A Randomized, Three-Treatment, Three-Period, Six-Sequence, Crossover, Placebo- and Active-Controlled, Double-Blind for ALXN1840 (Open-Label for Moxifloxacin) Thorough QT/QTc (TQT) Study to Evaluate the Effect of ALXN1840 on Cardiac Repolarization in Healthy Adult Participants

Unique Protocol ID:	ALXN1840-HV-107
NCT Number:	NCT04560816
Date of Protocol:	01 September 2020

CLINICAL STUDY PROTOCOL
IND 119,006

A RANDOMIZED, THREE-TREATMENT, THREE-PERIOD, SIX-SEQUENCE, CROSSOVER, PLACEBO- AND ACTIVE-CONTROLLED, DOUBLE-BLIND FOR ALXN1840 (OPEN-LABEL FOR MOXIFLOXACIN) THOROUGH QT/QTC (TQT) STUDY TO EVALUATE THE EFFECT OF ALXN1840 ON CARDIAC REPOLARIZATION IN HEALTHY ADULT PARTICIPANTS
PROTOCOL NO. ALXN1840-HV-107

Sponsor:	Alexion Pharmaceuticals, Inc. 121 Seaport Boulevard Boston, MA 02210
Medical Monitor and Sponsor Contact:	PPD PPD Telephone: PPD
Version of Protocol:	Amendment 1
Date of Protocol:	01 Sep 2020

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation Guideline E6(R2): Good Clinical Practice.

SIGNATURE PAGE

PROTOCOL TITLE: A Randomized, Three-Treatment, Three-Period, Six-Sequence, Crossover, Placebo- and Active-Controlled, Double-Blind for ALXN1840 (Open-Label for Moxifloxacin) Thorough QT/QTc (TQT) Study to Evaluate the Effect of ALXN1840 on Cardiac Repolarization in Healthy Adult Participants

PROTOCOL NUMBER: ALXN1840-HV-107 Amendment 1

PPD

09/02/2020
Date

Alexion Pharmaceuticals, Inc.

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree to conduct the study as outlined in protocol amendment 1 titled "A Randomized, Three-Treatment, Three-Period, Six-Sequence, Crossover, Placebo- and Active-Controlled, Double-Blind for ALXN1840 (Open-Label for Moxifloxacin) Thorough QT/QTc (TQT) Study to Evaluate the Effect of ALXN1840 on Cardiac Repolarization in Healthy Adult Participants" in accordance with the guidelines and all applicable government regulations, including US Title 21 of the Code of Federal Regulations Part 54. I have read and understand all sections of protocol amendment 1.

PPD

Principal Investigator
PPD

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	12 Jun 2020
Amendment 1	01 Sep 2020

Amendment 1 (01 Sep 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

This amendment has been prepared to correct and align information regarding pregnancy and contraception with the latest Alexion-approved language, and to clarify ECG procedures. Additional, minor edits for clarification and consistency were also made.

Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
Protocol Synopsis Section 3.1, Schedule of Events Section 6.1.1, Continuous Holter Electrocardiograms	Addition of text regarding ECG extraction on Day -1 of Treatment Period 1	To clarify the ECG procedures
Protocol Synopsis Section 3, Study Design Section 6.1.1, Continuous Holter Electrocardiograms	Deletion of text referring to activity prior to extraction on Day -1 of Treatment Period 1	To clarify the ECG procedures
Section 3.1, Schedule of Events	12-lead Holter measurement at time 0 on Day 1 removed	12-lead Holter extraction for Day -1 will be performed at time point -0.25 instead of timepoint 0
Protocol Synopsis Section 4.1, Inclusion Criteria	Inclusion criterion 5 changed from 6 months to 6 weeks	To align with Alexion standards
	Inclusion criterion 6 updated to include female partners of male participants and breastfeeding females, add details regarding ova donation, and change reference from 1 menstrual cycle to 6 weeks	To correct and align with Alexion-approved language.
	Order of text in inclusion criterion 7 updated for clarity	
	Exclusion criterion 12 updated to include language regarding a positive serum pregnancy test	
Section 6.2.1, Pharmacokinetic and Pharmacodynamic Sample Collection	Window for collection of samples for PK evaluation added	To include the time window for PK sample collection
Section 6.3.1.5, Collection of Pregnancy Information	Addition of text on reporting of pregnancy	To clarify reporting requirements for pregnancy

Section 6.3.1.5.2, Female Participants who Become Pregnant		
Section 9.3.1, Definition of Adverse Event	Definition of adverse events revised	To align with latest Alexion-approved language
Section 9.3.2, Definition of Serious Adverse Event	Definition of suspected unexpected serious adverse reaction (SUSAR) added.	To align with latest Alexion-approved language
All	Minor editorial updates and corrections	For clarification, and to ensure accuracy and consistency throughout the protocol.

