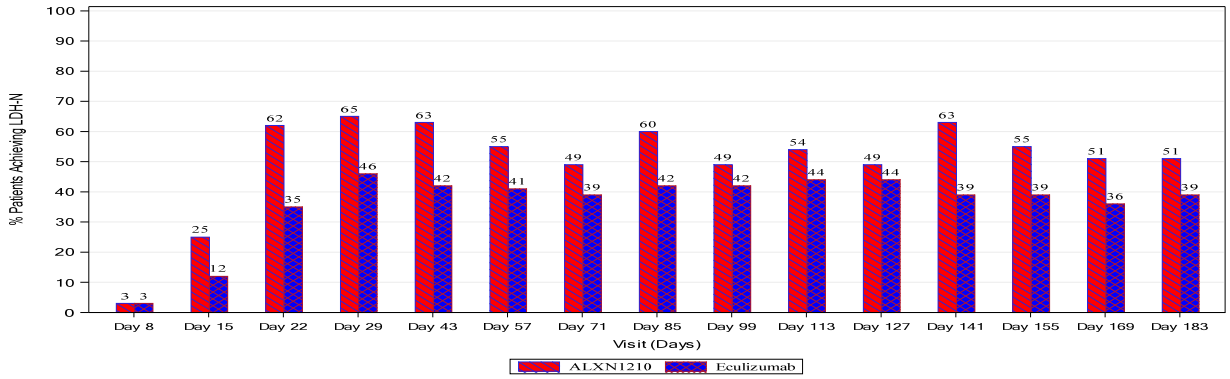
Note: X-axis is presented on log scale. LDH-N is LDH levels less than or equal to 1 × ULN, from Day 29 through Day 183. The ULN for LDH is 246 U/L. The red triangle indicates the non-inferiority margin.
Abbreviations: ALXN1210 = ravulizumab; CI = confidence interval; OR = odds ratio; LDH-N = normalization of lactate dehydrogenase levels; pRBC = packed red blood cell; ULN = upper limit of normal
Source: Module 2.7.3 Figure 11

The FDA's Assessment:

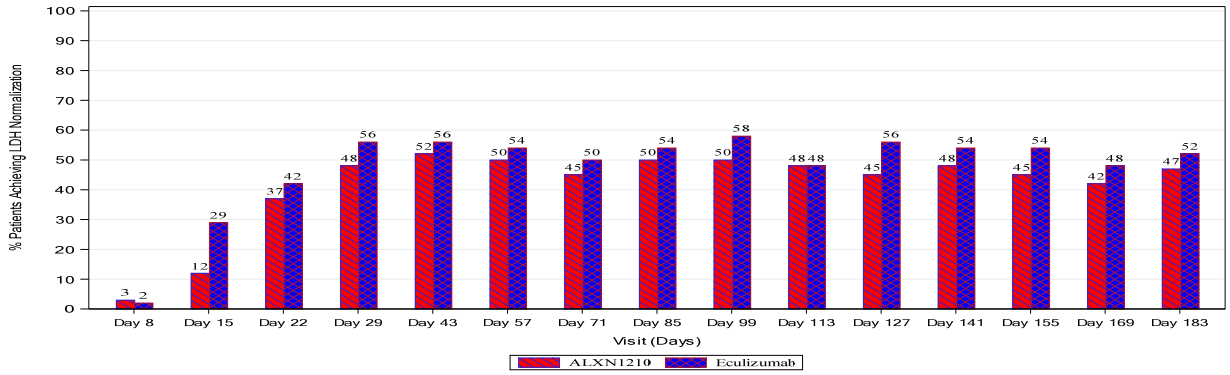
The FDA agree that no sensitive subgroups were identified for co-primary endpoint of TA. However, for co-primary endpoint of LDH-N, the point estimates for female patients favored control treatment of Eculizumab, and there is significant interaction between treatment and Sex with P-value of 0.0243 (> 0.05). Even using the Applicant prespecified NIM of 0.39, the non-inferiority of ravulizumab compared to eculizumab did not achieve in female patients because the lower bound of 95% CI of 0.36 is lower than the NIM of 0.39. The percentage of patients achieving LDH normalization by sex over time (Figure 16) also shows that consistently more male patients achieved LDH-D in ravulizumab (ALXN1210) group while more female patients in the eculizumab group achieved LDH Normalization.

Figure 16: Percentage of Patients Achieving LDH Normalization Over Time by Gender (FAS)

Male Patients Only



Female Patients Only



Source: FDA's Analyses

We conducted additional sensitivity analysis for coprimary endpoint of patients who achieved LDH-N at Day 183 using the stratified Newcombe CI method. The non-inferiority of ravulizumab compared to eculizumab at Day 183 did not achieve in female patients because the lower bound of 95% CI of -24.77% is even lower than the Applicant pre-specified NIM of -20%. It suggests that the treatment effect observed in overall population are driven by results in male patients.

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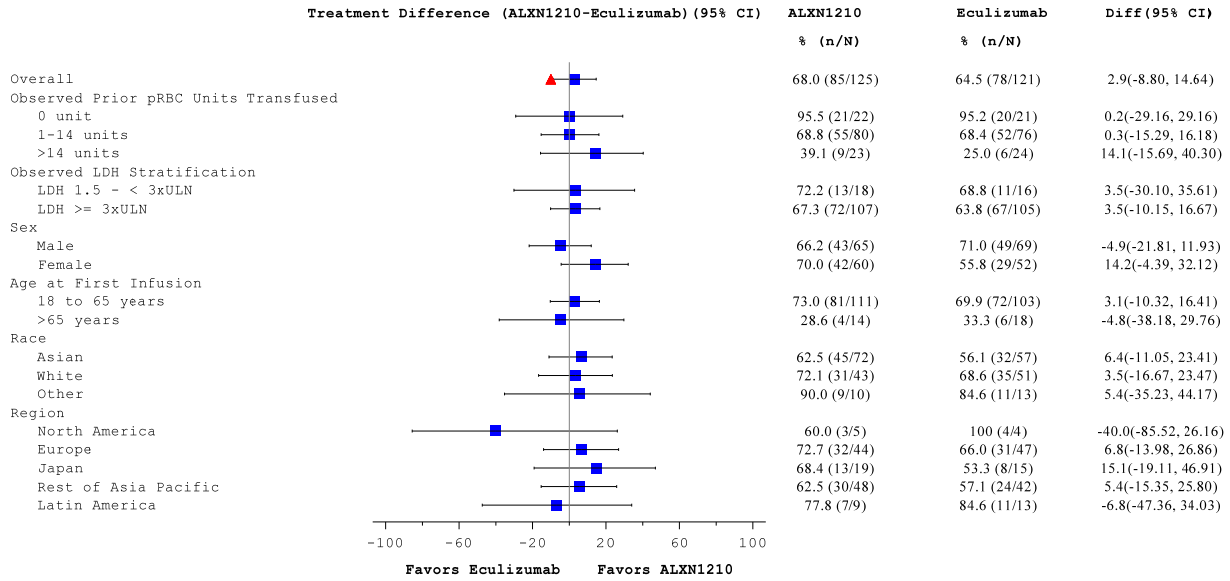
Table 16: Number (%) of Patients Achieving LDH Normalization by Sex (Full Analysis Set)

Variables	Ravulizumab	Eculizumab	Treatment Difference (Ravulizumab -Eculizumab)
Male			
Number of Patients (n)	65	69	
Percentage (%)	50.8	39.1	12.9
95% CI	(38.1, 63.4)	(27.6, 51.6)	(-4.20, 29.01)
Female			
Number of Patients (n)	60	52	
Percentage (%)	46.7	51.9	-6.4
95% CI	(33.7, 60.0)	(37.6, 66.0)	(-24.77, 12.39)

Source: FDA's Analyses

We also conducted subgroup analyses for clinical important endpoint of proportion of patients with stabilized hemoglobin through Day 183. As presented in Figure 17, while most the point estimates for subgroup analyses were generally consistent with the primary analysis which is favored ALXN121, the point estimate was favored eculizumab in male patients. The outlier observed from treatment effect by sex in LDH-N may not be clinical meaningful.

Figure 17: Study ALXN1210-PNH-301 Forest Plot of Patients with Hemoglobin Stabilization During the Primary Evaluation Period, Overall and by Subgroup (Full Analysis Set)



Note: Hemoglobin Stabilization was defined as avoidance of a ≥ 2 g/dL decrease in hemoglobin level from baseline in the absence of transfusion through Day 183 (Week 26).
Abbreviations: ALXN1210 = ravulizumab; CI = confidence interval; Diff = difference; pRBC = packed red blood cell; ULN = upper limit of normal
Source: FDA's Analyses

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Dose/Dose Response

No dose response analyses were performed.

Durability of Response

Efficacy responses were maintained throughout the 26-week randomized treatment period. This study measured the return of hemolysis using the endpoint of BTH. Due primarily to the differences in C5 excursions > 0.5 µg/mL, fewer ravulizumab-treated patients (4.0%, n = 5) experienced BTH during the 26-week treatment period compared with eculizumab-treated patients (10.7%, n = 13), representing more than a 2-fold difference between treatment groups.

Persistence of Effect

There were no discontinuations of ravulizumab; hence, it was not possible to analyze persistence of effect.

The FDA's Assessment:
The FDA agrees with the results in this section.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

In Study ALXN1210-PNH-301, for EORTC QLQ C-30, a higher percentage of patients in the ravulizumab group had at least a 10-point (i.e., clinically meaningful) 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.

Additional Analyses Conducted on the Individual Trial

Not applicable

The FDA's Assessment:
The Clinical Outcomes Assessment team was consulted regarding analysis of the secondary patient reported outcome endpoints. Please refer to the COA review by Dr. Julia Ju.

From the summary of the COA review, refer to section 8.1.5.

8.1.3. ALXN1210-PNH-302

The Applicant's Position:

Trial Design

Study ALXN1210-PNH-302 is an ongoing Phase 3, open label, randomized, active controlled, multicenter global study to evaluate the safety and efficacy of ravulizumab versus eculizumab administered by IV infusion to adult patients with PNH who were clinically stable after treatment with eculizumab for at least the previous 6 months. The objective of the development in the eculizumab-experienced patient population is to show that safety and efficacy are maintained after patients switch from eculizumab to ravulizumab.

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Study ALXN1210-PNH-302 enrolled patients who were clinically stable on eculizumab treatment and who might benefit from a treatment with a longer half-life that required fewer infusions while maintaining clinical disease stability. The primary objective of this study was to assess the non-inferiority of ravulizumab compared to eculizumab in adult patients with 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% CI for the difference (ravulizumab – eculizumab) in percent change in LDH level was less than 15%.

The study design, eligibility criteria, schedule of assessment, and dosing schedule of Study ALXN1210-PNH-302 was the same as that for Study ALXN1210-PNH-301 with the following exceptions:

- ALXN1210-PNH-302 enrolled patients who were clinically stable after having been treated with eculizumab for at least the past 6 months.
- In Study ALXN1210-PNH-302, the primary endpoint of change in LDH allowed 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.
- 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 ravulizumab during the 26 week Primary Evaluation Period. The randomization codes and treatments assigned are provided in ALX1210-PNH-302, Appendix 16.1.7.

Study Endpoints

<u>Primary</u>

- Hemolysis as directly measured by percent change in LDH from baseline to Day 183 (Week 26)

<u>Key Secondary (tested in a hierarchical manner)</u>

If non-inferiority was met for the primary endpoint, key secondary endpoints were tested for non-inferiority using a closed testing procedure in the following order so that the lack of significance of a test precluded assessment of subsequent tests:

1. Proportion of patients with BTH through Day 183 (Week 26)
2. Change from baseline to Day 183 (Week 26) in FACIT Fatigue
3. Transfusion avoidance (TA) through Day 183 (Week 26)
4. Proportion of patients with stabilized hemoglobin through Day 183 (Week 26)

If non-inferiority was established for all key secondary endpoints and a larger effect for ALXN1210 was observed, then superiority was assessed using a closed testing procedure in 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)

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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 hemoglobin through Day 183 (Week 26)
9. Transfusion avoidance

The key secondary study endpoints for the ALXN1210-PNH-302 Study are the same as in ALXN1210-PNH-301, however TA was a key secondary endpoint rather than coprimary and LDH-N was an "other" secondary endpoint. These modifications were made because patients were stable on eculizumab at baseline (i.e., LDH level ≤ 1.5 × the upper limit of normal at screening) and most patients were anticipated to be transfusion independent at study entry.

Statistical Analysis Plan

The statistical analysis plan (SAP) was finalized on 12 Dec 2017, prior to database lock for the Primary Evaluation Period. The final version of the SAP is provided in is provided in ALXN1210-PNH-302 CSR, Appendix 16.1.9.1.

Sample Size Determination

Approximately 192 patients were planned to be randomly assigned in a 1:1 ratio to continue on eculizumab (N = 96) or switch to ravulizumab (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 ravulizumab group to patients in the eculizumab group. The primary endpoint of hemolysis 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 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 ravulizumab 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%).

Endpoints and NIMs for the Phase 3 studies are presented in Table 17. The factors used to estimate sample size and determine NIMs are detailed in the statistical analysis plan appended to the clinical study report.

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Table 17: Study ALXN1210-PNH-302 Primary and Key Secondary Endpoints

Endpoint	Statistic for Treatment Comparison	NIM	Eculizumab Effect Preserved
Primary			
% Change in LDH	Difference in % change	15%[a]	89%
Key Secondary			
% Breakthrough Hemolysis	Difference in rate	20%[a,b]	51%
Change in FACIT-Fatigue	Difference in change	-3[b]	50%
% Transfusion Avoidance	Difference in rate	-20%[a]	60%
% Hemoglobin 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 NIM.

[b] 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.

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

Source: Module 2.7.3, Table 9

Analysis Populations

Efficacy analyses were performed using the FAS, the primary efficacy population. The primary efficacy endpoint analysis, as well as key secondary endpoint analyses, were repeated using the PP Set as a sensitivity analysis. Definition for the FAS was the same as Study ALXN1210-PNH-301. 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 criteria #2, 3, and 4 (ALXN1210-PNH-302 CSR Section 9.3.1)
- Did not meet exclusion criteria #1, 2, 3, 4, and 5 (ALXN1210-PNH-302 CSR Section 9.3.2)
- Never received the wrong randomized treatment
- Followed the protocol-specified transfusion guidelines

Analysis Methods

The primary efficacy endpoint was percent change from the difference between treatment groups in percent change in LDH from baseline to Day 183 (Week 26). Absolute LDH levels, and the change and percent change from baseline, were summarized at all study visits by treatment group.

The percent change in LDH was analyzed using a mixed-effect model for repeated measures (MMRM) (Mallinckrodt, 2001; Mallinckrodt, 2004) 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). An unstructured covariance matrix was used to model the within-patient errors. If this analysis failed to converge, the following structures were tested and the final covariance structure was determined by Akaike's

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information criterion; first order autoregressive, compound symmetry and Toeplitz method. The Kenward-Roger approximation (Kenward, 1997) was used to estimate denominator degrees of freedom. A difference in percent change in LDH between the ravulizumab and eculizumab treatment groups at Day 183 along with a 2-sided 95% CI were calculated.

If the upper bound of the 95% CI for the difference (ravulizumab -eculizumab) was less than the NIM of 15%, then ravulizumab treatment would be concluded to be no inferior to eculizumab.

Sensitivity Analyses

The following sensitivity analyses were produced for the primary endpoint of LDH-PCHG:

- The primary efficacy endpoint analysis was repeated using the PP set.
- The primary efficacy endpoint analysis, excluding the history of transfusion stratification factor, and baseline LDH level from the model as explanatory variables.

Additional analyses may be conducted for the primary endpoint of LDH-PCHG with consideration for the “missing not at random” assumption should the patient dropout rate exceed 5%.

The primary efficacy endpoint analysis, as well as key secondary endpoint analyses, were repeated using the PP Set as a sensitivity analysis. Sensitivity analyses for the primary endpoint of LDH-PCHG are described in the SAP.

Subgroup Analyses

Summaries of TA and LDH-N were produced for the subgroups of the randomization stratification variables. Summaries of the coprimary endpoints of TA and LDH-N and for the key secondary endpoints also were produced for subgroups based on sex, race, region, and age at first study drug infusion (18 to 65 and > 65 years).

Protocol Amendments

The original protocol (dated 27 Jan 2017) was globally amended 1 time during the Primary Evaluation Period of the study. Significant changes for this protocol amendment are provided below.

First global amendment (dated 23 Oct 2017):

- Revised the statistical analysis description regarding control of Type I error when testing the primary and secondary endpoints for non-inferiority and superiority
- To reduce the patient data collection burden, removed the exploratory endpoints of Patient-Reported PNH Symptoms and Healthcare Resource Utilization
- Clarified that transfusions administered in the inpatient or outpatient setting should not be captured as AEs or SAEs unless identified as such by the Investigator

Changes in Planned Analyses

For the analyses of subgroups utilizing MMRM, an unstructured covariance structure was used to model the within-patient errors for each category in a subgroup, and if that failed to converge for any category, then a Topelitz covariance structure was used for all categories.

The FDA's Assessment:

The trial design, study endpoints, protocol amendments and SAP described above by the Applicant are acceptable. Additional details regarding the SAP are presented below.

Non-inferiority Margin Derivation:

LDH-PCHG:

This margin is 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%).

Percent of patients with breakthrough hemolysis:

At week 26, 0% of patients on eculizumab had breakthrough hemolysis (LDH ≥ 2 × ULN) in TRIUMPH study. Based on data from the PNH Registry, 47% of patients who discontinued eculizumab had breakthrough hemolysis. A traditional choice of NIM is one with ≤ 50% loss of benefit. This would result in a NIM of 23% and rounded to a more clinically conservative value of 20%.

Change in FACIT-Fatigue:

The margin of -3 was selected based on data from the TRIUMPH study, in which patients on eculizumab had a mean (SD) FACIT-Fatigue score of 36.7 (10.5) at Baseline and a mean score of 42.9 (7.5) at Week 26. The baseline from the TRIUMPH study was used in constructing the NIM as very few patients who discontinued treatment in the PNH registry had data on FACIT-Fatigue (N = 4). A traditional choice of NIM is one with ≤ 50% loss of benefit. This would result in a NIM of -3.

Transfusion Avoidance Rate

The margin of -20% was selected based on data from the PNH Registry examining loss of benefit among patients who discontinued eculizumab compared to patients who remained on eculizumab treatment. The average TA rate was 87% at Week 26 after 12, 26, 52, and 78 weeks of eculizumab treatment. The rate of TA for patients who discontinued eculizumab was 37%. Using the traditional choice of NIM, with ≤ 50% loss of benefit, gives a margin of -25%; however, the more clinically conservative margin of -20% was selected. Again, the non-

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inferiority margin was based on the point estimate of the effect of eculizumab due to the feasibility of the trial sample size.

Percent of patients with stabilized hemoglobin:

The margin of -20% was selected based on data from the PNH Registry examining loss of benefit among patients who discontinued eculizumab compared to patients who remained on eculizumab treatment. The hemoglobin stabilization rate was 91% while on eculizumab and 46% for patients that discontinued eculizumab. Using the traditional choice of NIM, with ≤ 50% loss of benefit, a margin of -22.5% is obtained. The selected -20% margin is more clinically conservative.

Statistical Reviewer's comment:

- Non-inferiority margins for primary and secondary efficacy endpoints were never agreed in the IND meetings or correspondence between the applicant and FDA.
- In the Written Response of the Type C Guidance meeting sent to the Applicant on July 7, 2017, FDA stated that "As we communicated to you on December 15, 2016, we would accept a non-inferiority margin of no more than 10% given the established importance of the efficacy of eculizumab for the treatment of PNH. Your proposed margin of 15% in ALXN1210-PNH-302 for the endpoint percent change in lactate dehydrogenase level is greater than the largest clinically acceptable difference."

