NDA/BLA Multi-Disciplinary Review and Evaluation

<table>
<tr><td>Application Type</td><td>Biologic license application (BLA) Supplement</td></tr>
<tr><td>Application Number(s)</td><td>761108/ S-001</td></tr>
<tr><td>Priority or Standard</td><td>Priority</td></tr>
<tr><td>Submit Date(s)</td><td>April 19, 2019</td></tr>
<tr><td>Received Date(s)</td><td>April 19, 2019</td></tr>
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<tr><td>Division/Office</td><td>DHP/OHOP/OND</td></tr>
<tr><td>Review Completion Date</td><td>September 26, 2019</td></tr>
<tr><td>Established/Proper Name</td><td>Ravulizumab-cwvz</td></tr>
<tr><td>(Proposed) Trade Name</td><td>ULTOMIRIS</td></tr>
<tr><td>Pharmacologic Class</td><td>Selective Immunosuppressant/terminal complement inhibitor</td></tr>
<tr><td>Code name</td><td>ALXN1210</td></tr>
<tr><td>Applicant</td><td>Alexion Pharmaceuticals, Inc.</td></tr>
<tr><td>Formulation</td><td>300mg/30mL (10mg/mL) formulation for IV administration</td></tr>
<tr><td>Applicant proposed Dosing Regimen</td><td>Recommended dosing regimen in adult and pediatric patients one month of age and older weighing 5 kg or greater with aHUS consists of a loading dose followed by a maintenance dosing, administered by intravenous infusion. Dosing is based on the patient’s body weight.
<table>
<tr><th>Body Weight Range (kg)</th><th>Loading Dose (mg)</th><th colspan="2">Maintenance Dose (mg) and Dosing Interval</th></tr>
<tr><td>greater than or equal to 5 to less than 10</td><td>600</td><td>300</td><td rowspan="2">Every 4 weeks</td></tr>
<tr><td>greater than or equal to 10 to less than 20</td><td>600</td><td>600</td></tr>
<tr><td>greater than or equal to 20 to less than 30</td><td>900</td><td>2,100</td><td rowspan="5">Every 8 weeks</td></tr>
<tr><td>greater than or equal to 30 to less than 40</td><td>1,200</td><td>2,700</td></tr>
<tr><td>greater than or equal to 40 to less than 60</td><td>2,400</td><td>3,000</td></tr>
<tr><td>greater than or equal to 60 to less than 100</td><td>2,700</td><td>3,300</td></tr>
<tr><td>greater than or equal to 100</td><td>3,000</td><td>3,600</td></tr>
</table>
Maintenance doses should be administered once every 8-week interval, starting 2 weeks after loading dose administration.</td></tr>
<tr><td>Applicant Proposed Indication(s)/Population(s)</td><td>For the treatment of patients with complement mediated thrombotic microangiopathy to include atypical hemolytic uremic syndrome.</td></tr>
<tr><td>Recommendation on Regulatory Action</td><td>Regular Approval</td></tr>
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Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA)

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Bernetta Lane, DHS(c), MBA, RN
Nonclinical Reviewer	Rama Gudi, PhD
Nonclinical Team Leader	Brenda Gehrke, PhD
Office of Clinical Pharmacology Reviewer(s)	Lauren Price, PharmD
Office of Clinical Pharmacology Team Leader(s)	Olanrewaju Okusanya, PharmD, MS
Clinical Reviewer	Qin Ryan, MD, PhD
Clinical Team Leader	Tanya Wroblewski, MD
Statistical Reviewer	Jiaxi Zhou, MS
Statistical Team Leader	Yeh-Fong Chen, PhD
Office of Biostatistics Deputy Division Director	Thomas Gwise, PhD
Cross-Disciplinary Team Leader	Tanya Wroblewski, MD
Supervisory Associate Division Director (DHP)	Albert Deisseroth, MD, PhD

Additional Reviewers of Application

Deputy Director of Labeling (DHP)	Virginia E. Kwitkowski, MS, ACNP-BC
OPQ	Xuhong Li, PhD TL Kelley Burridge, PhD
OPDP	Robert Nguyen, PharmD TL Susannah O'Donnell, MPH, RAC
OSE/DRISK	Mei-Yean Chen, PharmD; Kate Oswell, MA TL Elizabeth Everhart, MSN, RN, ACNP
DMPP	Sharon Mills, BSN, RN, CCRP TL Barbara Fuller, RN, MSN, CWOCN

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMPP= Division of Medical Policy Programs
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADA	antidrug antibody
ADAMTS13	a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
aHUS	atypical hemolytic uremic syndrome
ALT	alanine aminotransferase
AMR	antibody-mediated rejection
AST	aspartate aminotransferase
AR	adverse reaction
BLA	biologics license application
BP	blood pressure
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
C5	complement component 5
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CKD	chronic kidney disease
Cmax	maximum observed serum concentration
CMC	chemistry, manufacturing, and controls
CNI	calcineurin inhibitor
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
cRBC	chicken red blood cells
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	concentration at the end of the dosage interval
CV	coefficient of variation
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document

eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOI	end of infusion
ESKD	end-stage kidney disease
EQ-5D-3L	EuroQol 5-Dimension 3-Level
ETASU	elements to assure safe use
FACIT	Functional Assessment of Chronic Illness Therapy
FAP	Full analysis population
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GRMP	good review management practice
Hib	Hemophilus influenzae type b
HUS	hemolytic uremic syndrome
ICF	informed consent form
ICH	International Conference on Harmonization
ICU	intensive care unit
IEC	Institutional (or Independent) Ethics Committee
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat IV intravenous(ly)
IVIg	intravenous immunoglobulin
IWRS	Interactive Voice/Web Response System
LDH	lactate dehydrogenase
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MMRM	mixed model for repeated measures
mTORi	mammalian target of rapamycin inhibitor
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information

PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PK	pharmacokinetic(s)
PNH	paroxysmal nocturnal hemoglobinuria
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
QoL	quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
q8w	once every 8 weeks
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SGE	special government employee
SOC	standard of care
SP	Safety population
TEAE	treatment emergent adverse event
sTNFR1	soluble tumor necrosis factor receptor 1
sVCAM-1	soluble vascular adhesion molecule 1
TMA	thrombotic microangiopathy
ULN	upper limit of normal
US TTO	time trade-off value set for the United States

1 Executive Summary

1.1. Product Introduction

ULTOMIRIS (ravulizumab-cwvz) is a humanized monoclonal antibody and is a terminal complement inhibitor that binds to the complement protein C5 and inhibits its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]) thus preventing the generation of the terminal complement complex C5b9.

The Agency's proposed indication for ULTOMIRIS is the treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

The proposed limitations of use include: ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).

The recommended dosing regimen in adult and pediatric patients (one month of age and older with aHUS weighing 5kg or greater) is a weight-based dosing regimen as shown in Table 1.

Table 1: ULTOMIRIS Weight-Based Dosing Regimen

Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg) and Dosing Interval	
greater than or equal to 5 to less than 10	600	300	Every 4 weeks
greater than or equal to 10 to less than 20	600	600	
greater than or equal to 20 to less than 30	900	2,100	Every 8 weeks
greater than or equal to 30 to less than 40	1,200	2,700	
greater than or equal to 40 to less than 60	2,400	3,000	
greater than or equal to 60 to less than 100	2,700	3,300	
greater than or equal to 100	3,000	3,600	

Maintenance dosing should begin once every 8 weeks or every 4 weeks (depending upon body weight) starting 2 weeks after initial loading dose. For patients switching from eculizumab to ULTOMIRIS, administer the loading dose of ULTOMIRIS 2 weeks after the last eculizumab

infusion and then administer maintenance doses once every 8 weeks or 4 weeks (depending upon body weight), starting two seeks after loading dose administration.

In this review document, ravulizumab refers to ravulizumab-cwvz.

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 of treatment of adult and pediatric patients one month and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complemented mediated thrombotic microangiopathy (TMA). The data submitted by the applicant provides for substantial review of effectiveness.

The approval recommendation is supported by the results of two open-label, single-arm, multicenter trials (ALXN1210-aHUS 311 and ALXN1210-aHUS-312). Study ALXN1210-aHUS-311 (Study 311) enrolled 56 adult patients with evidence of TMA due to aHUS who were naïve to complement inhibitor treatment prior to enrollment. Study ALXN1210-aHUS-312 (Study 312) enrolled 14 patients less than 18 years of age with complement inhibitor treatment-naïve aHUS. Efficacy was established based on complete TMA response defined as normalization of platelet count and lactate dehydrogenase and ≥ 25% improvement in serum creatinine from baseline during the 26-week Initial Evaluation Period. A complete TMA Response was achieved by 30 of 56 (53.6%; [95% CI: 39.7%, 67.0%]) adult patients in Trial 311 and 10 of 14 (71.4%; [95% CI: 41.9%, 91.6%]) pediatric patients in Trial 312. The median duration of complete TMA response was 7.97 months (range: 2.52 to 16.69 months) for Study 311 and 5.08 months (range: 3.08 to 5.54 months) in Study 312.

Supportive efficacy was demonstrated by platelet count change from baseline, dialysis requirement, and renal function as evaluated by estimated glomerular filtration rate (eGFR). In Study 311, 17 of the 29 patients (59%) who required dialysis at study entry discontinued dialysis at end of available follow. In Study 312, four of the five patients who required dialysis at study entry were able to discontinue dialysis after first month and for duration of treatment. The results from Study 312 also support the conclusion of effectiveness of ULTOMIRIS in pediatric patients age 1 month and greater. The youngest patient enrolled was 10 months and supports use of ULTOMIRIS in patients ages 1 month or greater as no differences in efficacy, safety, or PK are expected for patients aged 1 month to 2 years.

In summary, the results from studies 311 and 312 in a rare disease are acceptable for demonstration of effectiveness of this product in patients with aHUS. The ability to conduct formal randomized controlled trials or non-inferiority trials may not be feasible for the aHUS population in the US. The two single-arm trials (Study 311 and Study 312) demonstrated a sustainment of response supported by clinically meaningful secondary endpoints (improvement in renal function and decreased dialysis requirements) and provide sufficient evidence to support conclusion of effectiveness for ULTOMIRIS in adult and pediatric patients with aHUS.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening condition characterized by hemolytic anemia, thrombocytopenia and renal failure. Patients with aHUS often require one or more renal transplants or chronic dialysis and have an increased risk for death and serious thrombotic events such as stroke. Eculizumab, a selective humanized monoclonal antibody that targets C5 of the terminal complement cascade, is currently the only approved drug for the treatment of aHUS. Prior to the approval of eculizumab, plasma therapy was the standard of care for treatment of aHUS. 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 safety and efficacy of ULTOMIRIS in patients with aHUS was assessed in two open-label single arm studies (Study ALXN1210-aHUS-311 and Study ALXB1210-aHUS-312). In both studies, ULTOMIRIS was dosed intravenously based on weight-based dosing and patients were vaccinated against meningococcal infections prior to or at the time of initiating treatment with ULTOMIRIS. In both studies, enrollment criteria excluded patients presenting with TMA due to a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency, Shiga toxin *Escherichia coli* related hemolytic uremic syndrome (STEC-HUS) and genetic defect in cobalamin C metabolism. Patients with confirmed diagnosis of STEC-HUS after enrollment were excluded from the efficacy evaluation.

Study 311 enrolled 56 adult patients with aHUS who were naïve to complement inhibitor treatment prior to study entry and displayed signs of thrombotic microangiopathic angiopathy (TMA). To qualify for enrollment, patients were required to have a platelet count ≤150 x 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal or required dialysis. The median age at time of first infusion of ravulizumab-cwvz was 42 years(range 19.5, 76.6). The median platelet count was 95 (range 18,473) and median LDH was 508 (range 229.5, 3249). Demonstration of efficacy was based on complete TMA response during the 26-week initial evaluation period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Complete TMA Response was observed in 30 of the 56 patients (54%) during the 26-week Initial Evaluation Period. The median duration of Complete TMA Response was 7.97 months (range: 2.52 to 16.69 months).

The demonstration of efficacy was supported by platelet count change from baseline, , dialysis requirement, and renal function as evaluated by estimated glomerular filtration rate (eGFR). An increase in mean platelet count was observed after commencement of ULTOMIRIS, increasing from 118.52 × 10^9/L at baseline to 240.34 ×10^9/L at Day 8 and remaining above 227 × 10^9/L at all subsequent visits in the Initial Evaluation

Period (26 weeks). Renal function, as measured by eGFR, was improved or maintained during ULTOMIRIS therapy. The mean eGFR (+/- SD) increased from 15.86 (14.82) at baseline to 51.83 (39.16) by 26 weeks. Seventeen of the 29 patients (59%) who required dialysis at study entry discontinued dialysis by the end of the available follow-up.

Study 312 enrolled 14 pediatric patients who displayed signs of TMA. In order to qualify for enrollment, patients were required to have a platelet count ≤150 x 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine level ≥ 97.5% percentile at screening or required dialysis. The mean age at time of first infusion was 6.1 years with range of 10 months to 17 years. The demonstration of efficacy was based upon Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Complete TMA Response was observed in 10 of the 14 patients (71%) during the 26-week Initial Evaluation Period. The median duration of Complete TMA Response was 5.08 months (range: 3.08 to 5.54 months). The demonstration of efficacy was supported by platelet count change from baseline, dialysis requirement, and renal function as evaluated by eGFR. An increase in mean platelet count was observed after commencement of ULTOMIRIS, increasing from 60.50 × 10^9/L at baseline to 296.67 × 10^9/L at Day 8 and remained above 296 × 10^9/L at all subsequent visits in the Initial Evaluation Period (26 weeks). The mean eGFR (+/- SD) increased from 28.4 (23.11) at baseline to 108.0 (63.21) by 26 weeks. Four of the 5 patients who required dialysis at study entry were able to discontinue dialysis after the first month in study and for the duration of ULTOMIRIS treatment. The results from Study 312 support the conclusion of effectiveness of ULTOMIRIS in pediatric patients age 1 month and greater. The youngest patient enrolled was 10 months and supports use of ULTOMIRIS in patients ages 1 month or greater as no differences in efficacy, safety, or PK are expected for patients aged 1 month to 2 years.

In both studies, the adverse event profile did not identify any new risks for the use of ULTOMIRIS in this population. The most commonly reported TEAES (≥20%) were upper respiratory tract infections, diarrhea, nausea, vomiting, headache, hypertension and pyrexia. Serious adverse reactions were reported in 52 (57%) patients with aHUS. Four patients died during Study 311 with cause of death sepsis in two patients and intracranial hemorrhage in one patient. The fourth patient who was excluded from the trial after diagnosis of STEC-HUS died due to pretreatment cerebral arterial thrombosis. There was a low incidence of immunogenicity in both 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 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. To mitigate this risk, a Risk Evaluation and Mitigation Strategy (REMS)

is in place and the prescribing information includes a box warning for serious meningococcal infections. Overall the benefit-risk profile for ULTOMIRIS in adult and pediatric patients age one month of age with aHUS appears acceptable.

In summary, results of both trials in pediatric and adult patients with aHUS, demonstrate a favorable benefit-risk profile for ULTOMIRIS for the proposed indication. Adult and pediatric patients with aHUS experienced substantial benefits with 53.6% and 71.4% achieving complete TMA response, respectively. Improvements were also demonstrated in renal function and patients no longer requiring dialysis. Complete terminal complement inhibition was achieved and maintained throughout an extended dosing interval, enabling convenient q8w or q4w weight-based dosing that reduced treatment burden. The results from these single-arm trials in a rare disease are acceptable for demonstration of effectiveness of this product in patients with aHUS. The ability to conduct formal randomized controlled trials or non-inferiority trials may not be possible for the aHUS population. The two single-arm trials (Study 311 and Study 312) demonstrated a sustainment of response supported by clinically meaningful secondary endpoints (improvement in renal function and decreased dialysis requirements) were sufficient to support a conclusion of effectiveness for ULTOMIRIS in adult and pediatric patients with aHUS. The safety profile in patients with aHUS was acceptable and similar to the previously approved same class agent, with no meningococcal infections reported in aHUS trials. In conclusion, the totality of the data supports a favorable benefit-risk profile for ravulizumab in treatment of patients with aHUS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Atypical hemolytic uremic syndrome (aHUS) is a rare, progressive, and life-threatening disorder characterized by hemolytic anemia, thrombocytopenia, acute renal injury, and extra-renal complications. • The predominant underlying cause of aHUS is dysregulation of the alternative pathway of complement, resulting in uncontrolled complement activation, which causes inflammation, endothelial activation and damage, and a prothrombotic /procoagulant state resulting in systemic thrombotic microangiopathy (TMA)s . • In pediatric and adult patients with aHUS, 46% of adults and 17% of children progressed to end-stage kidney disease (ESKD) or death by 1 month after clinical manifestation, and 56% of adults and 29% of children progressed to ESKD or death by 1 year (Fremeaux-Bacchi,	• **aHUS is a rare and serious life-threatening condition with increased mortality and morbidity.** • **aHUS is a chronic disease that requires lifelong treatment.** .

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	2013).	
Current Treatment Options	• Terminal complement inhibition provides an effective therapy for patients with aHUS. • Eculizumab was approved in 2011 for the treatment of aHUS . Eculizumab is dosed weekly for 4 weeks followed by maintenance dosing every 2 weeks. The dosing regimen may impose a burden on patients to include missed days of work or school. • Plasma therapy and steroids has limited efficacy in aHUS.	**An additional effective therapy but with reduced burdensome dosing regimen for patients with aHUS would be a benefit.**
Benefit	• In Study 311, Complete TMA Response was observed in 30 of the 56 patients (54%) during the 26-week Initial Evaluation Period. The median duration of Complete TMA Response was 7.97 months (range: 2.52 to 16.69 months). • The demonstration of efficacy was supported by platelet count change from baseline, , dialysis requirement, and renal function as evaluated by estimated glomerular filtration rate (eGFR). An increase in mean platelet count was observed after commencement of ULTOMIRIS, increasing from 118.52 × 10^9/L at baseline to 240.34 ×10^9/L at Day 8 and remaining above 227 × 10^9/L at all subsequent visits in the Initial Evaluation Period (26 weeks). • Renal function, as measured by eGFR, was improved or maintained during ULTOMIRIS therapy. The mean eGFR (+/- SD) increased from 15.86 (14.82) at baseline to 51.83 (39.16) by 26 weeks. Seventeen of the 29 patients (59%) who required dialysis at study entry discontinued dialysis by the end of the available follow-up. • In study 312, Complete TMA Response was observed in 10 of the 14	**The basis for conclusion of efficacy of ULTOMIRIS in adult and pediatric patients age 1 month and greater with aHUS was established on sustained complete TMA response and improvement in a meaningful clinical endpoint (decrease in dialysis requirements) in patients who were naïve to complement inhibitor treatment.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients (71%) during the 26-week Initial Evaluation Period. The median duration of Complete TMA Response was 5.08 months (range: 3.08 to 5.54 months). The demonstration of efficacy was supported by platelet count change from baseline, dialysis requirement, and renal function as evaluated by eGFR. • The most meaningful clinical benefit to patient with aHUS is improvements in renal function and sustainment of complete TMA response dialysis requirements and durability of the complete TMA response.	
Risk and Risk Management	• The most important risk associated with complement C5 inhibition or deficiency is increased susceptibility to infectious or caused by Neisseria meningitidis infections. The risk has been well characterized with the approval of ravulizumab for PNH and other C5 inhibitors. Ravulizumab is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) because of the risk of meningococcal infections. • The safety profile is notable for SAEs observed in more than trial patients, 56.8% as of 90-day safety update cut-off. The most common adverse events were various infections, hypertension, headache, diarrhea, and vomiting. Based on the previous experience in ravulizumab and agents of the same class, the most serious safety concern is *Neisseria* meningococcal infection that lead to meningitis that observed in the previous trials. However, Neisseria meningitis was not reported in the two trials reviewed in this submission. • Treatment emergent antibodies to ravulizumab-cwvz were detected in 1 of 71 (1.4%) patients with aHUS. There was no apparent correlation of antibody development to altered PK profile, clinical	**• Overall, the risk of ULTOMIRIS appears acceptable for the treatment of adult and pediatric patients with aHUS. The biggest risk is serious meningococcal infections.** **• To mitigate the risk of serious meningococcal infections, ULTOMIRISULTOMIRIS will only be available through a restricted program under a Risk Evaluation and Mitigation Strategy (REM).** **• Additional mitigation strategies for the serious meningococcal infections include a box warning in the prescribing information.** **• The prescribing information includes information to immunized patients with meningococcal vaccine at least 2 weeks prior to administering first dose of**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	response or adverse events observed.	**ULTOMIRIS.** • **Healthcare Professionals and patients and caregivers 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.**

1.4. Patient Experience Data

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

			Section of review where discussed, if applicable
x	**The patient experience data that were submitted as part of the application include:**		
	x	Clinical outcome assessment (COA) data, such as	See Section 8
		x Patient reported outcome (PRO)	See Section 8
		☐ 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 were not submitted in the application, but were considered in this review:**		
	☐	Input informed from participation in meetings with patient stakeholders	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	
	☐	Observational survey studies designed to capture patient experience data	
	☐	Other: (Please specify):	
☐	**Patient experience data was not submitted as part of this application.**		

Two single-arm, multi-center trials were submitted to support this application. The patient reported outcome data is difficult to interpret given single-arm and open-label trial designs. Only descriptive conclusions can be drawn from the review of the data (b) (4)

2 Therapeutic Context

2.1. Analysis of Condition

Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy (TMA) characterized by hemolytic anemia, thrombocytopenia and renal failure (Nester 2015). Historically, hemolytic uremic syndrome (HUS) has been divided into typical HUS (primarily STEC-HUS due to Shiga toxin-producing Escherichia coli) or other micro-organisms that produce verotoxin (VTEC), and atypical HUS, referring to non-STEC mediated HUS. Newer classification systems have been proposed, including a division of HUS into primary causes due to mutations in complement genes or autoantibodies against complement regulatory proteins (aHUS), or secondary causes, including infection, drug toxicity, autoimmune disorders, transplants, or pregnancy. Other systems have proposed naming of TMAs based on causes, for example, utilizing "complement-mediated TMA" to refer to aHUS to ameliorate confusion when discussing TMAs (George and Nester 2014, Baines 2017, Scully 2017, Garvriilaki 2019, Berger 2018, Padmanabhan 2019), however, there is no universally accepted naming convention at this time.

aHUS is estimated to have an incidence rate of approximately 1-2 cases per million in the United States. Although rare, it is a serious and life-threatening condition caused by uncontrolled complement activation resulting in endothelial damage. Uncontrolled complement activation may be due to genetic mutations or acquired autoantibodies in the alternative pathway of complement (Noris 2010, Feitz 2018), however, pathologic gene mutations or autoantibodies are only identified in at most 50% to 60% of patients (Fakhouri 2017, Schaefer 2018).

Atypical HUS tends to be a disease of childhood with most patients developing the disease before 10 years of age. There are, however patients that present with disease in adults even older adults (over age 60). Approximately 50% patients with aHUS require maintenance dialysis and aHUS frequently recurs after kidney transplant (Schmidtko 2013). In addition, patients with aHUS may have chronic overt disease or subclinical disease with unpredictable relapses.

A key contrast of aHUS with thrombotic thrombocytopenia purpura (TTP) is that in aHUS the lactate dehydrogenase (LDH) and creatinine frequently do not normalize with the use of plasma exchange. In aHUS there is persistent platelet activation and a continued decline in estimated glomerular filtration rates (eGFR). Approximately 30-80% of these patients advance to end-stage renal disease or death despite hematological responses to plasma exchange (Laurence 2013, Tsai 2014, Loirat 2016). Although patients with aHUS may have hematologic responses to plasma-based therapy, long-term renal outcomes remain poor, with 50-77% of patients developing ESRD or dying after 3-year follow-up (Noris 2010).

The endothelial damage due to increased complement activity in aHUS, including damage caused by the formation of the C5b-9 membrane attack complex and C5a anaphylatoxin, initiates a cascade of events. These result in thrombosis, thrombocytopenia secondary to platelet consumption, hemolysis, and end-organ, renal and extra-renal, damages. The prognosis of aHUS in the pre-complement inhibitor therapy era was poor.

An aHUS registry (Schaefer 2018) reported that without eculizumab, 31% of adult patients developed ESKD within 1 year of aHUS diagnosis and required dialysis or kidney transplant. Within 6 months of aHUS diagnosis in non-eculizumab-treated patients, 25% of patients were receiving chronic dialysis, 19% had received a kidney transplant, and approximately 67% had incurred further manifestations of aHUS, despite the use of plasma exchange. In addition, extra-renal manifestations persisted even 6 months after diagnosis: gastrointestinal in 24%, cardiovascular in 17%, pulmonary in 12%, and central nervous system in 22%. In summary, without complement inhibitor therapy, aHUS can lead to early mortality and significant morbidities such as ESKD.

A French study reported in pediatric patients with aHUS, 17% of children progressed to end-stage kidney disease (ESKD) or death by 1 month after clinical manifestation, and 29% of children progressed to ESKD or death by 1 year (Fremeaux-Bacchi 2013). Therefore, early recognition and treatment of aHUS in both adult and pediatric patients is important to minimize irreversible damage. Patients treated sooner with complement inhibitor therapy have better outcomes, including greater renal recovery (Vande Walle 2017).

As shown in the Table below, the only approved therapy for aHUS is the C5 inhibitor eculizumab. Treatments of corticosteroids and plasma exchange/plasma infusion have limited benefit for aHUS (Kavanagh 2012, Laurence 2013, Laurence 2016, Azoulay 2017).

2.2. Analysis of Current Treatment Options

Available therapies for aHUS are summarized in Table 2.

Table 2: Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
SOLIRIS (eculizumab) IND 011075 / BLA 125166	atypical hemolytic uremic syndrome (aHUS) to inhibit complement-	2011	IV For patients 18 years of age and older: 900 mg weekly for the first 4 weeks, followed by 1200	Median exposure 26 weeks. -complete response 65% at 26 weeks, 77% at 2 year -Median EGFR improved > 15	Risk of life-threatening and fatal meningococcal infections. Other infections, hypertension,	Patient population: PI/PE> 4 or intolerance, Platelet < $150x10^9$, evidence of hemolysis but need in need of chronic

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
	mediated thrombotic microangiopathy.		mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter. Under age 18 see pediatric dosing	ml/min/1.73M^2 53% at 26 weeks, 59% at 2 years -Reduction of complement activity? -platelet counts normalized 76% at 26 weeks, 88% at 2 years. TMA Event free 88% TMA intervention 0 Median exposure 26 weeks.	Headache, nasopharyngitis, back pain and nausea.	dialysis. Median age 28. Second adult study population and efficacies are similar
Other Treatments – [Combine by Pharmacologic Class, if relevant]						
PE/PI, apheresis	Off label use	n/a	IV	Minimal effects	Allergic reaction, fatigue, nausea, dizziness, and hypotension	Minimal efficacy
Corticosteroids	Off label use	n/a	IV, PO	Minimal effects	Infections, hyperglycemia, hypertension, palpitation, gastritis, phycological changes.	Minimal efficacy

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

On Dec 21, 2018, FDA approved ULTOMIRISULTOMIRIS for adult patients with paroxysmal nocturnal hemoglobinuria (PNH). The safety and efficacy of ULTOMIRIS in patients with PNH was assessed in two open-label, randomized, active-controlled, noninferiority trials (ALXN1210 PNH 301 and ALXN1210 PNH 302) comparing ULTOMIRIS and eculizumab, which demonstrated the non-inferiority of ULTOMIRIS to eculizumab in patients with PNH. ULTOMIRIS appeared 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 is only be available through a REMS. Under the ULTOMIRIS REMS, providers must enroll in the program.

Reference submissions:

Orphan Drug Designation 15-5130: Treatment of Paroxysmal Nocturnal Hemoglobinuria. Designated January 4, 2017. Approved

(b) (4)

(b) (4)

IND 128367: Ravulizumab, original submission was dated December 16, 2015.

3.2. Summary of Presubmission/Submission Regulatory Activity

- Pre-IND Meeting – June 24, 2013: FDA concurred the applicant proposed approach on animal study based human dosing and advised that the first in man study should be conducted in patients, not healthy volunteers.

- Pre-IND Meeting – January 14, 2014: FDA rejected the applican (b) (4) study (b) (4)

- Pre-IND Meeting – December 10, 2015: Discussed a single arm trial protocol in PNH patients for a proposed IND to FDA.

- Type C Meeting – March 24, 2016: End of phase 2 discussion on clinical trial developments for PNH and aHUS indications.

- Type B End-of-Phase 2 Meeting – July 20, 2016: Discussed phase 3 trial design for patients with PNH and aHUS.

- Type B Pre-sBLA Meeting – April 08, April 2019: Discussed the plane of the BLA submission for aHUS indication.

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

4.1. Office of Scientific Investigations (OSI)

Please see the multi-Disciplinary review for BLA 761108 dated Dec 20, 2018 in DARRTS.

4.2. Product Quality

Please see the multi-Disciplinary review for BLA 761108 dated Dec 20, 2018 in DARRTS.