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PROTOCOL SYNOPSIS

PROTOCOL NO.: ALXN1840-HV-107 Amendment 1

TITLE: A Randomized, Three-Treatment, Three-Period, Six-Sequence, Crossover, Placebo- and Active-Controlled, Double-Blind for ALXN1840 (Open-Label for Moxifloxacin) Thorough QT/QTc (TQT) Study to Evaluate the Effect of ALXN1840 on Cardiac Repolarization in Healthy Adult Participants

STUDY PHASE: 1

STUDY SITE: One clinical site in the United States

OBJECTIVES:

Primary: The primary objective of this study is to evaluate the effect of a supratherapeutic dose of ALXN1840 on the heart rate (HR)-corrected QT interval (QTc) with the intent to exclude a 10 ms effect.

Secondary: The secondary objectives of the study are:

- To demonstrate assay sensitivity of the study to detect an effect on the mean QT/QTc interval of approximately 5 ms using moxifloxacin as a positive control.
- To evaluate the safety and tolerability of a single oral supratherapeutic dose of ALXN1840 in healthy participants.
- To assess the pharmacokinetics (PK) of ALXN1840 following administration of a single oral supratherapeutic dose in healthy participants.
- To evaluate the effects of a single oral supratherapeutic dose of ALXN1840 on HR, PR and QRS intervals, treatment-emergent T-wave morphology abnormalities, and appearance of U-waves.

STUDY DESIGN: This is a randomized, 3-treatment, 3-period, 6-sequence, crossover, placebo- and active-controlled, double-blind for ALXN1840, open-label for moxifloxacin, in healthy adult participants. Moxifloxacin will be used as the active control.

Approximately 54 participants will be randomized to ensure there will be 45 evaluable participants with data from all treatment periods. To ensure sequences are balanced within sex, participant randomization will be stratified by sex. Study interventions will be given in randomized sequences: ABC, ACB, BAC, BCA, CAB, and CBA, with each treatment administered with 240 mL of water following an overnight fast of at least 10 hours. No food will be allowed for at least 4 hours postdose. Water can be allowed as desired except for 1 hour before and after drug administration. Treatment A is a single oral dose of ALXN1840 120 mg administered as 15-mg enteric-coated tablets (supratherapeutic dose); Treatment B is a single oral dose of enteric-coated placebo tablets matching ALXN1840; and Treatment C is a single oral dose of moxifloxacin 400 mg tablet.

Cardiodynamic assessment will be performed for approximately 25 hours on Day –1 of Treatment Period 1 and Day 1 to Day 2 of each treatment period. Blood samples for PK will be collected predose and at specified times up to 96 hours after the Day 1 dose in each treatment period.

Twelve-lead electrocardiograms (ECGs) will be extracted from a continuous (Holter) recording by the central laboratory. To support high quality data for extraction, participants will be resting in the supine position for at least 15 minutes prior to and 5 minutes after each nominal time point for ECG extraction. Blood for plasma PK will be collected as close as possible to nominal time but after completion of ECG extraction period with actual times for blood sample collections recorded.

Participants will be domiciled in the clinic for 7 days in Treatment Period 1 and for 6 days in Treatment Periods 2 and 3, starting on Day –2 for Treatment Period 1 and on the day before dosing (Day –1) for Treatment Periods 2 and 3, until safety procedures have been completed and reviewed on Day 5. There will be a washout of at least 14 days between dose administration in each period.

All participants (including participants who terminate the study early) will return to the study site 14 days (±2 days) after the last administration of study intervention for follow-up procedures and to determine if any adverse event (AE) has occurred since the last study visit.

Duration of participant participation from the Screening Visit to the End-of-Study (EOS) Visit will be approximately 70 days. This includes up to 29 days for the Screening Period, study intervention administration on Day 1 of each treatment period, a minimum of a 14-day washout between study intervention administration in each treatment period, and 14 days (±2 days) for the EOS Visit.