Due to the clinical important of preserving treatment effect, we use NIMs of 10% in this review to establish the efficacy for efficacy endpoint LHD-PCHG, TA, Proportion of patients with stabilized hemoglobin, and proportion of patients with breakthrough hemolysis.

FDA Clinical Reviewer's comments:

The study population, trial design and study endpoints described above by the Applicant are acceptable. The primary efficacy endpoint of percent change in LDH from baseline to Day 183 adequately represent the pathophysiology of PNH and the clinically important disease parameters relevant to patients with PNH. TA was a key secondary endpoint rather than coprimary endpoint in Study ALXN1210-PNH-302. The secondary study endpoints for Study ALXN1210-PNH-302 were otherwise the same as in ALXN1210-PNH-301.

The sample size estimate for Study ALXN1210-PNH-302 was based on a non-inferiority design comparing patients in the ravulizumab group to patients in the eculizumab group. A NIM of 15% was used by the Applicant based on data from Alexion's PNH Registry which showed that for patients who discontinued eculizumab, the mean percent change in LDH was +134%. Preserving 50% of the benefit would give a margin of 67%; however, the more conservative margin of 15% was selected by the Applicant to preserve a more substantial amount of treatment effect. Use of a more conservative NIM would have required a larger sample size which may have negatively affected the feasibility of the study given the rarity of PNH. Sensitivity analyses using a 10% NIM were conducted by the FDA. The results are presented in Section 8.1.2 below.

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8.1.4. Study Results

The Applicant's Position:

Compliance with Good Clinical Practices

Study ALXN1210-PNH-302 was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH E6 Guidelines for GCP and applicable regulatory requirements. Ethics Committees and Institutional Review Boards reviewed and approved the protocol, protocol amendments, and patient informed consent forms. All patients or their legal representatives voluntarily consented prior to study enrollment.

Financial Disclosure

Disclosure information is presented in Section 19.2. Given the distribution of patients across multiple investigative sites, the randomized study design, and the objective nature of the primary and most key secondary endpoints, it is unlikely for any 1 investigator to influence overall outcomes.

The FDA's Assessment:

The FDA agrees with the statements in this section. Refer to appendix 19.2 for financial disclosure forms.

Patient Disposition

A total of 197 patients were randomized at 49 sites in 11 countries (Australia, Canada, France, Germany, Italy, Japan, Netherlands, Republic of Korea, Spain, United Kingdom, and United States). Of the 197 randomized patients, 195 patients were treated and 191 patients completed the Primary Evaluation Period; 1 patient in the ravulizumab group and 3 patients in the eculizumab group prematurely discontinued study drug (Figure 18).

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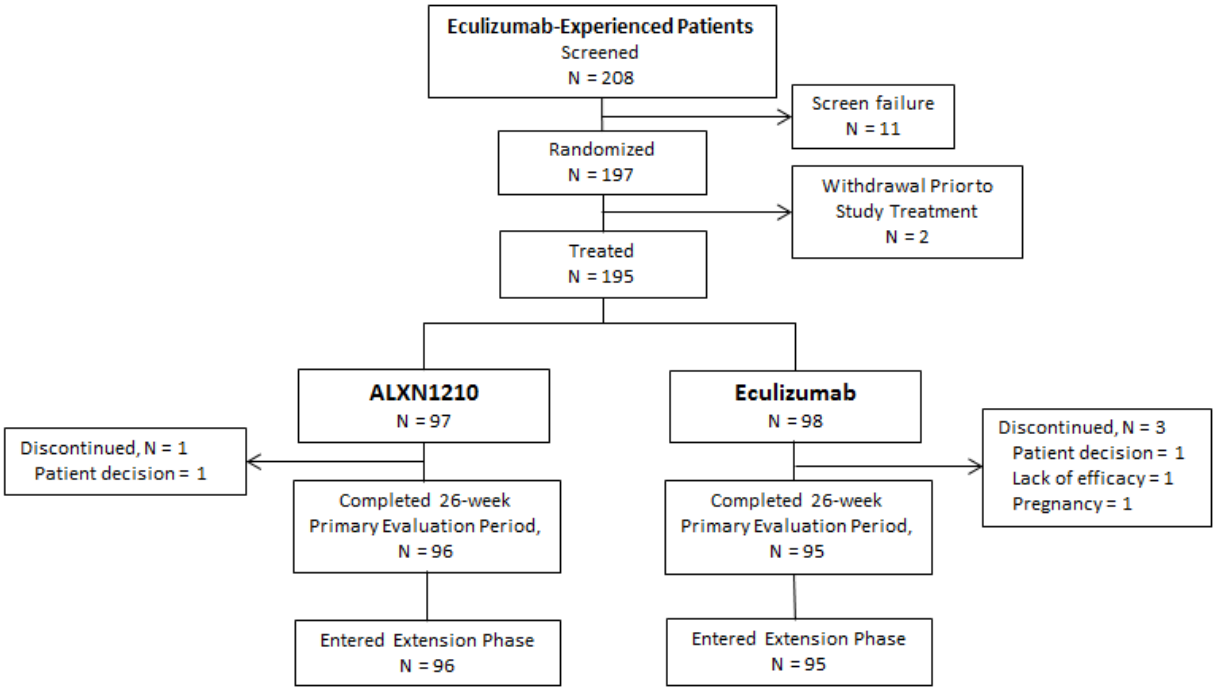
Figure 18 Study ALXN1210-PNH-302 Patient Disposition – Primary Evaluation Period



Source: ALXN1210-PNH-302 CSR, Figure 3

Of the 197 randomized patients, 195 treated patients (97 patients in the ravulizumab group and 98 patients in the eculizumab group) were included in the FAS. Nine treated patients from the FAS were excluded from the PP Set; 2 patients in the ravulizumab group were determined to not meet the criteria of being treated with eculizumab according to the labelled dosing recommendation for PNH (eculizumab infusion every 14 ± 2 days) within 6 months prior to Day 1 since a few of the eculizumab doses had been administered outside of the ± 2 day window; 2 patients in the eculizumab group were determined to have had an LDH value > 2 × ULN within 6 months prior to Day 1; and 5 patients (ravulizumab: n = 2, eculizumab: n = 3) met the protocol-specified criteria for pRBC transfusion (hemoglobin ≤ 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.

Protocol Violations/Deviations

Any departure from the approved protocol was considered a protocol deviation. Major deviations were those that could potentially impact the rights, welfare, or safety of the patient and/or the integrity of study data; all others were considered minor. A total of 30 patients had major protocol deviations in the Primary Evaluation Period. None of these protocol deviations were considered to impact the safety of the patients or the interpretation of efficacy and safety results from this study.

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The FDA's Assessment:

The FDA agrees with the results presented in this section. Major protocol deviations by treatment are presented below.

Table 18: Study ALXN1210-PNH-302 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)

Source: ALXN1210-PNH-302 CSR, Table 9

Demographic Characteristics

Study entry criteria were carefully selected to reflect an adult patient population consistent with the population likely to be treated with ravulizumab in clinical practice. Patients in Study ALXN1210-PNH-302 had stable disease determined by LDH ≤ 1.5 × ULN after having been treated for at least 6 months with eculizumab according to the labelled dosing recommendation for PNH. A minority (12%) of patients were transfusion-dependent at baseline due to the fact that their disease was controlled by eculizumab.

There were no noteworthy differences in the demographic characteristics between the ravulizumab and eculizumab treatment groups (Table 19).

Table 19: Study ALXN1210-PNH-302 Demographic Characteristics

Characteristic	Ravulizumab (N = 97)	Eculizumab (N = 98)	Total (N = 195)
Age (years) at first infusion in study			
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
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)
Hispanic or Latino	3 (3.1)	4 (4.1)	7 (3.6)
Not reported	15 (15.5)	17 (17.3)	32 (16.4)
Missing/unknown	3 (3.1)	0	3 (1.5)
Race, n (%)			
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)
White	50 (51.5)	61 (62.2)	111 (56.9)
Other	2 (2.1)	1 (1.0)	3 (1.5)
Not reported	13 (13.4)	13 (13.3)	26 (13.3)
Black or African American	5 (5.2)	3 (3.1)	8 (4.1)
Multiple	1 (1.0)	0	1 (0.5)
Unknown	3 (3.1)	1 (1.0)	4 (2.1)
Body weight (kg)			
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
Body weight (kg) category, n (%)			
≥ 40 to < 60	27 (27.8)	22 (22.4)	49 (25.1)
≥ 60 to < 100	62 (63.9)	74 (75.5)	136 (69.7)
≥ 100	8 (8.2)	2 (2.0)	10 (5.1)

Abbreviations: max = maximum; min = minimum; SD = standard deviation
Source: Module 2.7.3, Table 24

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Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

PNH medical history and baseline disease characteristics were similar between ravulizumab and eculizumab treatment groups (Table 20).

Table 20: Study ALXN1210-PNH-302 Baseline Disease Characteristics

Parameter	Statistics	Ravulizumab (N = 97)	Eculizumab (N = 98)
Age (years) at PNH diagnosis	Mean (SD) Median Min, max	34.1 (14.41) 32.0 6, 73	36.8 (14.14) 35.0 11, 74
Age (years) at first infusion in study	Mean (SD) Median Min, max	46.6 (14.41) 45.0 18, 79	48.8 (13.97) 49.0 23, 77
Sex (n, %)	Male Female	50 (51.5) 47 (48.5)	48 (49.0) 50 (51.0)
Pre-treatment LDH levels	Mean (SD) Median	228.0 (48.71) 224.0	235.2 (49.71) 234.0
Number of patients with pRBC/whole blood Transfusions within 12 months prior to first dose	n (%)	13 (13.4)	12 (12.2)
pRBC/whole blood Transfusions within 12 months prior to first dose	Total Mean (SD) Median	64 4.9 (5.51) 3.0	30 2.5 (2.32) 1.5
Units of pRBC/whole blood transfused within 12 months prior to first dose	Total Mean (SD) Median	103 7.9 (8.78) 4.0	50 4.2 (3.83) 2.5
Patients with any PNH conditions prior to informed consent Anemia Hematuria or hemoglobinuria Aplastic anemia Renal failure Myelodysplastic syndrome Pregnancy complication Other[a]	n (%)	90 (92.8) 64 (66.0) 47 (48.5) 34 (35.1) 11 (11.3) 3 (3.1) 4 (4.1) 14 (14.4)	96 (98.0) 67 (68.4) 48 (49.0) 39 (39.8) 7 (7.1) 6 (6.1) 9 (9.2) 14 (14.3)

Abbreviations: BMI = body mass index; max = maximum; min = minimum; SD = standard deviation
Source: Module 2.7.3, Table 25

The FDA's Assessment:

The FDA agrees with the results presented in this section. Demographic characteristics and baseline disease characteristics were balanced between ravulizumab and eculizumab treatment groups.

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Randomization was stratified by transfusion history (received a transfusion of pRBC within 12 months prior to Day 1, yes or no). Observed stratification factors are summarized in **Table 21**. Stratification seems to be balance among treatment arms.

Table 21: Study ALXN1210-PNH-302 Stratification Factor by Treatment (FAS)

Observed Stratification Groups	ALXN1210 (N = 98)	Eculizumab (N = 99)	Total (N = 197)
Yes	13 (13.3)	12 (12.1)	25 (12.7)
No	85 (86.7)	87 (87.9)	172 (87.3)

Source: Reviewer's Analysis

Treatment Compliance and Concomitant Medications

All patients in both treatment groups received all of the planned infusions during the Primary Evaluation Period. One patient in the eculizumab group received 1 unscheduled additional dose of eculizumab on Day 176; the investigator administered the extra dose to this patient in the setting of BTH following an serious adverse event (SAE) of acute pyelonephritis on Day 173.

During the study, 97.9% of patients (97.9% in the ravulizumab group and 98.0% in the eculizumab group) took at least 1 concomitant medication. The prior and concomitant medications used were consistent with a PNH patient population.

The FDA's Assessment:

The FDA agrees with the results presented in this section.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Patients who switched from eculizumab to ravulizumab maintained reductions in LDH levels. The primary endpoint, percent change in LDH from baseline to Day 183, met the primary objective of statistically significant non-inferiority of ALXN1210 compared to eculizumab. The point estimate for the difference between treatment groups favored ALXN1210 (Figure 19 with treatment difference displayed as eculizumab - ravulizumab).

Mean percent change in LDH from baseline to Day 183 showed a decrease of 0.82% for the ravulizumab group and an increase of 8.39% for the eculizumab group with a treatment difference (ravulizumab - eculizumab) of -9.21% (95% CI: -18.84%, 0.42%).

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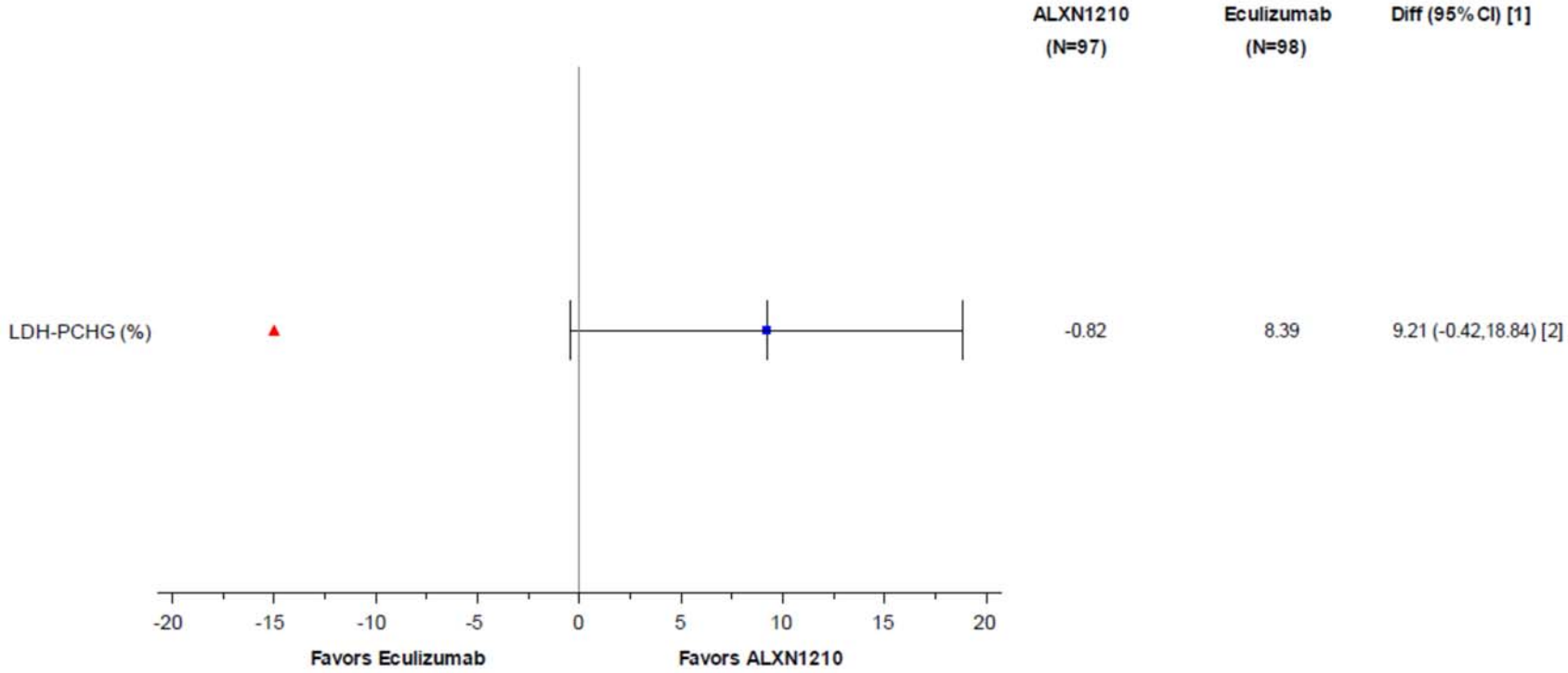
Figure 19: Study ALXN1210-PNH-302 Forest Plot of Primary Endpoint – Primary Evaluation Period (Full Analysis Set)



Note: The red triangle indicates the non-inferiority margin.
[1] Diff (95% CI) was based on estimated differences in percent with 95% CI.
[2] Treatment difference was estimated for eculizumab - ravulizumab.
Abbreviations: ALXN1210 = ravulizumab; CI = confidence interval; Diff = difference; LDH = lactate dehydrogenase; LDH-PCHG = percent change in LDH
Source: Module 2.7.3 Figure 6

Efficacy Results – Secondary and other relevant endpoints

Ravulizumab achieved statistically significant non-inferiority for all 4 key secondary endpoints (Figure 20). All 4 key secondary endpoints had point estimates which favored ravulizumab over eculizumab:

- Breakthrough hemolysis was experienced by none of the patients in the ravulizumab group and 5 (5.1%) of the patients in the eculizumab group. The difference between treatment groups was -5.1% (95% CI: -18.99%, 8.89%). The incidence of breakthrough hemolysis was higher in the eculizumab group (7 events) than in the ravulizumab group (0 events). Of the 7 breakthrough hemolysis events seen in the eculizumab group, 4 were associated with elevated free C5 above 0.5 µg/mL. There were no breakthrough hemolysis events in the ravulizumab group, and no patients in the ravulizumab group had elevations of free C5 levels above 0.5 µg/mL.
- LS mean change in FACIT-Fatigue total score from baseline to Day 183 was 2.01 for the ravulizumab group and 0.54 for the eculizumab group. The LS mean difference between treatment groups was 1.47 (95% CI: -0.21, 3.15). Both treatment groups showed improvement in fatigue as measured by FACIT-Fatigue over time, with ravulizumab better than eculizumab at all time points following Day 8.
- Transfusion avoidance was achieved by 87.6% of patients on ravulizumab compared to 82.7% of patient on eculizumab by Day 183. 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%).
- Hemoglobin stabilization through Day 183 was achieved by 76.3% of patients in the ravulizumab group and 75.5% of patients in the eculizumab group. The difference between treatment groups was 1.4% (95% CI: -10.41%, 13.31%).

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 favoring 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.