4.3. Clinical Microbiology

Please see the multi-Disciplinary review for BLA 761108 dated Dec 20, 2018 in DARRTS.

4.4. Devices and Companion Diagnostic Issues

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

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Please see the multi-Disciplinary review for BLA 761108 dated Dec 20, 2018 in DARRTS.

5.2. Referenced NDAs, BLAs, DMFs

Please see the multi-Disciplinary review for BLA 761108 dated Dec 20, 2018 in DARRTS.

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

5.3. Pharmacology

Please see the multi-Disciplinary review for BLA 761108 dated Dec 20, 2018 in DARRTS.

5.4. ADME/PK

Please see the multi-Disciplinary review for BLA 761108 dated Dec 20, 2018 in DARRTS.

5.5. Toxicology

5.5.1. General Toxicology

Please see the multi-Disciplinary review for BLA 761108 dated Dec 20, 2018 in DARRTS.

5.5.2. Genetic Toxicology

Please see the multi-Disciplinary review for BLA 761108 dated Dec 20, 2018 in DARRTS.

5.5.3. Carcinogenicity

Please see the multi-Disciplinary review for BLA 761108 dated Dec 20, 2018 in DARRTS.

5.5.4. Reproductive and Developmental Toxicology

Please see the multi-Disciplinary review for BLA 761108 dated Dec 20, 2018 in DARRTS.

5.5.5. Other Toxicology Studies

Please see the multi-Disciplinary review for BLA 761108 dated Dec 20, 2018 in DARRTS.

X	X
Primary Reviewer Qin Ryan, MD, Ph.D	Team Leader Tanya Wroblewski, MD

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking approval of ravulizumab-cwvz (ravulizumab) for the treatment of patients with complement-mediated thrombotic microangiopathy (TMA) including atypical hemolytic uremic syndrome (aHUS). Ravulizumab was previously approved for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) on December 21, 2018. The proposed dosing regimen in patients with aHUS is a loading dose followed by maintenance dosing starting 2 weeks after loading dose administration. The loading dose, maintenance dose, and maintenance dosing frequency are determined by body weight.

Clinical pharmacology information submitted in S-001 included ravulizumab pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity data from two clinical trials: ALXN1210-aHUS-311 and ALXN1210-aHUS-312. In addition, a population PK (PopPK) analysis including data from both trials and a pre-specified interim PK/PD analysis from Study ALXN-aHUS-312 were submitted.

Recommendations
The Office of Clinical Pharmacology has reviewed the information contained in BLA 761108/S-001. This sBLA is approvable from a clinical pharmacology perspective for the revised indication "*treatment of adults and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA)".* The key review issues with specific recommendations and comments are summarized below.

<table>
<tr><th>REVIEW ISSUE</th><th>RECOMMENDATIONS/COMMENTS</th></tr>
<tr><td>Pivotal or supportive evidence of effectiveness</td><td>In the two pivotal aHUS studies (ALXN1210-aHUS-311 and ALXN1210-aHUS-312), complete inhibition of serum complement protein (C5; terminal complement) was observed (as defined by serum free C5 concentrations of <0.5 µg/mL) by the end of the first ravulizumab infusion and sustained throughout the 26-week treatment period in the majority (93%) of adult and pediatric patients with aHUS. The Complete TMA Response Rates were 53.6% and 71.4% in Study ALXN1210-aHUS-311 and Study ALXN1210-aHUS-312, respectively.</td></tr>
<tr><td>General dosing instructions</td><td>The recommended dosing regimen for patients with aHUS 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 herein. Starting 2 weeks after the loading dose administration, begin maintenance doses.
<table>
<tr><th>Body Weight Range (kg)</th><th>Loading Dose (mg)</th><th colspan="2">Maintenance Dose (mg) and Dosing Interval</th></tr>
<tr><td>≥5 to <10</td><td>600</td><td>300</td><td rowspan="2">Every 4 Weeks</td></tr>
<tr><td>≥10 to <20</td><td>600</td><td>600</td></tr>
<tr><td>≥20 to <30</td><td>900</td><td>2,100</td><td rowspan="5">Every 8 Weeks</td></tr>
<tr><td>≥30 to <40</td><td>1,200</td><td>2,700</td></tr>
<tr><td>≥40 to <60</td><td>2,400</td><td>3,000</td></tr>
<tr><td>≥60 to <100</td><td>2,700</td><td>3,300</td></tr>
<tr><td>≥100</td><td>3,000</td><td>3,600</td></tr>
</table>
</td></tr>
</table>

Dosing in patient subgroups (intrinsic and extrinsic factors)	No dose modification is needed for specific populations based on sex, age (10 months to 83 years), race, hepatic impairment, or any degree of renal impairment, including patients with proteinuria or receiving dialysis. Body weight was a clinically significant covariate on the PK of ravulizumab, supporting body weight-based dosing.
Labeling	Modifications to the Dosage and Administration, Immunogenicity, and Clinical Pharmacology sections of the label were recommended based on results of the two pivotal studies in patients with aHUS and to improve clarity.

Post-Marketing Requirements (PMR)
The following issues should be addressed as PMRs:

1. Provide safety, efficacy, PK, and PD data in pediatric patients with aHUS and a weight of greater than or equal to 5 kg to less than 10 kg treated with the recommended dosing regimen of ravulizumab (600 mg loading dose followed 2 weeks later by 300 mg maintenance doses every 4 weeks).
2. Provide safety, efficacy, PK, and PD data in patients with aHUS who switch from treatment with eculizumab to treatment with ravulizumab.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Ravulizumab is a terminal complement inhibitor that binds to the complement protein C5, thereby inhibiting its cleavage to C5a (the proinflammatory anaphylatoxin) and C5b (the initiating subunit of the terminal complement complex [C5b-9]) and preventing the generation of the terminal complement complex C5b-9.

The PK of ravulizumab in patients with aHUS was consistent with that observed in patients with PNH (BLA 761108, original BLA). Ravulizumab Cmax and Ctrough following the loading dose and maintenance doses in adult and pediatric patients with aHUS are shown in Table 3.

Table 3: Mean (%CV) PK Parameters of Ravulizumab in Pediatric and Adult Patients with aHUS

		Pediatric Patients (ALXN1210-aHUS-312)				Adult Patients (ALXN1210-aHUS-311)	
		N	< 20 kg MD given Q4W	N	≥ 20 to < 40 kg MD given Q8W	N	≥ 40 kg MD given Q8W
C_{max} (µg/mL)	LD	8	656 (38.1)	4	600 (17.3)	52	754 (35 2)
	MD	7	1,467 (37.8)	6	1,863 (15.3)	46	1,458 (17.6)
C_{trough} (µg/mL)	LD	9	241 (52.1)	5	186 (16.5)	55	313 (33 9)
	MD	7	683 (46.1)	6	549 (34.1)	46	507 (42 5)

LD = Loading Dose; MD = Maintenance Dose; Q4W = Every 4 Weeks; Q8W = Every 8 Weeks
Source: ALXN1210-aHUS-311 CSR, Tables 25 and 26; ALXN1210-aHUS-312 CSR, Tables 22 and 23

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended ravulizumab dosing regimen for adult and pediatric patients with aHUS consists of a loading dose followed by maintenance dosing, administered as an IV infusion. The loading dose, maintenance dose, and maintenance dosing interval are based on the patient's body weight. Maintenance doses should be administered starting 2 weeks after loading dose administration. The recommended ravulizumab dosing regimen for patients with aHUS is shown in Table 4.

Table 4: Ravulizumab Weight-Based Dosing Regimen in Patients with aHUS

Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg) and Dosing Interval	
≥5 to <10	600	300	Every 4 Weeks
≥10 to <20	600	600	
≥20 to <30	900	2,100	Every 8 Weeks
≥30 to <40	1,200	2,700	
≥40 to <60	2,400	3,000	
≥60 to <100	2,700	3,300	
≥100	3,000	3,600	

The recommended ravulizumab dosing regimen resulted in complete inhibition of serum C5 (as defined by serum free C5 concentrations of <0.5 µg/mL) by the end of the first ravulizumab infusion and sustained throughout the 26-week treatment period in the majority (93%) of adult and pediatric patients with aHUS. Six total events of breakthrough free C5 (serum free C5 concentrations ≥0.5 µg/mL) occurred in five patients and these higher free C5 concentrations were associated with ravulizumab concentrations falling below the target threshold (175 µg/mL).

Therapeutic Individualization

The results of the PopPK analysis support body weight tier-based dosing, as body weight was shown to impact both ravulizumab clearance and volume of distribution. No additional dose individualization is recommended based on sex, age, race, hepatic impairment, or any degree of renal impairment including patients with proteinuria or on dialysis.

Blood transfusion transiently increases the clearance of ravulizumab. However, there is no experience with supplemental doses of ravulizumab.

Outstanding Issues

The loading dose for patients weighing ≥5 to <10 kg was modified during Study ALXN1210-aHUS-312 after the pre-specified interim PK/PD analysis. The initial loading dose in these patients (300 mg) was not adequate to maintain plasma ravulizumab concentration above the

target threshold concentration of 175 µg/mL. Simulations were performed to support a new higher loading dose (600 mg) in these patients. Clinical data was not available for any patients weighing ≥5 to <10 kg after administration of the 600 mg loading dose. The Applicant has agreed to complete Study ALXN1210-aHUS-312 and provide clinical data from patients weighing ≥5 to <10 kg who receive the recommended loading dose of 600 mg as a PMR.

Data to support switching from treatment with eculizumab to treatment with ravulizumab in patients with PNH was included in the original BLA. Study ALXN-1210-aHUS-312 is evaluating the switch from eculizumab to ravulizumab in pediatric patients with aHUS in Cohort 2. Only preliminary data was available from Cohort 2 during review of this sBLA. The Applicant has agreed to provide complete data from Cohort 2 to support the safety and efficacy of switching treatment in patients with aHUS. There are no anticipated safety or efficacy differences between patients with PNH and patients with aHUS in regards to switching treatment.

There are no other outstanding clinical pharmacology issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The general pharmacology and pharmacokinetics of ravulizumab in healthy volunteers and adult patients with PNH has been previously reviewed (BLA 761108, original BLA). A summary of new information included in the current supplement and comparison to previous experience is provided below.

<table>
<tr><td colspan="2">Dose and Exposure</td></tr>
<tr><td>Therapeutic dosing regimen</td><td>The recommended dosage of ravulizumab is a body weight tier-based loading dose followed two weeks later by body weight tier-based maintenance doses. The maintenance dose is administered every 4 weeks for patients weighing <20 kg and every 8 weeks for patients weighing ≥20 kg.
The dosing regimens for patients with aHUS weighing ≥40 kg are the same as the approved recommended dosing regimens for adult patients with PNH.</td></tr>
<tr><td>Drug exposure at steady-state following the therapeutic dosing regimen</td><td>Therapeutic concentrations were achieved following the first dose of ravulizumab in pediatric and adult patients with aHUS. The steady-state exposures were similar to that observed in adult patients with PNH.
<table>
<tr><th>Mean (%CV)</th><th>Weight <20 kg
MD given Q4W</th><th>Weight ≥20 kg
MD given Q8W</th></tr>
<tr><td>Cmax,ss (µg/mL)</td><td>1,467 (37.8)</td><td>1,863 (15.3)</td></tr>
<tr><td>Ctrough,ss (µg/mL)</td><td>683 (46.1)</td><td>549 (34.1)</td></tr>
</table></td></tr>
<tr><td colspan="2">Pharmacokinetics and Dosing Considerations</td></tr>
</table>

Volume of distribution	The mean (%CV) volume of distribution at steady state for pediatric and adult patients with aHUS at the recommended dosing regimen was 2.12 (45.0) and 6.01 (16.4) L, respectively. The volume of distribution in adults with aHUS was similar to that observed in adult patients with PNH.
Terminal elimination half-life	The mean (%CV) terminal elimination half-life for pediatric and adult patients with aHUS was 44.4 (26.4) and 53.7 (31.1) days, respectively at the recommended dosing regimen. The terminal elimination half-life in patients with aHUS was similar to that observed in adult patients with PNH.
Immunogenicity	Pre-existing antibodies to ravulizumab were observed in both pediatric (12/16, 75%) and adult (18/57, 31.6%) patients with aHUS . After treatment with ravulizumab, ADA was detectable in one patient with pre-existing anti-ravulizumab antibodies. The incidence of treatment-emergent anti-ravulizumab antibodies was low (1/71, 1.4%). There was no evidence of neutralization and no apparent impact of pre-existing or treatment-emergent ADA on PK, PD, safety, or efficacy. The incidence of pre-existing ADA was higher in patients with aHUS than that observed in adult patients with PNH. However, the incidence of treatment-emergent ADA and lack of impact on outcomes was consistent with previous experience.
Special populations	Sex, age (10 months to 83 years), race, hepatic impairment, or any degree of renal impairment, including patients with proteinuria or receiving dialysis, has no significant impact on ravulizumab PK.
Interactions	Blood transfusion transiently increased the clearance of ravulizumab by 7.6-fold over a 24-hour period. In patients with aHUS, blood transfusions were common during the loading dose period (13/14 pediatric patients and 21/56 adult patients). However, there is no experience with administration of supplemental doses of ravulizumab.
Analytical Methods	
Pharmacokinetics	A liquid chromatography with tandem mass spectrometry (LC-MS/MS) method (LCMSF 777) was utilized to quantify ravulizumab. Method performance was acceptable. The same method was used in the Phase 3 studies in patients with PNH.
Pharmacodynamics	A Gyros-based fluorescence assay was utilized to quantify free C5. Method performance was acceptable. The same method was used in the Phase 3 studies in patients with PNH.
Immunogenicity	An electrochemiluminescence ligand-binding assay (ECL LBA) was utilized to detect and semi-quantitatively measure ADA. A

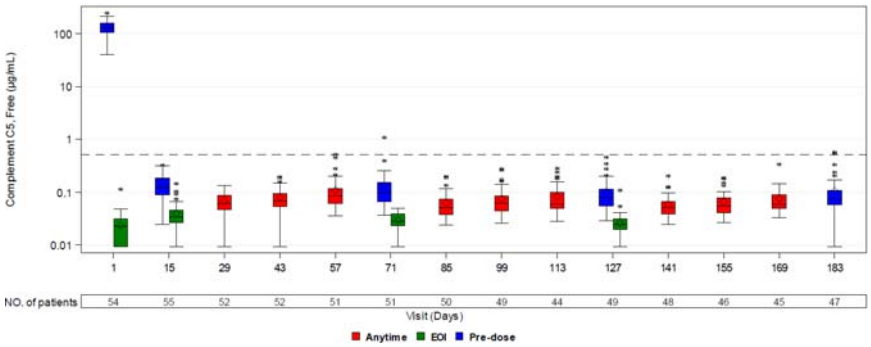
	competitive inhibition ECL LBA was utilized to measure NAb. In the NAb assay, the low positive control was changed from 0.3 µg/mL to 0.5 µg/mL. The assays were otherwise the same as those used in the Phase 3 studies in patients with PNH. Method performance was acceptable. The drug tolerance of the ADA method was validated up to 500 µg/mL ravulizumab.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

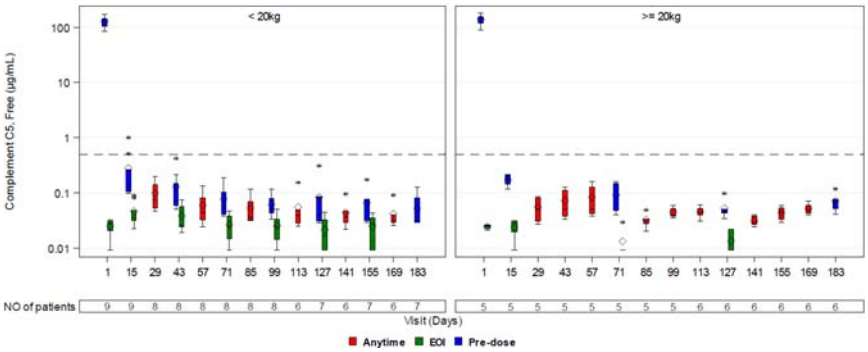
Yes. The ravulizumab body weight-based tiered dosing regimen studied in patients with aHUS was selected based on previous experience in healthy volunteers and adult patients with PNH. Utilizing the same ravulizumab serum concentration target threshold (≥175 µg/mL) for both patient populations, the dosing regimen was predicted to maintain effective ravulizumab concentration in nearly all patients (>97.5%) with aHUS and PNH. Complete TMA Response was achieved in 53.6% and 71.4% of patients with aHUS in Study ALXN1210-aHUS-311 and Study ALXN1210-aHUS-312, respectively. Refer to **Section 8.1** for detailed review of efficacy outcomes. The serum free C5 concentration over time throughout the 26-week treatment period for Study ALXN1210-aHUS-311 and Study ALXN1210-aHUS-312 are shown in Figure 1 and Figure 2, respectively.

Figure 1: Serum Free C5 Concentration-Time Profiles, Study ALXN1210-aHUS-311



Source: BLA 761108/S-001, ALXN1210-aHUS-311 CSR, Figure 14.2.5.2.8.4.s

Figure 2: Serum Free C5 Concentration-Time Profiles, Study ALXN1210-aHUS-312



Source: BLA 761108/S-001, ALXN1210-aHUS-312 Interim CSR, Figure 14.2.5.2.8.4

As shown in Table 5, complete TMA response rate was lower in patients who had any post-baseline ravulizumab concentration <175 µg/mL compared to patients with all post-baseline ravulizumab concentrations ≥175 µg/mL.

Table 5: Complete TMA Response Rate by Ravulizumab Concentration Throughout Treatment

Ravulizumab Concentration	Study -311	Study -312
Always ≥175 µg/mL, n/N (%)	28/45 (62.2)	8/10 (80)
Ever <175 µg/mL, n/N (%)	2/11 (18.2)	2/4 (50)
Overall, n/N (%)	30/56 (53.6)	10/14 (71.4)

Source: FDA Analysis

In Study ALXN1210-aHUS-311, three patients experienced four total events of incomplete terminal complement inhibition (serum free C5 ≥0.5 µg/mL). One patient had persistently low serum ravulizumab trough concentrations during maintenance dosing (<175 µg/mL) and experienced two free C5 excursions (Days 71 and 183) when the serum ravulizumab concentrations were 89 and 86.6 µg/mL, respectively. Another patient had repeated plasma infusions and low serum ravulizumab concentration (136 µg/mL) and the third patient had recurrent urinary tract infections. The remaining 53 patients maintained complete terminal complement inhibition throughout the 26-week treatment period.

In Study ALXN1210-aHUS-312, two patients each experienced a single event of incomplete terminal complement inhibition. One free C5 excursion occurred in a patient weighing 8.4 kg who received the original lower loading dose (300 mg) and had a low serum ravulizumab concentration (57.9 µg/mL). The other excursion occurred in a patient weighing 16.3 kg who received a loading dose of 600 mg and had a low serum ravulizumab concentration (121 µg/mL) at the time of the free C5 excursion. The remaining 12 patients maintained complete terminal complement inhibition throughout the 26-week treatment period.

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

Yes. Following the recommended ravulizumab dosing regimen, terminal complement inhibition (serum free C5 <0.5 µg/mL) was achieved and sustained throughout the 26-week treatment period in the majority (65/70, 93%) of adult and pediatric patients with aHUS. As described above, the ravulizumab target threshold to achieve complete serum free C5 inhibition (<0.5 µg/mL) for patients with aHUS was the same as for adult patients with PNH (175 µg/mL). The dosing regimen maintained ravulizumab Ctrough,ss above the target threshold and free C5 <0.5 µg/mL in adult and pediatric patients with aHUS.

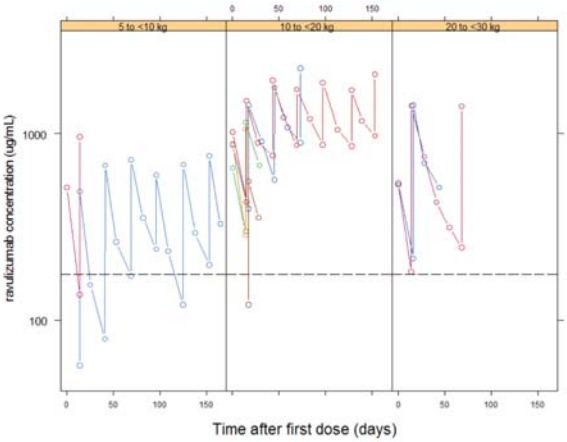
Exposure-response analyses for safety were conducted for both studies. No exposure-response relationships were observed in adult patients with aHUS for any treatment-emergent adverse events reported in >5% of patients. Similarly, no exposure-response relationships were observed in pediatric patients with aHUS for any treatment-emergent adverse events reported in 2 or more pediatric patients.

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

Body Weight: Body weight had a clinically significant impact on ravulizumab PK in the population PK analysis. The recommended dosing regimen is a body weight-based tiered dosing strategy to achieve similar ravulizumab exposure across weight ranges.

Age: After adjusting for body weight, age had no impact on the pharmacokinetics of ravulizumab, supporting the weight-based dosing regimen regardless of age in patients with aHUS. Based on the observed data and population PK assessment at a pre-specified interim PK analysis in Study ALXN1210-aHUS-312, the original loading dose of 300 mg ravulizumab in the lowest weight band (≥5 to <10 kg) was insufficient to maintain serum ravulizumab concentrations above the target threshold (Figure 3).

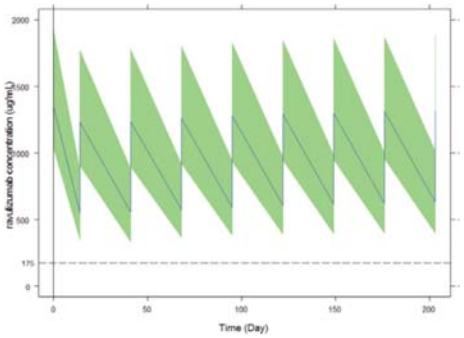
Figure 3: Ravulizumab Concentration-Time Profiles Stratified by Body Weight Group, Study ALXN1210-aHUS-312 Interim PK Analysis



Source: BLA 761108/S-001, Initial PK/PD Analysis, Figure 1

Simulations were conducted to determine an increased loading dose for use in these patients. Simulated ravulizumab concentration-time profile for pediatric patients with aHUS and body weight ≥5 to <10 kg after administration of a 600 mg loading dose followed 2 weeks later by 300 mg maintenance doses every 4 weeks is shown in Figure 4. As a result, the loading dose in patients weighing ≥5 to <10 kg was increased from 300 mg to 600 mg via protocol amendment. The maintenance dose and maintenance dosing interval (300 mg Q4W) were not changed.

Figure 4: Simulated Ravulizumab Concentration-Time Profile for Pediatric Patients with aHUS and Body Weight of ≥5 to <10 kg After Administration of Recommended Dosing Regimen



Source: Source: BLA 761108/S-001, Initial PK/PD Analysis, Figure 5

After the protocol amendment, no further patients in the lowest weight band were enrolled prior to submission of the current sBLA. Therefore, there is no clinical experience with the increased loading dose (600 mg) in patients weighing ≥5 to <10 kg. The 600 mg loading dose is

supported by the PopPK assessment and PK/PD data establishing the ravulizumab target threshold in patients with aHUS. (b) (4) As a PMR, the Applicant has agreed to complete Study ALXN1210-aHUS-312 and provide clinical safety, efficacy, PK, and PD data from patients weighing ≥5 to <10 kg who receive the recommended loading dose of 600 mg.

Renal Impairment: Any degree of renal impairment (including patients with proteinuria or on dialysis) did not significantly impact ravulizumab PK. The degree of renal impairment observed in patients with aHUS was broader than previous experience. Patients with any degree of renal dysfunction, including patients on dialysis, were eligible for both studies.

In Study ALXN1210-aHUS-311, 29 patients (51.8%) were on dialysis at baseline and in Study ALXN1210-aHUS-312, 5 patients (35.7%) were on dialysis at baseline. The rate of hematologic normalization (normalization of both platelets and LDH) was similar regardless of baseline dialysis status. However, the rate of renal function improvement (the third criterion for complete TMA response) was lower in adults on dialysis at baseline compared to adults not on dialysis at baseline. Renal function improvement in pediatric patients was similar regardless of baseline dialysis status.

A summary of hematologic normalization and renal function improvement by baseline dialysis status is shown in Table 6. Ravulizumab steady-state Ctrough was similar regardless of dialysis status (Table 7), suggesting that differences in response were not driven by differences in ravulizumab exposure.

Table 6: Response Criteria by Baseline Dialysis Status

	Study -311		Study -312	
Baseline Dialysis Status	**No**	**Yes**	**No**	**Yes**
Hematologic Normalization, n/N (%)	20/27 (74.1)	21/29 (72.4)	7/9 (77.8)	5/5 (100)
Renal Function Improvement, n/N (%)	18/27 (66.7)	15/29 (51.7)	7/9 (77.8)	4/5 (80)

Source: FDA Analysis

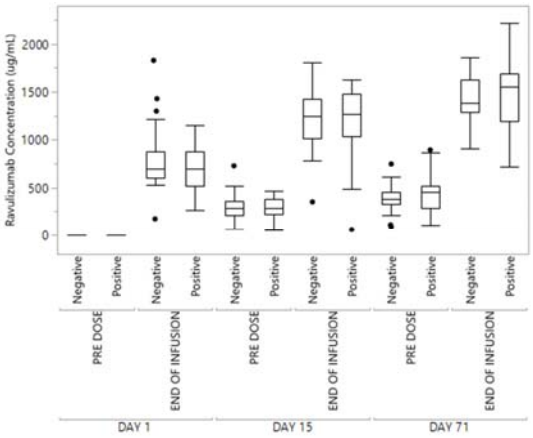
Table 7: Serum Ravulizumab Steady-State Trough Concentration by Dialysis Status

Dialysis Status	**Study -311**	**Study -312**
Never on dialysis, mean (%CV), µg/mL	561.0 (37.5)	662.4 (42.6)
Baseline dialysis, mean (%CV), µg/mL	470.3 (43.8)	568.6 (52.5)
Dialysis initiated during treatment, mean (%CV), µg/mL	470.3 (49.8)	---

Source: FDA Analysis

Anti-drug antibody: The incidence of baseline anti-drug antibody (ADA) positivity was high in patients with aHUS: 31.6% (18/57) of adults and 75% (12/16) pediatric patients. In contrast, the incidence of baseline ADA positivity was <10% in both pivotal studies of ravulizumab in adult patients with PNH. However, baseline ADA positivity did not impact PK, PD, safety, or efficacy of ravulizumab in patients with aHUS. A comparison of ravulizumab Cmax and Ctrough throughout treatment by baseline ADA status is shown in Figure 5 and a comparison of complete TMA response rate in efficacy evaluable patients by baseline ADA status is shown in Table 8.

Figure 5: Ravulizumab Concentration Before and After Infusion by Baseline ADA Status



Source: FDA Analysis

Table 8: Complete TMA Response Rate by Baseline ADA Status

Baseline ADA Status	Study -311	Study -312
Negative, n/N (%)	20/39 (51.3)	2/3 (66.7)
Positive, n/N (%)	10/17 (58.8)	8/11 (72.7)
Overall, n/N (%)	30/56 (53.6)	10/14 (71.4)

Source: FDA Analysis

One adult patient with aHUS had persistent ADA (positive at baseline and Day 73) with decreasing titer. The incidence of treatment-emergent ADA was low (1/71, 1.4%) in patients with aHUS, similar to past experience in patients with PNH (1/206, 0.5%), and no neutralizing antibodies were detected. Given that the drug tolerance of the ADA method was validated up to 500 µg/mL ravulizumab and positive ADA was not detected in patients with aHUS whose serum ravulizumab concentration fell below the target threshold (<175 µg/mL), the development of ADA does not appear to impact ravulizumab PK and PD.

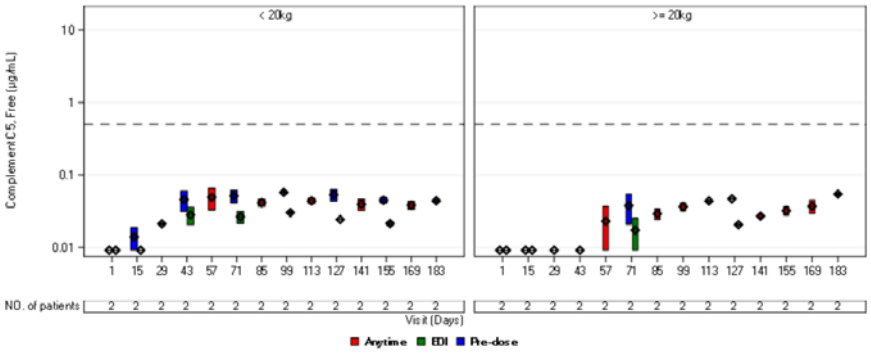
Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The impact of concomitant medications from assorted drug classes (anabolic agents, antithrombotic agents, antianemic preparations, antihypertensives, corticosteroids, antibacterials, antimycotics, and immunosuppressants) on subject-level variability of ravulizumab CL and Vc were assessed in the population PK analysis. The assessment showed that the studied concomitant drugs do not appear to impact ravulizumab PK, consistent with previous experience in adult patients with PNH (BLA 761108, original BLA).