STUDY POPULATION:

Inclusion Criteria: Each participant must meet all of the following criteria to be enrolled in this study:

1. Participant is a healthy adult male or female, 18 to 50 years of age, inclusive, at Screening.
2. Participant is a continuous nonsmoker and or an individual who has not used tobacco or nicotine-containing products (eg, electronic vapor cigarettes, cigarettes, cigars, chewing tobacco, snuff, nicotine gum, nicotine patches) for at least 3 months prior to the first dose of study intervention and for the duration of the study. A cotinine test performed during Screening and Check-in must be consistent with continuous nonsmoking status.
3. Participant must weigh at least 60 kg for males or 52 kg for females and have a body mass index ≥18.0 and ≤30.0 kg/m^2 at Screening.
4. Participant must have a medical assessment with no clinically significant or relevant abnormalities as determined by medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory evaluation (hematology, serum chemistry, coagulation, and urinalysis) that are reasonably likely to interfere with the participant's participation in or ability to complete the study, or to potentially confound interpretation of study results, as assessed by the Investigator.
5. Female participants of nonchildbearing potential must have undergone 1 of the following sterilization procedures and have official documentation of these occurring more than 6 weeks prior to the first dose of study intervention:
   a. Hysteroscopic sterilization;
   b. Bilateral tubal occlusion, including Essure®;

c. Bilateral tubal ligation or bilateral salpingectomy;

d. Hysterectomy;

e. Bilateral oophorectomy;

or be postmenopausal with amenorrhea for at least 1 year prior to the first dose of study intervention and have serum follicle-stimulating hormone levels consistent with postmenopausal status.

6. Female participants or female partners of male participants of childbearing potential (including breastfeeding females), if heterosexually active, must use highly effective contraception starting at least 6 weeks before the first dose of study intervention and continuing for at least 3 months after the end of systemic exposure of the study intervention. Female participants must not donate ova for at least 3 months after the end of systemic exposure of the study intervention. Highly effective contraceptive methods for females are as follows:
   a. Progestogen-only hormonal contraception associated with inhibition of ovulation as follows:
      i. Oral
      ii. Injectable
      iii. Implantable
   b. Intrauterine device
   c. Intrauterine hormone-releasing system
   d. Male partner vasectomized (with documented evidence of azoospermia if possible)
   e. Abstinence (note: sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study interventions. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant).
7. Male participants, if heterosexually active and with a female spouse or partner of childbearing potential or a pregnant or breastfeeding spouse or partner, must agree to use barrier contraception (male condom) for the duration of the study and for at least 3 months after the end of systemic exposure of the study intervention. Male participants must not donate sperm for at least 3 months after the end of systemic exposure of the study intervention.

   Female spouses or partners of male participants who are of childbearing potential must use highly effective contraception as previously defined, starting at least 6 weeks before (the male participant's) first dose of study intervention and continuing until at least 3 months after the end of their male partner's systemic exposure to the study intervention.

   For male participants who have had a vasectomy (with documented evidence of azoospermia if possible) and agree to use a male condom for the stated time period, no

additional contraceptive method is required by their female partner. Male condom is required even with documented medical assessment of surgical success of a vasectomy.

8. Participant has no clinically significant history or presence of ECG findings as judged by the Investigator at Screening and Check-in, including each criterion as follows:
   a. Normal sinus rhythm (HR between 45 beats per minute [bpm] and 100 bpm inclusive)
   b. QT interval corrected for HR using Fridericia's formula (QTcF) ≤ 450 ms
   c. QRS interval ≤ 110 ms; and confirmed by manual over read if > 110 ms
   d. 120 ms ≤ PR interval ≤ 220 ms

Exclusion Criteria: Participants meeting any of the following criteria will be excluded from the study:

1. Participant has a significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, psychiatric, or neurologic disorders.
2. Participant has a history of gastric bypass, other surgical procedure, or medical condition that may significantly alter absorption, metabolism, or excretion of drugs.
3. Participant has had lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years; or has a history of breast cancer within the past 10 years.
4. Participant has abnormal blood pressure, defined as a supine blood pressure <90/50 mm Hg or >140/90 mm Hg at Screening and predose vital signs; if either systolic or diastolic components of blood pressure meet these criteria, then the participant must be excluded. Blood pressure should be taken after a minimum of 5 minutes in the supine position.
5. Participant has serum potassium, calcium, or magnesium levels outside the normal range at Screening and/or Check-in, confirmed by repeat.
6. Participant has serum copper and/or ceruloplasmin values below the lower limit of normal at Screening.
7. Female participant has hemoglobin <10.8 g/dL and male participant has hemoglobin <12.5 g/dL at Screening or Check-in.
8. Participant has history of alcoholism or history of regular alcohol consumption within 24 months prior to the study, defined as an average weekly intake of >7 units. One unit is equivalent to 1 pint of beer, 1 glass of wine, or 1 measure (single shot) of spirits.
9. Participant has clinically significant multiple or severe drug allergies, food allergies, or allergies to study intervention, this class of drug, its derivatives, or to medical products that may be used in the study (eg, allergy to ALXN1840, any sulfur containing drugs, moxifloxacin, fluoroquinolone antibiotics, latex, band-aids, adhesive dressing, medical tape).
10. Participant has alanine aminotransferase, aspartate aminotransferase, serum creatinine, or total bilirubin greater than upper limit of normal (ULN) for the testing laboratory.

Participant's with confirmed Gilbert's syndrome may be included with total bilirubin >ULN if the participant has a measured direct bilirubin <ULN.

11. Participant has used any prescribed or over-the-counter medication (including dietary supplements, herbal remedies, and medications known to prolong the QTc interval) without the approval of the Investigator Alexion within 14 days (or 5 half-lives, whichever is longer) before the first dose of study intervention and during the study.
12. Female participant is pregnant, as evidenced by a positive serum pregnancy test at screening or check-in, or lactating.
13. Participant has positive urine drug or alcohol results at Screening or Check-in.
14. Participant has presence of hepatitis B surface antigen or positive hepatitis C antibody or ribonucleic acid (RNA) test result at Screening or within 3 months prior to first dose of study intervention. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C RNA test is obtained. NOTE: The RNA test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.
15. Participant has positive syphilis or human immunodeficiency virus (HIV)-1 and HIV-2 antigen/antibody immunoassay at Screening.
16. Participant has been on a diet incompatible with the on-study diet (including an extreme diet which resulted in a significant weight change for any reason), in the opinion of the Investigator, within the 29 days prior to the first dose of study intervention, and throughout the study.
17. Participant has donated blood or has had a significant blood loss of more than 500 mL within 56 days prior to the first dose of study intervention.
18. Participant has donated plasma within 7 days prior to the first dose of study intervention.
19. Participant is currently enrolled or has had past participation (within the last 30 days before signing of consent, 5 half-lives of the study intervention, or twice the duration of the biological effect of the study intervention [whichever is longer]) in this or any other clinical study involving an investigational study intervention or any other type of medical research.
20. Participant has participated in a previous clinical study where the participant received ALXN1840.
21. Participant has history or presence of:
    a. Hypokalemia, in the opinion of the Investigator
    b. Risk factors for torsades de pointes (eg, heart failure, cardiomyopathy, or family history of long QT syndrome)
    c. Sick sinus syndrome, second- or third-degree atrioventricular block, myocardial infarction, pulmonary congestion, cardiac arrhythmia, prolonged QT interval, or conduction abnormalities
    d. Repeated or frequent syncope or vasovagal episodes
    e. Hypertension, angina, bradycardia (if assessed as clinically significant by the Investigator), or severe peripheral arterial circulatory disorders.

STUDY INTERVENTION:

- Treatment A: A single oral dose of ALXN1840 120 mg administered as 15-mg enteric-coated tablets (supratherapeutic dose)
- Treatment B: A single oral dose of enteric-coated placebo tablets matching ALXN1840
- Treatment C: A single oral dose of moxifloxacin 400 mg tablet

STUDY PROCEDURES:

Cardiodynamic Assessments and Endpoints: Twelve-lead ECGs will be extracted from approximately 25-hour continuous (Holter) recordings on Day –1 of Treatment Period 1 and on Days 1 and 2 in each treatment period. Participants should be resting supinely for at least 15 minutes before and 5 minutes after each time point for ECG extraction, which should precede PK blood samples, when applicable.