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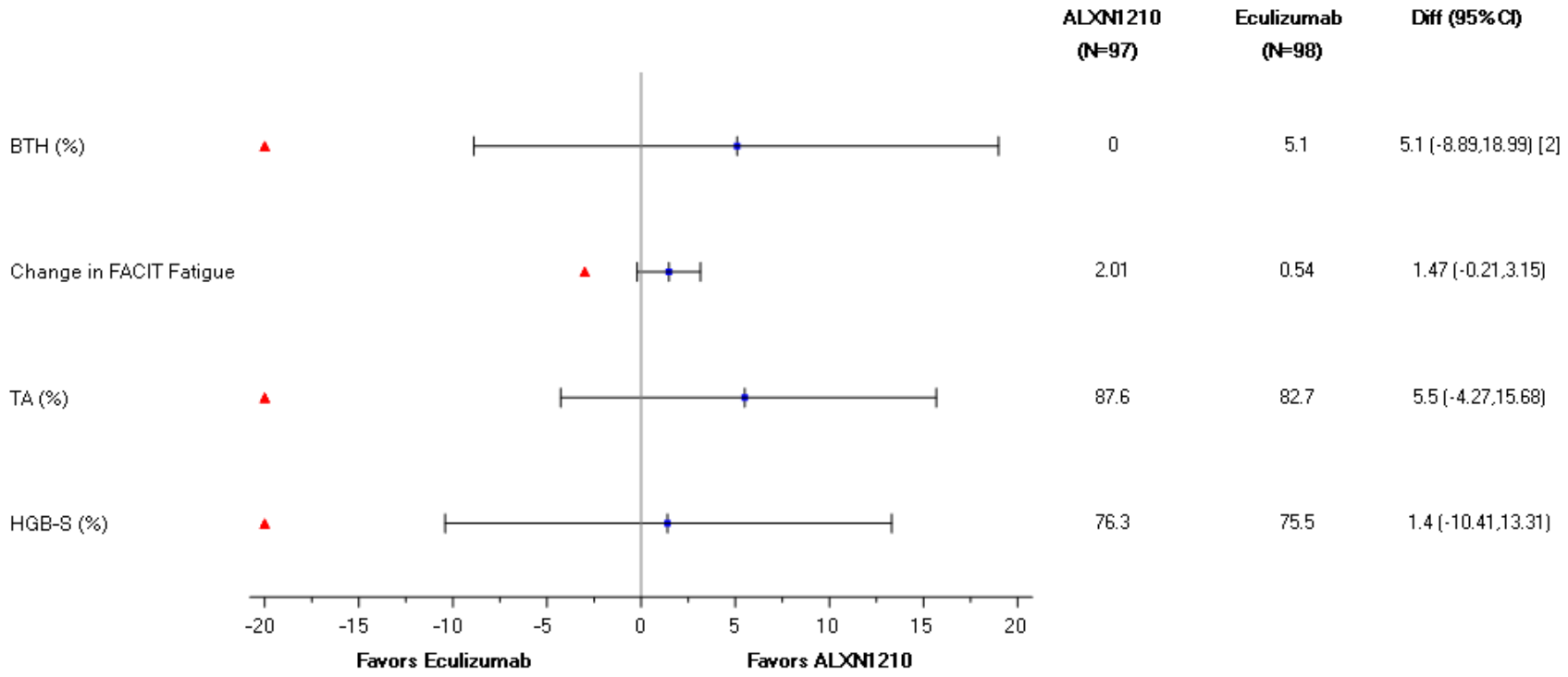
Figure 20: Study ALXN1210-PNH-302 Forest Plot of Key Secondary Endpoints – Primary Evaluation Period (Full Analysis Set)



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 BTH where treatment difference was based on eculizumab - ravulizumab.
Abbreviations: ALXN1210 = ravulizumab; BTH = breakthrough hemolysis; CI = confidence interval; Diff = difference; FACIT = Functional Assessment of Chronic Illness Therapy; HGB-S = hemoglobin stabilization; LDH-PCHG = percent change in lactate dehydrogenase; TA = transfusion avoidance
Source: Module 2.7.3, Figure 8

The FDA's Assessment:

Efficacy was established based on hemolysis as measured by LDH percent change from baseline to Day 183. Supportive efficacy data included transfusion avoidance, proportion of patients with stabilized hemoglobin, and breakthrough hemolysis through Day 183.

As presented in Table 22, non-inferiority of ravulizumab versus eculizumab was demonstrated in the patients with PNH previously treated with eculizumab using FDA recommended NIMs of -10% with regard to efficacy endpoints of LDH percent change from baseline, transfusion avoidance, and proportion of patients with breakthrough hemolysis. Note that ravulizumab did not achieve non-inferiority for key secondary endpoint hemoglobin stabilization based on FDA analysis of NIM of -10% because the lower bound of 95% CI is -10.4%, exceeding FDA recommended margin of -10%.

FDA Clinical Reviewer's comments:

(b) (4)

Please refer to the discussion in Section 8.1.5 regarding the patient reported outcome endpoint.

Table 22: Efficacy Results in Study ALXN1210-PNH-302 (Full Analysis Set)

	Ultomiris (N=97) n (%)	Eculizumab (N=98) n (%)	Ultomiris vs. Eculizumab Difference (95% CI)
Transfusion Avoidance (%)	85 (87.6)	81 (82.7)	5.5 (-4.3, 15.7)
Hemoglobin Stabilization (%)	74 (76.3)	74 (75.5)	1.4 (-10.4, 13.3)
Breakthrough Hemolysis (%)	0 (0.0)	5 (5.1)	-5.1 (-19.0, 8.9)
LDH Percent Change [1]	LS Mean(SEM) -0.8 (3.0)	LS Mean(SEM) 8.4 (3.0)	Difference (95% CI) -9.2 (-18.8, 0.4)

Note: LDH = lactate dehydrogenase; MMRM=Mixed Model for Repeated Measures; LS=Least square; CI=Confidence Interval; SEM=Standard error of the mean.
[1]: Estimates are based on MMRM that includes treatment group, observed transfusion history (yes/no within 1 year prior to first dose of study drug), baseline LDH level (as a continuous variable), study visit and study visit by treatment group interaction.
Source: FDA's Analyses

Subgroup Analyses

Subgroup analyses were performed for the randomization stratification variables of transfusion history and screening LDH levels and for sex, race, region, and age for the primary and key secondary endpoints. No sensitive subgroups were identified. The resulting point estimates for subgroups were consistent with the primary analysis: point estimates for all subgroups favored

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ALXN1210. Results for subgroup analyses in Study ALXN1210-PNH-302 are presented graphically for percent change in LDH (Figure 21).

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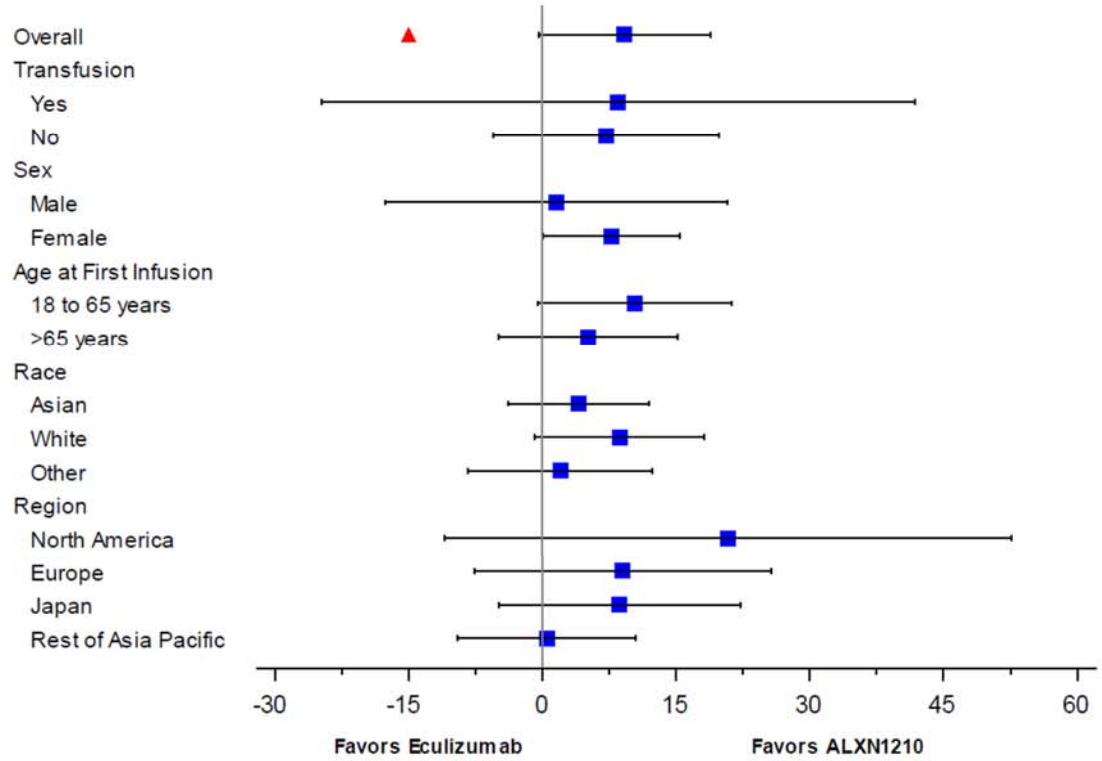
Figure 21: Study ALXN1210-PNH-302 Forest Plot of Percent Change to Day 183 (Week 26) in LDH Treatment Difference During the Primary Evaluation Period, Overall and by Subgroup (Full Analysis Set)



	ALXN1210 (N=97)	Eculizumab (N=98)	Diff (95% CI)
Overall	-0.82	8.39	9.21 (-0.42,18.84)
Transfusion			
Yes	1.04	9.56	8.52 (-24.81,41.85)
No	-1.20	5.94	7.14 (-5.52,19.79)
Sex			
Male	5.62	7.24	1.62 (-17.61,20.85)
Female	-3.81	3.96	7.77 (0.08,15.45)
Age at First Infusion			
18 to 65 years	-0.09	10.29	10.38 (-0.53,21.30)
>65 years	-3.77	1.37	5.13 (-4.89,15.15)
Race			
Asian	2.50	6.61	4.11 (-3.82,12.04)
White	-0.78	7.91	8.69 (-0.83,18.20)
Other	-5.25	-3.23	2.02 (-8.30,12.35)
Region			
North America	2.49	23.33	20.84 (-10.98,52.67)
Europe	-6.34	2.68	9.01 (-7.60,25.63)
Japan	7.48	16.13	8.65 (-4.88,22.17)
Rest of Asia Pacific	4.83	5.30	0.47 (-9.50,10.44)

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
Source: Module 2.7.3 Figure 12

The FDA's Assessment:

The FDA agree that no sensitive subgroups were identified for primary endpoint percent change in LDH. We also conducted subgroup analyses for clinical important endpoint achieving transfusion avoidance and proportion of patients with hemoglobin stabilization through Day 183. As presented in Table 24, most point estimates for percent of patients achieving transfusion avoidance by subgroups were generally consistent with the primary analysis which is favored ALXN121. For subgroup analysis of proportion of patients with hemoglobin stabilization, the point estimate was favored eculizumab in male patients and white patients.

Table 23: Subgroup Analysis for Number (%) of Patients Achieving Transfusion Avoidance in Study ALXN1210-PNH-302 (Full Analysis Set)

	ALXN1210 (N=97) % (n/N)	Eculizumab (N=98) % (n/N)	Treatment Difference (ALXN1210-Eculizumab)
Transfusion			
Yes	30.8 (4/13)	58.3 (7/12)	-27.6 (-62.39, 14.12)
No	96.4 (81/84)	86.0 (74/86)	10.4 (-5.03, 25.02)
Sex			
Male	92.0 (46/50)	89.6 (43/48)	2.4 (-17.19, 22.50)
Female	83.0 (39/47)	76.0 (38/50)	7.0 (-13.24, 26.61)
Age at First Infusion			
18-65 years	89.4 (76/85)	84.5 (71/84)	4.9 (-10.31, 19.62)
> 65 years	75.0 (9/12)	71.4 (10/14)	3.6 (-33.91, 40.68)
Race			
Asian	82.6 (19/23)	78.9 (15/19)	3.7 (-26.59, 32.78)
White	88.0 (44/50)	83.6 (51/61)	4.4 (-14.29, 22.73)
Other	91.7 (22/24)	83.3 (15/18)	8.3 (-22.59, 38.14)
Region			
North America	91.7 (11/12)	91.7 (11/12)	0.0 (-41.75, 41.75)
Europe	88.7 (55/62)	83.3 (55/66)	5.4 (-12.01, 22.60)
Japan	83.3 (5/6)	57.1 (4/7)	26.2 (-28.79, 72.34)
Rest of the Pacific	82.4 (14/17)	84.6 (11/13)	-2.3 (-36.71, 33.20)

Source: FDA's Analyses

Table 24: Subgroup Analysis for Number (%) of Patients with Stabilized Hemoglobin Through Day 183 in Study ALXN1210-PNH-302 (Full Analysis Set)

	ALXN1210 (N=97) % (n/N)	Eculizumab (N=98) % (n/N)	Treatment Difference (ALXN1210-Eculizumab)
Transfusion			

Yes	15.4 (2/13)	41.7 (5/12)	-26.3 (-59.77, 15.09)
No	85.7 (72/84)	80.2 (69/86)	5.5 (-9.75, 20.15)
Sex			
Male	78.0 (39/50)	81.3 (39/48)	-3.2 (-22.62, 16.68)
Female	74.5 (35/47)	70.0 (35/50)	4.5 (-15.68, 23.87)
Age at First Infusion			
18-65 years	77.6 (66/85)	76.2 (64/84)	1.5 (-13.82, 16.14)
> 65 years	77.6 (8/12)	71.4 (10/14)	-4.8 (-41.14, 33.65)
Race			
Asian	69.6 (16/23)	68.4 (13/19)	1.1 (-28.81, 30.79)
White	74.0 (37/50)	78.7 (48/61)	-4.7 (-23.11, 13.94)
Other	87.5 (21/24)	72.2 (13/18)	15.3 (-15.91, 44.34)
Region			
North America	66.7 (8/12)	91.7 (11/12)	-25.0 (-62.40, 18.81)
Europe	79.0 (49/62)	75.8 (50/66)	3.3 (-14.11, 20.63)
Japan	66.7 (4/6)	28.6 (2/7)	38.1 (-20.89, 80.47)
Rest of the Pacific	76.5 (13/17)	84.6 (11/13)	-8.1 (-41.97, 27.86)

Source: FDA's Analyses

Dose/Dose Response

No dose response analyses were performed.

Durability of Response

Efficacy responses were maintained throughout the 26-week randomized treatment period for ravulizumab. This study measured the return of hemolysis using the endpoint of BTH. No events of BTH were observed during the 26-week treatment period for the ravulizumab group. In contrast, 5 patients in the eculizumab group experienced BTH events.

Persistence of Effect

There was only 1 discontinuation of ravulizumab; hence, it was not possible to analyze persistence of effect.

The FDA's Assessment:

The FDA agrees with the assessment here.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

At Baseline, for both treatment groups, mean EORTC QLQ-C30 subscale scores reflected a patient population with stable disease: Global Health Status and Physical Functioning subscale scores were high, ranging from 69% to 88% across treatment groups, and Fatigue subscale scores were low, 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.

Additional Analyses Conducted on the Individual Trial

Not applicable

The FDA's Assessment:

The Clinical Outcomes Assessment team was consulted regarding analysis of the secondary patient reported outcome endpoints. Please refer to the COA review by Dr. Julia Ju.

From the summary of the COA review, refer to section 8.1.5.

8.1.5. Assessment of Efficacy Across Trials

The Applicant's Position:

Primary Endpoints

There were no pooled or integrated analyses performed since the two Phase 3 studies enrolled different patient populations. Across both Phase 3 studies, ravulizumab achieved statistically significant non-inferiority compared to eculizumab in reducing and maintaining control of hemolysis in patients with PNH. Eculizumab performed as expected in these studies, consistent with the results of the registrational eculizumab studies. For all primary efficacy endpoints, the large differences between the boundaries of the CIs and the NIMs establish the strength of evidence of the study results. Point estimates consistently favored ravulizumab over eculizumab for the primary efficacy endpoints in both Phase 3 studies, where eculizumab demonstrated its expected high level of efficacy.

Secondary and Other Endpoints

Point estimates consistently favored ravulizumab over eculizumab for all of the key secondary efficacy endpoints in the Phase 3 studies.

Importantly, the incidence of BTH was more than 2-fold higher in the eculizumab group compared to the ravulizumab group in both studies.

The consistency and robustness of results demonstrated across all efficacy endpoints representing the continuum of PNH pathophysiology strengthens the conclusion that ravulizumab is effective in the treatment of PNH. Efficacy was demonstrated in adult patients with PNH regardless of transfusion history or previous eculizumab treatment history.

It is important to include all of the primary and key secondary endpoints in labeling, in order to give physicians a full and broad understanding of the effect of ravulizumab on PNH disease. The primary and key secondary endpoints measure different aspects of PNH disease that are important to the evaluation of efficacy. LDH is a direct measure of hemolysis, the central pathophysiological feature of PNH disease. Transfusions and hemoglobin levels are clinically meaningful results of this hemolysis. Quality of life and breakthrough hemolysis are additional

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key measures of efficacy for a complement inhibitor that blocks C5 and therefore the consequences of PNH disease.

Subpopulations

The primary efficacy endpoints and key secondary efficacy endpoints were analyzed by the study-specific disease severity stratification factors. Treatment effects were consistent across all subpopulations regardless of other baseline and demographic factors.

In Study ALXN1210-PNH-301, the results for the subgroup analyses for the primary endpoints of TA and LDH-N were consistent across subgroups, and the point estimates for most groups favored ravulizumab. In Study ALXN1210-PNH-302, the results for the subgroup analyses for the primary endpoint of percent change in LDH were consistent across subgroups, and the point estimates for all groups favored ravulizumab.

Comparison of efficacy results from the two Phase 3 studies demonstrates that complement inhibitor-naïve and eculizumab-experienced patients with PNH both respond to ravulizumab treatment. Patients taking eculizumab can switch to ravulizumab without loss of efficacy.

Studies of ravulizumab in specific patient subpopulations, including pediatric patients, pregnant and breastfeeding patients, renal impaired patients, and hepatic-impaired patients, have not been conducted. However, there is no evidence from the PK/PD modeling to indicate that dosage needs to be adjusted in these populations.

Additional Efficacy Considerations

The Applicant's Position:

Although there were a limited number of patients in the U.S. in Study ALXN1210-PNH-301, the study captured data across a broad range of geographies including North America, Europe, and Asia and results were similar across the different regions. Therefore, similar to eculizumab, results would be expected to be similar in the U.S. population to the results observed globally. Furthermore, there were no intrinsic or extrinsic factors that would influence the efficacy of ravulizumab. The similarity in outcomes across regions in Study ALXN1210-PNH-302, in which the U.S. had higher representation, further support the global consistency of ravulizumab efficacy outcomes.

The FDA's Assessment:

The FDA agrees no pooled or integrated efficacy analyses are necessary because the two Phase 3 studies enrolled different patient populations.

The Division requested COA Staff input on the adequacy of the FACIT-Fatigue scale (b) (4) This review concludes the following:

- The open-label trial design limits interpretability of the PRO data because patient's knowledge of treatment assignment may lead to systematic overestimation or underestimation of treatment effect of which is currently unknown. With regard to the

non-inferiority design, the non-inferiority margins were not agreed upon based on discussion with the Biostatistical reviewer.

- The FACIT-Fatigue scale includes concepts that are content relevant to PNH patients based on discussion with Clinical and previous applications that labeled data from this instrument (BLA 125166), however, Studies 301 and 302 were not enriched with patients who sufficiently experienced fatigue-related symptoms and impacts as noted by floor effects in several items across both studies.
- While Study 301 generates data that shows improvement in the FACIT-Fatigue total score, there are only select items within the FACIT-Fatigue scale that contribute more to the change observed in the total score based upon review of item-level analyses
- Study 302 demonstrates none to minimal changes in the FACIT-Fatigue total score, however this is expected as patients were clinically stable and previously treated with eculizumab.
- The Applicant defined a clinically meaningful score change in the FACIT-Fatigue total score as 3-points, however there is insufficient data to support this threshold. While one anchor-based empirical cumulative distribution function (eCDF) curve potentially supports a threshold for within-patient meaningful change of 3-points (on a 0-52 scale) if anchored to "A little" response category on the EORTC QLQ-C30 item 12 ("Have you felt weak?"), the other anchor-based eCDF curves suggests that thresholds for within-patient meaningful change range from 5-7 points (on a 0-52 scale) based on "A little" to "Not at all" anchor response categories in EORTC QLQ-C30 item 18 ("Were you tired?") and item 12, respectively. However, the anchor-based eCDF curves should be interpreted cautiously as change is not observed in all FACIT-Fatigue items; further the anchors are not the typical anchors recommended for these types of analyses but were the only items administered in Studies 301 and 302 that could serve as anchors.

