CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761108Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 10, 2018
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761108
Product Name and Strength:	Ultomiris (ravulizumab-cwvz) Injection 300 mg/30 mL (10 mg/mL)
Applicant/Sponsor Name:	Alexion Pharmaceuticals, Inc.
FDA Received Date:	November 15, 2018
OSE RCM #:	2018-1309-1
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Hematology Products (DHP) requested that we review the revised container label and carton labeling for Ultomiris (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container label and carton labeling for Ultomiris are acceptable from a medication error perspective. We have no further recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[a] Garrison N. Label and Labeling Review for ULTOMIRIS (BLA 761108). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 08. RCM No.: 2018-1309-1.

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/s/

NICOLE B GARRISON
12/10/2018

HINA S MEHTA
12/11/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 02, 2018

To: Natasha Kormanik, MSN, RN, OCN, Regulatory Project Manager, Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Robert Nguyen, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ULTOMIRIS™ (ravulizumab-cwvz) injection, for intravenous use

BLA: 761108

In response to DHP's consult request dated July 6, 2018, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for the original BLA submission for Ultomiris.

PI: OPDP's comments on the proposed labeling are based on the draft PI accessed on Sharepoint on October 30, 2018 and are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on November 1, 2018.

Thank you for your consult. If you have any questions, please contact Robert Nguyen at (301) 796-0171 or Robert.Nguyen@fda.hhs.gov.

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/s/

ROBERT L NGUYEN
11/02/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 1, 2018
To:	Anne Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Robert Nguyen, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ULTOMIRIS (ravulizumab)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761108
Applicant:	Alexion Pharmaceuticals, Inc.

1 INTRODUCTION

On June 18, 2018, Alexion Pharmaceuticals, Inc. submitted for the Agency's review an original Biologics License Application (BLA) 761108 for ULTOMIRIS (ravulizumab) injection. The Applicant proposes the following indication: For the treatment of adult patients with paroxysmal nocturnal hemoglobinuria.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on July 6, 2018 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for ULTOMIRIS (ravulizumab) injection.

2 MATERIAL REVIEWED

- Draft ULTOMIRIS (ravulizumab) injection MG received on June 18, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 19, 2018.
- Draft ULTOMIRIS (ravulizumab) injection Prescribing Information (PI) received on June 18, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on October 19, 2018, and on October 26, 2018, accessed from SharePoint on October 29, 2018.
- Approved SOLIRIS (eculizumab) injection comparator labeling July 25, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
11/01/2018

ROBERT L NGUYEN
11/01/2018

LASHAWN M GRIFFITHS
11/01/2018

CLINICAL INSPECTION SUMMARY

Date	October 16, 2018
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Rosanna Setse, M.D., Ph.D., Medical Officer Tanya Wroblewski, M.D., Clinical Team Leader Ann Farrell, M.D., Director Natasha Kormanik, R.N., M.S.N., Regulatory Project Manager Division of Hematology Products
BLA	761108
Applicant	Alexion Pharmaceuticals, Inc
Drug	ravulizumab
NME	Yes
Therapeutic Classification/Status	recombinant humanized protein
Proposed Indication	Treatment of paroxysmal nocturnal hemoglobinuria
Consultation Request Date	June 29, 2018 (Priority Review)
Summary Goal Date	October 22, 2018
Action Goal Date	November 30, 2018
PDUFA Date	December 18, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Kulasekararaj and de Latour) were selected for inspection in support of BLA 761108. The sponsor (Alexion Pharmaceuticals, Inc.) was also inspected. The study data from these clinical sites, as reported by the sponsor to the BLA, are considered to be reliable in support of the requested indication.

The preliminary regulatory classification of Dr. Kulasekararaj and Dr. de Latour is No Action Indicated. The final regulatory classification of Alexion Pharmaceuticals, Inc. is No Action Indicated.

2. BACKGROUND

Ravulizumab (ALXN1210) is a recombinant humanized protein, produced in Chinese hamster cells and designed through targeted engineering to substitute four amino acids in the eculizumab heavy chain. Ravulizumab was engineered from eculizumab to preserve immediate and complete C5 inhibition while providing sustained complement inhibition throughout a prolonged dosing interval (≥1 month).