Electrocardiograms will be extracted from the continuous recording by a central ECG laboratory (ERT, Rochester, NY) on Day –1 of Treatment Period 1 and each of these days at the following time points: Day 1 at predose (–45, –30, and –15 minutes) and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 (Day 2) hours postdose, for a total of 15 (3 predose and 12 postdose) time points in each treatment period. For HR-corrected QTc calculation in case of a substantial HR effect due to ALXN1840, ECG extraction from the Holter recording on Day -1 of Treatment Period 1 will include continuous ECG extraction for optimized QT interval (QTcI) calculation, and if needed, ECG extraction at timepoints that precisely match the extraction timepoints for Day 1 of Periods 1, 2 and 3 for individual HR-corrected QT interval (QTcS) calculation.

The following ECG parameters will be measured and calculated: HR, PR interval, QTcF, QRS interval, treatment-emergent T-wave morphology abnormalities, and appearance of U-waves.

The primary endpoint is placebo-corrected change from Baseline QTcF (ΔΔQTcF) for ALXN1840 using the by-time point analysis. The secondary endpoints are the ΔΔQTcF for moxifloxacin; the change from Baseline in HR, QTcF, PR, QRS (ΔHR, ΔQTcF, ΔPR and ΔQRS); the placebo-corrected change from Baseline HR, PR, and QRS (ΔΔHR, ΔΔPR and ΔΔQRS); categorical outliers for QTcF, HR, PR, and QRS; and the frequency of treatment-emergent changes of T-wave morphology and U-wave presence. The exploratory endpoint is the ΔΔQTcF for ALXN1840 using the concentration-QTc analysis by concentration of total Mo or PUF Mo (as surrogate measures of ALXN1840 PK) in plasma.

For all continuous ECG parameters from each period, Baseline is defined as the average of the measured ECG intervals from the 3 predose time points (–45, –30, and –15 minutes before dosing) on Day 1 for the respective period. For T-wave morphology and U-wave presence, Baseline includes findings observed in any replicates from the 3 predose time points (–45, –30, and –15 minutes) on Day 1 in each period.

Pharmacokinetic Assessments and Endpoints: Blood samples for PK analysis of total molybdenum (Mo) and PUF Mo (as surrogate measures of ALXN1840 PK) will be collected at the following time points: within 1.5 hour before dosing and postdose at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, and 96 hours in each period. Only samples collected predose and following ALXN1840 administration will be analyzed for plasma total Mo and PUF Mo.

Samples collected predose and after placebo and moxifloxacin administration will be saved for analysis, if needed.

The following plasma PK parameters will be calculated as endpoints for total Mo and PUF Mo using noncompartmental methods with Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) Version 8.0 or higher or SAS® (SAS® Institute Inc., Cary, North Carolina) Version 9.4 or higher, as applicable. Calculations will be based on the actual sampling times elapsed from the reference dosing time in the period as recorded during the study.

- Time delay between the time of dosing and time of appearance of Mo concentration in plasma (T_{lag})
- Maximum observed concentration in plasma (C_{max})
- Time to reach maximum observed concentration in plasma (T_{max})
- Area under the concentration in plasma versus time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t})
- AUC from time 0 to 96 hours postdose (AUC_{0-96})
- AUC from time 0 extrapolated to infinity (AUC_{0-inf})
- Apparent terminal-phase elimination rate constant (λ_z)
- Terminal elimination half-life ($t_{1/2}$)
- Apparent total clearance from plasma after oral administration of ALXN1840 (CL/F)
- Apparent volume of distribution during the terminal phase (V_z/F)

Pharmacokinetic samples may be used for the quantification of pharmacodynamic endpoints such as total Cu, PUF Cu, labile bound Cu, ceruloplasmin, and ceruloplasmin-bound Cu.

Additional PK parameters may be calculated if deemed appropriate.

Safety Assessments and Endpoints: Safety and tolerability will be assessed by the following endpoints: monitoring and recording of AEs, clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital sign measurements, 12-lead safety ECG results, and physical examination findings.

For all safety assessments, the Investigator will determine whether results are clinically significant, which is defined as any variation in a result that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If clinical significance is noted, the result and reason for significance will be documented and an AE will be reported on the AE page of the participant's eCRF. The Investigator will monitor the participant until the result has reached the reference range or the result at Screening, or until the Investigator determines that follow-up is no longer medically necessary.