Blood transfusion transiently increases the clearance of ravulizumab (7.6-fold over a 24-hour period by population PK). However, during the loading dose period (first two weeks), blood transfusion was common in pediatric (13/14, 93%) and adult (21/56, 38%) patients with aHUS. Despite increased ravulizumab clearance, the majority of patients (30/34, 88%) maintained ravulizumab Ctrough above the target threshold ($\geq$175 µg/mL) prior to the first maintenance dose without supplemental doses of ravulizumab. Of the four patients with blood transfusions who fell below the target threshold during the loading dose period, two weighed $\geq$5 to <10 kg and were treated with the initial lower 300 mg loading dose. Blood transfusions were less common after the loading dose period, occurring in 2 pediatric patients (14%) and 10 adult patients (18%). Both pediatric patients and 9 of 10 adult patients who received blood transfusions after the loading dose period did not achieve a complete TMA response. However, there is no experience with administration of supplemental doses of ravulizumab to mitigate the decreased ravulizumab exposure.

Data to support the safety and efficacy of switching from treatment with eculizumab to treatment with ravulizumab in adult patients with PNH was previously reviewed (BLA 761108, Original BLA). Study ALXN-1210-aHUS-312 is evaluating the switch from eculizumab to ravulizumab in pediatric patients with aHUS in Cohort 2. Preliminary data from the first 4 eculizumab-experienced patients in Cohort 2 was submitted during the review cycle. In all 4 patients, complete terminal complement inhibition (serum free C5 <0.5 µg/mL) was achieved and sustained throughout the 26-week treatment period. The serum free C5 concentration over time throughout the 26-week treatment period for the first 4 Study ALXN1210-aHUS-312 Cohort 2 patients is shown in Figure 6.

Figure 6: Serum Free C5 Concentration-Time Profiles, Study ALXN1210-aHUS-312 Cohort 2 Preliminary Data



Source: BLA 761108/S-001, 30 Sep. 2019 Response to Labeling Negotiation, Figure 1

A total of 10 patients are planned to be enrolled in Cohort 2. The Applicant has agreed to provide complete data from this Cohort to support the safety and efficacy of switching treatment in patients with aHUS (see Post-Marketing Requirements). There are no anticipated safety or efficacy differences between patients with PNH and patients with aHUS in regards to switching treatment.

Based on experience with eculizumab, the Applicant believes that plasma exchange/plasma infusion will increase the clearance of ravulizumab. Plasma exchange/plasma infusion was excluded during treatment with ravulizumab in both ALXN1210-aHUS-311 and ALXN1210-aHUS-312 and therefore there is no data on the impact of plasma exchange/plasma infusion on ravulizumab PK.

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Primary Reviewer
Lauren Price, Pharm D

X

Team Leader
Oalnrewaju Okusanya Pharm D, MS

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Table 9 lists the clinical trials that are relevant to this sBLA review. Two trials, ALXN1210-

aHUS-311 (trial 311) and ALXN1210-aHUS-312 (trial 312) provided data for efficacy and safety assessments in adult and pediatric patients with aHUS for proposed indication. The trial 311 enrolled 58 adult patients and the study has been completed. The trial 312 enrolled 16 pediatric patients and still ongoing.

Table 9: Listing of Clinical Trials Relevant to this BLA*

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

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

* No controlled study for this application.
Source: BLA 761108-S1

7.2. Review Strategy

This sBLA review was conducted by multi-disciplinary reviewers, including but not limited to clinical, statistical, clinical pharmacology, OBP and consultants for patient reported outcome. Two trials, 311 and 312, were submitted under BLA 761108 S-1 to provide the basis of this review for the new indication in treating adult and pediatric patients with aHUS.

Clinical, clinical pharmacology and immunogenicity data, including clinical study reports, case report forms, and datasets were reviewed for trials 311 and 312. In addition, the 90-day safety update and applicant's responses to clinical and statistical inquiries during the review process were reviewed. The principal review activities for this sBLA included:

- Review of the electronic submission of the sBLA.
- Review of applicant responses to clinical queries
- Reproduction or auditing of key efficacy and safety analysis with JMP or SAS using derived datasets provided by the applicant
- Additional exploratory analyses of safety and efficacy data using the JMP tool

No new chemistry manufacturing and controls (CMC), clinical microbiology, or preclinical pharmacology/toxicology (PT) data were included in this sBLA submission. and focused on the safety and efficacy data.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trials ALXN1210-aHUS-311 (311) and ALXN1210-aHUS-312 (312)

Trial Design

As summarized in Table 10, both trials were open label, single arm, non-comparative studies (Trial 311 in adult patients and Trial 312 in pediatric patients with aHUS). The patient selection is summarized in Table 11.

Table 10: Overview of clinical trials

Trial ID	ALXN1210-aHUS-311	ALXN1210-aHUS-312
Trial Title	Single Arm Study of ALXN1210 in Complement Inhibitor Treatment-naïve Adult and Adolescent Patients with Atypical Hemolytic Uremic Syndrome (aHUS)	A Phase 3, Open-Label, Multicenter Study of ALXN1210 in Children and Adolescents with Atypical Hemolytic Uremic Syndrome (aHUS)
Overview	This is a single arm international multicenter trial to evaluate the safety and efficacy of ULTOMIRIS in aHUS. All patient must be naïve to complement inhibitor treatment.	This is a single arm, multicenter study to evaluate the safety efficacy, PK, and PD of ALXN1210 administered by intravenous (IV) infusion in at least 16 (and no more than 24) pediatric patients, from birth to < 18 years of age, with confirmed diagnosis of aHUS. Initially enrolled patient must be naïve to complement inhibitor treatment but changed to eculizumab treatment > 90 days.
Objectives	The primary objective: To assess the efficacy of ALXN1210 in complement inhibitor treatment-naïve	
	Adolescent and adult	New born to adolescent
	patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA) as characterized by thrombocytopenia, hemolysis, and renal impairment.	
	Secondary objectives: 1. To characterize the safety and tolerability of ALXN1210 in this patient population 2. To evaluate the efficacy of ALXN1210 by additional efficacy	Secondary objectives: 1. To characterize the safety and tolerability of ALXN1210 in this patient population

Trial ID	ALXN1210-aHUS-311	ALXN1210-aHUS-312
	measures 3. To characterize the pharmacokinetics (PK)/pharmacodynamics (PD) of ALXN1210 4. To evaluate the long-term safety and efficacy of ALXN1210	2. To evaluate the efficacy of ALXN1210 by the following additional measures: a. Dialysis requirement status b. Time to Complete TMA Response c. Complete TMA Response status over time d. Observed value and change from baseline in estimated glomerular filtration rate (eGFR) e. Chronic kidney disease (CKD) stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline f. Observed value and change from baseline in hematologic parameters (platelets, lactate dehydrogenase [LDH], hemoglobin) g. Increase in hemoglobin of ≥ 20 g/L from baseline, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between h. Change from baseline in quality of life (QoL), as measured by Pediatric Functional Assessment of Chronic Therapy (FACIT) Fatigue questionnaire 3. To characterize the pharmacokinetics (PK)/pharmacodynamics (PD) of ALXN1210 by the following measures: a. Changes in serum ALXN1210 concentration over time b. Changes in free complement component 5 (C5) concentrations over time 4. To evaluate the long-term safety and efficacy of ALXN1210
Started	3/18/2017	9/1/2017
Stopped*	11/16/2018	n/a, ongoing
Data cut-off	5/23/2018	10/30/2018
Extension Period data cut-off	10/15/2018	n/a, the trials is still on going.

* The end of the trial is defined by the last patient's last visit.
Source: BLA 761108-S1

Table 11: Patient eligibility for Trials 311 and 312

Trial ID	ALXN1210-aHUS-311	ALXN1210-aHUS-312
Patient	Adolescent (12 to < 18 years of age) and adult (≥ 18 years of age) patients with aHUS who were naïve to complement inhibitor treatment	Patients with aHUS from birth up to < 18 years of age, weighing ≥ 5 kg at the time of consent, and not previously treated with eculizumab
Inclusion	1. Male or female patients ≥ 12 years of age and weighing ≥ 40 kg at the time of consent. 2. Evidence of TMA, including thrombocytopenia, evidence of hemolysis, and kidney dysfunction, based on the following Screening Visit laboratory findings: a. Platelet count < 150 per microliter (μL), and b. LDH ≥ 1.5 × upper limit of normal (ULN), and hemoglobin ≤ lower limit of normal (LLN) for age and gender, and c. Serum creatinine level ≥ ULN in adults (≥18 years of age), or ≥ 97.5th percentile for age at Screening in adolescents (≥ 12 to < 18 years of age) (patients who require dialysis for acute kidney injury are also eligible). 3. Among patients with a kidney transplant: a. Known history of aHUS prior to current kidney transplant, or b. No known history of aHUS, and persistent evidence of TMA after suspension of dosing of calcineurin inhibitor ([CNI]; eg, cyclosporine, tacrolimus) or mammalian target of rapamycin inhibitor ([mTORi]; eg, sirolimus, everolimus) for a minimum of 4 days and a maximum of 7 days. 4. Among patients with onset of TMA postpartum, persistent evidence of TMA for > 3 days after the day of childbirth. 5. To reduce the risk of meningococcal infection (Neisseria meningitidis), all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who receive a meningococcal vaccine less than 2 weeks before initiating ALXN1210 treatment must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients who have not been vaccinated prior to initiating ALXN1210 treatment should receive prophylactic antibiotics prior to and for at least	1. Patients from birth up to < 18 years of age and weighing ≥ 5 kg at the time of consent. 2. Evidence of TMA, including thrombocytopenia, evidence of hemolysis, and kidney injury, based on the following Screening Visit laboratory findings: a. Platelet count < 150,000 per microliter (μL), and b. LDH ≥ 1.5 × upper limit of normal (ULN), and hemoglobin ≤ lower limit of normal (LLN) for age and gender, and c. Serum creatinine level ≥ 97.5th percentile for age at Screening (patients who require dialysis for acute kidney injury are also eligible). 3. Among patients with a kidney transplant: a. Known history of aHUS prior to current kidney transplant, or b. No known history of aHUS, and persistent evidence of TMA at least 4 days after modifying the immunosuppressive regimen (eg, suspending or reducing the dose) of calcineurin inhibitor ([CNI]; eg, cyclosporine, tacrolimus) or mammalian target of rapamycin inhibitor ([mTORi]; eg, sirolimus, everolimus). 4. Among patients with onset of TMA postpartum, persistent evidence of TMA for > 3 days after the day of childbirth. 5. To reduce the risk of meningococcal infection (Neisseria meningitidis), all patients must be vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who receive a meningococcal vaccine less than 2 weeks before initiating ALXN1210 treatment must receive treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients who have not been vaccinated prior to initiating ALXN1210 treatment should receive prophylactic antibiotics prior to and for at least 2 weeks after meningococcal vaccination. Patients who cannot be vaccinated must receive antibiotic prophylaxis for the entire treatment period and for 8 months following last dose.

Trial ID	ALXN1210-aHUS-311	ALXN1210-aHUS-312
	2 weeks after meningococcal vaccination. 6. Patients < 18 years of age must have been vaccinated against Hemophilus influenzae type b (Hib) and Streptococcus pneumoniae according to national and local vaccination schedule guidelines. 7. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy while on treatment and for 8 months after last dose of study drug. 8. Willing and able to give written informed consent and comply with the study visit schedule. For patients < 18 years of age, patient's legal guardian must be willing and able to give written informed consent and the patient must be willing to give written informed assent (if applicable as determined by the central or local Institutional Review Board [IRB]/Institutional (or Independent) Ethics Committee [IEC]).	6. Patients must have been vaccinated against Hemophilus influenzae type b (Hib) and Streptococcus pneumoniae according to national and local vaccination schedule guidelines. 7. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy while on treatment and for 8 months after last dose of study drug. 8. Patient's legal guardian must be willing and able to give written informed consent and the patient must be willing to give written informed assent (if applicable as determined by the central or local Institutional Review Board [IRB]/Institutional (or Independent) Ethics Committee [IEC]) and comply with the study visit schedule.
Exclusion	1. Known familial a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency (activity < 5%). 2. Shiga toxin-related hemolytic uremic syndrome (STEC-HUS). 3. Streptococcal pneumoniae-related hemolytic uremic syndrome (HUS), as evidenced by a positive direct Coombs test and infection by Streptococcal pneumoniae (eg, culture, antigen test). 4. Known Human Immunodeficiency Virus (HIV) infection. 5. Unresolved systemic meningococcal disease. 6. Patients with a confirmed diagnosis of ongoing sepsis defined as positive blood cultures within 7 days prior to the start of Screening and untreated with antibiotics. 7. Presence or suspicion of active and untreated systemic bacterial infection that, in the opinion of the Investigator, confounds an accurate diagnosis of aHUS or impedes the ability to manage the aHUS disease. 8. Pregnancy or lactation. 9. Heart, lung, small bowel, or liver transplant. 10. Among patients with kidney transplant, any of the	1. Known familial or acquired 'a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13' (ADAMTS13) deficiency (activity < 5%). 2. Known Shiga toxin-related hemolytic uremic syndrome (ST-HUS) as demonstrated by a positive test for Shiga toxin or culture of Shiga toxin producing bacteria. 3. Positive direct Coombs test. 4. Known Human Immunodeficiency Virus (HIV) infection. 5. Unresolved meningococcal disease. 6. Patients with a confirmed diagnosis of ongoing sepsis defined as positive blood cultures within 7 days prior to the start of Screening and untreated with antibiotics. 7. Presence or suspicion of active and untreated systemic bacterial infection that, in the opinion of the Investigator, confounds an accurate diagnosis of aHUS or impedes the ability to manage the aHUS disease. 8. Pregnancy or breastfeeding. 9. Heart, lung, small bowel, pancreas, or liver transplant. 10. Among patients with a kidney transplant, acute kidney dysfunction within 4 weeks of transplant consistent

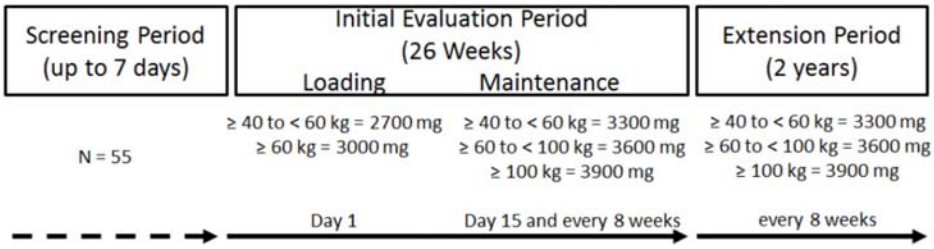
Trial ID	ALXN1210-aHUS-311	ALXN1210-aHUS-312
	following: a. Acute kidney dysfunction within 4 weeks of transplant consistent with the diagnosis of acute antibody-mediated rejection (AMR) according to Banff 2013 criteria, or b. Acute kidney dysfunction within 4 weeks of transplant and a rising donor-specific antibody (DSA) consistent with a clinical diagnosis of acute AMR. c. History of polycystic kidney disease. 11. Among patients ≥18 years of age presenting with systolic blood pressure (SBP) ≥ 170 mmHg, or patients 12 to < 18 years of age presenting with a clinical diagnosis of hypertension, , any of the following: a. Persistent evidence of TMA (inclusion criterion number 2) after less than 4 days of blood pressure reduction to ≤ 140 mmHg. b. Known left ventricular hypertrophy. c. Known small and hyperechoic kidneys on ultrasound. 12. Identified drug exposure-related HUS. 13. Receiving plasma exchange/plasma infusion (PE/PI), for 28 days or longer, prior to the start of Screening for the current TMA. 14. History of malignancy within 5 years of Screening with the exception of a nonmelanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence. 15. Bone marrow transplant (BMT)/hematopoietic stem cell transplant (HSCT) within the last 90 days prior to the start of Screening. 16. HUS related to vitamin B12 deficiency. 17. Known systemic sclerosis (scleroderma), systemic lupus erythematosus (SLE), or antiphospholipid antibody positivity or syndrome. 18. Chronic dialysis (defined as dialysis on a regular basis as renal replacement therapy for end-stage kidney disease [ESKD]).	with the diagnosis of acute antibody-mediated rejection (AMR) according to Banff 2013 criteria. 11. Among patients without a kidney transplant, history of kidney disease other than aHUS, such as: a. Known kidney biopsy finding suggestive of underlying disease other than aHUS b. Known kidney ultrasound finding consistent with an alternative diagnosis to aHUS (eg small kidneys for age) c. Known family history and/or genetic diagnosis of noncomplement mediated genetic renal disease (eg, focal segmental glomerulosclerosis) 12. Identified drug exposure-related HUS. 13. Receiving plasma exchange/plasma infusion (PE/PI), for 28 days or longer, prior to the start of Screening for the current TMA. 14. History of malignancy within 5 years of Screening with the exception of a non-melanoma skin cancer or carcinoma in situ of the cervix that has been treated with no evidence of recurrence. 15. Bone marrow transplant (BMT)/hematopoietic stem cell transplant (HSCT) within the last 6 months prior to the start of Screening. 16. HUS related to vitamin B12 deficiency. 17. Known systemic sclerosis (scleroderma), systemic lupus erythematosus (SLE), or antiphospholipid antibody positivity or syndrome. 18. Chronic dialysis (defined as dialysis on a regular basis as renal replacement therapy for end-stage kidney disease [ESKD]). 19. Patients receiving chronic intravenous immunoglobulin (IVIg) within 8 weeks prior to the start of Screening, unless for unrelated medical condition (eg, hypogammaglobinemia); or chronic rituximab therapy within 12 weeks prior to the start of Screening. 20. Patients receiving other immunosuppressive therapies such as steroids, mTORi (eg, sirolimus, everolimus), CNI (eg, cyclosporine or tacrolimus) are excluded unless: a. part of an established post-transplant antirejection regimen, or b. patient has confirmed anti-complement factor antibodies requiring immunosuppressive therapy, or

Trial ID	ALXN1210-aHUS-311	ALXN1210-aHUS-312
	19. Patients receiving chronic intravenous immunoglobulin (IVIG) within 8 weeks prior to the start of Screening, unless for unrelated medical condition (eg, hypogammaglobinemia); or chronic rituximab therapy within 12 weeks prior to the start of Screening. 20. Patients receiving other immunosuppressive therapies such as steroids, mTORi (eg, sirolimus, everolimus), CNI (eg, cyclosporine or tacrolimus) are excluded unless: a) part of an established post-transplant antirejection regime, or b) patient has confirmed anti-complement factor antibodies requiring immunosuppressive therapy, or c) steroids are being used for a condition other than aHUS (eg, asthma). 21. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater. 22. Prior use of eculizumab or other complement inhibitors 23. Hypersensitivity to murine proteins or to one of the excipients. 24. Any medical or psychological condition that, in the opinion of the Investigator, could increase the risk to the patient by participating in the study or confound the outcome of the study. 25. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening.	c. steroids are being used for a condition other than aHUS (eg, asthma). 21. Participation in another interventional treatment study or use of any experimental therapy within 30 days before initiation of study drug on Day 1 in this study or within 5 half-lives of that investigational product, whichever is greater. 22. Prior use of eculizumab or other complement inhibitors 23. Hypersensitivity to any ingredient contained in the study drug, including hypersensitivity to murine proteins. 24. Any medical or psychological condition that, in the opinion of the Investigator, could increase the risk to the patient by participating in the study or confound the outcome of the study. 25. Known or suspected history of drug or alcohol abuse or dependence within 1 year prior to the start of Screening. 26. Use of tranexamic acid within 7 days prior to Screening is prohibited.

Source: BLA 761108 S1

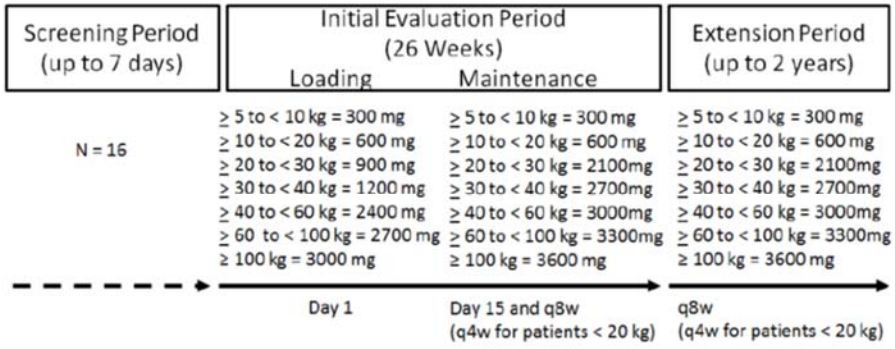
The treatment design in both trials 311 and 312 consisted of a 7-day Screening Period, a 26-week Initial Evaluation Period and an Extension Period of up to 2 years, as illustrated in Figure 7 and Figure 8. The treatment dosing regimens of the both trials were weight based. Patients enrolled to either trial were to receive a weight-based loading dose of ULTOMIRISULTOMIRIS on Day 1, followed by weight-based maintenance doses of ULTOMIRISULTOMIRIS IV on Day 15 and once every 4 or 8 weeks (q4w or q8w) depending on patient's body weight thereafter for a total of 26 weeks of treatment. After the Initial Evaluation Period, patients were entered into an Extension Period to receive ALXN1210 until the product is registered or approved (in accordance with country specific regulations) or for up to 2 years, whichever occurs first.

Figure 7: Trial 311 treatment and dosing plan



Source: BLA 761108 S1

Figure 8: Trial 312 treatment and dosing plan



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

Source: BLA 761108 S1

The designed loading and maintenance doses are summarized in Table 12. For Trial 311, weight-based dosing was based on patients' last recorded study visit body weight.

Table 12: Trial ALXN1210-aHUS-311 dosing schema

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

Source: BLA 761108-S1

However, in the pediatric trial 312, dosages were based on patients' body weight recorded on Dose Regimen Decision Days (if the Dose Regimen Day is a dosing day, body weight will be recorded predose), as shown in Table 13:

Table 13: Trial ALXN1210-aHUS-312 Dosing

Body Weight Range (kg)[a]	Loading Dose (mg)	Maintenance Doses (mg)	Maintenance Dosing Frequency, day 15 and then
≥ 5 to < 10	300	300	q4w
≥ 10 to < 20	600	600	q4w
≥ 20 to < 30	900	2100	q8w
≥ 30 to < 40	1200	2700	q8w
≥ 40 to < 60	2400	3000	q8w
≥ 60 to < 100	2700	3300	q8w
≥ 100	3000	3600	q8w

Abbreviations: q4w = once every 4 weeks; q8w = once every 8 weeks
a. Body weight as recorded on Dose Regimen Decision Days. If the Dose Regimen Day is also dosing day, body weight will be recorded predose with dosing that day based on the previous Dose Regimen Day body weight.
Source: BLA 761108 S1

During the Initial Evaluation Period of the pediatric trial 312, changes to dose or dosing frequency, i.e., q4w vs q8w, was based on patients' body weight on the "Dose Regimen Decision Day (patients on q4w or q8w schedules)" preceding the day of administration.

Scheduled study assessments from screening to the end of the initial evaluation period of trials 311 and 312 are summarized in the Table 14 and Table 15.

Table 14: Trial 311 Schedule of Study Visits and Assessments: Screening Through End of Initial Evaluation Period

Period	Screening	Initial Evaluation Period															
Study Day	**–7 to –1**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183[x]/ET**
Window (day)	**NA**		**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±2**
Informed consent	X																
Confirmation or administration of meningococcal vaccination[a]	X																
Medical history and demographics	X																
ADAMTS13	X																
Stool Shiga toxin test[b]	X																
Direct Coombs test	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
FACIT-Fatigue questionnaire/Pediatric FACIT-Fatigue questionnaire[d,e]		X	X			X			X				X				X
EQ-5D-3L questionnaire[e]		X	X			X			X				X				X
Patient-reported aHUS symptoms questionnaire[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Resource utilization patient questionnaire[e]		X				X			X				X				X
Physical examination	X																X
Abbreviated physical examination[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assessment of extra-renal signs or symptoms of aHUS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety 12-lead ECG[h]	X							X									X
Chemistry[i]	X[w]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LDH isozymes[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology including free hemoglobin and coagulation[k]	X[w]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis and urine chemistry	X	X		X		X		X		X		X		X			X
PK/PD sampling[l]		X[l]		X[l]		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]
Exploratory APC activity[m]		X		X			X		X		X		X		X		X
Exploratory serum and plasma biomarkers[n]		X		X					X				X				X
Exploratory urine biomarkers[o]		X		X					X				X				X
Exploratory urine ALXN1210[p]		X		X		X			X								
Exploratory autoantibody[q]		X							X								
Exploratory genetic sample[r]		X															
Immunogenicity (ADA)[s]		X							X				X				X
Review safety card[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[u]		←Monitor continuously→															

Period	Screening	Initial Evaluation Period															
Adverse events		←Monitor continuously→															
ALXN1210 administration[v]		X		X				X				X					

a All patients must have been vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiated study drug treatment < 2 weeks after receiving a meningococcal vaccine must have received treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients who had not been vaccinated prior to initiating ALXN1210 treatment should have received prophylactic antibiotics prior to and for at least 2 weeks after meningococcal vaccination.
b Stool sample.
c Female patients of childbearing potential only. Serum pregnancy test at Screening and Day 183/ET; urine or serum pregnancy test at all other required time points. A negative pregnancy test result was required prior to administering study drug to female patients of childbearing potential at the indicated study visits.
d FACIT-Fatigue version 4 was used for patients ≥ 18 years of age at Screening. Pediatric FACIT-Fatigue was used for patients < 18 years of age at Screening.
e On dosing days, patient-reported assessments were performed prior to dosing.
f Abbreviated physical examination consisted of a body system relevant examination based upon Investigator judgment and patient symptoms. At least 1 body system must have been checked for an abbreviated examination.
g Vital sign measurements were taken after the patient had been resting for at least 5 minutes and included systolic and diastolic BP (mm Hg), pulse oximetry, heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (°C or °F). On dosing days, vital signs were taken predose.
h Single 12-lead ECG were collected at Screening, Day 57, predose on Day 183 and anytime at ET. Patients must have been supine for approximately 5 to 10 minutes before ECG collection and remained supine but awake during ECG collection.
i Clinical safety laboratory measurements were collected predose on dosing days. The LDH level for eligibility was determined from the chemistry assessment. Follicle-stimulating hormone levels were measured during screening only in order to confirm postmenopausal status.
j Serum sample for LDH isozyme testing was only collected at selected sites at any/all timepoints prior to ALXN1210 dosing, dependent on sample testing availability.
k Assessment for safety as well as the primary and secondary endpoints.
l Serum samples for PK/PD analyses were collected at the indicated visits. For indicated visits falling on dosing days, samples were collected predose (within 0.5 hour prior to the start of infusion) and at EOI (within 0.5 hour after the EOI from the patient's opposite, noninfused arm). In order to minimize needle sticks to the patient, the predose sample may have been drawn through the venous access created for the dose infusion, prior to administration of the dose. As noted, the postdose sample must have been drawn from the opposite, noninfused arm. For indicated visits not falling on dosing days, samples may have been collected at any time that visit day. All collection times will be recorded in the eCRF.
m Collection was predose on days of dosing and for days without dosing, at any time that visit day. All collection times were recorded in the eCRF.
n Collection was predose. All collection times were recorded in the eCRF.
o Collection was predose and combined with urine stabilizing buffer. All collection times were recorded in the eCRF.
p Urine sample for drug measurement was collected at EOI (within 0.5 hour after the EOI) on Days 1, 15, and 71; and at any time on Day 29.
q Collection was predose.
r A single whole blood collection from those patients who consented to genetic testing was collected anytime during the study.
s ADA serum samples were collected predose on Days 1, 71, and 127. Day 183 collection occurred prior to first dose in the Extension Period. All collection time points occurred at any time on the visit day. All collection times were recorded in the eCRF.
t Reviewed the Clinical Trial Participant Safety Information Card with the patient and discussed the importance of carrying the safety card at all times, and the

risks of ALXN1210 treatment, including the risk of meningococcal infection.
u Concomitant medications were collected at all study visits and checked against the prohibited medication defined by the protocol (see section 8.1.2 for concomitant medication).
v The dose of ALXN1210 was based on the patient's last recorded study visit body weight (Day 1 dosing was based on the body weight at Screening).
w If a local laboratory was used to define eligibility, additional samples were collected during the Screening Period for LDH, platelet count, hemoglobin, and serum creatinine and tested at the central laboratory.
x The primary efficacy endpoint assessment was before dosing on Day 183. Dosing on Day 183 is the start of the Extension Period.
Abbreviations: ADA = antidrug antibody; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS = atypical hemolytic uremic syndrome; APC = alternative pathway of complement; BP = blood pressure; ECG = electrocardiogram; eCRF = electronic case report form; EOI = end of infusion; EQ-5D-3L = EuroQol 5-Dimension 3-Level; ET = early termination; FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase; NA = not applicable; PD = pharmacodynamics; PK = pharmacokinetics.
Source: BLA781108-S1

Table 15: Trial 312 Schedule of Study Visits and Assessments: Screening Through End of Initial Evaluation Period

Period	**Screening**	**Initial Evaluation Period**															
Study Day	**–7 or -28[a] to – 1**	**1**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**	**183[b]/ET**
Window (day)	**NA**		**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±2**
Informed consent	X																
Confirmation or administration of meningococcal vaccination[c]	X																
Medical history and demographics	X																
ADAMTS13[d]	X																
Stool Shiga toxin test[d, e]	X																
Direct Coombs test[d]	X																
Head circumference (patients up to 2 years of age)	X	X		X			X		X		X		X		X		X
Height and weight[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[g]	X	X		X					X				X				X
Pediatric FACIT-Fatigue Questionnaire[h]		X	X			X			X				X				X
Physical examination	X																X
Abbreviated physical examination[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assessment of extra-renal signs or symptoms of aHUS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety 12-lead ECG[k]	X							X									X
Chemistry[l, f]	X[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Period	Screening	Initial Evaluation Period															
Hematology including free hemoglobin and	X[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis and urine chemistry	X	X		X		X		X		X		X		X			X
PK/PD sampling[o]		X		X		X	X	X	X	X	X	X	X	X	X	X	X
Exploratory serum and plasma biomarkers[p]	X					X			X				X				X
Exploratory urine biomarkers[q]		X		X					X				X				X
Exploratory urine ALXN1210[r]		X		X		X			X								
Exploratory autoantibody[s]	X																
Exploratory genetic sample[t]	X																
Immunogenicity (ADA)[u]		X							X				X				X
Review safety card[v]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[w]		←Monitor continuously→															
Adverse events		←Monitor continuously→															
ALXN1210 administration (patients weighing < 20		X		X			X		X		X		X		X		
ALXN1210 administration (patients weighing ≥ 20		X		X					X				X				
Dose Regimen Decision Day (patients on q4w or q8w schedules)[y]	X		X					X				X				X	

a The Screening Period was up to 7 days for complement inhibitor treatment-naïve patients.