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic disorder that occurs most frequently in adults. The disease begins with the clonal expansion of a hematopoietic stem cell that has acquired a somatic mutation in the PIG-A gene. Consequently, PNH blood cells lack the glycophosphatidylinositol anchor protein and are deficient in the membrane-bound complement inhibitory proteins CD55 and CD59. In the absence of CD55, there is increased deposition of complement protein C3 cleavage products on blood cell membrane surfaces, in turn leading to cleavage of component 5 (C5) into C5a and C5b. The pathology and clinical presentations in patients with PNH are driven by uncontrolled terminal complement activation on red blood cells (RBCs). The primary clinical manifestations of paroxysmal nocturnal hemoglobinuria are hemolytic anemia, marrow failure, and thrombophilia. Involvement of unusual sites (hepatic, mesenteric, cerebral, dermal veins) is characteristic of the thrombophilia of PNH.

The only approved treatment for PNH is eculizumab (Soliris®). Eculizumab is a humanized monoclonal antibody that specifically binds to the complement protein C5 with high affinity.

Study ALXN1210-PNH-301

Study ALXN1210-PNH-301 is an ongoing Phase 3, open-label, randomized, active-controlled, multicenter study to evaluate the safety and efficacy of ravulizumab (ALXN1210) versus eculizumab administered by intravenous (IV) infusion to adult patients with PNH who are naïve to complement inhibitor treatment. The primary objective of this study is to assess the noninferiority of ravulizumab compared to eculizumab in adult patients with PNH who have never been treated with a complement inhibitor. The co-primary study endpoints for this study are: (a) transfusion avoidance, defined as the proportion of patients who remain transfusion-free and do not require a transfusion per protocol-specified guidelines through Day 183 (Week 26), and (b) hemolysis, as directly measured by the normalization of LDH from Day 29 (first scheduled evaluation status post-initiation of the maintenance dose through Day 183 [Week 26]).

This multicenter, multinational study was conducted at 123 sites in 25 countries. The primary efficacy population consisted of 246 patients (125 in the ravulizumab treatment group and 121 in the eculizumab group). The first subject enrolled on December 20, 2016. The last patient completed the primary evaluation period on January 25, 2018.

Study ALXN1210-PNH-302

Study ALXN1210-PNH-302 is an ongoing Phase 3, open-label, randomized, active-controlled, multicenter study to evaluate the safety and efficacy of ravulizumab (ALXN1210) versus

eculizumab administered by intravenous (IV) infusion to adult patients with PNH who were clinically stable after treatment with eculizumab for at least the previous 6 months. The primary objective of this study was to assess the noninferiority of ravulizumab compared to eculizumab in adult patients with paroxysmal nocturnal hemoglobinuria (PNH) who were clinically stable after having been treated with eculizumab for at least the past 6 months.

This multicenter, multinational study was conducted at 52 sites in 12 countries that screened patients. The primary efficacy population consisted of 195 treated patients; 97 in the ravulizumab group and 98 in the eculizumab group. The first subject enrolled on June 5, 2017. The last patient completed the primary evaluation period on March 8, 2018.

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	**Protocol #/ Site #/# Subjects enrolled**	**Inspection Dates**	**Classification**
Austin Kulasekararaj, M.D. Denmark Hill King's College Hospital NHS Foundation Trust London, NA SE5 9RS Great Britain	Study ALXN1210-PNH-302 Site #223 26 subjects	September 17-21, 2018	Preliminary: NAI*
Régis Peffault de Latour, M.D. Hôpital Saint-Louis Service hématologie Greffes de Mölle 1 Avenue Claude Vellefaux Paris, Cedex 10, 75475 France	Study ALXN1210-PNH-302 Site #263 20 subjects	September 24-28, 2018	Preliminary: NAI*
Alexion Pharmaceuticals, Inc 100 College Street New Haven, CT 06510	Sponsor of: Study ALXN1210-PNH-301 Study ALXN1210-PNH-302	August 2-10, 2018	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
* Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Investigator

1. Austin Kulasekararaj, M.D.

A total of 26 subjects were screened and 26 subjects were enrolled and randomized. All subjects received and completed study treatment. The study is ongoing.

For this inspection, a complete review of all regulatory documentation at the study site was performed, as well as the source records for all 26 subjects enrolled at the site prior to the database lock. A 100% review of informed consent forms was completed. The source records reviewed included medical records, regulatory binder documents, source data worksheets, informed consent forms, monitoring follow-up reports, and pharmacy records.

Source documents for all 26 enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings, in part, for primary efficacy endpoints, adverse events and serious adverse event reporting. A complete compliance review was conducted for 10 study subject records. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. There was no under-reporting of adverse events noted during this site audit. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. A Form FDA 483 (Inspectional Observations) was not issued at the end of the inspection.