STATISTICAL ANALYSIS PLANS:

Sample Size: A sample size of approximately 54 participants was chosen to obtain 45 evaluable participants to complete the study. Assuming a 1-sided 5% significance level and a within-participant standard deviation of 8 ms for ΔQTcF for all treatment groups and a true mean difference of 3 ms in ΔQTcF between ALXN1840 and placebo, based on the

calculation of the sample size for a TQT study, a sample size of 45 evaluable participants will provide a power of 90% to demonstrate that the upper bound of all the 2-sided 90% CIs on ΔΔQTcF will fall below 10 ms for up to 12 postdose time points. To account for a drop-out rate of approximately 16%, 54 participants will be enrolled.

Based on the calculation of the sample size for a TQT study, as the test is performed at 3 time points separately (1, 2, and 3 hours), a 1-sided 5% significance level (with adjusted 1-sided significance levels of 5%, 2.5%, and 1.67%) is used along with a within-participant standard deviation of 8 ms for ΔQTcF and a true effect of moxifloxacin of 10 ms, a sample size of 45 evaluable participants will provide greater than 98% power to demonstrate assay sensitivity of excluding a mean difference of 5 ms in ΔQTcF between moxifloxacin and placebo groups.

Analysis Sets: The analysis populations are as follows:

- The Safety Set will include all participants who receive at least 1 dose of study intervention (ALXN1840, moxifloxacin, or placebo) and for whom any postdose data are available.
- The QT/QTc Set will include all participants in the Safety Set with measurements at Baseline as well as on-treatment with at least 1 postdose time point with a valid ΔQTcF value. The QT/QTc Set will be used for the by-time point, assay sensitivity, and categorical analyses of the cardiodynamic ECG parameters.
- The PK Set will include all participants who receive at least 1 dose of ALXN1840 and have evaluable PK data for total Mo and PUF Mo (as surrogate measures of ALXN1840 PK) in plasma. The PK Set will be used for PK analysis.
- The PK/QTc Set will include all participants who are in both the QT/QTc and PK Sets with at least 1 pair of postdose PK and QTcF data from the same time point as well as participants in the QT/QTc Set who received placebo. The PK/QTc Set will be used for the exploratory concentration-QTc analysis.

Cardiodynamic Analyses: Cardiodynamic analyses will be based on the QT/QTc Set. The primary analysis will be based on by-time point analysis to evaluate the effect of ALXN1840 on the ΔΔQTcF at each postdosing time point ("by-time point" analysis) using the intersection union test (IUT). The effect of ALXN1840 on placebo-corrected change from Baseline in HR, PR, and QRS (ΔΔHR, ΔΔPR, and ΔΔQRS) will also be evaluated using the IUT.

The statistical hypothesis to be tested for the primary assessment of QT prolongation for the ALXN1840 treatment is:

H_0: $\cup\{\mu_{D(i)} - \mu_{P(i)}\} \geq 10$, $i = 1,2,\ldots,12$

H_1: $\cap\{\mu_{D(i)} - \mu_{P(i)}\} < 10$, $i = 1,2,\ldots,12$

where $\mu_{D(i)}$ and $\mu_{P(i)}$ are the least squares (LS) mean of ΔQTcF for ALXN1840 and placebo at postdose time point i, respectively.

The by-time point analysis for QTcF will be based on a mixed-effects model for repeated measures (MMRM) with change from Baseline QTcF (ΔQTcF) as the dependent variable; period, sequence, time (ie, postdose time point: categorical), treatment (supratherapeutic dose of ALXN1840, moxifloxacin, and placebo), and time-by-treatment interaction as fixed effects

and Baseline QTcF and sex as covariates. An unstructured covariance matrix will be used to model within-participant error. If the model with unstructured covariance matrix fails to converge, other covariance structure such as Toeplitz with heterogeneity (TOEPH), auto-regressive with heterogeneity (ARH), compound symmetry with heterogeneity (CSH), TOEP, AR, and CS will be considered in decreasing complexity in parameterization. The final model selection will be based on Akaike information criterion (AIC). The degrees of freedom estimates will be determined by the Kenward-Roger method. The model will also include a participant-specific random effect. Least squares mean difference and 2-sided 90% CI will be calculated for the contrast of ALXN1840 versus placebo at each postdose time point, separately. If the upper bound of the 2-sided 90% CI of LS mean ΔΔQTcF lies below 10 ms at all 12 postdose time points, ALXN1840 will be concluded not to have a significant effect on QT interval prolongation.