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

c All patients must have been vaccinated against meningococcal infections within 3 years prior to, or at the time of, initiating study drug. Patients who initiated study drug treatment less than 2 weeks after receiving a meningococcal vaccine must have received treatment with appropriate prophylactic antibiotics until 2 weeks after vaccination. Patients who had not been vaccinated prior to initiating ALXN1210 treatment should have received prophylactic antibiotics prior to and for at least 2 weeks after meningococcal vaccination. Patients who could not be vaccinated must have received antibiotic prophylaxis for the entire treatment period and for 8 months following last dose.

d For Cohort 2 patients, historical test results via chart review were utilized, and if not available, this assessment was omitted.

e Stool sample.

f Predose on dosing days.

g Female patients of childbearing potential only. Serum pregnancy test at screening and Day 183/ET; urine (or serum if required per site policy) pregnancy test at all other required time points. A negative pregnancy test result was required prior to administering study drug to female patients of childbearing potential at the indicated study visits.

h On dosing days, assessment was performed prior to dosing. Pediatric FACIT-Fatigue only in patients ≥ 5 years of age (patient-reported for patients who were ≥ 8 years of age at
the time of enrollment; caregiver-reported or caregiver assistance for patients who were 5 to < 8 years of age at the time of enrollment).

i 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 must have been checked for an abbreviated examination.

j Vital sign measurements were taken after the patient had been resting for at least 5 minutes and included systolic and diastolic blood pressure (BP; mm Hg), pulse oximetry,
heart rate (beats/minute), respiratory rate (breaths/minute), and temperature (°C or °F). On dosing days, vital signs were taken predose.

k Single 12-lead ECG were collected at screening, Day 57, predose on Day 183, and at any time at ET. Patients must have been supine for approximately 5 to 10 minutes before ECG collection and must have remained supine but awake during ECG collection.
l Clinical safety laboratory measurements were collected predose on dosing days. The LDH level for eligibility was determined from the chemistry assessment.
m Local laboratory or central laboratory analysis was used for determining eligibility at screening. However, if local laboratory tests were to be used, duplicate samples for LDH, platelet count, hemoglobin, and serum creatinine were collected at this visit for central laboratory testing.
n Assessment for safety as well as the primary and secondary endpoints.
o Serum samples for PK/PD analyses were collected at the indicated visits. For indicated visits falling on dosing days, samples were collected predose (within 0.5 hours prior to the start of infusion) and at EOI (within 0.5 hours after the EOI from the patient's opposite, noninfused arm). In order to minimize needle sticks to the patient, the predose sample was drawn through the venous access created for the dose infusion, prior to administration of the dose. As noted, the post-dose sample was drawn from the opposite, noninfused arm. For indicated visits not falling on dosing days, samples were collected at any time that visit day. If a supplemental dose was administered, PK/PD samples were collected predose and at EOI. If a loading dose was administered as 2 separate infusions < 24 hours apart, PK/PD samples were collected before the first infusion (ie, the predose sample) and after the second infusion (ie, the EOI sample). All collection times were recorded in the eCRF.
p Baseline samples were obtained during the Screening Period or on Day 1 in accordance with daily blood volume restrictions. Collection was predose on dosing days. For indicated visits not falling on dosing days, samples were collected at any time that visit day. All collection times were recorded in the eCRF. An alternative blood sampling schedule for infants, for whom less blood volume should have been collected, was used as detailed in the Study Operations Manual.
q Collection was predose and combined with urine stabilizing buffer. All collection times were recorded in the eCRF.
r Urine sample for drug measurement was collected at EOI (within 0.5 hours after the EOI) on Days 1, 15, and 71; and at any time on Day 29.
s Collection was at any time during the study.
t A single whole blood collection from those patients who consented to genetic testing was collected anytime during the study. u The ADA serum samples were collected predose on Days 1, 71, and 127. Day 183 collection occurred prior to first dose in the Extension Period. The ET collection occurred at any time on the visit day. All collection times were recorded in the eCRF.
v The Clinical Trial Participant Safety Information Card was reviewed with the patient/caregiver. The importance of carrying the safety card at all times and the risks ALXN1210 treatment, including the risk of meningococcal infection, were discussed with the patient/caregiver.
w Concomitant medications were collected at all study visits and checked against the prohibited medication defined by the protocol (see section 8.1.2 for concomitant medication).
x The dose of ALXN1210 was based on the patient's body weight on the preceding "Dose Regimen Decision Day (patients on q4w or q8w schedules)".
y Dose Regimen Decision Day for patients currently on a q4w or q8w schedule: Changes to dose regimen (dose level [ie, mg] or dose frequency [ie, q4w vs q8w]) were based on the patient's body weight on the "Dose Regimen Decision Day (patients on q4w or q8w schedules)" preceding the day of administration. Patients changing from q4w to q8w were administered their first q8w dose on the ALXN1210 administration day ("ALXN1210 administration [patients weighing > 20 kg]") following the "Dose Regimen Decision Day (patients on q4w or q8w schedules)". Patients changing from q8w to q4w were administered their first q4w dose on the ALXN1210 administration day ("ALXN1210 administration [patients weighing < 20 kg]") following the "Dose Regimen Decision Day (patients on q4w or q8w schedules)".
Abbreviations: ADA = antidrug antibody; ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; AE = adverse event; aHUS = typical hemolytic uremic syndrome; ECG = electrocardiogram; eCRF = electronic case report form; EOI = end of infusion; ET = early termination; FACIT = Functional Assessment of Chronic Illness Therapy; LDH = lactate dehydrogenase; NA = not applicable; PD = pharmacodynamics; PK = pharmacokinetics; q4w = once every 4 weeks; q8w = once every 8 weeks.

Source: BLA761108-S1

Special procedures were made to reduce the risk of infections, patients must have been vaccinated or revaccinated according to current national vaccination guidelines or local practice for vaccination use with complement inhibitors.

Patients who had not been vaccinated prior to initiating ULTOMIRISULTOMIRIS treatment must have received prophylactic antibiotics from the time of initiating ULTOMIRISULTOMIRIS until at least 2 weeks after meningococcal vaccination.

Because vaccination may not be sufficient to completely prevent meningococcal infection, investigators were instructed to consider official guidance and local practice on the appropriate use of antibacterial agents. All patients were monitored for early signs of meningococcal infection, evaluated immediately if infection was suspected, and treated with appropriate antibiotics, if necessary.

To increase risk awareness and promote prompt disclosure of any potential signs or symptoms of infection experienced by the patients during the course of the study, patients were provided a safety card to carry with them at all times and for 8 months after the last dose of ULTOMIRIS.

Study Endpoints

The endpoints of both trials 311 and 312 are summarized in Table 16.

Table 16: Study endpoints of trials 311 and 312

Trial ID	ALXN1210-aHUS-311	ALXN1210-aHUS-312
Primary	Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Patients must meet all Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between.	
Secondary	1. Time to Complete TMA Response 2. Complete TMA Response status over time 3. Dialysis requirement status 4. Observed value and change from baseline in eGFR 5. Chronic kidney disease (CKD) stage, as evaluated by eGFR at select target days and classified as improved, stable (no change), or worsened compared to baseline 6. Observed value and change from baseline in hematologic parameters (platelets, LDH, hemoglobin) 7. Increase in hemoglobin of ≥ 20 g/L from baseline, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between	
	8. Change from baseline in quality of life (QoL), as measured by EuroQol 5-Dimension 3-Level (EQ-5D-3L; all patients), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Questionnaire version 4 (patients ≥ 18 years of age), and Pediatric FACIT-Fatigue Questionnaire (patients < 18 years of age)	8. Change from baseline in QoL, as measured by Pediatric FACIT Fatigue questionnaire (patients ≥ 5 years of age)
Pharmacokinetic and pharmacodynamics	- Changes in serum ALXN1210 concentration over time - Changes in serum free complement component 5 (C5) concentrations over time	
Safety	The long-term safety and tolerability of ALXN1210 was evaluated by physical examinations, vital signs, electrocardiograms (ECGs), laboratory assessments, and incidence of adverse events (AEs) and serious adverse events (SAEs). The proportion of patients who developed antidrug antibodies (ADA) was also assessed.	
		physical growth (height, weight, and head circumference)

Source: BLA 761108 S1

Statistical Analysis Plan

The analysis population and sample size planned for trial 311 and 312 are summarized in Table 17.

Table 17: Analysis population

Trial ID	ALXN1210-aHUS-311	ALXN1210-aHUS-312
Analysis Population	Efficacy analyses were performed on the Full Analysis Set (FAS). The FAS was based on a	The FAS was based on a modified intent-to-treat approach. With this approach,

Trial ID	ALXN1210-aHUS-311	ALXN1210-aHUS-312
	modified intent-to-treat approach. This specifically applies to Inclusion Criterion 2c (must be confirmed via a central laboratory), Exclusion Criterion 1 (may be confirmed via a central or local laboratory), and Exclusion Criterion 2 (may be confirmed via a central or local laboratory). Based on the above, the FAS included all patients who received at least 1 dose of ALXN1210, had at least 1 post-baseline efficacy assessment, met Inclusion Criterion 2c, and did not meet Exclusion Criteria 1 or 2. The Per Protocol (PP) Set included all patients in the FAS who met the following criteria: • Received 100% of the planned number of infusions during the 26-week Initial Evaluation Period • Did not take any prohibited medications or undergo any prohibited procedures • Met Inclusion Criteria 2 and 8 • Did not meet Exclusion Criteria 3, 7, 10, 11, 12, 13, 15, 16, 17, 18, 21, 22, and 26	confirmation of eligibility in patients may have occurred after receiving study drug. This specifically applies to Inclusion Criterion 2c (confirmed via a central laboratory), Exclusion Criterion 1 (confirmed via a central or local laboratory), and Exclusion Criterion 2 (confirmed via a central or local laboratory). Based on the above, the FAS included all patients who received at least 1 dose of Clinical Study Report (Initial Analysis) had at least 1 post-baseline efficacy assessment, and met all of the following criteria: − Met Inclusion Criterion 2c − Did not meet Exclusion Criterion 1 or 2
Sample size	55 planned, 58 enrolled, 56 in FAS, 49 entered extension period(>26 weeks)	original planned 16, then increase to 23-28 for addition of cohort 2, 16 in FAS, 14 entered extension period (>26 weeks)

Source: BLA 761108 S1

An overview of the statistical plan for both trial 311 and 312 are summarized in Table 18.

Table 18: Statistical analysis plan overview

Trial ID	ALXN1210-aHUS-311	ALXN1210-aHUS-312
Efficacy: Primary analysis	Complete TMA Response during the 26-week Initial Evaluation Period, the primary analysis consisted of estimating the proportion of complete TMA responders among ALXN1210-treated patients. This was performed by calculating the point estimate and a 95% confidence interval (CI) for the proportion of complete TMA responders in ULTOMIRIS-treated patients. The 95% CI was based on exact confidence limits using the Clopper-Pearson method.	The primary efficacy endpoint for Cohort 1 was Complete TMA Response during the 26-week Initial Evaluation Period. The primary analysis consisted of estimating the proportion of complete TMA responders among ULTOMIRIS-treated patients. This was performed by calculating the point estimate and a 95% confidence interval (CI) for the proportion of complete TMA responders in ULTOMIRIS-treated patients. The 95% CI was based on exact confidence limits using the Clopper-Pearson method.
Efficacy: Secondary analysis	For the secondary efficacy endpoint of time to Complete TMA Response, a Kaplan-Meier cumulative distribution curve was generated along with a 2-sided 95% CI. Complete TMA Response was summarized over time by presenting the number and proportion of responders along with a 2-sided 95% CI for each post-baseline time point. A similar approach was used to summarize the number and proportion of patients with an increase from baseline in hemoglobin ≥ 20 g/L, observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. Kidney function (dialysis requirement status, eGFR, CKD stage) and hematologic parameters (platelets, LDH, hemoglobin) were summarized at baseline and each post-baseline time point. Descriptive statistics for continuous variables (eGFR, platelets, LDH, hemoglobin) were used to summarize the observed value as well as the change from baseline. A mixed model for repeated measures (MMRM) with the fixed, categorical effect of visit and fixed, continuous effect of the specific test's baseline value as covariates was fit to test whether changes differ from zero at each time point. Dialysis requirement status and CKD stage were summarized over time. Dialysis requirement status was summarized among patients receiving dialysis within 5 days prior to ALXN1210 treatment initiation by presenting the number and proportion of those patients receiving and not receiving dialysis at each time point. A 2-sided 95% CI for the proportion of patients receiving dialysis was provided. The CKD stage was summarized over time by presenting the number and proportion of patients that improved (excluding those with Stage 1 at baseline as they cannot improve), worsened (excluding those with Stage 5 at baseline as they cannot worsen), and stayed the same compared to CKD stage at baseline. Stage 5 was considered the worst category, while Stage 1 was considered the best category. A 2-sided 95% CI for the proportion was provided for each category. Quality of life was evaluated using EQ-5D-3L (all patients), FACIT-Fatigue version 4 (patients ≥ 18 years of age), and Pediatric FACIT-Fatigue (patients < 18 years of age) questionnaires. These measures were summarized at baseline and each post-baseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline. A MMRM with the fixed, categorical effect of visit and fixed, continuous effect of the specific test's baseline value as covariates may have been fit to test whether changes differ from zero at each time point.	

Trial ID	ALXN1210-aHUS-311	ALXN1210-aHUS-312
Safety	Safety analyses included exposure to ALXN1210, all AEs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements, and were presented using descriptive statistics. No formal hypothesis testing was performed for the safety parameters. For all safety parameters, baseline was the last available assessment prior to administration of the first dose of study drug.	The safety and tolerability of ALXN1210 were assessed by the following measures: all AEs that occurred after the ICF had been signed, including serious AEs (SAEs); laboratory results for hematology, blood chemistry, coagulation, and urinalysis measurements; vital signs measurements; physical examinations; and electrocardiograms (ECGs). The proportion of patients who developed antidrug antibodies (ADAs) was also assessed. The timing of the clinical and laboratory assessments to be performed was specified in the schedule of assessments
Immunogenicity	The number and percentage of patients with positive titers for ADAs to ALXN1210 and different titer categories was summarized over time. The proportion of patients ever positive and the proportion of patients always negative were also summarized.	
Pharmacokinetic	Graphs of mean serum ULTOMIRIS concentration-time profiles were constructed. Descriptive statistics were calculated for PK serum concentration data at each sampling time, as appropriate.	
Pharmacodynamics	For PD parameters, summary tabulations of mean, SD, median, minimum, and maximum values were presented for actual, change and percentage change from baseline. The relationship between changes in PD parameters, exploratory biomarkers, and the effects of treatment outcome were evaluated.	For PD parameters, effects of ULTOMIRIS were evaluated by assessing the absolute values and changes and percentage changes from baseline in serum free C5 serum concentrations over time, as appropriate. Descriptive statistics were calculated for the PD data at each sampling time, as appropriate. Assessments of PK/PD relationships were explored using data from this study or in combination with data from other studies.

Source: BLA 761108 S1

Statistical reviewer comment: No formal hypothesis test was used in the sample size calculation. The applicant used an asymptotic Gaussian approximation method with a continuity correction to calculate 95% CI of the primary efficacy endpoint of Trail 311. In statistical reviewer's analysis, the exact 95% confidence intervals in both trials are calculated with the use of the Clopper–Pearson method.

Protocol Amendments

The amendments of both trial protocols are summarized in Table 19 below.

Table 19: Protocol amendments of trials 311 and 312

Amendments	ALXN1210-aHUS-311	ALXN1210-aHUS-312
1	9/28/2016: Weight-based doses were adjusted	3/16/2017: Removal of genetic language.
2	1/23/2017: Revision to primary endpoint description to clarify that patients must meet all Complete TMA Response criteria at two separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. • Clarifications to secondary objectives (CKD stage as evaluated by eGFR; hemoglobin increase observed at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between) • Minor revisions to inclusion and exclusion criteria for clarity and alignment with clinical practice • Addition of benefit/risk assessment text • Withdrawal criteria clarified to specify serious infusion reaction, severe uncontrolled infection, and pregnancy. • Minor corrections and clarifications were made to the schedule of assessments and language describing drug packaging, storage, and preparation; prior/concomitant medications/ procedures; prohibited medications; vaccination; contraception; medical history; vital signs; immunogenicity; SUSAR reporting, adverse events; PK/PD assessment; genetics; statistical analysis; DMC; regulatory considerations; references; appendices	3/21/2017: Targeted adverse events broadened.
3	7/19/2017: • Broaden inclusion criteria to include platelet count, LDH, and hemoglobin laboratory results during the Screening Period or within 28 days prior to the start of the Screening period from a local lab; these changes allow patients with recent PE/PI (which alters lab results) to enter the study based on labs prior to PE/PI. • Continue to require that serum creatinine results for inclusion must be based on central laboratory results from a specimen collected during the Screening Period. Since the primary endpoint is a change from baseline in creatinine, it is important to have both baseline and on-treatment serum samples from the same laboratory. • Added a requirement to enroll at least 30 patients who meet all 4 TMA requirements at Day 1 (platelet count of < 150,000 per microliter, LDH ≥ 1.5 × upper limit of normal (ULN), hemoglobin ≤ lower limit of normal (LLN), and serum creatinine level ≥ ULN) to ensure that a majority of patients enrolled will have abnormal baseline lab values.	10/19/2017: to allow enrollment of patients previously treated with eculizumab for at least the past 3 months. Significant changes include revisions to the entry criteria (to enroll patients previously treated with eculizumab), the addition of a new objective (to evaluate the safety and efficacy of patients previously treated with eculizumab), and updates to the statistical language (to clarify that patients previously treated with eculizumab will be excluded from the main analyses and summarized separately, as appropriate). This amendment is a Japan-specific amendment, and only patients that satisfy the global study inclusion and exclusion criteria will be included in the global study population.

Amendments	ALXN1210-aHUS-311	ALXN1210-aHUS-312
	• Clarify standard care for the treatment of TMA may include tests noted in exclusion criteria 1, 2 and 3. These test results may be used for determination of eligibility, even if performed prior to informed consent. • Clarify patients with genetic defects in vitamin B12 metabolism (a rare cause of HUS not related to complement), rather than a deficit in vitamin B12, are excluded. • Provide Sponsor opportunity to exclude patients on basis of risk to patient or outcome of study. • Clarified the direct Coombs test (already included in protocol) is conducted at Screening. • Provided the option for serum pregnancy tests to be used at any timepoints. • Removed the option for "a designee" to perform the physical exam. • Added pregnancy test assessment prior to the first dose in Extension Period; removed requirement for pregnancy test to use urine (serum may now be used at all indicated timepoints). • Clarified terminology on "meeting" vs "satisfying" inclusion and exclusion criteria and added option for the patient's legally authorized representative to provide informed consent. • Correct use of "assent" vs "consent". • Clarified that there are separate tests for urine chemistry and urinalysis.	
4	8/4/2071: Indicate change of amendment 3 in Japan.	2/2/2018: change from eculizumab naïve to allow enrollment of patients previously treated with eculizumab for at least the past 90 days into Cohort 2. Significant changes include revisions to the entry criteria (to enroll Cohort 2), the addition of new Cohort 2 objectives and endpoints (to evaluate the safety and efficacy of ALXN1210 in Cohort 2), and updates to the statistical language (to clarify that data from Cohort 2 patients will be excluded from the main analyses and presented separately, as appropriate). Patients enrolled in Cohort 1 of this Japan-specific amendment will be included in the global study population. Patients enrolled in Cohort 2 of this Japan-specific amendment will not be included in the global study population and will only be included in the Japan-specific version of the study.
5	None.	8/23/2018: ALXN1210-aHUS-312, a protocol enrolling patients not previously treated with eculizumab, was changed by way of

Commented [RQ1]: Details?

Amendments	ALXN1210-aHUS-311	ALXN1210-aHUS-312
		ALXN1210-aHUS-312 Amendment 5 (Global), to allow enrollment of adolescent patients previously treated with eculizumab for at least the past 90 days into Cohort 2. Significant changes include revisions to the loading dose for patients 5 to < 10 kg (increased from 300 mg to 600 mg), the entry criteria (to enroll Cohort 2), the addition of new Cohort 2 objectives and endpoints (to evaluate the safety and efficacy of ALXN1210 in Cohort 2), modifications in the study design to account for the screening period of 28 days for Cohort 2, and updates to the statistical language (to clarify that the analyses for Cohort 1 and Cohort 2 will be conducted and reported separately).

Source: BLA 761108

8.1.2. Study Results

Compliance with Good Clinical Practices

Institutional Review Board (IRB)/Institutional (or Independent) Ethics Committee (IEC) approval to conduct the study was obtained at all participating sites. The initial and amended IRB/IEC protocol approvals, and all materials that were submitted and approved by the IRB/IEC for this study, including the informed consent form (ICF) and recruitment materials, were maintained by the Investigator and made available for inspection.

Both trials were 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.

The investigators or designees ensured that an informed consent was given to each patient or the patient's legal representative. This included obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product. The investigator retained the original signed ICF and a copy of the signed ICF was given to the patient.

Financial Disclosure

The study sites for both trials are summarized in the Table 20.

Table 20: Summary of study sites

Trial	ALXN1210-aHUS-311	ALXN1210-aHUS-312
Initiated study sites/Country	178 sites/16 countries	69 sites/not available
Study site enrolled Patients	41	12 (ongoing)
Country enrolled Patients	14 (Australia, Austria, Belgium, Canada, France, Germany, Italy, Japan, Korea, Russia, Spain, Taiwan, the United Kingdom, and the United States)	6 (Belgium, Germany, Japan, Korea, Spain, and the United States)

Source: BLA 761108 S1

Of the 1082 Investigators who involved in the two trials, 1077 provided certification for financial disclosure. There were 235 investigators treated patients in trial ALXN1210-311, 53 treated patients in trial ALXN1210-312, and 794 investigators and their sites never enrolled or treated any patients in either trial. All investigators but five sub-investigators from three study sites failed to provide financial disclosure. These sub-investigators were from the study sites did not screen or enroll any patients. These sub-investigators also did not perform any study related activities.

Five investigators received Alexion grants of $10,000 – $170,000 USD, , as shown in Table 21. These investigators were from four sites of 312 (b) (6), 312 (b) (6), 311- (b) (6)), 311- (b) (6)). Investigator (b) (6) of the study site 312 (b) (6) enrolled one patient (312 (b) (6)).

Table 21: Investigators with financial interests disclosed

Study (Site #)	Investigator Name (Role) Site Name (Country)	Cumulative Disclosure Amount [a]	Nature of Disclosure	Steps Taken to Minimize Bias on Clinical Study Results
ALXN1210-aHUS-312 (b) (6)	(b) (6)	See footnote [b]	External consultant and participation in speakers bureau	ALXN1210-aHUS-312 study design [a]
ALXN1210-aHUS-311 (b) (6) ALXN1210-aHUS-312 (b) (6)		£ 8,000 GBP per year maximum ($ 10,520 USD per year maximum)	Compensation as member of (b) (6) (b) (6) Scientific Advisory Board	ALXN1210-aHUS-311 and ALXN1210-aHUS-312 study design [a], Site did not screen or enroll any patients.
ALXN1210-aHUS-311 (b) (6)		£ 128,762 GBP ($ 169,362 USD)	See footnote [4]	ALXN1210-aHUS-311 study design [a]
ALXN1210-aHUS-311 (b) (6)		$ 30,000 CAD ($ 22,381 USD)	Unrestricted educational grant	ALXN1210-aHUS-311 study design [a]
ALXN1210-aHUS-311 (b) (6)		>$ 25,000 USD [a]	See fotnoote [a]	ALXN1210-aHUS-311 study design [a]

[a]: Disclosure amounts provided in local currency were converted to USD on 22-March-2019

[b]: No payments were made to the investigator during the conduct of the ALXN1210-aHUS-312 trial. The last payment made was in 2015.

[c]: ALXN1210-aHUS-311 and ALXN1210-aHUS-312 are multi-centered, global clinical studies with a primary endpoint based on central laboratory results only, namely the Complete Thrombotic Microangiopathy (TMA) Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Alexion utilized an independent Contract Research Organization (CRO) who performed 100% Source Data Verification on other site specific data generated. In addition, Alexion conducted clinical site audits, some of which were performed by a 3rd party vendor. Alexion organized an independent Data Monitoring Committee.

[d]: Indirectly, as (b) (6) holds a grant from the (b) (6) research network called (b) (6) Alexion funds this research network.

[e]: Non restricted educational grants, $ 45,000 USD per year in 2011-2013. Honoraria and ad board etc which could exceed $ 25,000 USD per year during the conduct of the trial.

[f]: Dr. (b) (6) received to date £17,900 GBP ($ 23,542 USD) for compensation as member of (b) (6) Scientific Advisory Board.

Source: BLA 761108-S1, 1.3.4 financial disclosure, Table 5.

Reviewer Comment: In response to FDA information request(IR), the applicant clarified that (b) (6) received a total of $15,991.64 between 2012 and 2015 for her role as an external consultant and participation in the Speakers Bureau. This payment included speaker and consultancy fees as well as reimbursement of lodging, food /drink and travel.

Patient Disposition

The patient disposition of both Trials 311 and 312 are summarized in the Table 22 below. For Trial 311, the planned enrollment and initial evaluation period were completed, and the extension period is ongoing. Trial 312 is still enrolling.

Table 22: Trials 311 and 312 patient disposition

	ALXN1210-aHUS-311 (N = 58)	ALXN1210-aHUS-312 (N = 16)	Total (N = 74)
Treated, n (%)	58 (100 0)	16 (100 0)	74 (100 0)
Completed Initial Evaluation Period, n (%)	49 (84 5)	13 (81 3)	62 (83 8)
Completed study, n (%)	0	0	0
Initial Evaluation Period (Week 26), n (%)			
Discontinued from study during Initial Evaluation Period	9 (15 5)	3 (18 8)	12 (16 2)
Adverse event	3 (5 2)	1 (6 3)	4 (5 4)
Death	2 (3 4)	0	2 (2 7)
Physician decision	1 (1 7)	0	1 (1 4)
Protocol violation	1 (1 7)	1 (6 3)	2 (2 7)
Deemed ineligible post treatment	2 (3 4)	1 (6 3)	3 (4 1)
Extension Period, n (%)			

	ALXN1210-aHUS-311 (N = 58)	ALXN1210-aHUS-312 (N = 16)	Total (N = 74)
Entered into Extension Period	49 (84 5)	13 (81 3)	62 (83 8)
Received treatment during Extension Period	46 (79 3)	13 (81 3)	59 (79 7)
Ongoing in Extension Period at data cutoff	47 (81 0)	13 (81 3)	60 (81 1)
Discontinued from study during Extension Period	2 (3 4)	NA	2 (2 7)
Physician decision	1 (1 7)	NA	1 (1 4)
Withdrawal by subject	1 (1 7)	NA	1 (1 4)

Source: sNDA 761108-S1

Protocol Violations/Deviations

Protocol deviation was approximately 70% for both trials, as summarized in the Table 23. The major protocol deviations of trial 311 and 3212 are summarized in Table 24 and Table 25.