2. Régis Peffault de Latour, M.D.

A total of 21 subjects were screened, and 20 subjects were enrolled, and randomized. Twenty subjects completed the treatment phase of this study. The study is ongoing.

The inspection evaluated the following documents: source records, screening and enrollment logs, physician clinical notes, eligibility criteria, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for 20 enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings, in part, for patient inform consent documentation, primary study endpoint assessment, adverse event and serious adverse event reporting. A comprehensive audit of the inclusion and exclusion criteria for patient enrollment was evaluated at this site inspection. Source documents for the raw data used to assess the primary safety study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 was issued.

Sponsor

3. Alexion Pharmaceuticals, Inc.

Records reviewed included but were not limited to: organizational charts; vendor list; vendor oversight plans; transfer of obligations; investigator agreements; financial disclosures; monitoring plans; monitoring reports; monitor qualifications, safety reports; adverse events; protocol deviations; and standard operating procedures. Monitoring reports for Study ALXN1210-PNH-301 and Study ALXN1210-PNH-302, respectively, were reviewed. At the end of the inspection, a Form FDA 483 was not issued. Data from this sponsor appear to be reliable.

{See appended electronic signature page}

Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
10/16/2018

KASSA AYALEW
10/16/2018

MEMORANDUM
NONPROPRIETARY NAME SUFFIX

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 2, 2018
Responsible OND Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761108
Product Name and Strength:	Ultomiris (ravulizumab-cwvz) Injection, 300 mg/30 mL (10 mg/mL)
Product Type:	Single Ingredient Product
Applicant/Sponsor Name:	Alexion Pharmaceuticals, Inc. (Alexion)
OSE RCM #:	2018-1819
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, BS Pharm
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the four-letter suffix for inclusion in the nonproprietary name and communicates our recommendation for the nonproprietary name for BLA 761108.

1.1 Regulatory History

Alexion was notified of the Agency's intention to designate a nonproprietary name that includes a four-letter distinguishing suffix that is devoid of meaning for their product in an Advice Letter[a].

2 ASSESSMENT OF THE NONPROPRIETARY NAME

ravulizumab-cwvz

FDA generated a four-letter suffix, -cwvz. This suffix was evaluated using the principles described in the applicable guidance[b].

We determined that the FDA-generated suffix -cwvz, is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, that the suffix is devoid of meaning, does not include any abbreviations that could be misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of this product.

3 COMMUNICATION OF DMEPA'S ANALYSIS

These findings were shared with OPDP. In email correspondence dated October 2, 2018, OPDP did not identify any concerns that would render this suffix unacceptable. DMEPA also communicated our findings to the Division of Hematology Products (DHP) via e-mail on October 2, 2018.

4 CONCLUSION

We find the suffix -cwvz acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to ravulizumab-cwvz.

4.1 Recommendation for Alexion Pharmaceuticals, Inc.

We find the nonproprietary name, ravulizumab-cwvz, conditionally acceptable for your proposed product. Should your 351(a) BLA be approved during this review cycle,

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[a] Harris, D. General Advice Letter for BLA 761108. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US) 30 Aug 2018.

[b] See Section VI which describes that any suffixes should be devoid of meaning in Guidance for Industry: Nonproprietary Naming of Biological Products. 2017. Available from:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf

ravulizumab-cwvz will be the proper name designated in the license and you should revise your proposed labels and labeling accordingly. However, please be advised that if your application receives a complete response, the acceptability of this suffix will be re-evaluated when you respond to the deficiencies. If we find the suffix unacceptable upon our re-evaluation, we would inform you of our finding.

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/s/

CARLOS M MENA-GRILLASCA
10/02/2018

DANIELLE M HARRIS
10/04/2018

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: August 23, 2018

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Natasha Kormanik, RPM
DHP

Subject: QT-IRT Consult to BLA 761108

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 07/03/2018 regarding the sponsor's submitted concentration-QTc analysis from Phase 1/2 studies and data from two Phase 3 studies for ravulizumab, and any potential labeling recommendations. The QT-IRT reviewed the following materials:

- Sponsor's E-R analysis report;
- CSR for Phase 3 studies ALXN1210-PNH-301 and ALXN1210-PNH-302; and
- Sponsor's proposed label.

1. QT-IRT Responses

Ravulizumab, being a large targeted protein (mAb), has a low likelihood of direct ion channel interactions (ICH E14 Q&A (R3), Section 6.3) and data from clinical studies do not suggest the potential for proarrhythmic risk. Thus, similar to the labeling for other approved monocloncal antibodies, a QT related labeling language is not necessary for this mAb product. In this regard, the sponsor has also not proposed any language related to QT in their labeling proposal and that seems reasonable.