FDA Clinical Comment: Given the concerns with the open-label trial design, lack of enrichment of patients with fatigue at baseline and defining a meaningful score change (b) (4)

8.1.6. Integrated Assessment of Effectiveness

<u>The Applicant's Position:</u>

Ravulizumab treatment addresses the unmet medical needs in PNH by allowing for treatment q8w compared to the q2w schedule for eculizumab, and by reducing the incidence of breakthrough hemolysis compared to eculizumab. Ravulizumab was statistically noninferior to eculizumab in 2 well-controlled randomized Phase 3 studies conducted in a population likely to receive ravulizumab in clinical practice. Ravulizumab performed consistently better on all primary and key secondary endpoints in 2 distinct and complementary Phase 3 studies in patients with PNH, regardless of prior treatment history and history of transfusions. These consistent results suggest a clinically differentiated efficacy profile for ravulizumab compared to

the standard of care.

With its immediate, complete, and sustained C5 inhibition, treatment with ravulizumab can be effectively and safely initiated in complement inhibitor-naïve patients with active disease, and eculizumab-experienced patients with stable disease can be effectively and safely switched to ravulizumab. Compared to the q2w eculizumab regimen, the q8w ravulizumab regimen lessens the treatment burden for patients by reducing the number of infusions from 26 per year to 6 per year.

Ravulizumab provides improved control of disease compared to eculizumab, as evidenced by consistently favorable results across a spectrum of biochemical, clinical, and quality of life measures that address different aspects of PNH disease. Despite the robust efficacy achieved by eculizumab in the Phase 3 studies, results for 6 of 6 coprimary and key secondary endpoints in Study ALXN1210-PNH-301 and 5 of 5 primary and key secondary endpoints in Study ALXN1210-PNH-302 consistently favored ravulizumab even for measures where eculizumab is highly effective.

Long term data available from the Extension Phases of the Phase 1b and Phase 2 studies demonstrate sustained reduction of hemolysis with ongoing ravulizumab treatment for up to 100 weeks.

Ravulizumab prevents intravascular hemolysis over an extended q8w dosing interval both in patients who are naïve to complement inhibitor treatment and in patients who have previously been treated with eculizumab. By blocking intravascular hemolysis, ravulizumab ameliorates the sequelae of PNH disease, including transfusions (and the burden and risks associated with transfusions), anemia, and the devastating sequelae of breakthrough hemolysis, and enables a better quality of life through a less burdensome treatment regimen.

The FDA's Assessment:
The efficacy of ravulizumab in patients with PNH was assessed in two open-label, randomized, active-controlled, non-inferiority phase 3 studies: Study 301 and 302. Study 301 enrolled patients with PNH who were complement inhibitor naïve and had active hemolysis. Study 302 enrolled patients with PNH who were clinically stable after having been treated with eculizumab for at least the past 6 months.

Non-inferiority of ravulizumab compared to eculizumab was demonstrated across all efficacy endpoints in the complement inhibitor naïve treatment population using both sponsor's and FDA recommended NIMs. Non-inferiority of ravulizumab versus eculizumab was demonstrated in the patients with PNH previously treated with eculizumab using FDA recommended NIMs of -10% with regard to efficacy endpoints of LDH percent change from baseline, transfusion avoidance, and proportion of patients with breakthrough hemolysis. Note that ravulizumab did not achieve non-inferiority for key secondary endpoint hemoglobin stabilization because the lower bound of 95% CI is -10.4%, exceeding FDA recommended margin of -10%.

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FDA Clinical Comments

Non-inferiority of ravulizumab compared to eculizumab was demonstrated across all efficacy endpoints in the complement inhibitor naïve treatment population using the Applicants pre-specified NIMs. In sensitivity analyses conducted by the FDA ravulizumab did not achieve non-inferiority for the key secondary endpoint hemoglobin stabilization using the FDA recommended margin of -10%.

Nevertheless, given the otherwise robust and consistent efficacy findings across the primary and all key secondary endpoints in Study ALXN1210-PNH-301, as well as in all other endpoints for Study ALXN1210-PNH-302, the totality of the evidence weighs heavily is in favor of the conclusion of non-inferiority between ravulizumab and eculizumab. (b) (4) given limitations of open-label trial design and lack of enriched population.

The intent of the non-inferiority studies was to demonstrate that the experimental treatment (Ultomiris)is not substantially worse than a control treatment (eculizumab). Superiority studies were not feasible in this setting as ravulizumab has similar mechanism of action compared to eculizumab and non-inferiority studies to placebo were not ethical or feasible as effective therapy as eculizumab is the existing standard of care for patients with PNH. In these studies the efficacy of the active control was preserved thus a meaningful conclusion can be drawn regarding the non-inferiority of Ultomiris to eculizumab.

8.2. Review of Safety

The Applicant's Position:

The ravulizumab clinical development program, the largest conducted to date in this ultra-rare disease, includes 480 patients with PNH who are broadly representative of the patient population expected to receive ravulizumab in clinical practice. Patients had comorbidities typical of the PNH population (one-third of patients had aplastic anemia), patient age at first infusion ranged up to 86 years, and there were no prohibited concomitant medications.

In the Phase 3 studies, 222 patients with PNH received up to 26 weeks of ravulizumab treatment (110 patient-years of experience) at the weight-based dose regimen to be marketed. In the Phase 1b and 2 studies, 39 patients have been treated with ravulizumab for up to 104 weeks (67 patient-years) with a median duration of 634 days (range: 478 to 727 days) as of the data cutoff for this submission. Overall, the exposure to ravulizumab at submission (177 patient-years) provides an adequate database to assess the safety of ravulizumab in patients with PNH.

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The FDA's Assessment:
FDA agrees that the overall size of the safety database appears sufficient to characterize the safety of ravulizumab for treatment of PNH. The duration of treatment and exposure to ravulizumab at submission (177 patient-years) is adequate and consistent with the duration of treatment used in the TRIUMPH trial which supported approval of eculizumab.

8.2.1. Safety Review Approach

The Applicant's Position:

The safety evaluation of ravulizumab administered IV for the treatment of patients with PNH was based on 4 clinical studies:

- Two Phase 3, active-controlled (eculizumab) studies in patients with PNH, Study ALXN1210-PNH-301 and Study ALXN1210-PNH-302
- One Phase 1b and 1 Phase 2 study in patients with PNH, Study ALXN1210-PNH-103 and Study ALXN1210-PNH-201

In these 4 studies, 480 patients with PNH were enrolled and treated, 261 of who received ravulizumab. The clinical review of safety for this BLA is based on the following:

- Clinical Study Reports for the 4 studies listed above
- Integrated Summary of Safety and integrated datasets based on the 4 PNH clinical studies listed above
- Case Report Forms and Safety Narratives for Deaths, SAEs, and other Significant AEs
- A planned 90-Day Safety Update that will include data from the extension periods of all 4 clinical studies stated above

The FDA's Assessment:
FDA's review of the safety of ravulizumab was based on:

- Clinical Study Reports for studies ALXN1210 PNH 301, ALXN1210 PNH 302, ALXN1210-PNH-103 and Study ALXN1210-PNH-201
- The Integrated Summary of Safety and integrated datasets based on the 4 PNH clinical studies listed above
- Case Report Forms and Safety Narratives for Deaths, SAEs, and other Significant AEs
- The 90-Day Safety Update to the Summary of Clinical Safety and Integrated Summary of Safety

The two Phase 3, active-controlled (eculizumab) studies in patients with PNH (Study ALXN1210 PNH 301 and Study ALXN1210 PNH 302) serve as the primary safety data for this submission. Data from studiesALXN1210 PNH 103 and ALXN1210 PNH 201 are supportive. This reviewer agrees with the Applicant's pooling of data from these PNH clinical studies in the integrated datasets and the integrated safety analysis.

The Applicant submitted a 90-Day Safety Update including data from the extension periods of

all 4 clinical studies. Updated safety data were provided through the indicated data cutoff dates for the 4 clinical studies in which the safety of ravulizumab was evaluated in patients with PNH:

- Randomized, controlled Phase 3 Study ALXN1210-PNH-301 (10 May 2018)
- Randomized, controlled Phase 3 Study ALXN1210-PNH-302 (17 May 2018)
- Uncontrolled Phase 2 Study ALXN1210-PNH-201 (15 May 2018)
- Uncontrolled Phase 1b Study ALXN1210-PNH-103 (23 Apr 2018

The Applicant's safety analyses were replicated for confirmation and supplemented where necessary by FDA. Statistical analyses by the clinical reviewer were performed using JMP 12.0 (SAS Institute, Inc., Cary, NC), and MedDRA Adverse Events Diagnostic (MAED) v1.2 (Clinical Trials & Surveys Corporation, Owings Mills, MD).

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

Safety data in the submission are presented and discussed by 3 population groupings (pooled data): Phase 3 PNH Population, All PNH Patients Population, and PNH Extension Population (Table 25).

- 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. The Phase 3 PNH Population included a total of 441 patients (218 patient-years of exposure).
  In the pooled analysis, data are included up to the end of the 26-week Primary Evaluation Period of the 2 studies. The pooled analysis of two Phase 3 studies allows for a comparison of safety between ravulizumab and eculizumab over a large PNH population, and includes both complement inhibitor-naïve and eculizumab-experienced patients. Therefore, Phase 3 PNH Population represents the primary pooled population for evaluating the comparative safety of ravulizumab to eculizumab.
- The All PNH Patients Population represents pooled data from all patients with PNH who have received treatment with ravulizumab IV in the two Phase 3 studies and, the Phase 1b and 2 studies. The All PNH Patients Population included a total of 261 ravulizumab-treated patients (177 patient-years of exposure); patients in the Phase 1b and Phase 2 studies have been treated for up to 100 weeks.
  The population includes patients with PNH treated with ravulizumab and excludes patients in the eculizumab treatment arms. Pooling all 4 studies provides an integrated safety profile across all patients with PNH who have been treated with ravulizumab. This population provides the most comprehensive assessment of all patients who have been exposed to ravulizumab.
- The PNH Extension Population includes a total of 39 patients (67 patient-years of exposure), who have been treated for up to 100 weeks. This population includes 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. Pooling patients in these Phase 1b and 2 studies who completed the Primary Evaluation Period and entered into the Extension Period enables the analysis of safety over a longer term in these 2 studies.

Table 25: Safety Population, Size, and Denominators

Safety Database for the Study Drug (ravulizumab)[1] Individuals exposed to ravulizumab in this development program for the indication under review N = 480 (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	New Drug (ravulizumab) (n = 261)	Active Control (eculizumab) (n = 219)	Placebo (n = 0)
Controlled trials conducted for this indication[2]	222	219	0
All other than controlled trials conducted for this indication[3]	39	0	0
Controlled trials conducted for other indications[4]	0	0	0

[1] *study drug* means the drug being considered for approval.
[2] to be used in product's labeling
[3] if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm
[4] include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n = 0 in this column if no patients treated for other indication(s) were included in this safety database.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of exposure. Pooling of data from the 2 phase 3 PNH non-inferiority studies allow for a comparison of the safety profile between ravulizumab and eculizumab treated PNH patients. The Phase 3 PNH Population included a total of 441 patients (218 patient-years of exposure) over a 26-week treatment period with ravulizumab or eculizumab. Inclusion of data up to the end of the 26-week Primary Evaluation Period of ravulizumab treatment (110 patient-years of experience) at the weight-based dose regimen to be marketed is justified consistent with the 26-week duration of treatment used in the TRIUMPH trial which supported approval of eculizumab (Soliris). The 26-week evaluation period is considered appropriate by the Agency because this allows sufficient time for assessment of the transfusion needs in eculizumab treated population. FDA considers the phase 3 PNH Population the primary pooled population for evaluating the comparative safety of ravulizumab to eculizumab.

FDA also agrees with the pooling of data from all 4 studies (the two Phase 3 studies and the Phase 1b and 2 studies) in the All PNH population. This database includes a total of 261 ravulizumab-treated patients (177 patient years of exposure) and provides the most

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comprehensive review of the safety of ravulizumab among both complement inhibitor naïve and eculizumab experienced patients with PNH patients.

Although the size of the PNH extension population is small, this population treated for up to 100 weeks in the Phase 1b and Phase 2 studies, provide an indication of the longer-term safety of ravulizumab among PNH patients. Through the Safety Update data cutoff dates across these 4 studies, 475 patients with PNH received ravulizumab (367.8 patient-years of exposure).

Relevant characteristics of the safety population:

The Applicant's Position:

Demographics and disease characteristics of the safety population that included both eculizumab-naive and eculizumab-experienced patients with PNH were representative of the broad geographic coverage of enrollment of patients across the 4 clinical studies and are adequately representative of the target population of patients with PNH likely to be treated in clinical practice. Patients had comorbidities typical of the PNH population, patient age ranged from 18 to 86 years, and there were no prohibited concomitant medications.

The FDA's Assessment:
FDA assessed the demographic characteristics of the safety population and agrees with the Sponsor's position that the demographic characteristics of the safety population is broadly representative of patients likely to receive ravulizumab in clinical practice. Majority of subjects were White or Asian. Although overall, the proportion of blacks or African Americans and American Indian or Alaskan Native racial groups was small, this is consistent with the broad geographic regions from which patients were enrolled for the phase 3 studies. A wide age range (18 to 86 years) of patients were enrolled including a considerable number 58 (13.2%) over 65 years old.

The baseline characteristics and disease characteristics of the study population were well balanced between the treatment arms. The phase 3 PNH population included both complement inhibitor-naive and complement inhibitor-experienced patients from 25 countries across the globe. Patients in the complement inhibitor-naïve study had evidence of active disease as evidenced by the baseline high LDH level [mean (SD)] in both ravulizumab [634 (778.8) U/L] and eculizumab ([1578 (727.1) U/L] treated patients. Patients in the switch study (Study ALXN1210-PNH-302) had stable disease as evidenced by the lower determined by the mean baseline LDH levels of 228.0 (48.7) and 235.2 (49.7) in ravulizumab and eculizumab treated patients.

Adequacy of the safety database:

The Applicant's Position:

The overall size of the safety database (i.e., 261 patients with PNH treated with ravulizumab across 4 PNH clinical studies) is deemed sufficient to characterize the safety of ravulizumab for treatment of PNH. Of the 261 patients, 173 were treated with ravulizumab for 6 months or less, 49 patients for > 6 to 12 months, and 39 patients were treated with ravulizumab for more than 12 months.

The overall exposure to ravulizumab at submission (177 patient-years) provides an adequate database to assess the safety of ravulizumab in patients with PNH.

The FDA's Assessment:
FDA agrees with the Applicant's assessment of the overall adequacy of the safety database.

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The overall duration of treatment and exposure to ravulizumab in this submission (177 patient-years) is consistent with the duration of treatment used in the TRIUMPH trial which supported approval of Soliris.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

The data submitted in this BLA are of adequate quality to perform the safety review. Overall, there are no concerns regarding the integrity of data in this submission.

The FDA's Assessment:
The Agency has no concerns about the quality and integrity of the data in this submission.

Categorization of Adverse Events

The Applicant's Position:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 20.1. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. Treatment-emergent adverse events (TEAEs) were defined as any event arising or worsening after the start of study drug administration until 60 days after the last study drug administration. Where indicated in the tables or text, some AEs are presented as group terms.

Definitions for SAEs and the reporting of the SAEs were based on the ICH guidance document E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Based on specific AEs previously observed across drugs in the same class (C5 inhibitors), the applicant determined that some adverse reactions were of particular interest in the evaluation of safety. These AEs, termed AEs of special interest (AESI), include meningococcal infections.

The FDA's Assessment:
The Agency agrees with the Applicants coding of adverse events using the most up to date version of MedDRA, version 20.1 and use of NCI-CTCAE), version 4.03 for AE grading. The agency has no concerns about the Applicants definition of TEAEs and SAEs based on the ICH guidance document E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

AESI selected by the Applicant were:

- **Infections:**
  - Meningococcal Infections: Defined as any TEAEs for the following MedDRA preferred terms: "Meningococcal bacteremia," "Meningitis meningococcal," "Meningococcal infection," "Meningococcal sepsis," "Meningococcal carditis,"

"Encephalitis meningococcal," "Endocarditis meningococcal," "Myocarditis meningococcal," "Optic neuritis meningococcal," "Pericarditis meningococcal,"
  - Aspergillus Infections: Defined as any TEAEs for the preferred terms in the MedDRA high level term (HLT): "Aspergillus infections" AND the preferred term of "Aspergillus test positive."
  - Sepsis: Defined as any TEAEs for the preferred terms in the HLT: "Sepsis, bacteremia, viremia and fungaemia NEC."
  - Other Serious Infections: Defined as any SAE for the preferred terms in the MedDRA System Organ Class "Infections and infestations," EXCLUDING the preferred terms listed for the AESIs of Meningococcal Infections, Aspergillus Infections, AND Sepsis

- **Infusion Reactions**: Defined as any treatment-related TEAEs for the preferred terms in the standardized MedDRA query [SMQ (N)]: "Anaphylactic reaction" and the SMQ (N): "Hypersensitivity," EXCLUDING preferred terms that are in the AESIs of Angioedema and Serious Cutaneous Adverse Reactions
- **Serious Cutaneous Adverse Reactions**: Defined as any SAEs for the preferred terms in the SMQ: "Severe cutaneous adverse reactions."
- **Cardiac Disorders:** Defined as any TEAEs for the preferred terms in the SMQ (N): "cardiac arrhythmia terms nonspecific" AND any SAEs for preferred terms in the system organ class "Cardiac disorders" EXCLUDING preferred terms related to tachycardia and bradycardia ("Atrial tachycardia," "Bradyarrhythmia," "Bradycardia," "Bradycardia fetal," "Bradycardia neonatal," "Heart block congenital," "Inherited cardiac conduction disorder," "Neonatal tachycardia," "Sinus bradycardia," "Sinus tachycardia," "Tachycardia," "Tachycardia fetal," and "Tachycardia paroxysmal").
- **Angioedema:** Defined as any TEAEs for the preferred terms in the SMQ (N): "Angioedema."

FDA agrees that the selected AESI for this application are consistent with expected AESI for C-5 compliment inhibitor drugs.

Major adverse vascular events

Major adverse vascular events (MAVE) were assessed as part of the planned evaluation for AEs. MAVE was defined as any of the following:

Thrombophlebitis/deep vein thrombosis	Mesenteric/visceral vein thrombosis or infarction
Pulmonary embolus	Mesenteric/visceral arterial thrombosis or infarction
Myocardial infarction	Cerebral arterial occlusion/cerebrovascular accident
Transient ischemic attack	Cerebral venous occlusion
Unstable angina	Renal arterial thrombosis

Renal vein thrombosis	Gangrene (nontraumatic; nondiabetic)
Acute peripheral vascular occlusion	Amputation (nontraumatic; nondiabetic)
Hepatic/portal vein thrombosis (Budd-Chiari syndrome)	Dermal thrombosis

Thrombosis is a major clinical manifestation of PNH and thrombotic complications account for a significant amount of morbidity and mortality in PNH patients. Although the pivotal studies supporting this application were not powered to evaluate the efficacy of ravulizumab for reducing likelihood of thrombosis in patients with PNH, this is an important endpoint and FDA agrees with the assessment of MAVEs as part of AE evaluation in the safety populations. FDA agrees with the definition of MAVEs (above) selected by the Applicant.

Routine Clinical Tests

The Applicant's Position:
The frequency of clinical assessments is adequate to assess the risks of safety signals.

The FDA's Assessment:
FDA agrees with the frequency of laboratory assessments in the PNH studies. In the PNH clinical studies 301 and 302, hematology labs including CBC's, free hemoglobin and coagulation were assessed at screening, Day 1, every week during the first month of treatment and every 2 weeks thereafter up to Day 183 or ET. Urinalysis and urine chemistries were assed at screening, day 1, every 2 weeks up to Day 71, and every 8 weeks thereafter up to Day 183 or ET.