For HR, PR, and QRS, the analysis will be based on the change from Baseline postdosing (ΔHR, ΔPR, and ΔQRS). The same (by-time point analysis) model will be used as described for QTcF. The LS mean, SE, and 2-sided 90% CI from the statistical modeling for both change from Baseline and placebo-corrected change from Baseline values will be listed in the tables and graphically displayed.

An analysis of categorical outliers will be performed for changes in HR, PR, QRS, QTcF, T-wave morphology, and U-wave presence. The results for categorical outliers, T-wave morphology, and U-wave presence will be summarized in frequency tables with counts (percentages) for both number of participants and number of time points. For categorical outliers, the number (percentage) of participants as well as time points who had absolute QTcF values >450 and ≤480 ms, >480 and ≤500 ms, or >500 ms, and changes from predose Baseline (ΔQTcF) of >30 and ≤60 ms, or >60 ms; increase in PR from predose Baseline >25% to a PR >200 ms; increase in QRS from predose Baseline >25% to a QRS >120 ms; decrease in HR from predose Baseline >25% to a HR <50 bpm; and increase in HR from predose Baseline >25% to a HR >100 bpm will be determined. For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed; ie, changes not present at Baseline. For each category of T-wave morphology and of U-waves, the category will be deemed as present if observed in any replicates at the time point.

Assay sensitivity will also be evaluated using by-time point analysis of the effect on ΔΔQTcF of moxifloxacin using a similar model as for the primary analysis. The analysis to show assay sensitivity will be based on the change from Baseline postdosing QTcF of moxifloxacin. For the 3 predefined time points (1, 2, and 3 hours postdose), the contrast in treatment ΔΔQTcF = moxifloxacin versus placebo will be tested against the 1-sided null hypothesis ΔΔQTcF ≤5 ms on the 5% level. Multiplicity will be controlled by using a Hochberg procedure. If after this procedure the LS mean of ΔΔQTcF is significantly larger than 5 ms for at least 1 time point of these 3 time points, assay sensitivity will be considered to have been demonstrated. In addition, 2-sided 90% CIs will be obtained for the contrast at all time points and used in the figures.

Other QT interval corrections such as QTcI may be performed, if justified, with details to be included in the Statistical Analysis Plan.

Pharmacokinetic Analyses: Pharmacokinetic analyses will be based on the PK Set. Plasma total Mo and PUF Mo (as surrogate measures of ALXN1840 PK) and time deviation data

will be presented in a data listing by participant. Concentration data will be summarized separately by analyte and time point for each treatment using the following descriptive statistics: number of participants, arithmetic mean, SD, coefficient of variation (CV), geometric mean, geometric CV, median, minimum, and maximum. Mean concentration versus scheduled time profiles will be presented in figures on both linear and semilogarithmic scales. Individual concentration versus actual time profiles will be presented similarly.

Pharmacokinetic parameters derived from plasma total Mo and PUF Mo using noncompartmental methods will be presented in data listings and summarized separately using the following descriptive statistics: number of participants, arithmetic mean, standard deviation, arithmetic CV, geometric mean, geometric CV, median, minimum, and maximum. Geometric mean and geometric CV will be presented for C_{max} and AUCs only.

Pharmacokinetic Concentration/QTc Analysis: Pharmacokinetic concentration/QTc analysis will be based on the PK/QTc Set. The relationship between total Mo or PUF Mo (as surrogate measures of ALXN1840 PK) concentrations in plasma and ΔΔQTcF will be explored graphically and using a linear mixed-effects modeling approach with ΔΔQTcF as the dependent variable, total Mo or PUF Mo concentration in plasma as the exploratory variate (0 for placebo), centered Baseline QTcF (ie, Baseline QTcF for individual participant minus the population mean Baseline QTcF for all participants in the same treatment period) as an additional covariate, treatment (active = 1 or placebo = 0) and time (ie, postdose time point) as fixed effects, and a random intercept and slope per participant. The degrees of freedom estimates will be determined by the Kenward-Roger method. From the model, the slope (ie, the regression parameter for the total Mo or PUF Mo concentration in plasma) and the treatment effect-specific intercept (defined as the difference between active and placebo) will be estimated together with 2-sided 90% CI. The estimates for the time effect will be reported with degrees of freedom and SE.