2. BACKGROUND

Product Information

Ravulizumab (ALXN1210) is a terminal complement inhibitor that specifically binds to the complement protein C5 with high affinity, 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 C5b9. By binding specifically to C5, ravulizumab antagonizes terminal complement-mediated inflammation, cell activation, and cell lysis while preserving the early components of complement activation that are essential for opsonisation of microorganisms and clearance of immune complexes.

It is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH). The recommended dosing regimen for adult patients (≥ 18 years of age) with PNH consists of a loading dose followed by maintenance dosing, administered by intravenous infusion. The doses to be administered are based on the patient's body weight, as shown in table below. Maintenance doses should be administered at a once every 8-week interval, starting 2 weeks after loading dose administration.

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

Summary of QTc data from sponsor's submission

The sponsor's submission contains the concentration-QTc analysis with ECG/PK data collected in Phase 1/2 studies, and the sponsor has also provided the QTc outlier analysis in the CSR for the two Phase 3 studies (ALXN1210-PNH-301 and ALXN1210-PNH-302).

Concentration-QTc analysis for Phase 1/2 studies

A total of 878 time-matched triplicate ECG means and ravulizumab concentrations from 78 subjects were pooled from 5 clinical studies and used for modeling. Ravulizumab doses administered via IV infusion ranged from 0 to 1800 mg q4w.

The concentration-QTc analyses showed that the 95% CI for the slope parameter (95% CI: -0.0045, 0.0087) included zero, supporting absence of a significant relationship between concentration and QTc (see sponsor's Table 6 below).

Of the 78 subjects in the pooled analysis, 2 patients with PNH had abnormal ECG readings (ALXN1210-PNH-103 CSR Section 12.5.2): Patient (b) (6) in Cohort 1 (900 mg q4w) had a QT interval increase of > 60 ms at 2 timepoints during the study (Days 113 and 141 after dosing); Patient (b) (6) in Cohort 2 (1800 mg q4w) had QT and/or corrected QT interval using Fridericia's formula (QTcF) values > 500 ms at 5 timepoints during the study (Days 15, 29, 113, and 141 after dosing, and Day 169 predose).

Table 6: Final Concentration-QT/QTc Model Parameter Estimates: Slope Model

Parameter, Units	Estimate	RSE (%)	95% CI	BSV (ms)	RSE (%)	Shrinkage (%)
intercept, ms	426	1.0	418, 434	17	21	4
Covariate for sex	-12.4	41	-22, -2	NA	NA	NA
Slope, ms/(µg/mL)	0.00212	159	-0.0045, 0.0087	0.013	63	24
Beta, correction factor	0.34	3	0.319, 0.361	13[a]	42	44
Correlations						
intercept~Slope	0.57	NA	NA	NA	NA	NA
intercept~Beta	0.22	NA	NA	NA	NA	NA
Slope~Beta	-0.55	NA	NA	NA	NA	NA
Residual Error (additive), ms	7.8	9	6.4, 9.1	NA	NA	6

Reviewer's comment: The sponsor seems to have used the absolute QTc values rather than our preferred response variable of ΔQTc. Nevertheless, the molecule, due to its large molecular weight (148 kDa), is unlikely to have any direct ion channel interaction and a direct effect model is not relevant here.

Phase 3 studies ALXN1210-PNH-301 and ALXN1210-PNH-302

ECGs were obtained at baseline, Day 57, and Day 183. Changes from baseline in mean HR, PR, QRS, and QTcF values were small in both treatment groups. QT and QTc abnormalities were infrequent in both treatment groups (sponsor's Table 37 for Study ALXN1210-PNH-301 and sponsor's Table 35 for Study ALXN1210-PNH-302 below). No AEs of QT prolongation, syncope, or torsades de pointes were reported in either treatment group in both the studies.