8.2.4. Safety Results

Deaths

The Applicant's Position:

Across the 4 clinical studies in patients with PNH, no deaths were reported in the pooled ravulizumab group up to the data cutoff for this submission.

One patient in the pooled eculizumab group died during the Extension Period in Study ALXN1210-PNH-301 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 chemotherapy. Subsequently, the patient died due to lung adenocarcinoma.

The FDA's Assessment:
FDA reviewed the case narrative of the patient in the pooled eculizumab group who died during the Extension Period in Study ALXN1210-PNH-301. The Agency agrees with the Applicant's conclusion that the event of lung adenocarcinoma is likely unrelated to eculizumab treatment.

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The 90-Day safety update provided by the Applicant revealed an additional death in the ravulizumab treatment arm in Study ALXN1210-PNH-301 (b) (6) This patient was a 73-year-old male patient diagnosed with PNH at age 69. His medical history included aplastic anemia renal insufficiency, transient ischemic attack, hypertension muscle spasms and spinal fusion surgery. He was randomized to the eculizumab arm of Study 301. On Day 136, while on a regimen of eculizumab IV 900 mg q2w, he was hospitalized for pyrexia, chills, and muscle pain. He was hospitalized and treated with antibiotics. During the hospitalization, no focus of infection was found. Blood cultures showed no growth of microorganisms. On Day 140, the serious event of pyrexia was considered resolved, and the patient was discharged from the hospital with oral antibiotics (amoxicillin/clavulanic acid). The patient continued to receive study drug. The Investigator assessed the event of pyrexia as unlikely related to eculizumab.

As permitted under the study protocol, he was switched to the ravulizumab study treatment arm on Study Day 183. On Day 429, while on a regimen of ravulizumab IV 3300 mg q8w, he presented with a productive cough and was diagnosed with atypical pneumonia. He was hospitalized and treated with intravenous antibiotics. Blood culture and throat swab culture were negative. During this hospitalization, erythrocyte and platelet transfusions were given. The event resolved on Study Day 437, and the patient was discharged. No action was taken with ravulizumab in response to the event. The Investigator assessed the event of pneumonia as unlikely related to ravulizumab.

On Day 478, while on a regimen of ravulizumab IV 3300 mg q8w, he experienced fever, and chills and was admitted to the intensive care unit with suspected sepsis, pneumonia, and thrombocytopenia. CT scan of the thorax was consistent with pneumonia. Two days later, he was intubated and required high doses of catecholamines. Cultures from blood, tracheal secretion, and pleural fluid were negative; however, the Investigator confirmed that the patient had received Augmentin and Clotrim prior to culture collection. Despite treatment with antibiotics, antimycotics, and respiratory support, the patient continued to deteriorate and developed a pneumothorax, atrial fibrillation and acute renal failure with anuria. He died on Study Day 496. The most recent dose of ravulizumab, prior to the onset of Sepsis was on Study Day 478. The reason for death was identified as sepsis caused by pneumonia complicated by neutropenia and renal failure. The Investigator assessed the event of sepsis as unlikely related to ravulizumab.

This patient developed sepsis while being treated with ravulizumab. C5 complement inhibition is specifically associated with an increased risk of meningococcal infections and not sepsis broadly. All cultures for this patient were negative; however, the reliability of this information is questionable since the patient received antibiotics prior to culture specimen collection. Therefore, FDA is unable to determine the causal association between sepsis and ravulizumab use in this patient.

Serious Adverse Events

The Applicant's Position:

The overall incidence of SAEs was low across the 4 clinical studies.

In the Phase 3 PNH Population, similar percentages of patients experienced SAEs in the 2 pooled treatment groups (pooled ravulizumab: 6.8%, pooled eculizumab: 7.8%). Pyrexia was the most commonly reported SAE (pooled ravulizumab: n = 1, pooled eculizumab: n = 5) followed by hemolysis (pooled ravulizumab: n = 0, pooled eculizumab: n = 2); all other SAEs were reported in no more than 1 patient in either of the pooled treatment groups. No meningococcal infection/sepsis was reported in the Phase 3 studies.

In the All PNH Patients Population, 26 (10%) patients experienced SAEs. The most frequently reported SAEs were anemia (3 patients) and pyrexia and meningococcal infection (2 patients each).

The FDA's Assessment:

FDA's analysis and assessment of serious adverse events (SAEs) in the 3 safety populations was consistent with the Applicant's results.

The table below shows the Agency's analyses of SAEs in the pooled Phase 3 PNH population.

Table 26: SAES Reported in Ravulizumab and Eculizumab-Treated Patients in Complement Inhibitor Naïve and Eculizumab-Experienced Studies (Phase 3 PNH Population)

Body System or Organ Class	Preferred Term	Pooled Ravulizumab	Pooled Eculizumab
Patients with at least one TEAE		15 (6.8%)	17 (7.8%)
Blood and lymphatic system disorders	Anaemia	1 (0.5%)	0 (0.0%)
	Aplastic anaemia	1 (0.5%)	0 (0.0%)
	Neutropenia	1 (0.5%)	0 (0.0%)
	Thrombocytopenia	1 (0.5%)	0 (0.0%)
Blood and lymphatic system disorders	Haemolysis	0 (0.0%)	2 (1.0%)
Cardiac disorders	Left ventricular failure	1 (0.5%)	0 (0.0%)
	Myocardial ischaemia	1 (0.5%)	0 (0.0%)
Cardiac disorders	Palpitations	0 (0.0%)	1 (0.5%)
Gastrointestinal disorders	Colitis	1 (0.5%)	0 (0.0%)
Gastrointestinal disorders	Ileus	0 (0.0%)	1 (0.5%)
	Neutropenic colitis	0 (0.0%)	1 (0.5%)
General disorders and administration site conditions	Hyperthermia	1 (0.5%)	0 (0.0%)
	Pyrexia	1 (0.5%)	5 (2.6%)
Hepatobiliary disorders	Cholelithiasis	0 (0.0%)	1 (0.5%)
Infections and infestations	Influenza	1 (0.5%)	0 (0.0%)
	Leptospirosis	1 (0.5%)	0 (0.0%)
	Lower respiratory tract infection	1 (0.5%)	0 (0.0%)
	Systemic infection	1 (0.5%)	0 (0.0%)

Infections and infestations	Abscess limb	0 (0.0%)	1 (0.5%)
	Cellulitis	0 (0.0%)	1 (0.5%)
	Infection	0 (0.0%)	1 (0.5%)
	Pneumonia	0 (0.0%)	1 (0.5%)
	Pyelonephritis acute	0 (0.0%)	1 (0.5%)
	Viral upper respiratory tract infection	0 (0.0%)	1 (0.5%)
Injury, poisoning and procedural complications	Laceration	1 (0.5%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uterine leiomyoma	1 (0.5%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma of colon	0 (0.0%)	1 (0.5%)
	Lung adenocarcinoma	0 (0.0%)	1 (0.5%)
Nervous system disorders	Epilepsy	1 (0.5%)	0 (0.0%)
Renal and urinary disorders	Renal colic	1 (0.5%)	0 (0.0%)
Renal and urinary disorders	Paroxysmal nocturnal hemoglobinuria	0 (0.0%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	Respiratory failure	1 (0.5%)	0 (0.0%)
Vascular disorders	Deep vein thrombosis	1 (0.5%)	0 (0.0%)

FDA reviewed the case narratives of patients who developed SAEs in the pooled Phase 3 PNH Population. All except 2 SAEs resolved during the Primary Evaluation Period: Deep vein thrombosis (Patient ALXN1210-PNH-301 (b) (6) in the pooled ravulizumab group) and lung adenocarcinoma (Patient ALXN1210-PNH-301 (b) (6) in the pooled eculizumab group) were ongoing at the end of the Primary Evaluation Period. Neither SAE was assessed by the Investigator to be related to the study drug. FDA agrees with this causality assessment.

Deep vein thrombosis is considered a MAVE. MAVEs are of interest for ravulizumab. The narrative for the ravulizumab treated patient, who had an SAE event of Deep vein thrombosis in the Primary Evaluation Period is summarized in Section 8.2.5 below.

In the Phase 3 PNH population, 42 (9.6%) ravulizumab treated patients experienced at least 1 SAE. Pyrexia (0.9%, n = 4), influenza (0.7%, n = 3) and aplastic anemia (0.7%, n = 3) were the most frequently reported SAEs. Pneumonia, hemolysis, and uterine leiomyoma were reported in 2 patients each; all other SAEs were reported in no more than 1 patient.

Through the Safety Update data cutoff dates, 54 (11.4%) patients in the pooled ravulizumab group across the 4 PNH studies experienced SAEs. No new safety trend was evident from the review of SAEs. Pyrexia was still the most frequently reported SAE (1.1%, n = 5). No new cases of meningococcal infection/sepsis were reported through the Safety Update data cutoff dates

Dropouts and/or Discontinuations Due to Adverse Effects

<u>The Applicant's Position:</u>

No patients in the pooled ravulizumab group discontinued study drug due to an AE up to the data cutoff date for this submission. During the Extension Period in Study ALXN1210-PNH-301, study drug was discontinued in one patient from the eculizumab group following an AE (lung adenocarcinoma). This patient died due to lung adenocarcinoma.

The FDA's Assessment:
FDA agrees with the Applicant's reported findings up to the original data cutoff date for this submission dated June 18, 2018.

The 90-Day safety update revealed an additional adverse event (myelodysplastic syndrome leading to discontinuation in a patient (ALXN1210-PNH-302 (b) (6)) treated with Ultomiris in the Extension Period.

Patient (b) (6) was a 58-year-old Asian male diagnosed with PNH at age 50 by flow cytometry. The patient was originally assigned to the Eculizumab treatment arm in Study 302. On Day 183, after completion of the primary evaluation period for Study 302, the patient entered the Extension Period and receive Ultomiris as permitted under the study protocol. On Day 232, while on a regimen of ALXN1210 3300 mg IV q8w, the patient experienced dyspnea and was subsequently diagnosed with myelodysplastic syndrome. Concomitant medication in use at study entry and at the time of onset of the event was Ultracet. Ultomiris was permanently discontinued because of the event. The Investigator assessed the event of myelodysplastic syndrome as not related to ALXN1210.

There have been no previous reports of a causal association between C5 complement inhibition and MDS. On the contrary, PNH clones occur more frequently in patients with MDS and AA which may subsequently evolve in classic PNH. Underlying bone marrow dysfunction can also complicate the clinical course of PNH. It is possible this patient had some baseline bone marrow dysfunction and/or MDS which had not yet been diagnosed however, the long duration (8years) between PNH and diagnosis of MDS, makes this unlikely. FDA assessed the event of myelodysplastic syndrome as likely unrelated to Ultomiris treatment.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

Across the 4 clinical studies, no patients had a permanent dose interruption/reduction due to AEs up to the data cutoff for this submission.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

A total of 4 patients had infusion interruptions due to AEs in the Phase 3 population. Infusion interruptions due to these AEs were temporary, and all infusions were ultimately completed.

In 3 patients, infusion interruptions occurred during the Extension Period (after switching from eculizumab to ravulizumab treatment) due to the following AEs - lower respiratory tract

infection muscle spasms, and maculopapular rash. In one patient who had received eculizumab in the Primary Evaluation Period and switched to ravulizumab, there was a 30-minute interruption of ravulizumab infusion on Day 183 due to a transient maculopapular rash (Grade 2, non-serious). This AE was assessed by the Investigator to be possibly related to the study drug.

None of the AEs led to infusion interruption in the PNH extension population.

Significant Adverse Events

The Applicant's Position:

A total of 3 patients in the ravulizumab clinical development program had meningococcal infections/sepsis (all in the Phase 1b and Phase 2 studies; none in the Phase 3 studies). All 3 patients recovered and continued treatment with ravulizumab.

In the Phase 3 PNH Population, the most frequently reported AESI grouping was infusion reactions (pooled ravulizumab group: 8.6%, pooled eculizumab: 5.9%). The AE preferred terms included under the category of infusion reactions were determined by a predefined algorithm, which did not take into account the causality of the AE or the timing of the AE with respect to the timing of study drug administration. Among the AESIs identified as infusion-related reactions (6 events, all Grade 1 or 2), 3 events (pooled ravulizumab group) occurred during study drug administration (verbatim: lower back pain, drop in blood pressure, and infusion-related pain). All infusion-related reactions were transient and resolved spontaneously or with a concomitant medication.

The FDA's Assessment:

FDA reviewed the case narratives for the 3 patients who experienced meningococcal infections/sepsis in the ravulizumab clinical development program.

*Patient **ALXN1210-PNH-201** (b) (6) is a 28-year-old White male diagnosed with PNH in (b) (6) At baseline, the patient's LDH value was 1184.7 U/L. The patient had no history of blood transfusions prior to ALXN1210 administration. He was enrolled in Study ALXN1210-PNH-201 and received an induction dose and maintenance doses of ravulizumab every 8 weeks thereafter as per the study protocol. He was vaccinated against meningococcal disease prior to study enrollment. He was given benzylpenicillin sodium as a prophylactic antibiotic and stated that he had adhered to the dosing regimen. He did not have a history of meningococcal infection.*

*He was hospitalized on Study Day 57 with a 12-hour history of malaise, muscle pain and fever, and arterial hypotension with sustained pulse and sweating. He was diagnosed with meningococcal infection on Day 57. Blood culture grew Neisseria meningitidis, serotype Y/W13**5**. Cerebrospinal fluid examination was not performed. He was treated with antibiotics - ceftriaxone. He was transferred to the ICU during that hospitalization for worsening of overall condition. An echocardiogram was performed that revealed an ejection fraction (EF) of 30% due to diffuse hypokinesia in the context of severe myocarditis from sepsis. The treating physician assessed the final diagnosis as septic shock with severe myocarditis secondary to*

meningococcus infection in context of PNH. After 48 hours in the ICU, he showed significant clinical and hemodynamic improvement. He completed 7 days of monitored ceftriaxone treatment. A follow up echocardiogram was performed on an unspecified date revealed normalization of his EF (65%). The SAE was reported resolved on Day 67.

The Investigator considered the event of meningococcal infection to be not related to ALXN1210. The Applicant assessed causality of the event as possibly related to ALXN1210. FDA agrees that the event of meningococcal infection in this patient is likely related to treatment with ALXN1210, a complement C5 inhibitor.

Patient ***ALXN1210-PNH-201*** (b) (6) *is an 18-year-old White male diagnosed with PNH in* (b) (6) *At baseline, the patient's LDH value was 1131 U/L. The patient had no history of packed red blood cells transfusion prior to ALXN1210 administration. He was enrolled in study ALXN1210-PNH-201 and received an induction dose and maintenance doses of ravulizumab IV every 8 weeks thereafter as per the study protocol. He was vaccinated against meningococcal disease prior to study drug administration. He did not have a previous history of a meningococcal infection. He was not on antibiotic prophylaxis.*

On Study Day 222, the patient experienced vomiting. The following day, he presented with the safety card to a healthcare clinic and was immediately hospitalized due to a fever of 38.8 °C. Clinical symptoms included vomiting, malaise, confusion/delirium, worsening of general health conditions, petechial rash and purpura on both arms, legs, and feet. He was treated with IV ceftriaxone. CSF exam was clear. On Day 225, the patient was transferred to the ICU. Blood culture confirmed Neisseria meningitidis. The final diagnosis was reported as meningococcal septicemia (Meningococcal sepsis). On Day 238 the patient had recovered from meningococcal septicemia with sequelae of a small lesion on his right heel. The patient continued to receive ravulizumab in the study. The patient continued to receive ravulizumab in the study.

The investigator considered the event meningococcal septicemia as possibly related to ALXN1210 therapy. FDA assessed the event of meningococcal sepsis as likely related to ALXN1210 treatment. Other possible risk factors for meningococcal infection in this patient was being a college student and living with several other students. However, he was not in contact with any person from an endemic area and did not travel to an endemic area. He did not have a history of high risk sexual behavior.

Patient ***ALXN1210-PNH-103*** (b) (6) *is a 40-year-old white male diagnosed with PNH. At the Baseline Visit, his LDH value was 1880 U/L (reference range 53-234 U/L). He received 2 pRBC transfusions in the year prior to enrollment. He was vaccinated against meningococcal disease prior to study drug administration. He did not have a previous history of a meningococcal infection. He was not on antibiotic prophylaxis. He was enrolled in study ALXN1210-PNH-103 and received an induction dose and maintenance doses of ravulizumab IV every 8 weeks thereafter as per the study protocol.*

On Day 601, while receiving ALXN1210 IV 3300 mg q8w, the patient experienced a non-serious event of Grade 3 influenza (considered unlikely related to ALXN1210). No treatment was reported for the event. On Day 615, the patient was hospitalized after reporting a 2-week

history of dry cough, rhinorrhea, arthralgia, and fatigue. At the time of hospital admission, the patient had a fever of 39.0 ºC, chills, malaise, dry cough, rhinorrhea, and hematuria. There were no signs of meningitis or rash upon physical examination. Respiratory swab was positive for influenza B. Blood cultures were obtained. Lumbar puncture and skin biopsy were not performed. On Day 617, blood cultures collected upon admission identified beta-lactamase negative Neisseria meningitidis, serotype Y/W135. The patient's reported risk factor for meningococcal infection was that he had young children; travel history was unknown. On Day 623, he was discharged from the hospital on prophylactic amoxicillin, and the serious event of meningococcal infection was considered resolved. The patient continued to receive ALXN1210 in the study. The investigator assessed the event of meningococcal infection as definitely related to ALXN1210. FDA assessed the event of meningococcal sepsis as likely related to ALXN1210 treatment.

A discussion of the recommended mitigation process for the risk of meningococcal infections or meningococcal sepsis associated with Ultomiris use is discussed in Section 8.2.5 below.

AESI: FDA agrees with the Applicants summary statements about AESI above. Further discussion on the infusion reactions which was the most common AESI reported in the phase 3 studies is detailed below.

Infusion reactions: Infusion of monoclonal antibodies has been associated with infusion reactions – (including hypersensitivity reactions or cytokine release syndrome and anaphylaxis), with onset typically during or shortly after completion of the infusion. Re-administration of some monoclonal antibodies has been associated with serum sickness-like reactions manifesting 1 to 14 days after drug administration. In the pivotal studies 301 and 302, patients were carefully observed during each infusion for infusion reactions and the protocol required the immediate discontinuation of infusion if Grade ≥ 2 allergic/hypersensitivity reactions (including drug fever) or Grade ≥ 3 cytokine release syndrome/acute infusion reaction occurred. For Grade 1 or Grade 2 infusion reactions, the protocol required temporarily infusion interruption and consideration of treatment with an antihistamine and acetaminophen.

In the PNH 3 population, FDA identified 5 infusion related events (in 4 patients) in the pooled ravulizumab group that occurred during the primary evaluation period. Of these, 3 events occurred during study drug administration (verbatim: lower back pain, drop in blood pressure, and infusion related pain). All infusion related reactions resolved spontaneously or with a concomitant medication and no infusion-related reaction required discontinuation of the infusion. FDA recommends inclusion of the following statement to section 5.7 of the label – "Interrupt Ultomiris infusion and institute appropriate supportive measures if signs of cardiovascular instability or respiratory compromise occur."

Although the frequency of infusion reactions was higher in the pooled ravulizumab compared to the pooled eculizumab group, FDA agrees that this is of no relevance because the AE preferred terms included under the category of infusion reactions did not consider the causality or the timing of the AE with respect to the timing of study drug administration.