Table 23: Protocol deviations or violations in the trial 311.

Categories of Deviation	ALXN1210-3 1 1 (N = 58)	
	Patients n (%)	Deviations (n)
Major deviations	40 (69 0)	90
Eligibility and entry criteria	25 (43 1)	36
Serious adverse event reporting criteria	12 (20 7)	18
Study drug compliance	10 (17 2)	17
Study procedures criteria	7 (12 1)	10
Informed consent procedures	5 (8 6)	5
Concomitant medication criteria	3 (5 2)	3
Laboratory assessment criteria	1 (1 7)	1
Deviations resulting in exclusion from the PP Set	11 (19 0)	13
Eligibility and entry criteria	8 (13 8)	10
Concomitant medication criteria	3 (5 2)	3

Note: Percentages were based on the total number of patients Patients could have been counted in more than 1 deviation category if the patient had more than 1 type of protocol deviation

[a] Patients that did not meet this inclusion criteria or met these exclusion criteria were excluded from the PP Set Abbreviation: PP = per protocol

Source: sNDA 761108-S1 5 3 5 2 Trial ALXN1210-311 study report, Table 11

Table 24: The trial 311 major deviations summary by subject ID

Major Deviations	n	Patient ID
Shiga test result delay	12	(b) (6)
Antibiotic prophylaxis delay or incomplete	9	
Hematological criteria (platelet, LDH or Cr) not met	5	
Pregnancy test delay	2	
Systolic blood pressure below requirement	2	

Major Deviations	n	Patient ID
Tranexamic acid within 7 days of screening	2	(b) (6)
Streptococcus pneumoniae test delay	1	
Coombs test delay	1	
History of Malignancy not excluded	1	
Unacceptable contraception	1	
Total	36	(b) (6) ome patients had > 1 deviations)

Source: sNDA 761108-S1 5 3 5 2 Trial ALXN1210-311 study report, Table 13

Table 25: Protocol deviations or violations in the trial 312.

Categories of Deviation	**(N = 16) n (%)**
Patients with major deviations	11 (68 8)
Type of major deviations	
Eligibility and entry criteria*	7 (43 8)
Serious adverse event reporting criteria	5 (31 3)
Informed consent procedures	3 (18 8)
Study drug compliance	1 (6 3)
Source document criteria	1 (6 3)

Note: Percentages were based on the total number of patients Patients could have been counted in more than 1 category
*In response to FDA IR, the applicant provided the ID of subjects with eligibility division, which were (b) (6) (b) (6)

Source: sNDA 761108-S1 5 3 5 2 Trial ALXN1210-312 study report, Table 10

Clinical reviewer comment: The protocol deviations of both trials did not appear affecting the efficacy outcomes except not all patients meeting hematological criteria in trial 311 (n = 5) and eligibility deviation in trial 312 (n=7). Sensitivity analyses for Completed TMA response were explored by the statistical reviewer. See section 8.1.2, primary endpoint analysis for detail.

Data sets reviewed

Analysis datasets are summarized in Table 26. For trial 311, there were 56 out of 58 enrolled patients (96.6%) in FAS population. For trial 312, there are 14 out of 16 enrolled patients (87.5%) in FAS population.

Table 26: Analysis datasets of trials 311 and 312.

	ALXN1210-311 n (%)	**ALXN1210-312 n (%)**
Enrolled patients	58 (100)	16 (100)
Full Analysis Set (FAS)	56 (96 6)	14 (87 5)
Per-Protocol Set (PP)	44 (75 9)	14 (87 5)
Safety Set	58 (100 0)	16 (100 0)
PK Analysis Set	55(94 8)	14(87 5)

Abbreviations: FAS = Full Analysis Set; PK = pharmacokinetics; PP = Per Protocol
Source: BLA761108-S1 ALXN1210-311 and 312 study reports, 11 1

Clinical reviewer Comments: Unlike the completed trial 311, the trial 312 is still enrolling. Only cohort 1 of the trial 312, complement inhibitor naive patients with TMA, was included for FAS and SP analyses in this supplement.

Patient Demographic and Characteristics

The patient demographics and characteristics of both trial 311 and 312 are summarized in Table 27 and Table 28, respectively.

Table 27: Trial ALXN1210-311 patient demographics (FAS)

Variable	ALXN1210-311 (N = 56)
Age at time of first infusion (years)	
Mean (SD)	42 2 (14 98)
Median (min, max)	40 1 (19 5, 76 6)
Age at time of first infusion (years) category, n (%)	
18 to < 30 years	11 (19 6)
30 to < 40 years	17 (30 4)
40 to < 50 years	15 (26 8)
50 to < 60 years	5 (8 9)
≥ 60 years	8 (14 3)
Sex, n (%)	
Male	19 (33 9)
Female	37 (66 1)
Ethnicity, n (%)	
Hispanic or Latino	3 (5 4)
Not Hispanic or Latino	41 (73 2)
Unknown	12 (21 4)
Race, n (%)[a]	
American Indian or Alaskan Native	1 (1 8)
Asian	15 (26 8)
Black or African American	2 (3 6)
White	29 (51 8)
Unknown	8 (14 3)
Other	1 (1 8)
Weight at time of first infusion (kg)	
N	55
Mean (SD)	72 9 (17 61)
Median	67 7
Min, max	46 1, 111 6
Height at baseline (cm)	
N	56
Mean (SD)	166 1 (9 21)
Median	164 5
Min, max	151 5, 189
Met TMA criteria[b] at Day 1 (based on central laboratory results)	30 (53 6)

Note: Percentages are based on the total number of patients
a Patients can have multiple races selected
b Platelet count < 150,000/μL, LDH ≥ 1 5 × ULN, hemoglobin ≤ LLN, serum creatinine level ≥ ULN

Abbreviations: FAS = Full Analysis Set; LDH = lactate dehydrogenase; LLN = lower limit of normal; max = maximum; min = minimum; SD = standard deviation; TMA = thrombotic microangiopathy; ULN = upper limit of normal
Source: BLA761108-S1 ALXN1210-311 study report, 11 2

Table 28: Trial ALXN1210-312 patient demographic (FAS)

Variable	ALXN1210 -3 1 2 (N = 14)
Age at time of first infusion (years)	
Mean (SD)	6 1 (4 52)
Median (min, max)	5 2 (0 9, 17 3)
Age at time of first infusion (years) category, n (%)	
Birth to < 2 years	2 (14 3)
2 to < 6 years	7 (50 0)
6 to < 12 years	4 (28 6)
12 to < 18 years	1 (7 1)
Sex, n (%)	
Male	5 (35 7)
Female	9 (64 3)
Ethnicity, n (%)	
Hispanic or Latino	2 (14 3)
Not Hispanic or Latino	12 (85 7)
Race, n (%)[a]	
American Indian or Alaskan Native	1 (7 1)
Asian	4 (28 6)
Black or African American	2 (14 3)
White	7 (50 0)
Unknown	1 (7 1)
Height at baseline (cm)	
Mean (SD)	108 5 (24 70)
Median (min, max)	108 5 (64, 138 1)
Weight at time of first infusion (kg)	
Mean (SD)	19 8 (9 94)
Median (min, max)	16 2 (8 4, 35 75)
Weight at time of first infusion (kg) category, n (%)	
≥ 5 to < 10 kg	2 (14 3)
≥ 10 to < 20 kg	7 (50 0)
≥ 20 to < 30 kg	2 (14 3)
≥ 30 to < 40 kg	3 (21 4)

Note: Percentages are based on the total number of patients
[a] Patients can have multiple races selected
Abbreviations: FAS = Full Analysis Set; max = maximum; min = minimum
Source: BLA761108-S1 ALXN1210-312 study report, 11 2

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

The disease characteristics of Trials 311 and 312 are summarized in Table 29.

Table 29: Disease characteristics of aHUS patients in trials 311 and 312

Variable	ALXN1210-311 (N = 56)	ALXN1210-312 (N = 14)
Age (years) at time of first aHUS symptoms		
Mean (SD)	41 49 (15 78)	4 94 (3 08)
Median (min, max)	40 05 (9 3, 76 6)	4 10 (0 8, 11 2)
Dialysis at baseline[a], n (%)	29 (51 8)	5 (35 7)
Any kidney transplant prior to entering the study[b], n (%)	8 (14 3)	1 (7 1)
Related to aHUS	0	1 (100 0)
Baseline platelets (10^9/L) blood [normal range 130 to 400 10^9/L]		
Mean (SD)	118 52 (86 44)	60 50 (33 28)
Median (min, max)	95 25 (18, 473)	64 00 (14, 125)
Baseline LDH (U/L) serum [normal range 120 to 246 U/L]		
Mean (SD)	702 38 (557 96)	2324 11 (1361 52)
Median (min, max)	508 00 (229 5, 3249)	2077 00 (772, 4985)
Baseline hemoglobin (g/L) blood [overall normal range 115 to 175 g/L]		
Mean (SD)	86 26 (14 87)	74 82 (19 52)
Median (min, max)	85 00 (60 5, 140)	74 25 (32, 106)
Baseline eGFR (mL/min/1 73 m^2) [normal range ≥ 60 mL/min/1 73 m^2]		
Mean (SD)	15 86 (14 82)	28 4 (23 11)
Median (min, max)	10 00 (4, 80)	22 0 (10, 84)
Baseline CKD stage, n (%)[c]		
1	0	0
2	3 (5 4)	2 (14 3)
3A	1 (1 8)	1 (7 1)
3B	2 (3 6)	0
4	9 (16 1)	6 (42 9)
5	40 (71 4)	5 (35 7)
Missing	1 (1 8)	0

a Dialysis at baseline was recorded as "yes" for patients who received dialysis within 5 days prior to study drug initiation.
b Percentage was based on the total number of patients.
c Baseline CKD stage was only available for 54 patients.
Abbreviations: aHUS = atypical hemolytic uremic syndrome; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; max = maximum; min = minimum; SD = standard deviation.
Source: FDA reviewer analysis

Patients with baseline pre-treatment signs or symptoms of aHUS were 92.9% in Trial 311 and 71.4% in Trial 312, as shown in Table 30.

Clinical Reviewer Comment: In Study 312, the youngest patient was 8 months of age. The proposed indication includes pediatric patients (age 1 month and older). The inclusion and evaluation of the youngest patient of 8 months supports indication to down to 1 month of age.

Table 30: Pretreatment Extra-renal Signs or Symptoms of aHUS (FAS)

	ALXN1210-311 (N = 56) n (%)	ALXN1210-312 (N = 14)
Any pretreatment extra-renal signs or symptoms of aHUS	**52 (92.9)**	**10 (71.4)**
Cardiovascular	39 (69 6)	7 (50)
Hypertension	34 (60 7)	5 (35 7)
Palpitations	2 (3 6)	-
Shortness of breath	4 (7 1)	-
Sinus tachycardia	3 (5 4)	1 (7 1)
Pericardial effusion	2 (3 6)	1 (7 1)
Cardiac insufficiency/failure	1 (1 8)	-
Other	23 (41 1)	1 (7 1)
Pulmonary	25 (44 6)	1 (7 1)
Shortness of breath	13 (23 2)	-
Tachypnea	3 (5 4)	-
Pulmonary edema	7 (12 5)	-
Pulmonary hemorrhage	1 (1 8)	1 (7 1)
Pleural effusion	9 (16 1)	1 (7 1)
Other	10 (17 9)	-
Central Nervous System	29 (51 8)	5 (35 7)
Lethargy	8 (14 3)	3 (21 4)
Irritability	1 (1 8)	2 (14 3)
Confusion	3 (5 4)	-
Headache	17 (30 4)	1 (7 1)
Visual deficit	9 (16 1)	-
Seizures	1 (1 8)	1 (7 1)
Other	12 (21 4)	1 (7 1)
Gastrointestinal	35 (62 5)	8 (57 1)
Nausea	21 (37 5)	4 (28 6)
Vomiting	19 (33 9)	5 (35 7)
Diarrhea	10 (17 9)	-
Abdominal pain	8 (14 3)	4 (28 6)
Colitis	1 (1 8)	-
Elevated transaminases (ALT/AST)	7 (12 5)	4 (28 6)
Pancreatitis	2 (3 6)	1 (7 1)
Poor glucose control	2 (3 6)	-
Other	13 (23 2)	4 (28 6)
Skin	17 (30 4)	7 (50 5)
Petechiae	8 (14 3)	5 (35 7)
Maculopapular rash	2 (3 6)	-
Other	11 (19 6)	4 (28 6)
Skeletal muscle	13 (23 2)	1 (7 1)
Myalgias	4 (7 1)	1 (7 1)
Other	9 (16 1)	1 (7 1)

Note: In summarizing symptoms (%), if a patient had multiple reports for a particular organ system/sign or symptom, he/she was counted only once for that organ system/sign or symptom. Patients may have been counted in more than 1 organ system/sign or symptom category.
Abbreviations: aHUS = atypical hemolytic uremic syndrome; ALT = alanine aminotransferase; AST = aspartate aminotransferase; max = maximum; min = minimum.
Source; BLA761108-S1

In the FAS populations, 94.6% and 100% patients in Trials 311 and 312, respectively, had ER visits or hospitalization prior to enrollment, as shown in Table 31.

Table 31: ER visit and hospitalization due to aHUS prior trial enrollment (FAS)

	ALXN1210-311 (N = 56) n (%)	ALXN1210-312 (N = 14) n (%)
Any emergency room-visits or hospitalizations, n (%)[a]	53 (94 6)	14 (100 0)
Visit type[b], n (%)		
Emergency room visit	16 (30 2)	3 (21 4)
Hospitalization	45 (84 9)	13 (92 9)
ICU level of care, n (%)[b]		
Yes	27 (50 9)	6 (42 9)
No	26 (49 1)	8 (57 1)
Number of days of ICU stay[c]		
N	31	8
Mean (SD)	10 1 (10 03)	10 0 (18 63)
Median	7 0	4 0
Min, max	1, 49	1, 56

Note: Patients could have been counted for both emergency room visit and hospitalization categories.
a Percentages were based on the total number of patients.
b Percentages were based on the total number of patients who had any emergency room visits or hospitalizations due to aHUS prior to the start of screening.
c Patient could have had more than 1 ICU stay.
Abbreviations: ER=emergency room; aHUS = atypical hemolytic uremic syndrome; ICU = intensive care unit; max = maximum; min = minimum.
Source: BLA761108-S1

The treatments that study patients received prior to trial enrollment are summarized in Table 32.

Table 32: Treatment history prior to trial enrollment (SP)

	ALXN1210-311 (N = 58) n (%)	ALXN1210-312 (N = 16) n (%)
Prior treatments	56 (96.6)	16 (100)
Prior pharmacologic therapies given > 12% Patients		
Meningococcal vaccines	35 (60 3)	8 (50)
Pneumococcal vaccines	9 (15.5)	14 (87.5)
Hemophilus Influenza B	4 (6.9)	12 (75)
Combined bacterial viral vaccines	-	5 (31.3)
Sulfonamides	27 (46.6)	7 (43.9)
Furosemide	25 (43.1)	7 (43.9)
Heparins	15 (25 9)	2 (12.5)
Benzodiazepine	13 (22.4)	5 (31.3)
Electrolyte solutions	22 (37 9)	6 (37.5)
Anilids	18 (31)	4 (25)
Alpha and beta blockers	11 (19)	3 (18.8)
Dihydropyridine derivatives	(31)	4 (25)
H2 blockers	7 (12.1)	4 (25)
Proton pump inhibitors	11 (19)	4 (25)
Penicillin's and beta-lactamase inhibitors	10 (17 2)	2 (12.5)
3rd generation cephalosporins	8 (13.8)	3 (18.8)

	ALXN1210-311 (N = 58) n (%)	ALXN1210-312 (N = 16) n (%)
Glucocorticoids	26 (44 8)	3 (18.8)
Antianemic (5HT3 antagonists)	10 (17 2)	3 (18.8)
Opioid anesthetics	7 (12.1)	3 (18.8)
Prior non- pharmacologic therapies	49 (84 5)	14 (87.5)
Plasma exchange	48 (82 8)	5 (31.1)
Dialysis	48 (82 8)	6 (37.5)
RBC transfusion	17 (29 3)	12 (75)
Platelet transfusion	6 (10.3)	2 (12.5)
Mechanical ventilation	5 (8.6)	1 (6.3)

Source: BLA761108-S1

Clinical reviewer comments: Overall, the baseline disease characters appear to be worse in adult patient.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Fifty-eight patients (SP) of Trial 311 and 16 patients of Trial 312 received the planned infusions for the initial evaluation period (26 weeks). The mean treatment duration of 14 evaluable patients (FAS) of Trial 312 was 24.5 weeks. Dosing errors of Trial 311 are summarized in Table 33.

Table 33: ULTOMIRIS dosing error during the initial evaluation period of trials 311 and 312

Dosing error	ALXN1210-311 (N = 58) n (%)	Subject ID
Additional dose received	2 (3.4)	(b) (6)
Lower than planned dose received	5 (8.6)	
Technical issue for temporary infusion interruption	8 (13.8)	Not provided

Source: BLA761108-S1

Concomitant medications were recorded from the first infusion of study drug through 56 days after the patient's last dose of study drug. All concomitant medication use, and procedures undertaken during the study were recorded in the patient's source document/medical chart and eCRF. This record included all prescription drugs, herbal products, vitamins, minerals, over-the-counter medications, and current medications. Any changes in concomitant medications were also recorded in the patient's source document/medical chart and eCRF. Any concomitant medication deemed necessary for the patient's standard of care during the study, or for the treatment of any AE, was given at the discretion of the Investigator.

Patients were prohibited from receiving any of the following medications and procedures at any time after the first dose of study drug:

- Eculizumab or other complement inhibitors
- Use of any other investigational drug or device as part of a clinical study
- Intravenous immunoglobulin (unless for an unrelated medical need, eg, hypogammaglobinemia)
- Rituximab

- Plasma exchange/plasma infusion
- New dialysis within the first 48-hour period following the first dose of ALXN1210 unless there was a compelling medical need as assessed by (1) hypervolemia unresponsive to diuretics, (2) refractory electrolyte imbalance, or (3) new-onset uremic encephalopathy. Exceptions must have been approved prior to administration of dialysis on a case-by-case basis by Alexion.

The following concomitant medications and procedures were allowed under certain circumstances and with the following restrictions:

- Use of other immunosuppressive therapies, such as steroids, mTOR inhibitors(e.., sirolimus, everolimus), calcineurin inhibitors (eg, cyclosporine or tacrolimus) prior to screening or during the study were not allowed unless: a) part of an established post-transplant antirejection regime, or b) patient had confirmed anti-complement factor antibodies requiring immunosuppressive therapy, or c) steroids were being used for a condition other than aHUS (e.g., asthma). Concomitant medications that used in about 20% or more study patients are summarized in Table 34.

Table 34: Concomitant medications in trials 311 and 312

	ALXN1210-311(N = 58) n (%)	ALXN1210-312(N = 16) n (%)
Dihydropyridine derivatives	50 (86.2)	11 (68.8)
Anilids	45 (77.6)	11 (68.8)
Meningococcal vaccines	40 (69.0)	11 (68.8)
Sulfonamides	40(69.0)	6 (37 5)
Fluoroquinolones	(63 8)	3 (18 8)
Proton pump inhibitors	(63.3)	5 (31 3)
Heparins	(53.4)	5 (31 3)
Antianemic	(53.4)	5 (31 3)
Alpha-adrenoreceptor antagonists	29 (50.0)	-
Glucocorticoids	28 (48.3)	6 (37 5)
Selective beta-blockers	(44 8)	
Folic acid and derivatives	(36 2)	
ACE inhibitors	(36 2)	3 (18.8)
Electrolyte solutions	(36 2)	10 (62.5)
Penicillin's and beta-lactamase inhibitors	(34.5)	12 (75.0)
Osmotically acting laxatives	(34.5)	9 (56 3)
Agents for treatment of hyperkalemia and hyperphosphatemia	(32 8)	3 (18 8)
Beta-lactamase sensitive penicillins	(31.0)	3 (18 3)
Calcium	(31 0)	-
H2 blocker	(31 0)	5 (31 3)
Vitamin D and analogues	(31.0)	5 (31 3)
Propulsive	(29 3)	-
ACE inhibitors	(27.6)	6 (37 5)
Alpha- and beta-blocking agents	(25.9)	4 (25 0)
Potassium	(25 9)	-
Benzodiazepine derivatives	(24.1)	7 (43.7)
Hydrazinophthalazine derivatives	(24.1)	6 (37 5)
Third generation cephalosporin	(24.1)	5 (31 3)

	ALXN1210-311(N = 58) n (%)	ALXN1210-312(N = 16) n (%)
Carbapenems	(22.4)	-
Combinations of sulfonamides and trimethoprim including derivatives	(22.4)	-
Parental iron	(20.7)	-
Serotonin antagonists	(20.7)	8 (50 0)
Selective immunosuppressants	-	6 (37 5)
First-generation cephalosporins	-	5 (31 3)
Enemas	-	(43.8)
Other general anesthetics	-	(43.8)
Topical anesthetics	-	4 (25 0)
Oral iron	-	4 (25 0)
Mucolytics	-	4 (25 0)
Opium	-	4 (25 0)
Phenylpiperidine derivatives	-	4 (25 0)
Pneumococcal vaccines	-	4 (25 0)
Beta-2-agonists	-	4 (25 0)
Influenza vaccine	-	3 (18 8)
Parental nutrition	-	3 (18 8)
Magnesium	-	3 (18 8)

Source: BLA781108-S1

Both trials addressed the issue of increased susceptibility to *N. meningitidis* that can be associated with ULTOMIRISULTOMIRIS use. All patients were vaccinated against *N. meningitidis* within 3 years prior to, or at the time of, receiving the first dose of ULTOMIRIS. Patients who initiated study drug treatment less than 2 weeks after receiving a meningococcal vaccine had received appropriate prophylactic antibiotics until 2 weeks after vaccination. Vaccines against serotypes A, C, Y, W135, and B, where available, were used to prevent common pathogenic meningococcal serotypes

Efficacy Results-Primary Endpoint

The primary efficacy endpoint was Complete TMA Response during the 26-week Initial Evaluation Period. The criteria for Complete TMA Response are as follows:

- Normalization of platelet count
- Normalization of LDH
- ≥ 25% improvement in serum creatinine from baseline

Patients must have met all Complete TMA Response criteria concurrently, and each criterion must have met at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. To be considered a responder during the 26-week Initial Evaluation Period, the latest time point a patient could first meet the response criteria was 28 days before the Day 183 assessment. Platelet values obtained from the day of a blood transfusion of platelets through 3 days after the transfusion were excluded from all analyses. All serum creatinine values obtained while a patient was on dialysis were excluded from all analyses. When a patient was on dialysis at baseline, then the first valid creatinine value used as the baseline value was the first

assessment ≥ 6 days post dialysis. If a patient was on dialysis during the entire 26-week Initial Evaluation Period, then the baseline creatinine was not calculated.

In Trial 311, Complete TMA Response was observed in 30 of the 56 patients in the FAS (53.6%; [95% CI: 39.7%, 67.0%]) during the 26-week Initial Evaluation Period.

In Trial 312, Complete TMA Response was observed in 10 of the 14 patients in the FAS (71.4%; [95% CI: 41.9%, 91.6%]) during the 26-week Initial Evaluation Period.

The Complete TMA response (CR) and relevant components are summarized in Table 35. The proportion of Complete TMA Response was obtained based on the responders among the FAS patients. The numerator was the number of patients achieving Complete TMA Response during the 26-week Initial Evaluation Period and the denominator was the number of patients in the FAS.

Table 35: Complete TMA response and Complete TMA Response Components During the 26-Week Initial Evaluation Period (FAS)

	ALXN1210-311 (N=56)		ALXN1210-312 (N=14)	
	n/N	Proportion (95% CI) [a]	n/N	Proportion (95% CI) [a]
Complete TMA Response	30/56	0.536 (0.397, 0.670)	10/14	0.714 (0.419, 0.916)
Components of Complete TMA Response				
Platelet count normalization	47/56	0.839 (0.717, 0.924)	13/14	0.929 (0.661, 0.998)
LDH normalization	43/56	0.768 (0.636, 0.870)	12/14	0.857 (0.572, 0.982)
≥25% improvement in serum creatinine from baseline	33/56	0.589 (0.450, 0.719)	11/14	0.786 (0.492, 0.953)
Hematologic normalization [b]	41/56	0.732 (0.597, 0.842)	12/14	0.857 (0.572, 0.982)

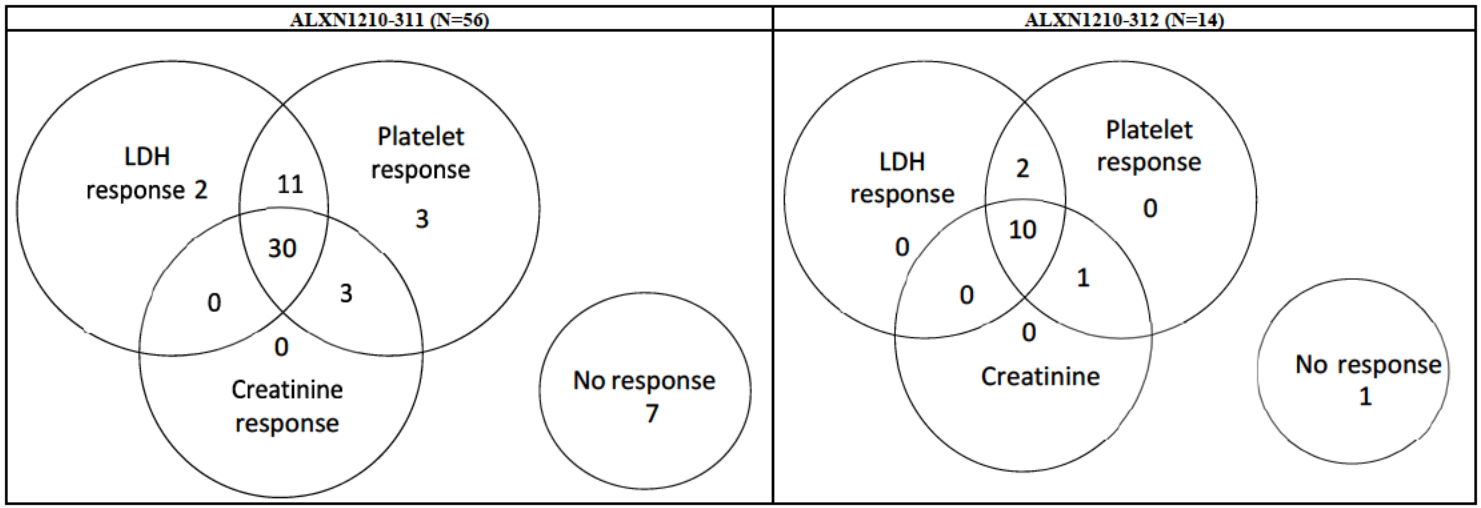
a. 95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.
b. Hematologic normalization includes normalization of platelet count (≥ 150 × 10^9/L) and normalization of LDH.
Abbreviations: CI = confidence interval; FAS = Full Analysis Set; LDH = lactate dehydrogenase; TMA = thrombotic microangiopathy.
Source: FDA reviewer analysis

In Trial 311, During the Initial Evaluation Period, 47 (83.9%) patients achieved platelet count normalization, 43 (76.8%) patients achieved LDH normalization, and 33 (58.9%) patients achieved renal function improvement. Seven patients (12.5%) in the FAS did not respond on any of the 3 components of the Complete TMA Response during the Initial Evaluation Period.

In Trial 312, with the exception of 1 patient who withdrew from the study on Day 21 after 2 doses of ULTOMIRIS, all 13 (100%) patients achieved platelet count normalization, 12 (92%) patients achieved LDH normalization and 11 (85%) patients achieved renal function improvement during the Initial Evaluation Period.

Figure 9 displays the components of Complete TMA response in FAS patients.

Figure 9: Complete TMA response in FAS patients



Source: BLA 761108-S1.

Clinical reviewer comments: The most frequent improvement among the response elements in both trials is platelet counts, followed by LDH normalization and creatinine response, respectively.

Sensitivity Analyses

Modified Complete TMA Response

To test the robustness of the primary analysis results, a sensitivity analysis was performed for patients in the FAS using a modified version of Complete TMA Response. The modification applied only to the patients who were on dialysis at baseline, the criterion requiring an improvement from baseline of 25% or more in serum creatinine was replaced by a post-baseline change in dialysis status (from requiring dialysis at baseline to no longer requiring dialysis) that was maintained for at least 4 weeks. The definition of Complete TMA Response remained the same for all other patients. The primary analyses were repeated on the PP Set as sensitivity analyses.

In Trial 311, for the Initial Evaluation Period, modified Complete TMA was observed in 32 of the 56 patients in the FAS (57.1%; [95% CI: 43.2%, 70.3%]). In the PP Set, modified Complete TMA Response was observed in 24 of the 44 patients during the Initial Evaluation Period (54.5%; [95% CI: 38.9%, 69.6%]).