Sponsor's Table 37 (Study ALXN1210-PNH-301): Number and Percentage of Patients by Electrocardiogram QT and QTcF Categories and Change from Baseline Categories Over Time (Safety Set)

Visit ECG Categories	QT n (%)		QTcF n (%)	
	ALXN1210 (N = 125)	Eculizumab (N = 121)	ALXN1210 (N = 125)	Eculizumab (N = 121)
Baseline				
≤ 450 ms	123 (98.4)	115 (95.0)	119 (95.2)	110 (90.9)
> 450 - ≤ 480 ms	0	3 (2.5)	4 (3.2)	6 (5.0)
> 480 - ≤ 500 ms	0	0	1 (0.8)	4 (3.3)
> 500 ms	1(0.8)	2 (1.7)	0	0
Day 57				
≤ 450 ms	117 (93.6)	112 (92.6)	120 (96.0)	109 (90.1)
> 450 - ≤ 480 ms	6 (4.8)	2 (1.7)	2 (1.6)	7 (5.8)
> 480 - ≤ 500 ms	0	1 (0.8)	1 (0.8)	0
> 500 ms	0	2 (1.7)	0	1 (0.8)
Day 183				
≤ 450 ms	112 (89.6)	102 (84.3)	112 (89.6)	99 (81.8)
> 450 - ≤ 480 ms	6 (4.8)	4 (3.3)	5 (4.0)	7 (5.8)
> 480 - ≤ 500 ms	0	1 (0.8)	1 (0.8)	1 (0.8)
> 500 ms	0	1 (0.8)	0	1 (0.8)
ECG Change From Baseline Categories				
Day 57				
≤ 0 ms	57 (45.6)	57 (47.1)	73 (58.4)	65 (53.7)
> 0 - ≤ 30 ms	50 (40.0)	45 (37.2)	42 (33.6)	47 (38.8)
> 30 - ≤ 60 ms	13 (10.4)	11 (9.1)	6 (4.8)	4 (3.3)
> 60 ms	2 (1.6)	3 (2.5)	1 (0.8)	0
Day 183				
≤ 0 ms	48 (38.4)	47 (38.8)	65 (52.0)	61 (50.4)
> 0 - ≤ 30 ms	51 (40.8)	44 (36.4)	46 (36.8)	42 (34.7)
> 30 - ≤ 60 ms	16 (12.8)	14 (11.6)	5 (4.0)	4 (3.3)
> 60 ms	2 (1.6)	2 (1.7)	1 (0.8)	0

Sponsor's Table 35 (Study ALXN1210-PNH-302): Number and Percentage of Patients by Electrocardiogram QT and QTcF Categories and Change from Baseline Categories Over Time (Safety Set)

Visit ECG Categories	QT n (%)		QTcF n (%)	
	ALXN1210 (N = 96)	Eculizumab (N = 98)	ALXN1210 (N = 95)	Eculizumab (N = 98)
Baseline				
≤ 450 ms	93 (96.9)	93 (94.9)	92 (96.8)	94 (95.9)
> 450 - ≤ 480 ms	3 (3.1)	4 (4.1)	3 (3.2)	4 (4.1)
> 480 - ≤ 500 ms	0	1 (1.0)	0	0
> 500 ms	0	0	0	0
Day 57				
≤ 450 ms	93 (96.9)	88 (89.8)	93 (97.9)	90 (91.8)
> 450 - ≤ 480 ms	2 (2.1)	5 (5.1)	2 (2.1)	4 (4.1)
> 480 - ≤ 500 ms	0	1 (1.0)	0	0
> 500 ms	0	0	0	0
Day 183				
≤ 450 ms	78 (81.3)	88 (89.8)	78 (82.1)	88 (89.8)
> 450 - ≤ 480 ms	3 (3.1)	1 (1.0)	3 (3.2)	1 (1.0)
> 480 - ≤ 500 ms	0	0	1 (1.1)	0
> 500 ms	1 (1.0)	0	0	0
ECG Change From Baseline Categories				
Day 57				
≤ 0 ms	60 (62.5)	52 (53.1)	54 (56.8)	42 (42.9)
> 0 - ≤ 30 ms	30 (31.3)	33 (33.7)	35 (36.8)	45 (45.9)
> 30 - ≤ 60 ms	4 (4.2)	4 (4.1)	4 (4.2)	4 (4.1)
> 60 ms	0	5 (5.1)	0	3 (3.1)
Day 183				
≤ 0 ms	51 (53.1)	53 (54.1)	51 (53.7)	50 (51.0)
> 0 - ≤ 30 ms	25 (26.0)	31 (31.6)	25 (26.3)	36 (36.7)
> 30 - ≤ 60 ms	5 (5.2)	3 (3.1)	4 (4.2)	1 (1.0)
> 60 ms	1 (1.0)	2 (2.0)	1 (1.1)	2 (2.0)

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

DHANANJAY D MARATHE
08/23/2018

CHRISTINE E GARNETT
08/23/2018