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Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

In the Phase 3 PNH Population, the incidence of TEAEs over 26 weeks of treatment was similar between the ravulizumab and eculizumab groups (87.8% vs 87.2%). The most commonly reported TEAE in both groups (pooled ravulizumab vs eculizumab) was headache (32.0% vs 26.0%). Other common TEAEs were among patients reporting upper respiratory tract infections (URTI: 38.7% vs 39.3%), where URTI was defined as any report of nasopharyngitis, URTI, viral URTI, oropharyngeal pain, rhinorrhea, pharyngitis, rhinitis, respiratory tract infection, or upper respiratory tract inflammation.

The overall PTs reported in the All PNH Patients Population were similar to those observed in the Phase 3 PNH Population (Table 27).

Table 27: Adverse Events Reported in 5% or More of Ravulizumab-Treated Patients in Complement Inhibitor Naïve and Eculizumab-Experienced Studies

System Organ Class Preferred Term	Number (%) of Patients	
	Ravulizumab (n = 222)	Eculizumab (n = 219)
Gastrointestinal disorders		
Diarrhoea	19 (8.6)	12 (5.5)
Nausea	19 (8.6)	19 (8.7)
Abdominal pain	13 (5.9)	16 (7.3)
General Disorders and Administration Site Conditions		
Pyrexia	15 (6.8)	18 (8.2)
Infections and Infestations		
Upper respiratory tract infection[a]	86 (38.7)	86 (39.3)
Musculoskeletal and Connective Tissue Disorders		
Pain in extremity	14 (6.3)	11 (5.0)
Arthralgia	11 (5.0)	12 (5.5)
Nervous System Disorders		
Headache	71 (32)	57 (26)
Dizziness	12 (5.4)	14 (6.4)

[a] Includes the preferred terms Nasopharyngitis, Upper respiratory tract infection, Oropharyngeal pain, Viral upper respiratory tract infection, Rhinitis, Respiratory tract infection, Rhinorrhoea, Pharyngitis and Upper respiratory tract inflammation

The FDA's Assessment:

The FDA agrees with the Applicant's analyses above. The FDA conducted independent analyses of the safety data from Phase 3 PNH Population and the findings were consistent with those described by the Applicant above.

Majority of patients in both ravulizumab (87.8) and eculizumab (87.2) treatment groups experienced at least one TEAE. The majority of AEs were Grade 1 or Grade 2 in severity. The

most frequently reported AE in ravulizumab treated patients was headache (32%). This is not unexpected since headache has been reported to be associated with terminal complement inhibition in patients with PNH.

FDA agrees with the Applicants aggregation of the preferred terms - Nasopharyngitis, Upper respiratory tract infection, Oropharyngeal pain, Viral upper respiratory tract infection, Rhinitis, Respiratory tract infection, Rhinorrhoea, Pharyngitis and Upper respiratory tract inflammation – under the preferred term URTI.

The percentage of patients with AEs of Grade 3 severity was similar between the pooled ravulizumab and eculizumab groups (9.9% vs 14.2%).

Nine patients (pooled ravulizumab: n = 7, pooled eculizumab: n = 2) reported AEs of Grade 4 severity. In 6 of the 7 patients in the pooled ravulizumab group, these were AEs associated with abnormal hematology values (See table below).

The table below shows FDA findings for the analyses of AEs of Grade 4 severity in the Phase 3 PNH population.

Table 28: Grade 4 TEAEs Reported in Ravulizumab and Eculizumab-Treated Patients in Complement Inhibitor Naïve and Eculizumab-Experienced Studies (Phase 3 PNH Population)

Dictionary Derived Term	ALXN1210	Eculizumab	Subjects(filtered)
Platelet count decreased	2 (0.9%)	1 (0.5%)	3 (0.6%)
Neutropenia	2 (0.9%)	0 (0.0%)	2 (0.4%)
Hyperthermia	1 (0.4%)	0 (0.0%)	1 (0.2%)
Epilepsy	1 (0.4%)	0 (0.0%)	1 (0.2%)
Respiratory failure	1 (0.4%)	0 (0.0%)	1 (0.2%)
Thrombocytopenia	1 (0.4%)	0 (0.0%)	1 (0.2%)
Neutrophil count decreased	0 (0.0%)	1 (0.5%)	1 (0.2%)
Aplastic anemia	1 (0.4%)	0 (0.0%)	1 (0.2%)
Subjects(filtered)	7 (3.0%)	2 (1.0%)	543 (100.0%)

In one patient (Patient ALXN1210-PNH-302 (b) (6), the Grade 4 AEs were epilepsy, respiratory failure, and hyperthermia. The case narrative for this patient is summarized below.

This patient was a 34-year-old White male diagnosed with PNH at age 19. His medical history included Budd-Chiari syndrome, aplastic anaemia, skin basal-cell carcinoma, iatrogenic cerebral hemorrhage, hemianopia, brain surgery requiring long-term antiseizure prophylaxis, post procedural hemorrhage, basal cell carcinoma, and hypertension. On Day 65, the patient received the Nimerix meningococcal vaccine A/C/Y/W and on Day 69, he received the Bexsero meningococcal vaccine. The patient received an earlier dose of the Bexsero meningococcal vaccine in (b) (6)

On Day 71, while on a regimen of ravulizumab 3300mg IV q 8 weekly, the patient presented with fever (temperature of > 40 ºC), convulsions, and diarrhea and was hospitalized in the

intensive care unit for epilepsy, hyperthermia and respiratory failure. The patient was intubated and treated with broad spectrum antibiotics and his antiseizure medication – levetiracetam dose was doubled. Full body computed tomography scan results were unremarkable. Polymerase chain reaction (PCR) testing for bacterial meningitis was negative. All cultures (aerobic and anaerobic blood, urine, rectal) subsequently showed no growth, except for tracheal aspirate, which grew saprophytic flora. Laboratory test results were notable for anemia (hemoglobin 10.1 g/dL and 8.3 g/dL), procalcitonin level within normal limits, low platelet count of 60,000-75,000, and low white blood cell count of 1900-2800 (units of measurement not provided).

On Day 72, the patient was extubated. Multiplex PCR was negative for cytomegalovirus, Epstein-Barr virus, Enterovirus, Herpes simplex virus 1, Herpes simplex virus 2, and Varicella Zoster Virus. The serious events of epilepsy, hyperthermia, and respiratory failure were considered resolved. No action was taken with ravulizumab in response to these events. The patient continued to receive ravulizumab in the study. On Day 73, the patient received 1 unit of pRBCs due to worsening anemia (7.4 g/dL). On Day 74, the patient was reported to be well. On Day 80, the patient was discharged from the hospital and antibiotic therapy was discontinued.

The Investigator assessed the events of hyperthermia, epilepsy, and respiratory failure as possibly related to ALXN1210 since the role of the C5 blockade as a contributing factor could not be entirely ruled out. However, the Investigator also suspected that the epilepsy was triggered by hyperthermia resulting from the administration of Bexsero vaccine.

The role of C5 complement blockade and ravulizumab in the causality of the events of hyperthermia, epilepsy, and respiratory failure is unclear. BEXSERO is a vaccine indicated for active immunization to prevent invasive disease caused by Neisseria meningitidis serogroup B. Fever is a frequently reported adverse event following immunization [Kohl et al, 2004]. Therefore, FDA agrees the event of epilepsy could have been triggered by hyperthermia from administration of the Bexsero vaccine.

Laboratory Findings

<u>The Applicant's Position:</u>

In both Phase 3 studies, clinical laboratory results were generally similar between ravulizumab and eculizumab groups, and reflected the laboratory profile of effectively treated PNH including normalized LDH and AST levels, improved or stable hemoglobin, and consistent bilirubin levels. Changes to laboratory parameters and all laboratory-related AEs were consistent with the known safety and efficacy profile of eculizumab in patients with PNH, or to the known underlying, concomitant diseases.

Apart from the sustained improvements from baseline in LDH and hematological parameters observed with ravulizumab treatment, there were no clinically significant changes in the laboratory parameters in the Phase 1b and Phase 2 studies.

<u>The FDA's Assessment:</u>

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The FDA agrees with the Applicants assessment that all laboratory related AEs were consistent with the known safety and efficacy profile of eculizumab in patients with PNH. There were no unexpected trends or differences in laboratory evaluations between the ravulizumab and eculizumab treatment groups.

Vital Signs

The Applicant's Position:

In all 4 clinical studies, mean changes in vital signs (temperature, HR, systolic BP, diastolic BP, and respiratory rate) were minor.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that there were no notable differences in vital signs between the two treatment groups in the clinical studies.

Electrocardiograms (ECGs)

The Applicant's Position:

There were no pertinent changes in ECG parameters in the ravulizumab clinical development program. In the two Phase 3 studies, changes in ECG parameters were similar in both ravulizumab and eculizumab groups. There were no AEs of QT prolongations, syncope, or torsades de pointes in either treatment group.

The FDA's Assessment:

In the phase 3 clinical studies ALXN1210-PNH-301 and Study ALXN1210-PNH-302, 12-lead ECG were performed at screening, Day 57, and Day 183 or at the early termination visit. No pooled analysis of ECG was performed. FDA agrees with the Applicants findings of similar changes in ECG parameters in both ravulizumab and eculizumab groups.

QT

The Applicant's Position:

Ravulizumab concentration versus QTc assessment confirmed the absence of an effect of ravulizumab on cardiac repolarization.

The FDA's Assessment:

For the phase 3 studies 301 and 302, the Applicant provided descriptive statistics by study visit and treatment group for absolute values and for change from baseline for ECG parameters (including PR, QRS, QT, and QT corrected by Fridericia's formula [QTcF]). FDA agrees that changes from baseline in mean HR, PR, QRS, and QTcF values at Day 57 and Day 183 were minimal and comparable in both treatment groups. QT and QTc abnormalities were infrequent and no AEs of QT prolongation, syncope, or torsades de pointes were reported in either

treatment group.

Immunogenicity

The Applicant's Position:

Across the 4 clinical studies in PNH patients treated with ravulizumab (N = 261), only 1 (0.38%) treatment-emergent ADA has been reported. This ADA was transient in nature with low titer and did not correlate with any effect on clinical response or AEs.

The FDA's Assessment:

FDA agrees with the Applicants position. In the Phase 3 PNH population, ravulizumab and eculizumab exhibited similar immunogenicity rates with no apparent impact on safety.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

No submission-specific issues were identified.

The FDA's Assessment:

Major Adverse Vascular Events (MAVE)
In the Phase 3 PNH population, three patients experienced a MAVE during the Primary Evaluation Period: Two events (DVT, thrombosis) were in the pooled ravulizumab treatment group and 1 event (thrombosis) in the pooled eculizumab group. In the 90 day safety Update, the Applicant reported 4 additional events in 4 patients in the ravulizumab group (Arterial embolism, jugular vein thrombosis, thrombophlebitis and cerebral infarction) during the Extension Periods of the 2 Phase 3 studies. An additional MAVE (deep vein thrombosis) occurred in a patient in the phase 2 Study ALXN1210-PNH-201.

In the TRIUMPH study for Soliris, no patient in the eculizumab treatment group experienced a thrombotic event and only one patient in the placebo group experienced a thrombotic event (hepatic vein thrombosis). In response to a query from FDA, the Applicant provided the following information and tables:-

- A Head-to-head comparison of ravulizumab and eculizumab during the randomized treatment period of the ravulizumab PNH Phase 3 studies.
- A Retrospective comparison of the MAVE rate in the 4 ravulizumab PNH studies through the 90-day Safety Update data cutoff with the rate reported in the eculizumab PNH clinical program.
- Analysis of data from eculizumab-treated PNH patients in the International PNH Registry from the first 15 months of eculizumab exposure, to approximate the duration of ravulizumab exposure at the time of the 90-day Safety Update.

Table 29: Treatment-emergent MAVEs in Phase 3 Ravulizumab PNH Studies

	Ravulizumab (N = 222)	Eculizumab (N = 219)
Number (%) of patients with events	2 (0.9)	1 (0.5)
Number of events	2	1
Patient-years (PY)	110.1	107.5
Rate per 100 PY	1.8	0.9
95% CI	(0.2, 6.6)	(0.02, 5.2)

Source: Ravulizumab BLA ISS Table 2.7.4.2.1.02.1, Table 2.7.4.1.9.02.1

Table 30: Comparison of MAVE Rates in PNH Studies and Registry

	Ravulizumab BLA All PNH Population N = 475	Eculizumab BLA PNH Population N = 195	Eculizumab E05-001 Per Protocol Population N = 184	Eculizumab PNH Registry N = 1036[a]
Number (%) of patients with events	7 (1.5)	2 (1.0)	6 (3.3)	20 (1.9)
Number of events	7	2	9	25
Patient-years (PY) of exposure	367.8	164.1	452.3	1200.2
Rate per 100 PYs	1.9	1.2	2.0	2.1
95% CI	(0.8, 3.9)	(0.2, 4.4)	(0.9, 3.8)	(1.4, 3.1)

[a] PNH patients in the International PNH Registry (M07-001) who had high-disease activity at initiation of eculizumab.

Source: Ravulizumab 90-day Safety Update Table 2.7.4.2.1.05.2; Eculizumab BLA Module 2.7.3 Table 2.7.3.3.2.6-1; E05-001 final CSR Table 14.2.3.1 and Table 14.2.3.3

FDA Assessment: The effect of C5 complement inhibition on thromboses in PNH patients is unknown. In the Phase 3 PNH Population 29.6% of eculizumab naïve patients and 23.7% of eculizumab experienced patients treated with ravulizumab received antithrombotic agents prior to start of ravulizumab treatment. These medications were continued during study treatment: antithrombotic agent use among ravulizumab treated patients during the randomized treatment period of Studies 301 and 302 was 29.6% and 26.8% respectively.

One of the 2 ravulizumab treated patients (Patient (b) (6)) who experienced a MAVE during the Primary Evaluation Period was receiving rivaroxaban for DVT prophylaxis prior to study enrolment. Three weeks after the first dose of study drug, rivaroxaban was discontinued. Subsequently, on Study Day 65 while on a regimen of ALXN1210 IV 3300 mg q8w, the patient experienced a non-serious event of thrombosis in his right lower leg. None of the other 4 ravulizumab treated patients who experienced a MAVE during the Extension Periods of the 2 Phase 3 studies had a history of antithrombotic agent use.

Because antithrombotic/anticoagulant use was relatively common and not controlled for and the thrombotic event rate in the controlled phase 3 studies was low, it is not possible to distinguish between the effect of anticoagulant management or withdrawal and any possible effect of ravulizumab on thromboses.

FDA agrees with the Applicants' argument that, from the retrospective comparison of the MAVE rate in the 4 ravulizumab PNH studies with the rate reported in the eculizumab PNH clinical program; as well as from the Applicants analysis of data from eculizumab-treated PNH patients in the International PNH Registry,- the exposure-adjusted MAVE rate for ravulizumab is comparable to that observed for eculizumab both in the clinical program and in the International PNH Registry over the 15-month period after initiation of eculizumab. However, this retrospective observational data is not sufficient to explain the effect of ravulizumab or C5 complement inhibition on thromboses in PNH patients. The PI for Soliris includes a statement that the effect of withdrawal of anticoagulant therapy during Soliris treatment has not been established. This reviewer recommends inclusion of a similar statement in the PI for ravulizumab. FDA proposed that the PI for ravulizumab should also include a statement that a total of 6 ravulizumab treated patients experienced thrombotic events in the Primary Evaluation Period and the extension period of Studies 301 and 302. The Applicant argued that the risk of thrombosis was related to the baseline disease in these patients and not necessarily due to Ultomiris use. FDA agreed with the Applicants Position. Under BLA 125166 for eculizumab, the Applicant had an agreement with the Agency to conduct as part of a PMC, a study to evaluate the effect of withdrawal of anticoagulation while on Soliris. However, this study was not feasible.

Meningococcal Infections

The Applicant's Position:
The most important risk associated with C5 complement inhibition is increased susceptibility to infections caused by *N. meningitidis.* The same effective risk mitigation processes in place for eculizumab have been applied in the ravulizumab clinical development program (Section 12).

The FDA's Assessment:

In the ravulizumab clinical development program, 3 patients (two in the phase 2 study ALXN1210-PNH-20 and one in the phase 1b study ALXN1210-PNH-103) with PNH experienced meningococcal infections/sepsis. All three received meningococcal vaccines prior to prior to study drug initiation treatment. One of these three patients received prophylactic antibiotics. All 3 patients recovered completely while remaining on ravulizumab without treatment interruption. The case narratives for these patients were summarized above.

No meningococcal infections/sepsis were reported in the Phase 3 studies. No additional meningococcal infections were reported through the Safety Update data cutoff date.

Use of eculizumab (Soliris), is estimated to be associated with a 1,000-fold to 2,000-fold increased incidence of meningococcal disease (FDA, 2014). Complement activation impairs the ability of the immune system to respond effectively to encapsulated organisms particularly Neisseria infections (Crew et. al. 2018). The approved prescribing information for eculizumab (Soliris,) includes a boxed warning regarding increased risk for meningococcal disease in eculizumab recipients. Alexion Pharmaceuticals has a REMS agreement with the Agency to educate health care providers and patients about the risk for and early signs of possible

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meningococcal infection and the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infection.

The REMS for Soliris also includes a key requirement to ensure that patients receiving Soliris receive meningococcal vaccines before beginning treatment. The Advisory Committee on Immunization Practices recommends that eculizumab recipients receive both quadrivalent meningococcal conjugate (MenACWY) and serogroup B (MenB) meningococcal vaccines (CDC 2017). Meningococcal vaccination however, does not prevent all cases of meningococcal disease. A recent CDC publication (McNamara L. et al. 2017) reported meningococcal infections caused by serogroups ACWY and B among Soliris treated patients who were previously vaccinated against these serogroups. Many clinicians and public health agencies, particularly in the United Kingdom and France, recommend antimicrobial prophylaxis with penicillin for the duration of eculizumab treatment. However, the effectiveness of this strategy for meningococcal disease prevention has not been established (McNamara L. et al. 2017).

In the phase 3 studies ALXN1210-PNH-301 and ALXN1210-PNH-302, meningococcal vaccination was required for all patients within the 3 years prior to receipt of Ultomiris. Patients who received study treatment less than 2 weeks after receiving a meningococcal vaccine were required to receive appropriate prophylactic antibiotics for at least 2 weeks after vaccination. Use of prophylactic antibiotics beyond 2 weeks was at the discretion of the treating provider.

Fifty-nine PNH patients in the Phase 3 PNH population initiated study drug less than 2 weeks after receiving a meningococcal vaccine; all received treatment with appropriate prophylactic antibiotics from Day 1 until at least 2 weeks after vaccination. In response to a query, the Applicant reported that the number and proportion of ravulizumab treated patients who received antibiotics as prophylaxis for meningococcal infection at any time beyond the two-week post immunization period during the randomized treatment period for Studies 301 and 302 were 47 (37.6%) and 54 (55.7%) respectively. However, the eCRF did not have a specific field encoded to capture whether antibiotic treatment was administered as prophylaxis for meningococcal infection. Therefore, the Applicant determined which antibiotics were used for meningococcal infection prophylaxis by performing a clinical review of the indication (free text field) for each antibiotic recorded in the eCRF, taking clinical context into account. The mean duration of exposure to prophylactic antibiotics in ravulizumab treated patients during the randomized treatment period in Studies 301 & 302 was 0.35 person-years.

Recommendations:

FDA recommends instituting a REMS for Ultomiris requiring the Applicant to educate health care providers and patients about the risk for and early signs of possible meningococcal infection and the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infection. Patients receiving Ultomiris should also be vaccinated against *Neisseria meningitides* at least 2 weeks prior to starting treatment with Ultomiris.

i. Box warning for the risk of serious meningococcal infections

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ii. There is insufficient evidence from the clinical studies for Ultomiris for FDA to recommend or not recommend the use of prophylactic antibiotics in patients treated with Ultomiris. The use of prophylactic antibiotics should remain at the discretion of the treating provider. FDA agrees with the CDC's recommendation that providers could consider use of antimicrobial prophylaxis for the duration of Ultomiris treatment to potentially reduce the risk for meningococcal disease.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

No such analysis for assessments specifically for safety/tolerability was performed in this submission.