As of the data cutoff date, modified Complete TMA Response was observed in 33 of the 56 patients (58.9%; [95% CI: 45.0%, 71.9%]) in the FAS. In the PP Set, modified Complete TMA Response was observed in 25 of the 44 patients as of the data cutoff date (56.8%; [95% CI: 41.0%, 71.7%])

In Trial 312, the Complete TMA Response was observed in 10 of the 14 patients (71.4%; [95% CI: 41.9%, 91.6%]) for both FAS and PP Sets.

Statistical reviewer Comments: Results of sensitivity analysis are consistent with primary analysis, which demonstrated the robustness of the data supporting the clinical benefits.

Complete TMA response – patients met/did not meet hematological eligibility criteria

The primary analysis of Complete TMA response in patients who met or did not meet all hematological eligibility criteria were also assessed. Since there are only 5 patients who did not meet all three hematological eligibility criteria, the response rates of the complete TMA and of its components for those without hematology deviation are very similar to those for the FAS as shown in Table 36.

Table 36: Analysis of Complete TMA responses with hematology deviations

		Total	Responder		
			n	Proportion	95% CI [a]
Complete TMA Response	FAS	56	30	0.536	0.397 0.670
	Without hematology deviations	51	26	0.510	0.366 0.653
	Hematology deviations	5	4	0.800	0.284 0.995
Components of Complete TMA Response					
Platelet count normalization	FAS	56	47	0.839	0.717 0.924
	Without hematology deviations	51	43	0.843	0.714 0.930
	Hematology deviations	5	4	0.800	0.284 0.995

		Total	Responder		
			n	Proportion	95% CI [a]
LDH normalization	FAS	56	43	0.768	0.636 0.870
	Without hematology deviations	51	38	0.745	0.604 0.857
	Hematology deviations	5	5	1.000	0.478 1.000
≥ 25% improvement in serum creatinine from baseline	FAS	56	33	0.589	0.450 0.719
	Without hematology deviations	51	29	0.569	0.423 0.707
	Hematology deviations	5	4	0.800	0.284 0.995
Hematologic normalization	FAS	56	41	0.732	0.597 0.842
	Without hematology deviations	51	37	0.726	0.583 0.841
	Hematology deviations	5	4	0.800	0.284 0.995

a. 95% CIs for the proportion were based on exact confidence limits using the Clopper-Pearson method.
Source: FDA reviewer analysis

Statistical Reviewer comments: The protocol deviation with respect to hematological eligibility did not appear to impact the primary analysis result. Due to the small sample size in the hematology deviations group, these data carried large variability and were inconclusive.

Data Quality and Integrity

The applicant incorporated the ethical principles of GCP to assure data quality and integrity. The applicant undertook a GCP audit program to ensure compliance with these procedures and to assess the adequacy of quality control procedures.

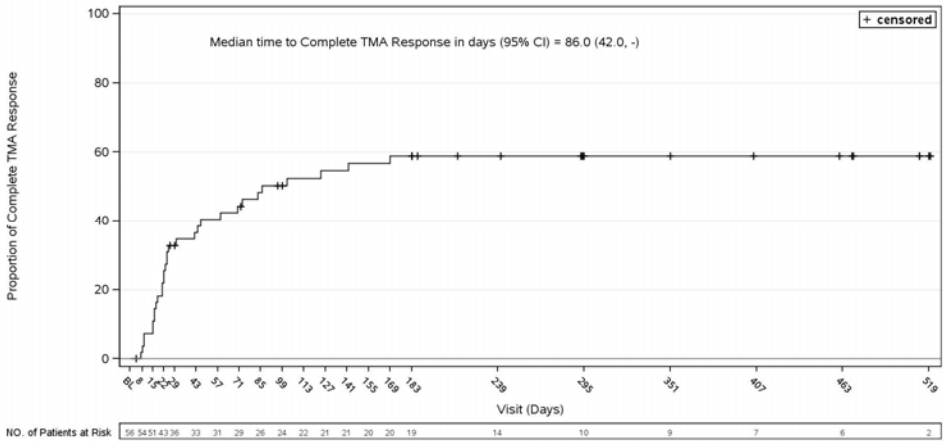
The overall quality and integrity of the application are acceptable. Upon further clarifications from the applicant's response to FDA's information requests, the statistical reviewer was able to confirm the applicant's analysis results for the efficacy endpoints and verify their lab data findings.

Efficacy Results – Secondary and other relevant endpoints

Time to Complete TMA response

For Trial 311, the median time to Complete TMA Response was 86 days, ranged from 7 to 169 days, following the first dose of ULTOMIRIS, as shown in Figure 10.

Figure 10: Time to Complete TMA response of Trial 311 (Kaplan Meier estimation, FAS)

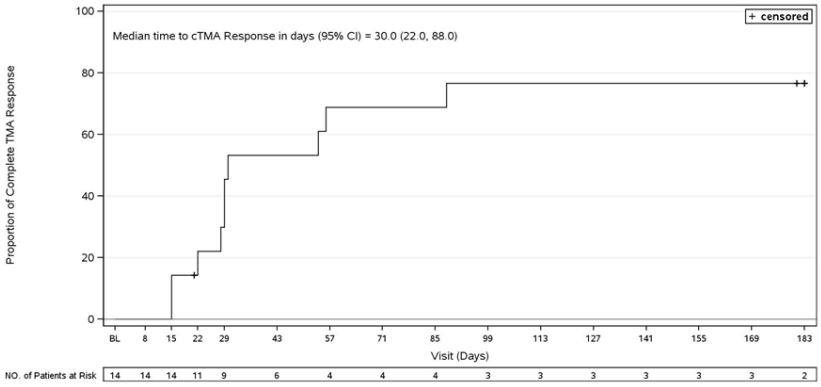


Source: BLA761108-S1.

Clinical reviewer comments: The latest response observed at 169 days was not counted in the primary analysis for the Initial Evaluation Period because it was confirmed after the Initial Evaluation Period by the response criteria. This case may be included in 120-day updates.

The median time to Complete TMA Response of Trial 312 during the Initial Evaluation Period was 30 days, ranged from 15 to 88 days following the first dose of ULTOMIRIS, as shown in Figure 11.

Figure 11: Time to Complete TMA response of Trial 312 (Kaplan Meier estimation, FAS)



Source: BLA761108_S1

Dose/Dose Response

See PK/PD section in the clinical pharmacology review for details.

Durability of Response

Duration of Complete TMA response

The Duration of Complete TMA response analysis was not prespecified in either of Trial 311 and 312 protocols; therefore, the definition for end of response was adapted from eculizumab studies C10-003 and C10-004. End of Complete TMA Response was considered to have occurred upon the observance of 2 consecutive measurements at least 4 weeks apart which each showed:

- Platelet count < lower limit of normal (LLN)
- Lactate dehydrogenase > upper limit of normal (ULN)
- Serum creatinine increased ≥ 25% from baseline and > ULN

Patients with no observed end of Complete TMA Response had their end of response value censored at the end of study or data cut-off date. Per the applied definition, no patients in either ravulizumab study lost response. The time available for each patient to lose response depended on duration of on-study follow-up, which varied among patients at data cut-off date. In Trial 311, the median duration of Complete TMA Response through data cutoff was 7.97 months (range: 2.52 to 16.69). In Trial 312, the median duration of Complete TMA Response through week 26 is 5.08 months (range: 3.08 to 5.54).

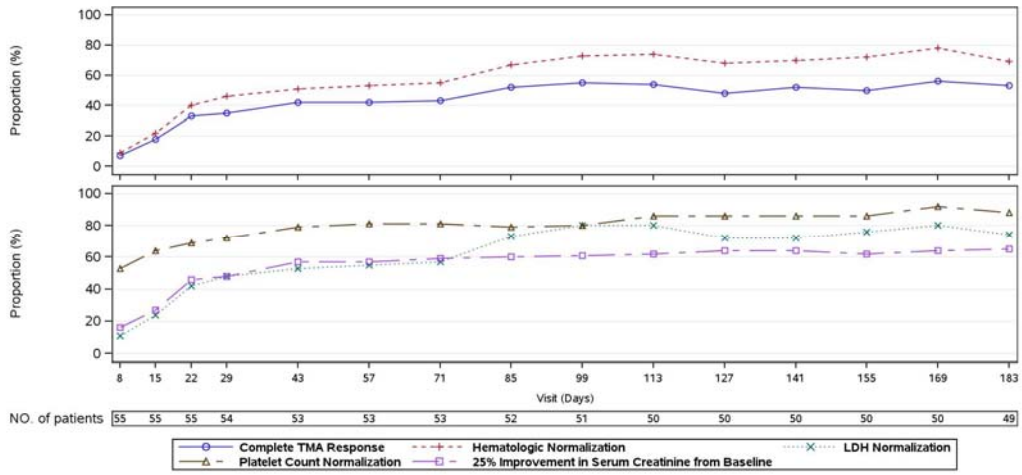
Statistical reviewer comment: As noted the duration of response analyses was not prespecified in either two protocols, therefore the analysis datasets and results were requested via the IR (dated on August 6th, 2019).

Persistence of Effect

1. Complete TMA Response Components and hematology normalization Status Over Time

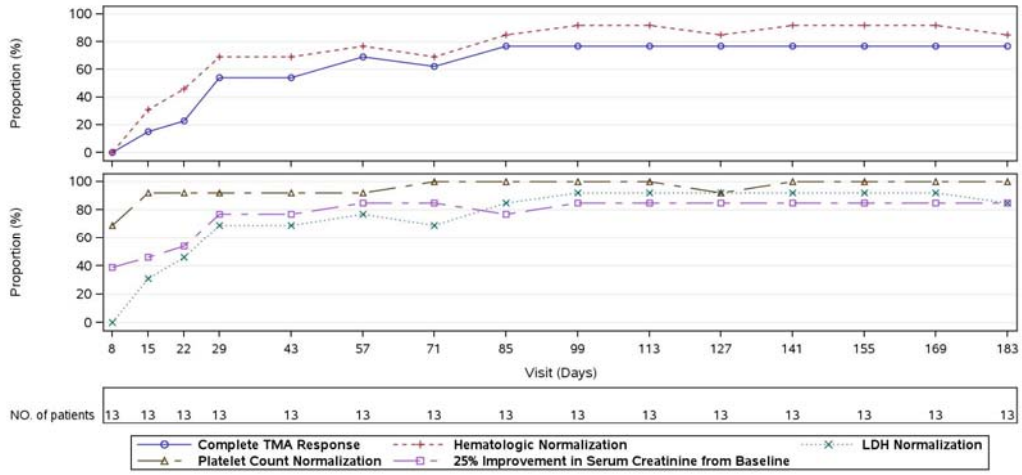
The Complete TMA Response and hematology normalization status over time for the FAS population is depicted in Figure 12 and Figure 13. Of the 3 Complete TMA Response components, platelets showed the earliest response, with more than half of patients achieving platelet count normalization by the Day 15 visit. Normalization of LDH and renal function required a longer duration of treatment to show improvement in general.

Figure 12: Trial 311 Complete TMA Response Components and Hematologic Normalization Status Over Time During the Initial Evaluation Period (FAS)



Source: BLA 761108-S1

Figure 13: Trial 312 Complete TMA Response Components and Hematologic Normalization Status Over Time During the Initial Evaluation Period (FAS)



Source: BLA761108-S1

2. Hemoglobin response
   During the Initial Evaluation Period, 71.4% (40/56, [95% CI: 58.7%, 84.2%]) and 85.7% (12/14, [95% CI: 57.2%, 98.2%]) FAS patients achieved a hemoglobin response in Trials 311 and 312, respectively. The trends of hemoglobin response in two trials are shown in the section above.

Clinical reviewer comments: Hematological and laboratory parameter improvements were observed in both trials. However, better improvements were seen in the pediatric trials, i.e., Trial 312.

3. Dialysis requirements

Dialysis Status changed during ULTOMIRIS treatment are summarized in Table 37. In Trial 311 at the cut-off of the end of study initial evaluation period, in patients who were on dialysis at baseline, 58.6% (17/29) have discontinued dialysis, and 41.4 % (12/29) remained on dialysis. For patients who were not on dialysis at baseline, 74% (20/27) remained dialysis free, 26% (7/27) initiated dialysis. Of seven patients who were initiated dialysis during the trial 311, six (86%) remained on dialysis at the end of the initial evaluation period. The overall status at the end of the evaluation period were 67.9% (38/56) adult patients with aHUS who were either free of dialysis (35.7%, 20/56) or discontinued dialysis (32.1%, 18/56). For patients required dialysis at the end of the initial evaluation period, 11 (19.6%) were continued dialysis from baseline and 7 (12.5%) were newly required dialysis during the ULTOMIRIS treatment.

Table 37: Dialysis status changed during the trials 311 and 312 (FAS, initial evaluation cut-off)

Dialysis Status	ALXN1210-311 (N=56), n (%)		ALXN1210-312 (N=14), n (%)	
Time	Baseline	Initial Evaluation End	Baseline	Initial Evaluation End
Dialysis	29 (58.8)	18 (32.1)	5 (35.7)	1 (7.1)
No Dialysis	27 (48.2)	38 (67 9)[1]	9 (64.3)	13 (92.9)
Initiated Dialysis	-	7 (12.1)	-	0
Discontinue Dialysis	-	18 (32.1)	-	0

1. There were 20 patients had never needed dialysis.
Source: BLA761108-S1.

In Trial 312, at the cut-off of the end of study initial evaluation period, in pediatric patients who were on dialysis at baseline, 80% (4/5) have discontinued dialysis, and 20% (1/5) remained on dialysis. For patients who were not on dialysis at baseline, 100% (9/9) remained dialysis free, no patients initiated dialysis during the study. At the end of the evaluation period, there were 92.9% (13/14) patients who were either continue free of dialysis (64.3%, 9/14) or discontinued dialysis (28.6%, 4/14), and one patient (7.1%) remained on dialysis.

4. EGFR changes from baseline

Renal function was assessed in both Trials 311 and 312 by eGFR. In both trials, the mean eGFR improved during the initial evaluation period, as shown in Table 38 below.

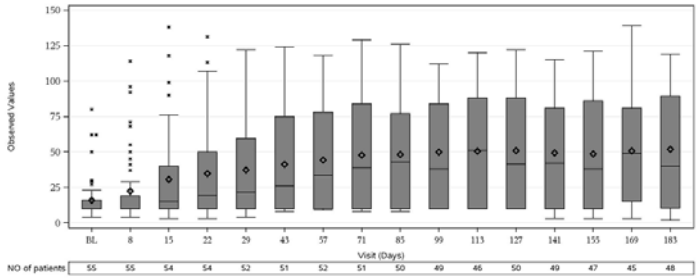
Table 38: Mean eGFR improvements during initial evaluation period in trial 311 and 312 (FAS)

Mean eGFR ($mL/min/1.73m^2$ ± SD)	ALXN1210-311 (N=56)	ALXN1210-312 (N=14)
Baseline	15.86 ± 14 82	28.40 ± 23.11
Day 8	22.35 ± 24 25	43.3 ± 34 31
Day 15	30.63 ± 31 27	63.2 ± 41 99
Day 85	48.20 ± 37 20	104.9 ± 56.36
Day 183 (Initial evaluation End)	51.83 ± 39.16	108.0 ± 63.21

Source: BLA 761108-S1

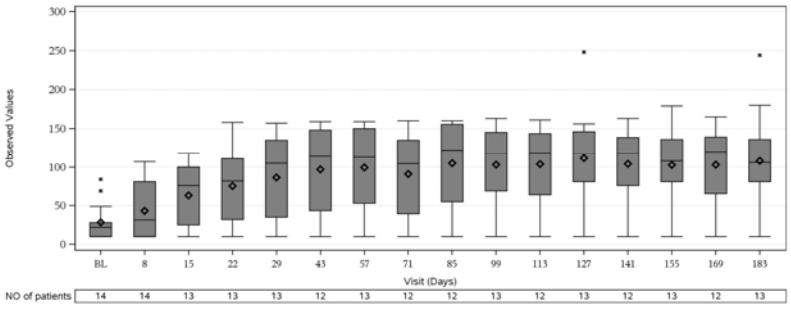
The trends of eGFR observed in both trials are shown in Figure 14 and Figure 15. Baseline value was defined as the average of the values from the assessments performed prior to the first study drug infusion (these could include results from screening and the Day 1 visit). For eGFR, 10 mL/min/1.73 m^2 was imputed for patients requiring dialysis for acute kidney injury. The horizontal line in the middle of individual box indicates the median, a diamond indicates the mean, and the top and bottom borders of the box mark the 75th and 25th percentiles, respectively. The whiskers represent the highest and lowest values within 1.5 times the interquartile range from the lower quartile and upper quartile. Outliers are represented by asterisk beyond the whiskers.

Figure 14: Trial 311 observed values of eGFR Over Time (FAS)



Abbreviations: BL = baseline; eGFR = estimated glomerular filtration rate; NO. = number.
Source: BLA 761108-S1

Figure 15: Trial 312 observed values of eGFR Over Time (FAS)



Abbreviations: BL = baseline; eGFR = estimated glomerular filtration rate; NO. = number.
Source: BLA 761108-S1

Clinical reviewer comment: A 25% greater free of dialysis were seen in pediatric patients with aHUS in Trial 312 (92.9%, 13/14) compared to adult patients in Trials 311 (67.9%, 38/56). This difference is likely contributed by the baseline renal function and disease manifestation differences between the adult and pediatric trial patients. The baseline mean eGFR of Trial 311 (15.86) is about 50% of the mean eGFR of Trial 312 (28.4). In addition, Trial 311 had 69.9% patients with stage 5 CKD at baseline, whereas Trial 312 had 35.7% patients with stage 5 CKD at baseline. However, the discontinuation of dialysis was 32% (18/56) in Trial 311 and 80% (1/5) in Trial 312, although both samples are very small. Therefore, possibility of the difference in renal improvements associated to age in ULTOMIRIS treatment could be further explored.

5. CKD stage shift

In Trial 311, 47 of 56 (83.9%) patients in the FAS had both baseline and Day 183 data. Of these 47 patients, 68.1% (32/47) patients had improvement in CKD stage compared to baseline, as shown in Table 39. Specifically, 6 patients were improved by 5 stages (i.e., from ESKD to normal renal function), 7 patients were improved by 4 stages, 5 patients were improved by 3 stages, 4 patients were improved by 2 stages, and 10 patients were improved by 1 stage. Eleven CKD stage 5 patients (23.4%) had no improvements. One CKD stage 2 patient (2.1%) also did not improve during the initial evaluation. Two patients (4.3%) progressed from CKD stage 4 to stage 5.

Table 39: Trial 311 CKD stage shift from baseline to end of Initial Evaluation Period (26 Weeks or Day 1-183)

Baseline CKD Stage	Post-Baseline CKD Stage at Day 183 (N = 47)					
	1 n (%)	2 n (%)	3A n (%)	3B n (%)	4 n (%)	5 n (%)
1 (n = 0)	0	0	0	0	0	0
2 (n = 3)	2 (4 3)	1 (2 1)	0	0	0	0
3A (n = 1)	1 (2 1)	0	0	0	0	0
3B (n = 2)	2 (4 3)	0	0	0	0	0
4 (n = 7)	1 (2 1)	0	0	3 (6 4)	1 (2 1)	2 (4 3)
5 (n = 34)	6 (12 8)	6 (12 8)	3 (6 4)	3 (6 4)	5 (10 6)	11 (23 4)
Total	12 (25 5)	7 (14 9)	3 (6 4)	6 (12 8)	6 (12 8)	13 (27 7)

Note: Dark shading indicates improvement compared to baseline and light shading indicates worsening compared to baseline. Baseline was derived based on the last available eGFR before starting treatment. Patients with both baseline and at least 1 value at post-baseline visits were included in the summary. Percentages were based on the total number of patients with non-missing data at both the baseline visit and the post-baseline visit. The CKD stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stages of CKD: Stage 1 = eGFR ≥ 90 (normal); Stage 2 = eGFR 60 to 89; Stage 3A = eGFR 45 to 59; Stage 3B = eGFR 30 to 44; Stage 4 = eGFR15 to 29; Stage 5: eGFR < 15 (including dialysis: end stage).
Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.
Source: BLA761108-S1

In Trial 312, 13 of 14 (92.8%) patients in the FAS had both baseline and Day 183 data. There were 11 patients of 13 (84.6%) patients had improvements of one or more CKD stages compared to baseline, as shown in Table 40. Two patients (15.4%), one stage 4 and one stage 5 at baseline, did not have improvement in CKD stages. However, no progression worsening in CKD stage was observed in Trial 312 at the data cutoff for this supplement submission.

Table 40: Trial 312 CKD stage shift from baseline to end of Initial Evaluation Period (26 Weeks or Day 1-183)

		Post-baseline CKD Stage at Day 183 (N = 13)[a]					
Baseline CKD Stage	Baseline n (%)	1 n (%)	2 n (%)	3A n (%)	3B n (%)	4 n (%)	5 n (%)
1	0	0	0	0	0	0	0
2	2 (14 3)	1 (7 7)	0	0	0	0	0
3A	1 (7 1)	1 (7 7)	0	0	0	0	0

3B	0	0	0	0	0	0	0
4	6 (42 9)	3 (23 1)	1 (7 7)	1 (7 7)	0	1 (7 7)	0
5	5 (35 7)	3 (23 1)	1 (7 7)	0	0	0	1 (7 7)
Total	14 (100 0)	8 (61 5)	2 (15 4)	1 (7 7)	0	1 (7 7)	1 (7 7)

Note: Dark shading indicates improvement compared to baseline and light shading indicates worsening compared to baseline. Baseline was derived based on the last available eGFR before starting treatment. Patients with both baseline and at least 1 value at post-baseline visits were included in the summary. Percentages were based on the total number of patients with non-missing data at both the baseline visit and the post-baseline visit. The CKD stage is classified based on the National Kidney Foundation Chronic Kidney Disease Stage. Stages of CKD: Stage 1 = eGFR ≥ 90 (normal); Stage 2 = eGFR 60 to 89; Stage 3A = eGFR 45 to 59; Stage 3B = eGFR 30 to 44; Stage 4 = eGFR 15 to 29; Stage 5: eGFR < 15 (including dialysis: end stage).
a The percentages for the post-baseline CKD stage at Day 183 are based on the 13 patients with available data. Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.
Source: BLA761108-S1

Clinical reviewer Comment: The down stage of CKD status is expected in concert to the improvements of eGFR and decreased dialysis requirements. Again, better CKD status improvements without any progressive worsening cases observed in Trial 312 pediatric patients compared to adults. These results reiterated the question of age associated response to ULTOMIRIS treatment and ability of response in disease recovery. However, the clinical pharmacology assessment did not suggest there is any PK/PD deference between adult and children. In addition, the baseline renal function and clinical characters of the pediatric patients in Trial 312 appeared to be better than the adult patients in trial 311.

Additional Efficacy Analyses and Results – Exploratory COA (PRO) Endpoints

PRO Instruments

The Applicant collected patient reported outcome (PRO) using the EQ-5D-3L (all patients), FACIT Fatigue version 4 Questionnaire (patients ≥ 18 years of age), Pediatric FACIT Fatigue Questionnaire (patients < 18 years of age). These measures were summarized at baseline and each postbaseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline. The FACIT Fatigue results were presented separately and combined for adults and pediatric patients. The number and proportion of patients with a 3 points improvement from baseline in the FACIT Fatigue score were summarized over time by the number and proportion of patients along with a 2-sided 95% CI for each post-baseline time point.

PRO Results

In Trial 311, the mean (SD) FACIT-Fatigue baseline score for the 51 patients in the FAS with available data is 24.03 (15.28). During the Initial Evaluation Period, patients in the FAS showed improvement in FACIT-Fatigue score over time. At Day 183, the 44 patients with available data had a mean improvement from baseline in FACIT-Fatigue score of 19.15 (16.21). An improvement of ≥ 3 points in FACIT-Fatigue score was observed in 37 (84.1%) of the 44 patients with available data.

At baseline, the mean (SD) EQ-5D-3L VAS score for the 52 patients in the FAS with available data is 46.17 (28.68). During the Initial Evaluation Period, patients in the FAS showed improvement in EQ-5D-3L VAS score

over time. At Day 183, the 45 patients with available data in the FAS had a mean (SD) improvement score of 32.33 (29.56).

In Trial 312, quality of life was assessed in patients ≥ 5 years of age by the Pediatric FACIT-Fatigue Questionnaire (patient-reported for patients who were ≥ 8 years of age at the time of enrollment; caregiver-reported or caregiver assistance for patients who were 5 to < 8 years of age at the time of enrollment). This measure was summarized at baseline and each post-baseline time point using descriptive statistics for continuous variables for the observed value as well as the change from baseline.

For the 7 treated patients who were > 5 years of age, QoL was assessed using the Pediatric FACIT-Fatigue Questionnaire. The mean (SD) Pediatric FACIT-Fatigue baseline score for the 7 patients with available data is 28.29 (13.97). During the Initial Evaluation Period, these 7 patients had a mean (SD) improvement in the Pediatric FACIT-Fatigue score of 19.00 (16.19) compared to baseline. Three (42.9%) of 7 patients had a 3-point improvement in the FACIT-Fatigue total score from baseline at Day 8, 6 (85.7%) patients had a 3-point improvement from baseline at Day 29, and all 7 patients had a 3-point improvement from baseline by Day 71.

Statistical Reviewer Comment: The PRO results in both trails showed patients' improvement in quality of life overtime, most of patients' measurement score improved by the end of the study or data cut-off date. Both trails are single-armed trials with no comparison group and thus limit the ability to interpret any PRO results, thus the PRO results are descriptive only.

8.1.3. Integrated Review of Effectiveness

The efficacy of ravulizumab-cwvz in patients with complement inhibitor treatment-naïve aHUS is supported by two open label, single arm, multicenter, international trials. Trial 311 was conducted in adult patients ≥ 18 years of age, and Trial 312 was conducted in pediatric patients < 18 years of age. Both trials used the same primary endpoint which is Complete TMA Response, and key secondary endpoints which are time to Complete TMA Response, Complete TMA Response status over time, dialysis requirement, CKD stage as evaluated by estimated glomerular filtration rate (eGFR), and hemoglobin response.

Study ALXN1210-aHUS-311 (Study 311) enrolled 56 adult patients with evidence of TMA due to aHUS who were naïve to complement inhibitor treatment prior to enrollment. Study ALXN1210-aHUS-312 (Study 312) enrolled 14 patients less than 18 years of age with complement inhibitor treatment-naïve aHUS. Efficacy was established based on complete TMA response defined as normalization of platelet count and lactate dehydrogenase and ≥ 25% improvement in serum creatinine from baseline during the 26-week Initial Evaluation Period. A complete TMA Response was achieved by 30 of 56 (53.6%; [95% CI: 39.7%, 67.0%]) adult patients in Trial 311 and 10 of 14 (71.4%; [95% CI: 41.9%, 91.6%]) pediatric patients in Trial 312. The median duration of complete TMA response was 7.97 months (range 2.52 to 16.69) months for Study 311 and 5.08 months (range: 3.08 to 5.54 months) in Study 312.

Supportive efficacy was demonstrated by platelet count change from baseline, dialysis requirement, and renal function as evaluated by estimated glomerular filtration rate (eGFR). In Study 311, 17 of the 19 patients (59%) who required dialysis at study entry discontinued dialysis at end of available follow. In Study 312, four of the

five patients who required dialysis at study entry were able to discontinue dialysis after first month and for duration of treatment.

In summary, the results from studies 311 and 312 in a rare disease are acceptable for demonstration of effectiveness of this product in patients with aHUS. The ability to conduct formal randomized controlled trials or non-inferiority trials may not be possible for the aHUS population. The two single-arm trials (Study 311 and Study 312) demonstrated a sustainment of response supported by clinically meaningful secondary endpoints (improvement in renal function and decreased dialysis requirements) and are sufficient to support conclusion of effectiveness for ULTOMIRIS in adult and pediatric patients with aHUS.

8.2. Review of Safety

8.2.1. Safety Review Approach

The clinical review of safety was based on the data from trials 311 and 312, provided in BLA761108-S1. Safety analyses were conducted on the datasets of each trial and pooled datasets with data cut-off dates of initial NDA submission and 90-days safety update.

8.2.2. Review of the Safety Database

Overall Exposure

Patients in both trials received a weight-based dosing regimen and schedule, as described in section 8.1.1. As of the data cut-off date, 74 patients received ravulizumab in the Initial Evaluation Period (58 patients in Trial ALXN1210-aHUS-311 and 16 patients in Trial ALXN1210-aHUS-312), of whom 62 patients completed the Initial Evaluation Period and continued into the Extension Period.

Of the 58 adult patients enrolled in Trial ALXN1210-311, 49 completed the Initial Evaluation Period; of the 9 patients who discontinued from the study, 3 discontinued due to AEs. Two patients were discontinued from the study after receiving the first dose of study drug as both patients were determined to be ineligible due to a positive stool Shiga toxin test result, which became available after the first dose of study drug was administered. Other reasons for discontinuation from study included death (2 patients), and physician decision and protocol violation (1 patient, each).

Of the 16 pediatric patients enrolled in Trial ALXN1210-312, 13 completed the Initial Evaluation Period; of the 3 patients who discontinued from the study, 1 discontinued due to AE. Two patients were withdrawn from the study after receiving the first dose of study drug; 1 due to protocol violation and the other being determined ineligible post-treatment.

As of the data cut-off date (5/23/2018 and 10/15/2018 for Trial 311 initiation and extension periods, 10/30/2018 for Trial 312), 74 patients received at least 1 dose of ravulizumab. Overall, the median treatment duration was 215 days (range: 4 to 568 days). The safety population, treatment follow up and duration are summarized in Table 41 by the applicant. The median treatment duration was 26.1 weeks for both trials 311 and 312. In addition, the trial 311 safety population (N = 58) had a later data cut-off during the extension period, also shown in Table 41.

Table 41: The applicant's analysis: Treatment exposure duration and follow up

Variable	ALXN1210-aHUS-311 (N = 58)	ALXN1210-aHUS-312 (N = 16)	Total (N = 74)
Treatment duration from Day 1 to data cutoff (days)[a]			
n	58	16	74
Mean (SD)	291 4 (158 42)	151 4 (68 25)	261 2 (154 66)
Median	262 5	183 0	215 0
Min, max	4, 568	7, 186	4, 568
Total PY of exposure (years)[a]	46 3	6 6	52 9
Treatment duration category, n (%)[a]			
0 to 6 months (≤ 182 days)	11 (19 0)	7 (43 8)	18 (24 3)
> 6 to 12 months	31 (53 4)	9 (56 3)	40 (54 1)
> 12 to 18 months	12 (20 7)	0	12 (16 2)
> 18 to 24 months	4 (6 9)	0	4 (5 4)
> 24 months	0	0	0
Number of infusions from Day 1 to data cutoff			
n	58	16[b]	74
Mean (SD)	6 4 (2 84)	5 8 (2 57)	6 3 (2 78)
Median	6 0	6 0	6 0
Min, max	1, 11	1, 8	1, 11
Number of patients with an infusion interruption from Day 1 to data cutoff, n (%)	9 (15 5)	2 (12 5)	11 (14 9)
Number of infusions interrupted from Day 1 to data cutoff			
Total	14	2	16
Mean (SD)	1 6 (1 33)	1 0 (0 00)	1 5 (1 21)
Median	1 0	1 0	1 0
Min, max	1, 5	1, 1	1, 5
Number of infusions interrupted due to adverse event from Day 1 to data cutoff			
Total	0	1	1
Mean (SD)	NA	1 0	1 0
Median	NA	1 0	1 0
Min, max	NA	1, 1	1, 1
Drug compliance from Day 1 to data cutoff, n (%)			
≥ 100%	58 (100 0)	16 (100 0)	74 (100 0)

The data cutoff dates were 15 Oct 2018 or the end of Initial Evaluation Period whichever came last for Study ALXN1210-aHUS-311 and the end of Initial Evaluation Period for Study ALXN1210-aHUS-312.

a Treatment duration = the earliest of (data cutoff date, study discontinuation date, or [treatment discontinuation date + 56 days]) - date of first ravulizumab infusion + 1.
b Patients weighing < 20 kg were dosed q4w and ≥ 20 kg were dosed q8w; therefore, the number of infusions were different.
Abbreviations: aHUS = atypical hemolytic uremic syndrome; max = maximum; Min = minimum; NA = not applicable; PY = patient-years; q4w = once every 4 weeks; q8w = once every 8 weeks; SD = standard deviation; TMA = thrombotic microangiopathy.
Source: BLA761108-S1, ISS.

The reviewer verified follow up and exposure data from initial submission and 90-date safety update (4/17/2019 cut-off), as shown in Table 42.

Table 42: Reviewer's analysis: Treatment exposure duration and follow up

Trial	ALXN1210-311			ALXN1210-312	
Data Cut-off	IEP 5/23/2018	ExtP 10/15/2018	90-day FU	10/30-2018	90-day FU
Parameter / SP	N = 58	N = 58	N=58	N = 16	N=16
Follow-up duration (weeks)[a]					
Mean (SD)	23 37 (7 3)	41 9 (22 6)	60 68 (30 6)	21 6 (9 8)	52 1 (26 5)
Median	26 1	39 6	63 8	26 1	62 2
Min, max	0 6, 27 1	0 6, 81 1	0 6, 107 4	1, 26 6	1, 83 1
Treatment duration[b] (weeks)					
Mean (SD)	23 4 (7 3)	41 6 (22 6)	60 68 (30 6)	21 64 (9 8)	52 1 (26 5)
Median	26 1	37 50	63 8	26 1	62 2
Min, max	0 6, 27 1	0 7, 81 1	0 6, 107 4	1, 26 6	1, 83 1
Number of infusions					
1	3 (5 2)	3 (5 2)	n/a	2 (12 5)	n/a
2	3 (5 2)	3 (5 2)		1 (6 3)	
3	2 (3 4)	2 (3 4)		-	
4	48 (82 8)	4 (6 9)		5 (31 3)	
5	2 (3 4)	13 (22 4)		-	
6	-	8 (13 8)		1 (6 3)	
7	-	5 (8 6)		7 (43 8)	
8	-	5 (8 6)		-	
9	-	4 (6 9)		-	
10	-	4 (6 9)		-	
11	-	7 (12 1)		-	

a Follow-up duration was defined as the number of weeks from date of first dose to completion of study/last available study visit/study discontinuation + 1 day.
b Treatment duration was defined as ([the date of last dose + 56 days] – [the date of first dose]) or ([study discontinuation date] – [the date of first dose]), if study discontinuation date is earlier than (the date of last dose + 56 days). The result was transferred to weeks.
Abbreviations: IEP = initial evaluation period, Ext P = extension Period, FU = follow up, max = maximum; min = minimum; Q1 = 25th percentile, Q3 = 75th percentile; SD = standard deviation.
Source: BLA761108-S1

Clinical reviewer comment: Two trials treatment duration and follow up appears to be in line with the study plan. The follow up and treatment duration for both adult and pediatric patients appears to be in adequate lengths for safety assessment

Adequacy of the safety database:

The safety database provided for safety analysis included following:

- Trial ALXN1210-aHUS-311: Safety data from the Initial Evaluation Period (through Week 26 visit or early withdrawal) for the 58 adult patients who received at least 1 dose of ravulizumab. In addition, safety data are included for patients who had a visit in the Extension Period through 15 Oct 2018. No adolescents were enrolled in this trial.

- Trial ALXN1210-aHUS-312: Safety data from the Initial Evaluation Period (through Week 26 visit or early withdrawal) for the first 16 pediatric patients enrolled in Cohort 1 who received at least 1 dose of ravulizumab. No patients from Cohort 2 are included in this analysis.

- Pooled dataset of Trials 3311 and 312 for integrated safety analyses.

The size of database of trials 311 and 312 is adequate to provide a reasonable estimate of adverse events that may occur with ULTOMIRIS exposure in patient with aHUS. However, the assessment of safety is limited by the single arm trial design.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

There is no issue concerning the data integrity and quality. The quality of the safety data submitted was adequate for substantive primary review. The applicant has provided sufficient safety information of patients enrolled in trials 311 and 312, including full datasets and narratives of deaths, serious adverse events or treatment emergent AE leading to permanent discontinuation of study treatment.

Categorization of Adverse Events

Treatment-emergent AEs (TEAEs) were coded using the MedDRA Version 21.0. Treatment-emergent AE was defined as any event not present prior to ravulizumab exposure or any event already present that worsens in either intensity or frequency following exposure to ravulizumab. An AE was considered a TEAE if the start date and time of the AE was on or after the start date and time of the first study drug infusion. Adverse events that do not meet the TEAE criteria were classified as pretreatment AEs.

The AEs were also categorized by severity using the Common Terminology Criteria for Adverse Events version 4.03 or higher and by relationship (unrelated and related) to the study drug as assessed by the Investigator.

Meningococcal infections were considered as AEs of special interest.

Base on the initial submission, 98.6% (73/74) patients across the 2 trials had at least 1 TEAE, as shown in Table 43. Overall, grade 3, 4 and 5 TEAEs were 45.9%, 20.3%, and 4.1%, respectively. At the time of 90-day safety updates, 100% of patients from two trials had at least 1 TEAE. Besides grade 3 AEs increased 7% percent, there were no other significant changes in AE reporting.

Table 43: Categorized adverse events of trials 311 and 312

Trials	311 (N = 58)		312 (N = 16)		Total (N = 74)	
	n (%)		n (%)		n (%)	
Submission	S1	90-day	sBLA	90-day	sBLA	90-day
Any TEAE	58 (100 0)	58 (100)	15 (93 8)	16 (100)	73 (98 6)	74 (100)
Grade 1	54 (93 1)	55 (94 8)	13 (81 3)	14 (87 5)	67 (90 5)	69 (93 2)
Grade 2	46 (79 3)	46 (79 3)	11 (68 8)	11 (68 8)	57 (77 0)	57 (77 0)
Grade 3	31 (53 4)	31 (53 4)	3 (18 8)	8 (50)	34 (45 9)	39 (52 7)
Grade 4	14 (24 1)	14 (24 1)	1 (6 3)	1 (6 3)	15 (20 3)	15 (20 3)
Grade 5	3 (5 2)	3 (5 2)	0	0	3 (4 1)	3 (4 1)
TEAE leading to study drug interruption	0	0	1 (6 3)	1 (6 3)	1 (1 4)	1 (1 4)
TEAE leading to study drug discontinuation	3 (5 2)	3 (5 2)	1 (6 3)	2 (12 5)	4 (5 4)	4 (5 4)
TEAE leading to study discontinuation	3 (5 2)	3 (5 2)	1 (6 3)	2 912 5)	4 (5 4)	4 (5 4)
Any serious TEAE (SAE)	30 (51 7)	31 (53 4)	8 (50 0)		38 (51 4)	42 (55 4)
SAE leading to study drug interruption	0	0	0		0	0
SAE leading to study drug discontinuation	3 (5 2)	3 (5 2)	1 (6 3)	1 (6 3)	4 (5 4)	4 (5 4)
SAE leading to study discontinuation	3 (5 2)	3 (5 2)	1 (6 3)	1 (6 3)	4 (5 4)	4 (5 4)
TEAE leading to death[a]	3 (5 2)	3 (5 2)	0	0	3 (4 1)	3 (4 1)

Source: BLA 761108-S1 and 90-day safety updates.

Reviewer comments: The frequency of overall adverse events are expected to the class of complement inhibitors and the patient population.

Routine Clinical Tests

The safety databases also collected clinical laboratory test results, vital signs measurements, physical examination findings, ECG parameters, or immunogenicity results was performed. The results for clinical laboratory tests, vital signs, physical examination, and ECG are discussed in the CSRs of individual clinical studies. The schedule of safety assessments for trials 311 and 312 was described in section 8.1.1. The frequency of safety of testing for safety monitoring was considered adequate within the context of the trials.

8.2.4. Safety Results

Deaths

In the 74-patient safety population of trials 311 and 312, 4 deaths were reported from Trial 311, and no deaths reported from Trial-312, as shown in Table 43. No additional deaths were reported from the 90-day safety updates. Therefore, a total 4 deaths occurred in the adult population evaluated and no deaths were observed in the pediatric population. .

The applicant reported that three of the four deaths (4.1%) were reported due to AEs that were considered not related to study drug by investigators. This reviewer reviewed the fatal cases for risk assessments and summarized case by case below.

1. Case (b) (6): A 77-year-old white female who had past medical history significant for squamous cell carcinoma of the lip, hypercholesterolemia, osteoporosis, and gastroesophageal reflux, presented with 3 weeks of diarrhea and was diagnosed cerebral arterial thrombosis on Day -7. Plasma exchange was initiated at day -2. The patient received 1 infusion of study drug after which she was found ineligible for the study because tested positive for Shiga toxin and was withdrawn from the study (Day 5). The patient continued with plasma exchange for Shiga toxin related HUS and died on Day 16.

   Reviewer comment: The patient was confounded by a pretreatment life threatening event for determination of the cause of death by the study drug. In addition, the patient was not eligible for the study by positivity of Shiga toxin, therefore, the applicant excluded this fatal event from the safety summary.

2. Case (b) (6): A 76-year-old Asian male with a past medical history of hypertension, diabetes mellitus, renal transplant on immunosuppression, myelofibrosis status post ruxolitinib treatment. On Day -23, the patient was admitted for respiratory failure, atypical pneumonia, and acute kidney injury. He was diagnosed with PCP and CMV pneumonia on day -22. Despite of appropriated treatment, the patient developed shock (both septic and volumic), acute respiratory distress syndrome with possible diffuse alveolar hemorrhage, and sepsis and was transferred to the intensive unit on day -16. The patient was intubated and receiving mechanical ventilation on day-15. Dialysis was started on day -7 due to renal failure. Plasmapheresis started on day -3 for progressive renal failure, hemolysis and thrombocytopenia. Day 4 after the first dose of ULTOMIRIS, central catheter and blood culture revealed Corynebacterium; on Day 6, a blood culture revealed *Candida lusitaniae*. Starting day 6, the patient had recurrent septic shock and died on Day 26. Persistent fungal infection with *Candida lusitaniae* and a catheter-related bloodstream infection caused by Corynbacterium were considered to be the cause of the septic shock. The patient had received 2 infusions of study drug in the study. The last infusion received prior to death was on Day 15.

   Reviewer comment: Given the multiple pretreatment comorbidities and clinical complications from underlying diseases, the role of testing drug in this patient's death cannot be determined.

3. Case (b) (6): The patient was a 73-year-old black male with past medical history significant for diabetes, hypertension, atrial fibrillation, congestive heart failure, coronary artery disease, obstructive sleep apnea, hyperlipidemia, anasarca, candida infection (thrush), and ITP, presented with 7 days diarrhea, weakness and worsening renal failure. At the time of aHUS diagnosis, he was also diagnosed with stroke, encephalopathy, bilateral pleural effusions, pseudomonas infection and a posterior thigh wound. Relevant concomitant medications included diltiazem, hydralazine, and metoprolol for hypertension; vasopressin for hypotension; levofloxacin and cefepime for pneumonia; Decadron and dexamethasone for ITP; hydrocortisone sodium succinate for adrenal insufficiency; methylprednisolone sodium succinate for aHUS; atorvastatin for hyperlipidemia; Humalog, Lantus, and dextrose for type 2 diabetes; insulin glargine for diabetes mellitus; ferrous sulfate for anemia; aspirin and nitroglycerin for coronary artery disease; omeprazole and pantoprazole for gastroesophageal reflux; and sodium bicarbonate for stage 5 chronic kidney disease. The patient was transfer to ICU for respiratory distress and was intubated for mechanical ventilation on day -1. After screening for trial 311, the patient received meningococcal vaccine A/C/Y/W and meningococcal

vaccine B on Day -1. The patient received 1 infusion of study drug on Day 1. He developed septic shock on Day 3 and died on Day 4. The Investigator reported patient's age, diabetes, renal failure, and recent use of highly potent corticosteroids as predisposing factors to septic shock.

Reviewer comment: The testing drug as the causality of this patient's death is confounded by preexisting comorbidities, pretreatment critical illness and complications.

4. Case (b) (6): The patient was a 46-year-old Asian female with a medical history of hypertension who presented with petechiae, anemia, thrombocytopenia, and acute kidney injury (eGFR 4 mL/min/1.73 m^2) on Day -15. The patient started hemodialysis on day 4. The patient had received 3 infusions of study drug on Days 1, 15 and 71. The patient did not response to testing drug by the TMA response criteria. On Day 92, she developed an intracranial hemorrhage. Medical care was withdrawn following the intracranial hemorrhage. The patient was withdrawn from the study on Day 96 and died on Day 106.

Reviewer comment: The patient's intracranial hemorrhage is most likely due to underlying disease, aHUS, which did not response to the study treatment.

Reviewer comment: In conclusion, there were 4 deaths in adult population studied (trial 311) and no death in the pediatric population studied (trial 312). None of the four on study deaths could be adequately assessed for association to the study drug because multiple confounding factors co-existed. As described above, one cases received one dose of study drug and had pretreatment event (Case (b) (6)) that lead to fatal outcome, two cases received one and two dose of study drug were critically ill with multiple clinical complications besides aHUS (Case (b) (6) and Case (b) (6)). The last case (Case (b) (6)) received three dose of study drug but did not have any clinical evidences of TMA response and likely die from the complication of aHUS. Based on review of narratives, it is unlikely these four deaths is related to the ULTOMIRIS therapy.

Serious Adverse Events

In the 74-patient safety population of trials 311 and 312, 51.4% (38/74) patients experienced serious adverse events evaluated by MedDRA, as shown in Table 43. Most frequent SAEs by SOC were Infections and Infestations, 19% (11/58) and 25% (4/16) in adult and pediatric patients, respectively. Other most frequently reported SAEs by PT were hypertension (5.4%, 4/74). Hypertension was expected in this population as a consequence of renal disease.

Based on the 90-day safety update report, 56.8% (42/74) patients crossing the 2 trials had at least 1 SAE, and 22 new SAEs reported during 90-day Safety Update period. Similar to the initial submission data, most frequent SAEs by SOC were Infections and infestations 24.1% (14/58) and 50% (8/16) in adult and pediatric patients, respectively, as of 17 Apr 2019. Other most frequently reported SAEs by PT were hypertension and pneumonia (5.4%, 4/74 each). At the time of safety update, no event of meningococcal infection was

reported as of the data cutoff date.

Clinical reviewer comment: The SAE profile observed in trials 311 and 312 in patients with aHUS is comparable to that described in eculizumab labeling for the same patient population. In addition, the overall incidence of SAEs reported was similar to overall incidence of SAEs reported during the initial submission of ULTOMIRIS for the PNH indication(PNH is also a complement mediated TMA).

Dropouts and/or Discontinuations Due to Adverse Effects

In the 74-patient safety population of trials 311 and 312, four (5.4%) patients had SAEs that led to discontinuation of study drug and withdrawal of patient from the study, as shown in Table 43. Interruption of study drug due to an AE occurred in 1 (1.4%) patient.

Significant Adverse Events

Based on previous clinical experience, patients receiving anti-complement drugs are at high risk of infection, especially meningococcal infection. This inherent risk with terminal complement inhibition has been well characterized with the use of complement inhibitors. However, in the 74-patient safety population of trials 311 and 312, no events of meningococcal infection were reported based on both initial submission and the 90-day safety updates.

In trials 311 and 312, 18.9% (14/74) patients experienced grade 3-4 infections, excluding 2 fatal infections. Patients observed with infections in both trials, ranked by frequency, were pneumonia (4.1%, 3/74), Escherichia pyelonephritis, septic shock, urinary tract infection and febrile neutropenia (each 2.7%, 2/74).

Based on the initial sBLA submission and 90-day safety updates, the observed grade 3 or higher adverse events that are > 2 % or clinically significant in trial 311 and 312 are summarized by body system and PT in Table 44. It is notable that cumulated grade 3 adverse events of gastrointestinal system and infections has increased at the 90-day safety update.

Table 44: Clinically significant or ≥ 2% Grade 3 or higher AEs observed in trials 311 and 312 (SP)

Trial ID	311			312	
Submission	Initial		90-Day	Initial	90-day
AE Grade	3-4	5	3-4	3-4	3-4
SOC/PT					
Blood and lymphatic system disorders	10 (17.2)	-	10 (17.2)	1 (6.3)	1 (6.3)
Anemia	*2 (3.4)*	-	*2 (3.4)*	*1 (6.3)*	*3 (18.8)*
Febrile neutropenia	*2 (3.4)*	-	*2 (3.4)*	-	-
Thrombocytopenia	*2 (3.4)*	-	*2 (3.4)*	-	-
Cardiac disorders	1 (1.7)	-	1 (1.7)	-	-
Congenital, familial and genetic disorders	-	-	-	-	--
Ear and labyrinth disorders	-	-	-	-	-
Endocrine disorders	-	-	-	-	-

Trial ID	311			312	
Eye disorders	2 (3.4)	-	2 (3.4)	-	-
Gastrointestinal disorders	9 (15.5)	-	11 (19)	1 (6.3)	2 (12.5)
Diarrhea	*2 (3.4)*	-	*2 (3.4)*	-	-
Vomiting	*2 (3.4)*	-	*2 (3.4)*	-	1 (6.3)
Nausea	*1 (1.7)*		*2 (3.4)*		
Abdominal pain	*1 (1.7)*		*2 (3.4)*		
General disorders and administration site conditions	1 (1.7)	-	1 (1.7)	-	-
Hepatobiliary disorders	-	-	-	-	-
Immune system disorders	1 (1.7)	-	2 (3.4)	-	-
Infections and infestations	12 (20.7)	2 (3.4)	15 (25.9)	2 (12.5)	7 (43.8)
Urinary tract infection	*5 (8.6)*	-	5 (8.6)	-	
Device related infection	*2 (3.4)*	-	2 (3.4)	-	
Gastrointestinal infection	*2 (3.4)*	-	2 (3.4)	-	
Pneumonia	*2 (3.4)*	*1 (1.7)*	2 (3.4)	-	1 (6.3)
Sepsis	*2 (3.4)*	*1 (1.7)*	2 (3.4)	-	
Injury, poisoning and procedural complications	3 (5.2)	-	6 (10.3)	-	1 (6.3)
Investigations	-	-		1 (6.3)	2 (2.5)
Metabolism and nutrition disorders	7 (12.1)	-	7 (12.1)	-	-
Hypokalemia	*1 (1.7)*	-	*1 (1.7)*	-	-
Hypocalcemia	*1 (1.7)*	-	*1 (1.7)*	-	-
Musculoskeletal and connective tissue disorders	3 (5.2)	-	3 (5.2)	-	-
Neoplasms benign, malignant and unspecified	1 (1.7)	-	1 (1.7)	-	-
Nervous system disorders	3 (5.2)	2 (3.4)	5 (8.6)	-	-
Seizure	*3 (5.2)*	-	*3 (5.2)*	-	-
Cerebral artery thrombosis	-	*1 (1.7)*	-	-	-
Hemorrhage intracranial	-	*1 (1.7)*	-	-	-
Product issues	1 (1.7)	-	1 (1.7)	-	-
Psychiatric disorders	1 (1.7)	-	1 (1.7)	-	-
Renal and urinary disorders	12 (20.7)	-	12 (20.7)	-	-
Chronic kidney disease	*3 (5.2)*	-	3 (5.2)	-	-
End stage renal disease	*3 (5.2)*	-	*3 (5.2)*	-	-
Acute kidney injury	*2 (3.4)*	-	*2 (3.4)*	-	-
Renal pseudoaneurysm	*2 (3.4)*	-	*2 (3.4)*	-	-
Reproductive system and breast disorders	-	-	-	-	-
Respiratory, thoracic and mediastinal disorders	8 (13.8)	-	9 (15.5)	1 (6.3)	1 (6.3)
Plural effusion	*1 (1.7)*	-	*1 (1.7)*	*1 (6.3)*	*1 (6.3)*
Skin and subcutaneous tissue disorders	2 (3.4)	-	2 (3.4)	-	-
Vascular disorders	11 (19.0)	-	13 (22.4)	2 (12.5)	2 (12.5)
Hypertension	*6 (10.3)*	-	*7 (12.1)*	*1 (6.3)*	*1 (6.3)*
Hypotension	*2 (3.4)*	-	*3 (5.2)*	-	-
Malignant hypertension	*2 (3.4)*	-	*3 (5.2)*	-	-
Hypertensive crisis	*1 (1.7)*	-	*1 (1.7)*	-	-

Source: BLA761108-S1.

Clinical reviewer comment: Infection is a clinically significant adverse event associated with terminal complement inhibition, as seen in trials 311 and 312. However, the experience of trials 311 and 312 suggest that adequate vaccination might be effective in preventing meningococcal infection in patients receiving ULTOMIRIS. Other frequent grade 3-4 adverse events were hyper/hypotension, cytopenias, renal and urinary disorders, GI and metabolism disorders, which were all observed in previous PNH trials with ULTOMIRIS except renal and urinary disorder.

Infusion-related reaction was reported, two patients in Trial 311 (3.4%) and one patient in Trial 312 (6.25%).

Total of 7 AEs were reported in these three patients, including hypertension, limb discomfort, muscle spasm, paresthesia, dysgeusia, and dizziness. Some events recurred in the same patient. Hypertension occurred in the patient of Trial 312 was led to interruption of the infusion for 10 minutes, nut was able to restart and completed after the interruption.

Infusion reactions that may lead to infusion interruptions were observed in previous reviewed PNH clinical trials with ravulizumab and in the current USPI for ULTOMIRIS includes a warning and precaution section. However, infusion related hypertension that could cause infusion interruption was not reported before. Also, limb discomfort is a new signal.

Treatment Emergent Adverse Events and Adverse Reactions

The frequent the adverse events were analyzed in datasets of two trials. Any grade common AEs > 10% were summarized by body systems or by preferred terms in Table 45.

Table 45: Common adverse events observed in clinical trials 311 and 312 (>10%)

SOC /PT	311 (N = 58) n (%)	312 (N = 16) n (%)	Total (N = 74) n (%)
Patients with TEAEs	48 (82.8)	12 (75)	60 (81.1)

SOC /PT	311 (N = 58) n (%)	312 (N = 16) n (%)	Total (N = 74) n (%)
Blood and lymphatic system disorders	20 (34.5)	5 (31 3)	25 (33 8)
Anemia	*8 (13.8)*	*2 (12.5)*	*10 (13.5)*
Cardiac disorders	11 (19.0)	2 (12.5)	13 (17.6)
Eye disorders	11 (19.0)	3 (18.8)	14 (18 9)
Gastrointestinal disorders	42 (72.4)	11 (68 8)	53 (71.6)
Diarrhea	*18 (31.0)*	*3 (18.8)*	*21 (28.4)*
Vomiting	*15 (25.9)*	*4 (25.0)*	*19 (25.7)*
Nausea	*13 (22.4)*	*2 (12.5)*	*15 (20.3)*
Constipation	*8 (13.8)*	*4 (25.0)*	*12 (16.2)*
Abdominal Pain	*7 (12.1)*	*2 (12.5)*	*9 (12.2)*
General disorders and administration site conditions	32 (55,2)	6 (37.5)	38 (51.4)
Pyrexia	*10 (17.2)*	*5 (31.1)*	*15 (20.3)*
Edema peripheral	*9 (15.5)*	*0 (0.0)*	*9 (12.2)*
Fatigue	*7 (12.1)*	*1 (6.3)*	*8 (10.8)*
Immune system disorders	8 (13.8)	0	8 (10.8)
Infections and infestations	34 (58.6)	9 (56.3)	43 (58.1)
Nasopharyngitis	*8 (13.8)*	*3 (18.8)*	*11 (14.9)*
Urinary Tract Infection	*10 (17.2)*	*1 (6.3)*	*11 (14.9)*
Injury, poisoning and procedural complications	18 ((31 0)	3 (18.8)	21 (28.4)
Investigations	21 (36.2)	6 (37.5)	27 (36 5)
Metabolism and nutrition disorders	26 (44.8)	4 (25.0)	30 (40 5)
Hypokalemia	*9 (15.5)*	*0 (0.0)*	*9 (12.2)*
Musculoskeletal and connective tissue disorders	23 (39.7)	4 (25.0)	27 (36 5)
Arthralgia	*10 (17.2)*	*1 (6.3)*	*11 (14.9)*
Nervous system disorders	35 (36.3)	4 (25.0)	39 (52.7)
Headache	*21 (36.2)*	*4 (25.0)*	*25 (33.8)*
Psychiatric disorders	14 (24.1)	2 (12.5)	16 (21.6)
Anxiety	*8 (13.8)*	*0 (0.0)*	*8 (10.8)*
Renal and urinary disorders	21 (36.2)	1 (6.3)	22 (29.7)
Reproductive system and breast disorders	13 (22.4)	0	13 (17.6)
Respiratory, thoracic and mediastinal disorders	30 (51.7)	7 (43.8)	37 (50 0)
Dyspnea	*10 (17.2)*	*2 (12.5)*	*12 (16.2)*
Cough	*10 (17.2)*	*0 (0.0)*	*10 (13.5)*
Skin and subcutaneous tissues disorders	25 (43.1)	7 (43 8)	32 (43 2)
Vascular disorders	25 (43.1)	7 (43.8)	32 (43 2)
Hypertension	*13 (22.4)*	*4 (25.0)*	*17 (23.0)*

Source: BLA761108-S1

Because the overall infection was 58%. This reviewer analyzed significant infections and pool the rate of infection by grouping locations or pathogens, as shown in Table 46.