The FDA's Assessment:
COA data were presented as part of this submission, however, no specific analysis for safety and tolerability were performed. Refer to the table in Section 1.4

The Applicant evaluated the effect of Ultomiris treatment on the concepts of fatigue and General cancer symptoms and impacts as efficacy outcomes using 2 COA instruments: 1) the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue; PRO) and 2) European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core – 30 (EORTC QLQ C30; PRO) . (b) (4)

(b) (4)

DHP requested the input of the COA division on the adequacy of the FACIT-Fatigue scale (b) (4)

(b) (4) The COA review concluded that (summarized),

- The open-label trial design of Studies 301 and 30 limits interpretability of the PRO data because patient's knowledge of treatment assignment may lead to systematic overestimation or underestimation of treatment effect of which is currently unknown.
- Studies 301 and 302 were not enriched with patients who sufficiently experienced fatigue-related symptoms
- Although Study 301 generates data that shows improvement in the FACIT-Fatigue total score, there are only select items within the FACIT-Fatigue scale that contribute more to the change observed in the total score based upon review of item-level analyses.
- Study 302 demonstrates none to minimal changes in the FACIT-Fatigue total score, however this is expected as patients were clinically stable and previously treated with eculizumab.
- The Applicant defined a clinically meaningful score change in the FACIT-Fatigue total score as 3-points, however there is insufficient data to support this threshold.

(b) (4)

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Overall, analysis of the safety profile across all 4 PNH clinical studies by demographic subgroup identified no sensitive subgroups that were considered to have an influence on the overall safety profile of ravulizumab.

The FDA's Assessment:
FDA's analyses are consistent with the Applicant's analysis above.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

No specific studies were conducted to evaluate any specific safety concern.

The FDA's Assessment:
Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

In the MedDRA System Organ Class Neoplasms benign, malignant and unspecified (including cysts and polyps), the Preferred Term of uterine leiomyoma was reported in 1 patient in the ravulizumab group, and Preferred Terms of adenocarcinoma of colon and lung adenocarcinoma were reported for 1 patient each in the eculizumab group.

Overall, there is no signal of increased malignancy with ravulizumab treatment.

The FDA's Assessment:
There is no apparent signal of increased malignancy associated with Ultomiris treatment. However, long-term animal carcinogenicity studies of ravulizumab have not been conducted and the length of follow up for the clinical studies is relatively short. This reviewer recommends that as part of the REMS for Ultomiris, all patients within the registry should be followed for safety including the detection of malignancies.

Human Reproduction and Pregnancy

The Applicant's Position:

Cumulatively, across the 4 PNH studies, 120 females with PNH were treated with ravulizumab (ages ranged from 18 to 79 years with a mean age of 46.1 years). The median duration of treatment in the female group was 230 days. No ravulizumab-treated patients became pregnant during the entire clinical development program as of each CSR cutoff date. Two partners of ravulizumab treated patients had a confirmed pregnancy, both of which occurred in Study ALXN1210-PNH-301.

The FDA's Assessment:

The FDA agrees with the information the Applicant provided. As included in the Prescribing Information, there are no available data on ULTOMIRIS use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Animal studies using a mouse analogue of the ULTOMIRIS molecule (murine anti-C5 antibody) showed increased rates of developmental abnormalities and an increased rate of dead and moribund offspring. Also, human IgG are known to cross the human placental barrier, and thus ULTOMIRIS may potentially cause terminal complement inhibition in the fetal circulation.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Ravulizumab was not studied in a pediatric population.

The FDA's Assessment:

The safety of Ultomiris in the pediatric population has not been established. An ongoing study (ALXN1210-PNH-304) is targeting enrollment of 12 pediatric patients with PNH.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

In the ravulizumab clinical development program, there were no AEs of overdose of ravulizumab.

There are no data to support an association of monoclonal antibodies, including ravulizumab, with the potential for addiction, abuse, withdrawal, or rebound. Therefore, the applicant did not evaluate abuse potential.

The FDA's Assessment:
FDA agrees with the Applicant's position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable; ravulizumab is not marketed in any country.

The FDA's Assessment:
None at this time.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Safety in the postmarketing setting is expected to be similar to that observed in the clinical studies reviewed in this application. Similar to eculizumab, the most important risk with ravulizumab as detailed above is increased susceptibility to infections caused by *N. meningitidis.* Currently, eculizumab has an approved REMS in place. Alexion recommends a REMS for ravulizumab based broadly on the REMS components currently in place for the approved eculizumab indications (PNH, aHUS, and gMG).

The FDA's Assessment:

The most important risk associated with ravulizumab is increased susceptibility to infections caused by N. meningitidis. This is because ravulizumab inhibits complement activation, impairs neutrophil and monocyte function and impairs the ability of the patient to clear infections with encapsulated organisms. The Agency agrees with the Applicants proposal to institute a REMS program for ravulizumab similar to the REMS currently in place for eculizumab. The goals of this REMS are to mitigate the occurrence and morbidity associated with meningococcal infections in patients treated with Ultomiris and to educate Healthcare Professionals (HCP) and patients regarding the increased risk of meningococcal infections, the early signs of invasive meningococcal infections, and the need for immediate medical evaluation of signs/symptoms consistent with possible meningococcal infections.

The 26-week Phase 3 studies, as well as the Phase 1b and 2 studies provide the majority of evidence that contributes to the overall safety of ravulizumab IV in patients with PNH. Both phase 3 studies include an Extension Period of up to 2 years. A PMC is recommended for the Applicant to for studies ALXN1210-PNH-301 and ALXN1210-PNH-302) up to the end of the 2 year extension/ follow-up period.

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8.2.11. Integrated Assessment of Safety

The Applicant's Position:

Ravulizumab was well tolerated, and in two Phase 3 studies, the safety profile was similar to that of eculizumab. The overall safety profile of eculizumab in both Phase 3 studies is similar to that observed for eculizumab (Soliris®) in the postmarketing PNH setting. The main safety concern for ravulizumab, meningococcal infection, is common to all C5 inhibitors and can be effectively managed with the same risk mitigation strategies (REMS) in place as for eculizumab. In the ravulizumab clinical development program, 3 patients with PNH experienced meningococcal infections/sepsis. All 3 patients recovered completely while remaining on ravulizumab without treatment interruption, suggesting that patients can safely continue treatment with ravulizumab during meningococcal infection. All 3 patients were in the Phase 1b and 2 studies. No meningococcal infections were reported in the Phase 3 studies.

Across the 4 clinical studies in patients with PNH, no patient discontinued study drug due to an AE. One eculizumab-treated patient who participated in Study ALXN1210-PNH-301 died during the Extension Period from lung adenocarcinoma, for which symptoms began during the Primary Evaluation Period; no other deaths were reported.

The FDA's Assessment:

FDA agrees with the Applicants' assessment above.

The ravulizumab clinical development program was designed to assess safety in a population broadly representative of patients likely to receive ravulizumab in clinical practice. The safety population consisting of 261 patients with PNH treated with ravulizumab across 4 PNH clinical studies with 177 patient-years of follow up is adequate to evaluate the safety of ravulizumab in this population.

FDA agrees 'that overall, Ultomiris was well tolerated and the safety profile of Ultomiris was similar to eculizumab.

There were no new safety findings identified in this submission.

In both phase 3 studies, the adverse event profile of Ultomiris was similar to eculizumab. No new risks were identified. The incidence of TEAEs over 26 weeks of treatment was 87.8% and 87.2% for ULTOMIRIS and eculizumab, respectively in the pooled safety population (n=441 patients). Most AEs were Grade 1 or Grade 2 in severity. The most commonly reported TEAEs(> 10%) in ULTOMIRIS treated patients were upper respiratory tract infections(39%) and headache (32.0%) %). Serious adverse reactions were reported in 15 (6.8%) patients receiving ULTOMIRIS. The serious adverse reactions in patients treated with Ultomiris included hyperthermia and pyrexia. No serious adverse reactions were reported in more than one patient treated with ULTOMIRIS. There was one case fatal case of sepsis identified in a patient treated with Ultomiris. Longer exposure to Ultomiris for up to 2 years (in Phase 1b and 2 studies) was not

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associated with an increase in the frequency or severity of AEs. There was a low incidence of immunogenicity in both complement inhibitor-naïve and eculizumab-experienced patients with PNH in the Phase 3 studies (0.5%). In the Ultomiris clinical development program, a total of 3 patients with PNH (in the Phase 1b and 2 studies) experienced meningococcal infections/sepsis. No meningococcal infection/sepsis was reported in the Phase 3 studies.

Three patients with PNH experienced meningococcal infections/sepsis in the ravulizumab clinical development program. The risk of meningococcal infection is common to all C5 inhibitors. All 3 patients with PNH who developed meningococcal infections/sepsis in the ravulizumab clinical development program, recovered completely while remaining on ravulizumab without treatment interruption. One death from sepsis was reported in a ravulizumab treated patient in the extension period of Study ALXN1210-PNH-301 however, this was not related to meningococcal infection. The safety profile of ravulizumab in the pivotal Phase 3 studies is consistent with thethat observed safety profile for eculizumab (in clinical trials and in the post-marketing PNH setting.

FDA recommends including a box warning and instituting a REMS program for ravulizumab to mitigate the risk of meningococcal infection in PNH patients. This should include the requirement for the administration of meningococcal vaccines to patients with PNH prior to treatment with ravulizumab. The Applicant should also educate health care providers and patients about the risk for and early signs of possible meningococcal infection and the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infection. The use of prophylactic antibiotics for the duration of Ultomiris treatment should be at the discretion of the treating provider.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The main issues of this review are:

- For two pivotal studies 301 and 302, the non-inferiority margins were never agreed between the applicant and FDA in the IND meetings and correspondence.
- The Statistical Analysis Plans for studies 301 and 302 have never been submitted and reviewed by the Agency.
- For study 301, the point estimates of co-primary endpoint of LDH-N in female patients favored control treatment of Eculizumab, and there is significant interaction between treatment and Sex with P-value of 0.0243 (> 0.05).
- For study 302, ravulizumab did not achieve non-inferiority for key secondary endpoint hemoglobin stabilization because the lower bound of 95% CI is -10.4%, exceeding FDA recommended margin of -10% based on FDA analysis

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8.4. Conclusions and Recommendations

The FDA's Assessment (statistics):

Study 301 demonstrates non-inferiority of ravulizumab over to eculizumab in the complement inhibitor naïve treatment population using both Applicant's and FDA recommended non-inferiority margins.

Study 302 demonstrates non-inferiority of ravulizumab over eculizumab in the patients with PNH previously treated with eculizumab using both sponsor's and FDA recommended NIMs of -10% with regard to efficacy endpoints of LDH percent change from baseline, transfusion avoidance, and proportion of patients with breakthrough hemolysis. Non-inferiority did not achieve for key secondary endpoint hemoglobin stabilization because the lower bound of 95% CI is -10.4%, exceeding FDA recommended margin of -10%.

In conclusion, the statistical reviewer confirms the applicant's results submitted for Study 301 and Study 302. The statistical reviewer also conducted additional sensitivity and subgroup analyses to explore the robustness of the efficacy results. The Agency concludes that ravulizumab was shown to be non-inferiority over eculizumab in the complement inhibitor naïve and PNH previously eculizumab treated population.

Clinical reviewer Assessment:
Study ALXN1210 PNH-301 enrolled 246 patients with complement inhibitor-naïve PNH with active hemolysis. Patients were randomized 1:1 to ravulizumab-cwvz or eculizumab. Efficacy was established based upon the transfusion avoidance and hemolysis as directly measured by normalization of LDH levels. Transfusion avoidance rate in the ULTOMIRIS arm was 73.6% compared to 66.1% in the eculizumab arm with a difference in rate of 6.8% (95% CI:, -4.66, 18.14) and LDH normalization of 53.6% in ULTOMIRIS arm compared to 49.4% in the eculizumab arm with odds ratio of 1.19 (95% CI: 0.80, 1.77). Supportive efficacy data included the percent change from baseline in LDH levels, the proportion of patients with breakthrough hemolysis defined as at least one new or worsening symptom or sign of intravascular hemolysis in the presence of elevated LDH ≥ 2 x upper limit of normal (ULN), after prior LDH reduction to < 1.5 x ULN on therapy and the proportion of patients with stabilized hemoglobin. Non-inferiority of ULTOMIRIS to eculizumab was demonstrated across the endpoints in the complement inhibitor naïve treatment population. Mean change in FACIT-fatigue total score from baseline to Day 183 was also evaluated and there was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared to baseline. The patient-reported fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment and are descriptive findings.

Study ALXN1210-PNH-302 enrolled patients with PNH who were clinically stable after receiving eculizumab for at least the past 6 months. In this study, 195 patients were randomized 1:1 to either continue eculizumab or to switch to ULTOMIRIS. Efficacy was established based on hemolysis as measured by LDH percent change from baseline to Day 183. The LDH percent

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change in the ULTOMIRIS arm was -0.82% compared to 8.4% with difference in percentage change from baseline of 9.2% (95% CI: -0.42, 18.8). Supportive efficacy data was transfusion avoidance [(87.6% in ravulizumab-cwvz arm and 82.7% in eculizumab arm with rate difference of 5.1 (95% CI: -8.9, 19.0)], proportion of patients with stabilized hemoglobin [(76.3% in ravulizumab-cwvz arm compared to 75.5% in eculizumab arm with rate difference of 1.4 (95% CI: -10.4, 13.3)] and the proportion of patients with breakthrough hemolysis through Day 183 [0% in the ravulizumab-cwvz arm, 5.1% in the eculizumab arm with rate difference of 5.1 (95% CI: -8.9, 19.0)]. Non-inferiority of ULTOMIRIS to eculizumab was demonstrated across endpoints in patients with PNH previously treated with eculizumab. Mean change in FACIT-fatigue total score from baseline to Day 183 was also evaluated and there was no observable difference in fatigue between ULTOMIRIS and eculizumab after 26 weeks of treatment compared to baseline. The patient-reported fatigue may be an under-or over-estimation, because patients were not blinded to treatment assignment and are descriptive findings.

Overall, there were no clinically meaningful differences in TEAE rates between complement inhibitor-naïve patients treated with Ultomiris or eculizumab, or between eculizumab-experienced patients treated with Ultomiris or eculizumab. The most important risk associated with ravulizumab is increased susceptibility to infections caused by *N. meningitidis*

FDA recommends including a box warning and instituting a REMS program for ravulizumab to mitigate the risk of meningococcal infection in PNH patients. This should include the requirement for the administration of meningococcal vaccines to patients with PNH prior to treatment with ravulizumab. The Applicant should also educate health care providers and patients about the risk for and early signs of possible meningococcal infection and the need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infection. The use of prophylactic antibiotics for the duration of Ultomiris treatment should be at the discretion of the treating provider.

In summary, the results from studies ALXN1210 PNH 301 and ALXN1210 PNH 302 demonstrate the non-inferiority of ULTOMIRIS to eculizumab in patients with PNH. ULTOMIRIS appears to retain the efficacy of eculizumab in patients with PNH with a less frequent (8 weekly versus 2 weekly) dosing regimen which may be less burdensome to patients.

Based on the demonstrated non-inferiority of ravulizumab over eculizumab in both complement inhibitor-naïve and eculizumab-experienced patients with PNH as well as the favorable risk-benefit profile of Ultomiris, the clinical and statistical reviewers recommend approval of:

ULTOMIRIS for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

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X	X
Kate Li Dwyer, PhD Primary Statistical Reviewer	Yeh-Fong Chen, PhD Statistical Team Leader
X	X
Rosanna Setse, MD, PhD Primary Clinical Reviewer	Tanya Wroblewski, MD Clinical Team Leader

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9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
This Application did not raise any concerns that required an Advisory Committee Meeting or other external consultations.

10 Pediatrics

The Applicant's Position:
The proposed indication is treatment of adults with PNH. The safety of ravulizumab in children with PNH aged 0 to < 18 years of age has not yet been established. An ongoing study (ALXN1210-PNH-304) initiated in 2018 is targeting enrollment of 12 pediatric patients with PNH. Ravulizumab is also being investigated in pediatric patients in (b) (4) ongoing Phase 3 studies in atypical hemolytic uremic syndrome.

The FDA's Assessment:
This application is exempt from the Pediatric Research Equity Act (PREA) requirements because ravulizumab has orphan drug designation for the sought indication.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant's Position:

The proposed labeling for ravulizumab is based broadly on the approved labeling for Soliris, most notably where precautionary statements reflect the shared risk of meningococcal infection, which is well understood and linked to the mechanism of action of C5 inhibitors. To mitigate the risk of meningococcal infection with ravulizumab treatment, the same effective risk mitigation processes in place for eculizumab have been applied in the ravulizumab development program (see Section 12). The proposed labeling specifically addresses this risk in Contraindications, Special Warnings and Precautions for Use, and Undesirable Effects.

The ravulizumab development program targets 2 distinct and complementary PNH populations, representing the patients who would likely receive ravulizumab in clinical practice: complement inhibitor naïve and eculizumab experienced. The populations are characterized differently in so far as naïve patients have active hemolytic disease and the patients on eculizumab have stable disease. Therefore, the endpoints in the 2 studies have been carefully selected to reflect this difference.

Study ALXN1210-PNH-301 enrolled patients who were complement inhibitor-naïve and had uncontrolled hemolysis; the majority of patients were transfusion-dependent, and a substantial proportion of patients had a history of major thrombosis. With its previously untreated patient population, Study ALXN1210-PNH-301 showed the magnitude of amelioration of PNH disease, which was critical to quantifying the efficacy of ravulizumab. Study ALXN1210-PNH-302 represented the disease population who had benefitted from access to treatment with eculizumab and thus enrolled patients with stable disease status.

The clinical trials descriptions in Section 14 of the proposed labeling are intended to convey information likely to be of use to a prescriber in understanding the clinical profile of the product

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as represented in the outcomes of the Phase 3 clinical studies. The efficacy of ravulizumab was evaluated across a continuum of inter-related endpoints that reflect the pathophysiology of PNH and collectively assess the multiple clinically important disease parameters relevant to the functional well-being of patients with PNH. Each of these endpoints reflects a specific, clinically relevant facet of the patient's experience and therefore is included in the proposed labeling. The data presentations, (b) (4) tabular (b) (4) have been chosen to represent these data in an accessible and applicable manner.

Across both Phase 3 studies, ravulizumab achieved statistically significant non-inferiority compared to eculizumab in reducing and maintaining control of hemolysis in patients with PNH. For all efficacy endpoints, the large differences between the boundaries of the CIs and the NIMs establish the strength of evidence of the study results (see Figure 10 and Figure 11 in Section 8.1). The consistency and robustness of results demonstrated across all efficacy endpoints representing the continuum of PNH pathophysiology strengthens the conclusion that ravulizumab is effective in the treatment of PNH.

In the Phase 3 studies, immediate and complete inhibition of serum complement component 5 (C5; terminal complement) was observed by the end of the first ravulizumab dose and sustained throughout the entire 26 week treatment period in all 222 ravulizumab treated patients (see Figure 5 and Figure 6 in Section 6). This complete terminal complement inhibition provided near maximal LDH suppression in complement inhibitor naïve patients (Study ALXN1210-PNH-301) and maintenance of LDH normalization in eculizumab experienced patients (Study ALXN1210-PNH-302). Given the importance in maintaining C5 inhibition throughout the dosing period to avoid incidence of breakthrough hemolysis and associated serious clinical sequelae, it is considered useful to describe the inhibitory effect of ravulizumab compared to eculizumab in labeling.