Table 46: Infections grouped by locations or pathogens

Infection group/ trial	311 (n=58) N (%)		312 (n=16) N (%)		Overall (n=74) N (%)	
Submissions	Initial	90-Day*	Initial	90-Day*	Initial	90-Day*
Urinary tract infection	14 (24.1)	21 (36.2)	1 (6.3)	2 (12.5)	15 (20.3)	23 (31.1)
Upper airway infection	13 (22.4)	45 (77.6)	6 (38)	9 (56.3)	19 (25.7)	54 (73)
Viral infection*	11 (19)	12 (20.6)	5 (31.3)	10 (62.5)	14 (18.9)	22 (29.7)
Gastrointestinal Infection	7 (12.1)	13 (22.4)	2 (12.5)	6 (37.5)	9 (12.2)	19 (25.7)
Lower respiratory tract and lung infections	7 (12.1)	9 (15.5)	0	2 (12.5)	7 (9.5)	16 (21.6)

* Viral infection included Cytomegalovirus, Herpes virus, Influenza virus, others.
**There may be more than one AE per patient.
Source: BLA761108-S1

Clinical reviewer Comments: The infections by specific groups have shown increase from initial report to the 90-day safety updates, indicating that overall infections and specific infections are important to monitor and manage in this disease setting during the ULTOMIRIS treatment, in addition to the meningococcus meningitis. This finding is expected based on the mechanism of the action of ULTOMIRIS.

Laboratory Findings

As described in Table 45, the most frequent laboratory abnormality is hypokalemia, 15.5% (9/58) in Trial 311 and none in Trial 312. Followed by abnormality of bicarbonate (11.6%, n=5), sodium (8.3%, n=4), chloride (8.3%, n=4), calcium (6.3%, n=3), and magnesium (4.3%, n=2). One patient has grade 4 hypokalemia and hypocalcemia.

At the end of the initial evaluation period (day 183), 5 patients (10.4%) had elevation of liver enzymes, ALT (n=2), AST (n=5), and GGT (n=3). Other abnormalities from normal baseline including amylase (12.6%. n = 6), urine phosphate (10.6%. n=5), uric acid (10.6%. n=5), c-reactive protein (6.3%, n=3). In addition, there is a shift of LDH isoenzyme 3 from baseline were noted (21.7%, n=5).

Clinical reviewer comment: Except hypokalemia, the denominator that the applicant used for calculating laboratory abnormality rates are not consistent with the safety population, but patients with available data. In addition, the applicant pooled abnormalities that were higher or lower than the normal limits of each electrolyte together. The clinically significant of electrolytes and other laboratory abnormalities and association with the study drug is not clear given the underlying disease, aHUS and other comorbidities.

Vital Signs

Overall, the mean (SD) systolic BP decreased from 143.74 (16.04) mm Hg at baseline to 125.54 (16.57) mm Hg at Day 183 and mean (SD) diastolic BP decreased from 82.48 (14.25) mm Hg at baseline to 77.71 (11.88) mm Hg at Day 183. Changes from baseline in mean temperature, mean heart rate, mean respiratory rate, and mean oxygen saturation did not show clinically important trends over time.

Electrocardiograms (ECGs)

Electrocardiograms were obtained at baseline, Day 57, and Day 183. Changes from baseline in mean PR, QT, QTcF, and RR interval values over time were not considered clinically important. No patients had any shift from normal or clinically insignificant abnormal ECG reading to clinically significant abnormal reading, as shown in Table 47.

Table 47: ECG changes

Category	Baseline[a]	Post-baseline Category[a]		
		Normal	Abnormal, NCS	Abnormal, CS
		Trial 311		
Normal	32 (60 4)	24 (45 3)	8 (15 1)	0
Abnormal, NCS	19 (35 8)	7 (13 2)	12 (22 6)	0
Abnormal, CS	2 (3 8)	1 (1 9)	0	1 (1 9)
Total	53 (100 0)	32 (60 4)	20 (37 7)	1 (1 9)
		Trial 312		
Normal	10 (71 4)	8 (57 1)	2 (14 3)	0
Abnormal, NCS	4 (28 6)	2 (14 3)	2 (14 3)	0
Abnormal, CS	0	0	0	0
Total	14 (100 0)	10 (71 4)	4 (28 6)	0

a Baseline was from the screening value.
Abbreviations: CS = clinically significant; ECG = electrocardiogram; NCS = not clinically significant.
Source: BLA761108-S1.

QT

No AEs of QT prolongation, syncope, or torsade's de pointes were reported in two trials.

Immunogenicity

See section 6, clinical pharmacology review.

8.2.5. Analysis of Submission-Specific Safety Issues

1. The most frequently reported AEs (reported by > 20% patients) were infections, headache, diarrhea, vomiting, nausea, and hypertension.

2. Four deaths were reported during the Initial Evaluation Period. One death was due to a pretreatment event (cerebral artery thrombosis), and 3 deaths were due to treatment-emergent SAEs (two patients with septic shock, one patient with intracranial hemorrhage) that were confounded by underlying disease and compilations.

3. Seventy-three (98.6%, 73/74) patients experience at least one adverse event. Thirty-eight patients (51.4%, 38/74) patients experienced 71 SAEs; the most frequently reported SAEs were pneumonia and hypertension (5.2% each, 3/74).

4. Four (5.4%, 4/74) patients discontinued study treatment and withdrew from the study due to an SAE (autoimmune hemolytic anemia, intracranial hemorrhage, and immune thrombocytopenic purpura).

5. Infections was observed in 58.1% (43/74) of study patients. Grade 3 infection was 20.7% (12/58) in Trial 311 and 12.5% (2/16) in Trial 312. Specific group of infection by locations or pathogens, such as urinary tract infections, upper airway infections, lower airway and lung infections, gastrointestinal infections and viral infections were higher than 10%.

6. With vaccination and appropriated antibiotic prophylaxis, no meningococcal infections were reported in the two trials.

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

See section 8.1.2 Exploratory COA (PRO) Endpoints

8.2.7. Safety Analyses by Demographic Subgroups

No formal safety analysis by demographic subgroups with ULTOMIRIS were conducted. The small number of patients limited the ability to conduct demographic subgroup analyses.

8.2.8. Specific Safety Studies/Clinical Trials

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

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No human carcinogenicity data were submitted with this application.

Human Reproduction and Pregnancy

No ravulizumab-treated patients became pregnant during the clinical trial as of each CSR cut-off date.

Pediatrics and Assessment of Effects on Growth

The median change in growth parameters in the pediatric patients as calculated by the difference between the last recorded (day 183) measurement and the baseline measurement are summarized in Table 48.

Table 48: Growth effect assessment in trial 312 pediatric patients

Growth parameters	Median change (range)		
	< 6 years N = 9	6 to < 18 years N = 7	All N = 16
Weight (kg)	1.6 (-0.5, 4.4)	0.8 (-7.2, 4.5)	1.5 (-7.2, 4.5)
Height (cm)	2.5 (-0.9, 7.6)	1.3 (0.5, 2.5)	2 (-0.9, 7.6)
Head circumference (cm)	-6.5 (-16, 15.5)	-17 (-22, -8)	-9 (-22, 15.5)

Changes from baseline in mean body weight and mean head circumference over time did not suggest a clinically significant impact of ULTOMIRIS on growth in pediatric patients enrolled in trial 312. However, the assessment of growth in pediatric patients is limited by the small number.

Analysis of the impact of ULTOMIRIS therapy on developmental parameters such as weight is complicated by the lack of a comparator arm, the chronic nature of aHUS that is likely to adversely impact development, and the comorbid renal impairment.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

In the ravulizumab clinical development program, no overdose of ravulizumab was reported. There are no data to support an association of monoclonal antibodies, including ravulizumab, with the potential for addiction, abuse, withdrawal, or rebound. Because of the REMS requirement for physician registration to obtain ULTOMIRIS, as well as the mechanism of action and method of administration, there is minimal potential for this drug to be used for non-therapeutic purpose.

It is possible that the discontinuation of ULTOMIRIS may make patients more vulnerable to an aHUS exacerbation. ULTOMIRIS

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Ravulizumab was recently approved under the trade name ULTOMIRIS for the treatment of PNH in adult patients in the US. No postmarketing data are available as of the data cutoff date.

Expectations on Safety in the Postmarket Setting

Safety in the postmarketing setting is expected to be similar to that observed in the clinical studies reviewed in this application. The most important risk with ravulizumab as detailed above is increased susceptibility to infections caused by N. meningitidis. 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. Currently, ravulizumab has an approved REMS in place for PNH indication. This submission included a ULTOMIRIS REMS revision for aHUS indication.

8.2.11. Integrated Assessment of Safety

In both studies, the adverse event profile did not identify any new risks for the use of ULTOMIRIS in this population. The most commonly reported TEAES (≥20%) were upper respiratory tract infections, diarrhea, nausea, vomiting, headache, hypertension and pyrexia. Serious adverse reactions were reported in 52 (57%)

patients with aHUS. Four patients died during Study 311 with cause of death sepsis in two patients and intracranial hemorrhage in one patient. The fourth patient who was excluded from the trial after diagnosis of STEC-HUS died due to pretreatment cerebral arterial thrombosis. There was a low incidence of immunogenicity in both 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 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. To mitigate this risk, a Risk Evaluation and Mitigation Strategy (REMS) is in place and the prescribing information includes a box warning for serious meningococcal infections. Overall the benefit-risk profile for ULTOMIRIS in adult and pediatric patients age one month of age with aHUS appears acceptable.

8.3. Statistical Issues

There is no major statistical issue identified in the review.

8.4. Conclusions and Recommendations

The efficacy and safety results of the adult trial 311 and pediatric trial 312 reviewed suggest the totality of the data support a favorable risk/benefit ratio for ULTOMIRIS use in treating patients with complement inhibitor naïve aHUS. Therefore, the clinical and statistical review teams recommend approval of ULTOMIRIS for treatment of patients with aHUS.

The approval recommendation is supported by the results of two open-label, single-arm, multicenter trials (ALXN1210-aHUS 311 and ALXN1210-aHUS-312). Study ALXN1210-aHUS-311 (Study 311) enrolled 56 adult patients with evidence of TMA due to aHUS who were naïve to complement inhibitor treatment prior to enrollment. Study ALXN1210-aHUS-312 (Study 312) enrolled 14 patients less than 18 years of age with complement inhibitor treatment-naïve aHUS. Efficacy was established based on complete TMA response defined as normalization of platelet count and lactate dehydrogenase and ≥ 25% improvement in serum creatinine from baseline during the 26-week Initial Evaluation Period. A complete TMA Response was achieved by 30 of 56 (53.6%; [95% CI: 39.7%, 67.0%]) adult patients in Trial 311 and 10 of 14 (71.4%; [95% CI: 41.9%, 91.6%]) pediatric patients in Trial 312. The median duration of complete TMA response was 7.97 months (range 2.52 to 16.69) months for Study 311 and 5.08 months (range: 3.08 to 5.54 months) in Study 312.

Supportive efficacy was demonstrated by platelet count change from baseline, dialysis requirement, and renal function as evaluated by estimated glomerular filtration rate (eGFR). In Study 311, 17 of the 19 patients (59%) who required dialysis at study entry discontinued dialysis at end of available follow. In Study 312, four of the five patients who required dialysis at study entry were able to discontinue dialysis after first month and for duration of treatment.

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 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. To mitigate this risk, a Risk Evaluation and Mitigation Strategy (REMS) is in place and the prescribing information includes a box warning for serious meningococcal infections. Overall the benefit-risk profile for ULTOMIRIS in adult and pediatric patients age one month of age with aHUS appears acceptable.

In summary, the results from studies 311 and 312 in a rare disease are acceptable for demonstration of effectiveness of this product in patients with aHUS. The ability to conduct formal randomized controlled trials or non-inferiority trials may not be possible for the aHUS population. The two single-arm trials (Study 311 and Study 312) demonstrated a sustainment of response supported by clinically meaningful secondary endpoints (improvement in renal function and decreased dialysis requirements) and are sufficient to support conclusion of effectiveness for ULTOMIRIS in adult and pediatric patients with aHUS. The most important risk associated with complement C5 inhibition is increased susceptibility to *Neisseria meningitides* infections. To mitigate this risk, a Risk Evaluation and Mitigation Strategy (REMS) is in place and the prescribing information includes a box warning for serious meningococcal infections. Overall the benefit-risk profile for ULTOMIRIS in adult and pediatric patients age one month of age with aHUS appears acceptable.

X

Primary Statistical Reviewer
Jiaxi Zhou, PhD

X

Statistical Team Leader
Yeh-Fong Chen, PhD

X

Primary Clinical Reviewer
Qin Ryan, MD

X

Clinical Team Leader
Tanya Wroblewski, MD

9 Advisory Committee Meeting and Other External Consultations

This application did not raise any concerns that required an Advisory Committee meeting.

10 Pediatrics

As detailed in the efficacy and safety sections of this review, the safety and effectiveness of ULTOMIRIS for the treatment of aHUS have been established in pediatric patients aged 1 months and older. Use of ULTOMIRIS in pediatric patients for treatment of complement mediated TMA for this indication is supported by evidence a study in adults and from one pediatric clinical study (14 patients aged 10 months to 17 years). The results from Study 312 support the conclusion of effectiveness of ULTOMIRIS in pediatric patients age 1 month and greater. The youngest patient enrolled was 10 months and supports use of ULTOMIRIS in patients ages 1 month or greater as no differences in efficacy, safety, or PK are expected for patients aged 1 month to 2 years.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information: The major proposed and approved labeling changes are summarized in Table 49: The major proposed and approved labeling changes.

Table 49: The major proposed and approved labeling changes

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
1 Indication and usage	ULTOMIRIS is (b) (4) indicated for (b) (4) • the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). (1) • the treatment of patients with complement-mediated thrombotic microangiopathy (TMA) including atypical hemolytic uremic syndrome (aHUS). (1) Limitation of Use: ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).	ULTOMIRIS is indicated for: • the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). • the treatment of adult and pediatric (one month and older) patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy. Limitations of Use: ULTOMIRIS is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS).
2.2 Recommended weight based dosage regimen	(b) (4)	Deleted

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
	(b) (4)	
2.3 Administration	(b) (4) .	Administer ULTOMIRIS (b) (4) as a (b) (4) intravenous infusion (b) (4)
4 Contraindications	n/a	Patients who are not currently vaccinated against Neisseria meningitidis, unless the risks of delaying ULTOMIRIS treatment outweigh the risks of developing a meningococcal infection [see Warnings and Precautions (5.1)].
5.1 Serious Meningococcal Infections	(b) (4)	Deleted
5.2 Other infections	n/a	Administer vaccinations for the prevention of Streptococcus pneumoniae and Hemophilus influenza type b (Hib) infections according to ACIP guidelines.
5.3 Monitoring Treatment discontinuation for aHUS	Treatment Discontinuation for (b) (4) ULTOMIRIS treatment to (b) (4) should be a minimum duration of 6 months. (b) (4) Patients who are at higher risk for TMA recurrence, as determined by the treating healthcare provider (or clinically indicated), may require chronic therapy. There are no specific data on ULTOMIRIS discontinuation. (b) (4)	There are no specific data on ULTOMIRIS discontinuation. After discontinuing treatment with ULTOMIRIS, monitor (b) (4) for signs and symptoms of (b) (4) . TMA complications post-discontinuation can be identified if any of the following is observed: Clinical (b) (4) symptoms of TMA include changes in mental status, seizures, angina, dyspnoea or thrombosis. In addition, at least two of the following laboratory (b) (4) observed concurrently: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during ULTOMIRIS treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment; (b) (4) an increase in serum LDH of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment;

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
	(b) (4) should be monitored for (b) (4) symptoms of TMA (b) (4). TMA complications post-discontinuation can be identified if any of the following is observed: (i) At least two of the following laboratory (b) (4) observed concurrently: a decrease in platelet count of 25% or more as compared to either baseline or to peak platelet count during ULTOMIRIS treatment; an increase in serum creatinine of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment; (b) (4) an increase in serum LDH of 25% or more as compared to baseline or to nadir during ULTOMIRIS treatment; (results should be confirmed by a second measurement 28 days apart with no interruption). Or (ii) (b) (4) symptoms of TMA: a change in mental status or seizures or (b) (4) or thrombosis. If TMA complications occur after ULTOMIRIS discontinuation, consider reinitiating of ULTOMIRIS treatment.	(results should be confirmed by a second measurement 28 days apart with no interruption). If TMA complications occur after ULTOMIRIS discontinuation, consider re-initiation of ULTOMIRIS treatment (b) (4) or appropriate organ-specific supportive measures.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
5.5 Infusion reaction	Administration of ULTOMIRIS may result in infusion reactions. In clinical trials, 5 out of 296 (b) (4) patients (b) (4) treated with ULTOMIRIS experienced infusion reactions (lower back pain, drop in blood pressure, (b) (4) infusion-related pain, elevation in blood pressure and limbs discomfort) during ULTOMIRIS administration.	(b) (4)
6.1 Safety	(b) (4) The data described below reflect exposure of 58 adult and 16 pediatric patients with (b) (4) in (b) (4) who received ULTOMIRIS at the recommended dos (b) (4) (b) (4) The most frequent adverse (b) (4) reactions reported with ULTOMIRIS were diarrhea, nausea, vomiting, headache, hypertension and pyrexia. Table (b) (4) describes adverse reactions that occurred at a rate of 10% or more among patients treated with ULTOMIRIS in (b) (4) studies. Serious adverse reactions were reported in (b) (4) %) patients with (b) (4) receiving ULTOMIRIS. Four patients died during the ALXN1210-aHUS-311 study. (b) (4) patient, excluded after a diagnosis of STEC-HUS, died due to pretreatment cerebral arterial thrombosis. Two (b) (4) patients died of septic shoc (b) (4) and (b) (4) patient died of intracranial hemorrhage.	The safety results described below reflect exposure of 58 adult and 16 pediatric patients with (b) (4) in single arm trials who received ULTOMIRIS at the recommended dos (b) (4) (b) (4) The most frequent adverse drug reactions reported with ULTOMIRIS were upper respiratory tract infections, (b) (4) (b) (4) diarrhea, nausea, vomiting, headache, hypertension and pyrexia. Table (b) (4) describes adverse reactions that occurred at a rate of (b) (4) 10% or more among patients treated with ULTOMIRIS in (b) (4) studies. Serious adverse reactions were reported in (b) (4) %) patients with (b) (4) receiving ULTOMIRIS.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
6.2 Immunogenicity	In clinical studies (b) (4) treatment-emergent antibodies to ravu zumab-cwvz were detected in 1 of 206 2 (0.5 (b) (4)) patients. No apparent correlation of antibody d velopment to altered pharmacokinetic profile, clinical response, or adverse events was observed.	In clinical studies, treatment-emergent antibodies to ravulizumab-cwvz were detected in 1 of 206 (0.5%) patients with PNH and 1 of 71 (1.4%) patients with aHUS. No apparent correlation of antibody development to altered pharmacokinetic profile, clinical response, or adverse events was observed.
8.4 Pediatric Use	The safety and efficacy of ULTOMIRIS for the treatment of PNH in pediatric patients have not been established. Use of ULTOMIRIS in pediatric patients for treatment of (b) (4) is supported by evidence from (b) (4) The safety and efficacy of ULTOMIRIS for the treatment of (b) (4) appear similar in pediatric and adult patients [see Adverse Reactions (6.1), and Clinical Studies (14.2)]. (b) (4)	The safety and efficacy of ULTOMIRIS for the treatment of PNH in pediatric patients have not been established. The safety and effectiveness of ULTOMIRIS for the treatment of aHUS have been established in pediatric patients aged one month and older. Use of ULTOMIRIS for this indication is supported by evidence (b) (4) in adults and (b) (4) pediatric clinical study (b) (4) The safety and efficacy of ULTOMIRIS for the treatment of aHUS appear similar in pediatric and adult patients *[see Adverse Reactions (6.1), and Clinical Studies (14.2)]*.
14. Efficacy	**14.2** (b) (4) The (b) (4) efficacy of ULTOMIRIS in patients with (b) (4) was assessed in two open-label, single-arm, Phase 3 studies. Study ALXN1210-aHUS-311 enrolled adult patients (b) (4) . Study ALXN1210-	**14.2 Atypical Hemolytic Uremic Anemia (aHUS)** The efficacy of ULTOMIRIS in patients with aHUS was assessed in 2 open-label, single-arm, studies. Study ALXN1210-aHUS-311 enrolled adult patients

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
	aHUS-312 enrolled pediatric patients (b) (4) (b) (4) TMA. **14.2.1 Study in Adult Patients with Complement-Mediated TMA** The adult study [ALXN1210-aHUS-311; NCT02949128] was (b) (4) conducted in patients who were naïve to complement inhibitor treatment prior to study entry. The study consisted of a 26-week Initial Evaluation Period and patients were allowed to enter an extension period for up to (b) years. A total of 5(b) patients with (b) (4) (b) (4) were of patients had extra-renal signs or symptoms of aHUS at baseline. At baseline, 71.4% (n=4(b) (4) of patients had Stage 5 chronic kidney disease. Table (b) (4) presents the demographics and baseline characteristics of the 56 adult patients enrolled in Study ALXN1210-aHUS-311 that constituted the FAS. (b) (4)	who displayed signs of thrombotic microangiopathy (TMA). In order to qualify for enrollment, patients were required to have a platelet count ≤150 x 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine above the upper limits of normal or required dialysis. Study ALXN1210-aHUS-312 enrolled pediatric patients who displayed signs of thrombotic microangiopathy. In order to qualify for enrollment, patients were required to have a platelet count ≤150 x 10^9/L, evidence of hemolysis such as an elevation in serum LDH, and serum creatinine level ≥ 97.5% percentile at screening or required dialysis. In both studies, enrollment criteria excluded patients presenting with (b) (4) due to a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency, Shiga toxin *Escherichia coli*-related hemolytic uremic syndrome (STEC-HUS) and genetic defect in cobalamin C metabolism. Patients with confirmed diagnosis of STEC-HUS after enrollment were excluded from the (b) (4) efficacy evaluation. Study in Adult Patients with aHUS The adult study [ALXN1210-aHUS-311; NCT02949128] was conducted in patients who were naïve to complement inhibitor treatment prior to study entry. The study consisted of a 26-week Initial

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
	(b) (4)	Evaluation Period and patients were allowed to enter an extension period for up to (b) (4) years. A total of 56 patients with (b) (4) aHUS were evaluated for efficacy. Ninety-three percent of patients had extra-renal signs (cardiovascular, pulmonary, central nervous system, gastrointestinal, skin, skeletal muscle) or symptoms of aHUS at baseline. At baseline, 71.4% (n = 40) of patients had Stage 5 chronic kidney disease (CKD). Fourteen percent had history of prior renal kidney transplant and 51.8% were on dialysis at study entry. Table (b) (4) presents the demographics and baseline characteristics of the 56 adult patients enrolled in Study ALXN1210-aHUS-311 that constituted the Full Analysis Set. The efficacy evaluation was based on Complete TMA Response during the 26-week Initial Evaluation Period, as evidenced by normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Patients had to meet each Complete TMA Response criteria at 2 separate assessments obtained at least 4 weeks (28 days) apart, and any measurement in between. Complete TMA Response was observed in 30 of the 56 patients (53.6%) during the 26-week Initial Evaluation Period as shown in Table (b) (4). One additional patient had a Complete TMA Response that was confirmed after the 26-week Initial Evaluation Period. Complete TMA Response was

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
	(b) (4) Renal function, as measured by eGFR, was improved or maintained during ULTOMIRIS therapy. (b) (4) **14.2.2 Study in Pediatric Patients with** (b) (4) The Pediatric Study [ALXN1210-aHUS-312; NCT03131219] is a 26-week ongoing, multicenter, single arm, Phase 3 study conducted in 16 pediatric patients. A total of 14 eculizumab-naïve patients with documented diagnosis of (b) (4) were enrolled and included in this interim	achieved at a median time of 86 days (range: 7 to 169 days). Other endpoints included platelet count change from baseline, (b) (4) dialysis requirement, and renal function as evaluated by estimated glomerular filtration rate (eGFR), An increase in mean platelet count was observed after commencement of ULTOMIRIS, increasing from 118.52 × 10^9/L at baseline to 240.34 ×10^9/L at Day 8 and remaining above 227 × 10^9/L at all subsequent visits in the Initial Evaluation Period (26 weeks). Renal function, as measured by eGFR, was improved or maintained during ULTOMIRIS therapy. The mean eGFR (+/- SD) increased from XX at baseline to XX by 26 weeks. Seventeen of the 29 patients who required dialysis at study entry (b) (4) discontinue dialysis by the end of the available follow-up and 6 of 27 patients were off dialysis at baseline were on dialysis at last available follow-up. (b) (4)

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
	analysis (b) (4) he (b) (4) age at the time of first infusion was (b) (4) years. The overall mean weight at Baseline was 19.8 kg; half of the patients were in the baseline weight category ≥ 10 to < 20 kg. The majority of patients had pretreatment extra renal signs or symptoms of aHUS at baseline. At baseline, 35.7% (n=5) of patients had a chronic kidney disease Stage 5. Table (b) (4) presents the baseline characteristics of the pediatric patients enrolled in ALXN1210-aHUS-312 Study. (b) (4)	(b) (4) (b) (4) Complete TMA Response during the Initial Evaluation Period was achieved at a median time of 30 days (range:15 to 88 days). .

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
	Complete TMA Response was observed in 10 of the 14 patients (71.4%) during the 26 week Initial Evaluation Period as shown in Table (b) (4). (b) (4)	Other endpoints included platelet count change from baseline, dialysis requirement, and renal function as evaluated by eGFR, An increase in mean platelet count was observed after commencement of ULTOMIRIS, increasing from 60.50×10^9/L at baseline to 296.67×10^9/L at Day 8 and remained above 296×10^9/L at all subsequent visits in the Initial Evaluation Period (26 weeks). Four of the 5 patients who required dialysis at study entry were able to discontinue dialysis after the first month in study and for the duration of ULTOMIRIS treatment. No patient started dialysis during the study.

12 Risk Evaluation and Mitigation Strategies (REMS)

The REMS for ULTOMIRIS was established at the time of ULTOMIRIS 2018 approval. The REMS mandates prescribers to be educated and enrolled for ULTOMIRIS use. The program ensures proper immunization with meningococcal vaccine and reducing patient's risk of meningococcal infection. This reviewer recommends REMS revision for aHUS indication. Please see DRISK review for further details.

13 Postmarketing Requirements and Commitment

The median follow-up for efficacy and safety of ULTOMIRIS in adult and pediatric patients with aHUS is limited, 37 weeks in trial ALXN1210-HUS-311 and 26 weeks in trial ALXN1210-HUS-312. Therefore, long-term follow up of safety and efficacy in the trial ALXN1210-HUS-311 and ALXN1210-HUS-312 is recommended.

Proposed PMRs
PMR 1: Submit the final clinical study report and datasets for the single arm trial of ULTOMIRIS in pediatric patients with aHUS (ALXN1210-HUS-312) to include the extension period of up to 4.5 years of follow-up on safety and efficacy.

PMR 2: Provide safety, efficacy, PK, and PD data in pediatric patients with aHUS and a weight of greater than or equal to 5 kg to less than 10 kg treated with the recommended dosing regimen of ravulizumab (600 mg loading dose followed two weeks later by 300 mg maintenance doses every 4 weeks).

PMR 3: Provide safety, efficacy, PK, and PD data in patients with aHUS who switch from treatment with eculizumab to treatment with ravulizumab.

PMR 4: Submit the final clinical study report and datasets for the single arm trial of ULTOMIRIS in adult patients with aHUS (ALXN1210-HUS-311) to include the extension period of up to 4.5 years of follow-up on safety and efficacy.

14 Division Director (OB)

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Thomas Gwise, PhD
Deputy Division Director

15 Division Director (Clinical)

Study ALXN1210-aHUS-311 and Study ALXN1210-aHUS-312 showed complete TMA responses in 30 of 56 (54%) and 10 of 14 (71%) enrolled patients respectively during the 26-week evaluation period. No new safety signals were identified.

Thus, I agree with the review divisions' recommendation for approval of Ultomiris for the treatment of adult and pediatric patients one month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

Albert Deisseroth MD, PhD

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16 Appendices

16.1. References

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16.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Trials 311 and 312

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1082		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5.		
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: No Significant payments of other sorts: No Proprietary interest in the product tested held by investigator: No		

Significant equity interest held by investigator in S Sponsor of covered study: No		
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) 1077		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

16.3. Nonclinical Pharmacology/Toxicology

16.4. OCP Appendices (Technical documents supporting OCP recommendations)

16.5. Additional Clinical Outcome Assessment Analyses

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/s/

THERESA A CARIOTI
10/18/2019 10:01:41 AM

QIN C RYAN
10/18/2019 10:21:57 AM

LAUREN S PRICE
10/18/2019 10:24:52 AM

OLANREWAJU OKUSANYA
10/18/2019 10:34:48 AM

JIAXI ZHOU
10/18/2019 10:35:55 AM

YEH FONG CHEN
10/18/2019 11:09:35 AM

THOMAS E GWISE
10/18/2019 11:17:44 AM

TANYA M WROBLEWSKI
10/18/2019 11:27:32 AM

ALBERT B DEISSEROTH
10/18/2019 11:39:23 AM