Overall, the proposed labeling is considered to provide important safety and efficacy information in a manner which allows for optimal communication to the prescriber.

The FDA's Assessment:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
Highlights, Product Title	Proprietary name in Title Case.	Revised to be ALL CAPS per Product Title guidance.
Global	-Proposed inclusion of ™ at every instance of proprietary name.	To avoid cluttering the label, we recommend inclusion of Trademark symbols only once in labeling; in the product title. Recommend removal of the rest of the TM symbols throughout the PI.

	-Passive voice language. -Use of symbols (≤, ≥, µ) that may be misinterpreted and lead to dosing errors. -Use of incorrect cross-reference format	-Revised to reflect active voice. - Requested replacement of the symbols "≥", "<", "±", and "µ" with their intended meanings to prevent misinterpretation and confusion. - Revised to reflect correct format per PLR guidance..[see Use in Specific Populations (8.1)].
Highlights and FPI, Boxed Warning	Missing statement that appears in Soliris BW "vaccination reduces, but does not eliminate, the risk of meningococcal infection"	Added this statement, as the risk is also relevant to this product.
Highlights, Adverse Reactions	Listed headache only.	Added "upper respiratory infection" term. In an actively controlled trial of two products from the same class, even adverse reactions that occurred more commonly in the control arm are important to understanding the toxicity profile of Ultomiris.
FPI, Warnings and Precautions (5.1 Serious Meningococcal Infections)	Proposed organization was not updated to recently approved Soliris labeling.	Revised this subsection to be consistent with recent revisions to Soliris PI and to keep the REMS information within the warning. Each warning should describe a discrete adverse reaction or risk.
FPI, Warnings and Precautions (b) (4)	Vaccination warning was included (b) (4)	Removed (b) (4)
FPI, Warnings and	Did not contain a warning on	Added a warning for

Precautions	thrombosis.	"Thrombosis Prevention and Management"
Highlights, General Formatting	Missing statement corresponding to asterisk on "Full Prescribing Information: Contents*"	Requested addition of: "*Sections or subsections omitted from the full prescribing information are not listed."
FPI, Section 2 (Dosage and Administration)	-Text included between Section 2 Heading and numbered subsection (2.1). (b) (4) Table 2 that described the (b) (4) maximum infusion rate. -Inclusion of negative statements (i.e., (b) (4)) -Trailing zeros on numbers	- Added this text under a new subheading (2.1 Recommended Vaccination and Prophylaxis) (b) (4) - We recommend deleting these statements due to post-marketing reports that (b) (4) - Remove the trailing zero (e.g. 2.0) to avoid a ten-fold misinterpretation.
FPI, Section 6	Included text on recommendations/advice.	Removed text advising clinicians to inform patients about infection risk (this text is relevant to sections 5 &17).
FPI, Section 6.1, Adverse Reactions	-Use of term (b) (4) -Use of MeDDRA terms (System Organ Class,	Per the Adverse Reactions guidance, avoid the use of the term (b) (4) and instead use "adverse reactions". -Replacement of MedDRA terms with clinically

	Preferred Term) -Use of non-US spellings of AR terms -Use of non-rounded integers for AR rates	meaningful terms "Body System, Adverse Reaction" -Revised to US spelling -Advised Applicant to round integers to nearest whole number.
FPI, Adverse Reactions Section, 6.2 Immunogenicity	-Background paragraph not consistent with current guidance. (b) (4) ; limitations of assays preclude inclusion.	-Revised to reflect the text in the Guidance for Industry: Labeling for Biosimilar Products, dated July 2018 -Deletion due to limitations (b) (4)
FPI, 8.1, Pregnancy	-Statement of available human pregnancy data not consistent with current approach. -No Clinical Considerations included (exist in Soliris PI) -Background risk of birth defects/miscarriage not included (per PLLR Final Rule)	Added statement: There are no available data on Ultomiris use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage -Added Clinical Considerations of disease-associated maternal and/or fetal/neonatal risk (similar to Soliris PI) -Added background risk statement (our current approach and per PLLR Final Rule and Guidance)
FPI, 8.2, Lactation	(b) (4) (b) (4)	-There are no data on the presence of ravulizumab in human milk, the effect on the breastfed child, or the effect on milk production -Deleted (b) (4) (per PLLR Guidance)
(b) (4)		
FPI, 8.4, Pediatric Use	Statement regarding "safety and efficacy not established" included (b) (4)	Deleted (b) (4) and provided standard statement "The safety and

	(b) (4)	efficacy of Ultomiris in pediatric patients have not been established.”
FPI, 8.5, Geriatric Use	Missing/deleted	We rejected the deletion of the Geriatric Use subsection. Specific statements on geriatric use of the drug for an approved adult indication are required (21CFR 201.57(c)(9)(v)(A). Per SCS, since only 58 patients in the Phase 3 population were 65 or over; this statement is the correct statement. We provided the required statement: Clinical studies of ULTOMIRIS did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.
(b) (4)		
FPI, Section 12.1, MOA	Detailed information not specific to MOA provided. (b) (4)	The mechanism of action text has been limited to the activity the drug has on the disease process itself. Deleted (b) (4)
FPI, Section 13.1, Carcinogenesis, Mutagenisis, Fertility	Included animal reprotox study findings.	Moved to section 8.1, per PLLR Guidance.
(b) (4)		

		(b) (4)
FPI, Section 14, Clinical Studies	-Text included between Section heading and numbered subsections.	- For all sections of the FPI, when a subsection heading is used, capture all information under a subsection heading. Section 14 revised for clarity and brevity. Added race to demographics table. Revised age (Demo table) to reflect time of first infusion in study. Added Trial names, NCT#s to trial descriptors to ease the identification of trials included in labeling by prescribers. -Revised Table 6: Include only Packed RBC/whole blood units transfused per patient within 12 months. This is similar to description in the eculizumab label. Deleted (b) (4) recommended providing data in tabular format. Removed text describing (b) (4)

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[redacted] (b) (4)		
FPI, Section 16, How Supplied/Storage and Handling	-Missing identifying characteristics. -Descriptor “sterile” included. -Inclusion of [redacted] (b) (4)	-Revised to include the identifying characteristics per 21 CFR 201.57(c)(17). -The reference to “sterile” is not necessary in this section. The reference to sterile is stated in section 11 - This statement is not necessary, [redacted] (b) (4)
FPI, Section 17, Patient Counseling Information	Missing statement on inform patients of increased risk of other types of infection (present in Soliris)	Added.

12 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant's Position:

The most important risk associated with C5 complement inhibition is increased susceptibility to infections caused by *N. meningitidis.* This inherent risk with terminal complement inhibition has been well characterized with the use of eculizumab. Meningococcal infection and meningococcal sepsis are listed as serious adverse drug reactions (ADRs) in the approved labels of eculizumab. Due to its identical binding epitope on C5 and mechanism of action of near complete terminal complement inhibition, ravulizumab carries the same risk of meningococcal disease as eculizumab.
Currently, eculizumab has an approved Risk Evaluation Mitigation Strategy REMS in place. Alexion recommends a REMS for ravulizumab based broadly on the REMS components currently in place for the approved eculizumab indications (PNH, aHUS, and gMG).

The goals of the REMS will be:

- To mitigate the occurrence and morbidity associated with meningococcal infections
- To educate Healthcare Professionals (HCPs) and patients regarding the:
  - increased risk of meningococcal infections with ravulizumab
  - early signs of invasive meningococcal infections
  - need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infections

The FDA's Assessment:

FDA agrees that there is the need for a REMS strategy/program for Ultomiris to mitigate the well characterized risk of meningococcal infection and meningococcal sepsis associated with C5 complement inhibition.

Soliris is approved with a REMS that includes elements to assure safe use to mitigate the risk of meningococcal infection. Prescribers must counsel patients about the risk of meningococcal infection, provide the patients with the REMS educational materials, and ensure patients are vaccinated with meningococcal vaccine(s) prior to starting Soliris.

The FDA REMS oversight committee recommends that, in accordance with section 505-1 of FDCA, a REMS is necessary for ULTOMIRIS. The goals of this REMS are as stated by the Applicant above. The REMS for Ultomiris should be identical to the REMS for Soliris with the exception that because this is a new REMS the timetable for submission of assessments should be 6 months, 12 months, and annually thereafter. The timetable for submission of assessments in the Soliris REMS was modified in 2015 to every 2 years.

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13 Postmarketing Requirements and Commitment

The FDA's Assessment:
The following PMCs are recommended:

Clinical PMC Description
"Submit the final clinical study reports and datasets for randomized controlled trials of Ultomiris in patients with paroxysmal nocturnal hemoglobinuria (ALXN1210-PNH-301 and ALXN1210-PNH-302) to include the extension period of up to 2 years of follow-up".

The timetable for fulfilling this PMC as agreed to by the Applicant on December 10, 2018 is:

Interim Report Submission:	06/2019
Final Report Submission:	09/2020

CMC PMC Description: Implement a two-tier Reference material system with (b) (4) storage condition for primary reference material.

Final Report Submission:	12/2019

CMC PMC Description: Explore alternative assay formats for the Hemolytic Assay in order to reduce method variability.

Final Report Submission	3/2019

CMC PMC Description: Quality the (b) (4) sample for the bioburden method using samples from three (b) (4) lots. Prove the qualification data.

Final Report Submission	6/2019

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14 Division Director (DHOT)

X

John Leighton, PhD, DABT
Division Director
Division of Hematology, Oncology, Toxicology

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15 Division Director (OCP)

X _____

Nam Atiqur Rahman, PhD
Division of Clinical Pharmacology V Director
Office of Clinical Pharmacology

Reference ID: 4366451

16 Division Director (OB)

X

Tomas E. Gwise, PhD
Deputy Director, Office of Biometrics

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17 Division Director (Clinical)

I concur with the review team regarding the evidence of effectiveness, safety, and labeling instructions for Ultomiris (ravulizumab-cwvz). The applicant submitted the results of two randomized, open-label phase 3 studies -Study ALXN1210 PNH 301 and ALXN1210 PNH 302 which demonstrated non-inferiority between ravulizumab-cwvz and eculizumab for both clinical and laboratory-based efficacy endpoints. Ravulizumab-cwvz and eculizumab have very similar mechanisms of action (MOA) and the safety profiles were similar between products. No unexpected safety issues were identified during the review. Due to the MOA, ravulizumab-cwvz is expected to carry the same risk of meningococcal disease. To mitigate this risk, a risk evaluation and mitigation strategy (REMS) is recommended. The benefit-risk profile for ravulizumab-cwvz in adult patients with PNH appears acceptable.

X _____

Ann T. Farrell, MD
Division Director
Division of Hematology Products

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18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

Amy McKee, MD
Acting Associate Office Director
Office of Hematology and Oncology Products (OHOP)

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19 Appendices

19.1. References

The Applicant's References:

Brodsky RA, Young NS, Antonioli E, et al. Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria. Blood. 2008;111(4):1840-1847.

Brodsky RA. Eculizumab: another breakthrough. Blood. 2017;129(8):922-923.

Brodsky RA. Complement in hemolytic anemia. Blood. 2015;126(22):2459-2465.

Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood. 2014;124(18):2804-2811.

Canalejo K, Riera Cervantes N, Felippo M, Sarandria C, Aixala M. Paroxysmal nocturnal haemoglobinuria. Experience over a 10 years period. Int J Lab Hematol. 2014;36(2):213-221.

Dale J, Myhre E. Lactate dehydrogenase and mechanical trauma of erythrocytes. Acta Med Scand. 1972;191(1-2):133-136.

de Latour R, Fremeaux-Bacchi V, Porcher R, et al. Assessing complement blockade in patients with paroxysmal nocturnal hemoglobinuria receiving eculizumab. Blood. 2015;125(5):775-783.

de Latour R, Mary J, Salanoubat C, Terriou L, Etienne G, Mohty M. Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories. Blood. 2008;112(8):3099-3106.

Hill A, Kelly R, Hillmen P. Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood. 2013;121(25):4985-4996.

Hill A, Platts P, Smith A, Richards S, Cullen M. The Incidence and Prevalence of Paroxysmal Nocturnal Hemoglobinuria (PNH) and Survival of Patients in Yorkshire. Blood. 2006;108(11):985-985.

Hill A, Rother RP, Wang X, et al. Effect of eculizumab on haemolysis-associated nitric oxide depletion, dyspnoea, and measures of pulmonary hypertension in patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol. 2010;149(3):414-425.

Hill A, Richards SJ, Hillmen P. Recent developments in the understanding and management of paroxysmal nocturnal haemoglobinuria. Br J Haematol. 2007;137(3):181-192.

Hillmen P, Lewis SM, Bessler M, Luzzatto L, Dacie JV. Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med. 1995;333(19):1253-1258.

Hillmen P, Muus P, Roth A, et al. Long-term safety and efficacy of sustained eculizumab treatment in patients with paroxysmal nocturnal haemoglobinuria. Br J Haematol. 2013;162(1):62-73.

Hillmen P, Young NS, Schubert J, et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006;355(12):1233-1243.

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Kanakura Y, Ohyashiki K, Shichishima T, et al. Safety and efficacy of the terminal complement inhibitor eculizumab in Japanese patients with paroxysmal nocturnal hemoglobinuria: the AEGIS clinical trial. Int J Hematol. 2011;93(1):36-46.

Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 1997;53(3):983-997.

Leach MW, Rottman JB, Hock MB, Finco D, Rojko JL, Beyer JC. Immunogenicity/hypersensitivity of biologics. Toxicol Pathol. 2014;42(1):293-300.

Lobo ED, Hansen RJ, Balthasar JP. Antibody Pharmacokinetics and Pharmacodynamics. J. Pharm Sci. 2004;93(11):2645-2668.

Mallinckrodt CH, Clark WS, David SR. Accounting for dropout bias using mixed-effects models. J Biopharm Stat. 2001;11(1-2):9-21.

Mallinckrodt CH, Kaiser CJ, Watkin JG, Molenberghs G, Carroll RJ. The effect of correlation structure on treatment contrasts estimated from incomplete clinical trial data with likelihood-based repeated measures compared with last observation carried forward ANOVA. Clin Trials. 2004;1(6):477-489.

Matis LA, Rollins SA. Complement-specific antibodies: designing novel anti-inflammatories. Nat Med. 1995;1(8):839-842.

Nakayama H, Usuki K, Echizen H, Ogawa R, Orii T. Eculizumab dosing intervals longer than 17 days may be associated with greater risk of breakthrough hemolysis in patients with paroxysmal nocturnal hemoglobinuria. Biol Pharm Bull. 2016;39(2):285-288.

Ohno H. Survey by research group to grasp the epidemiology image of the specific disease treatment study business for non-target disease. Collection of 1999 Study Achievements – Final Report. March 2000.

Parker C, Omine M, Richards S, et al. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood. 2005;106(12):3699-3709.

Risitano AM. Paroxysmal nocturnal hemoglobinuria and other complement-mediated hematological disorders. Immunobiology. 2012;217(11):1080-1087.

Rother RP, Rollins SA, Mojcik CF, Brodsky RA, Bell L. Discovery and development of the complement inhibitor eculizuamb for the treatment of paroxysmal nocturnal hemoglobinuria. Nat Biotechnol. 2007;25(11):1256-1264.

Schrezenmeier H, Muus P, Socie G, et al. Baseline characteristics and disease burden in patients in the international paroxysmal nocturnal hemoglobinuria registry. Haematologicea. 2014;99(5):922-929.

Sharma R, Keyzner A, Liu J, Bradley T, Allen SL. Successful pregnancy outcome in paroxysmal nocturnal hemoglobinuria (PNH) following escalated eculizumab dosing to control breakthrough hemolysis. Leuk Res Rep. 2015;4(1):36-38.

Reference ID: 4366451

Socie G, Mary JY, de Gramont A, et al. Paroxysmal nocturnal haemoglobinuria: long-term follow-up and prognostic factors. French Society of Haematology. Lancet. 1996;348(9027):573-577.

The FDA's References:

CDC. Meningococcal ACIP recommendations. Atlanta, GA: US Department of Health and Human Services, CDC; 2017. https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html

Food and Drug Administration. Alexion briefing information for the November 18, 2014, meeting of the Drug Safety and Risk Management Advisory Committee. https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm423029.htm

Katrin S. Kohl, Michael Marcy, Michael Blum, Marcy Connell Jones, Ron Dagan, John Hansen, David Nalin, EdwardRothstein, and the Brighton Collaboration Fever Working Group. Fever after Immunization: Current Concepts and Improved Future Scientific Understanding. Clinical Infectious Diseases, Volume 39, Issue 3, 1 August 2004, Pages 389–394

McNamara LA, Topaz N, Wang X, Hariri S, Fox L, MacNeil JR. High Risk for Invasive Meningococcal Disease Among Patients Receiving Eculizumab (Soliris) Despite Receipt of Meningococcal Vaccine. MMWR Morb Mortal Wkly Rep 2017;66:734-737. DOI: http://dx.doi.org/10.15585/mmwr.mm6627e1.

Page E Crew, Winston E Abara, Lynda McCulley, Peter E Waldron, Robert D Kirkcaldy, Emily J Weston, Kyle T Bernstein, S Christopher Jones, Susan J Bersoff-Matcha; Disseminated gonococcal infections in patients receiving eculizumab: a case series, Clinical Infectious Diseases, ciy958, November 2018. https://doi.org/10.1093/cid/ciy958

Reher D, Fuhrmann V, Kluge S, Nierhaus A. A rare case of septic shock due to Neisseria meningitidis serogroup B infection despite prior vaccination in a young adult with paroxysmal nocturnal haemoglobinuria receiving eculizumab. Vaccine. 2018 May 3;36(19):2507-2509.

19.2. Financial Disclosure

The Applicant's Position:

Financial Disclosure Forms (FDF) have been collected for all investigators who participated actively in the studies. The sponsor was unable to obtain FDFs from 8 investigators and subinvestigators (7 were from sites that never screened or enrolled any patients and 1 from a subinvestigator who left the study site before study initiation). Nine investigators who participated in Study ALXN1210-PNH-301 and 8 investigators who participated in Study ALXN1210-PNH-302 declared disclosable financial interests/arrangements, in most cases because they are part of a PNH Center of Excellence and have collaborated with the Applicant on PNH research since the early 2000's. The design of the Phase 3 studies, including endpoints

based on central laboratory results, 100% source data verification performed by an independent contract research organization, as well as sponsor audits, is considered adequate to minimize the risk for bias of study results.

The FDA's Assessment:

The applicant provided certification on FDA Form 3454 to indicate that there were no financial arrangements between the Sponsor and Investigators which could be affected by the outcome of the Phase 3 studies Study ALXN1210-PNH-301 and ALXN1210-PNH-302. For the 8 investigators and sub-investigators whose FDF's could not be obtained, the applicant provided a certification attesting to the sponsor's due diligence in attempting to obtain the information, and the reason why such information was not obtained.

FDA agrees with the Applicant's statement that – "the design of the Phase 3 studies, including endpoints based on central laboratory results, 100% source data verification performed by an independent contract research organization, as well as sponsor audits", is adequate to minimize the risk for bias of study results.

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Covered Clinical Study: ALXN1210-PNH-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 552		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 9		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 9 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 5		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study: ALXN1210-PNH-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 259		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): none		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 8		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 8 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:
All nonclinical pharmacology/toxicology information is presented in Section 5.

The FDA's Assessment:
Not applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

Not applicable .

Reference ID: 4366451

19.5. Additional Safety Analyses Conducted by FDA

Not Applicable

19.6. Appendix: Inspection History for Manufacturing/Testing Sites - Ravulizumab

The recent FDA and EMA inspection history of the sites involved in the manufacture and testing of ravulizumab is listed in Table 31.

Reference ID: 4366451

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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