The geometric mean of the individual C_{max} values for total Mo or PUF Mo (as surrogate measures of ALXN1840 PK) concentrations in plasma for participants in the active drug group will be determined. The predicted effect and its 2-sided 90% CI for ΔΔQTcF (ie, slope estimate × concentration + treatment effect-specific intercept) at this geometric mean C_{max} will be obtained.

Safety Analyses: Safety analyses will be based on the Safety Set. Adverse events will be coded by preferred term and system organ class using the Medical Dictionary for Regulatory Activities. All AE data will be presented in a data listing. Treatment-emergent AEs will be summarized by treatment and overall, as well as by severity and relationship to study intervention. Serious AEs and AEs leading to early discontinuation will also be presented in data listings.

Actual values and changes from Baseline for clinical laboratory test results, vital sign measurements, and 12-lead safety ECG results will be summarized by treatment at each time point using descriptive statistics (number of participants, mean, SD, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results. Clinical laboratory test results, vital sign measurements, 12-lead safety ECG results, and physical examination findings will be presented in data listings.

DATE OF PROTOCOL AMENDMENT 1: 01 Sep 2020

1. INTRODUCTION

1.1 BACKGROUND

Wilson disease (WD) is a rare, autosomal recessive disorder of impaired copper (Cu) transport that results in pathological Cu accumulation. It is caused by mutations in the adenosine triphosphate (ATP7B) gene, located on chromosome 13. The gene is highly expressed in the liver and encodes a trans-membrane protein adenosine triphosphatase 2 (ATPase2) involved in Cu transport (Pfeiffer 2007). The physiological role of ATP7B is to incorporate Cu in ceruloplasmin and to excrete excess Cu into bile. In WD, mutations in the ATP7B gene result in deficient production of ATPase2, which in turn leads to impaired biliary excretion of Cu and impaired incorporation of Cu into ceruloplasmin, a serum ferroxidase, which, in healthy humans, contains greater than 95% of the Cu found in plasma (Hellman 2002). Consequently, there is an increase of Cu in liver, brain, and other tissues with resultant organ damage and dysfunction (Pfeiffer 2007). Wilson disease genetic prevalence is approximately 1 per 30,000 population worldwide. An estimated 50% of people with an identified mutation will become symptomatic, diagnosed, and treated. Typical clinical presentation of WD is in adolescence to early adulthood. Initial signs and symptoms of WD are predominantly hepatic (approximately 40%), neurologic (approximately 40%), or psychiatric (approximately 20%), but patients often develop combined hepatic and neuropsychiatric disease. Untreated or inadequately treated patients have progressive morbidity, and mortality is usually secondary to hepatic cirrhosis. Liver transplantation is the only effective therapy for WD-associated acute liver failure; other causes of death associated with WD include hepatic malignancy and neurologic deterioration with severe inanition.

Current treatment goals for WD focus on compensating for impaired Cu metabolism, reducing free Cu, and maintaining normal Cu levels to improve patients' symptoms. The current treatments for WD are general chelator therapies that non-specifically chelate Cu and promote urinary Cu excretion. In addition, zinc, which blocks dietary uptake of Cu, is used mainly for maintenance treatment. Zinc impairs the absorption of Cu by the induction of metallothionein in the gastrointestinal (GI) tract. The currently available drugs have high rates of treatment discontinuation due to tolerability and efficacy issues. These therapies require frequent dosing (2 to 4 times per day) and must be taken in a fasted state. While ALXN1840 is also to be taken in a fasted state, it requires only once daily dosing. The adverse event (AE) profiles and complicated dosing regimens of currently available treatments leads to poor compliance and high rates of treatment failure, a major concern in WD, which requires life-long treatment.

ALXN1840 (bis-choline tetrathiomolybdate) is a novel, first-in-class, Cu-binding agent in development for the treatment of WD. ALX1840 preclinically has been shown to directly target and remove Cu from intracellular Cu stores, rapidly form stable Cu-tetrathiomolybdate (TTM) complexes, and promote biliary excretion of Cu to reduce Cu overload. ALXN1840 acts by improving control of Cu due to the rapid formation of the virtually irreversible TTM-Cu-albumin tripartite complexes (TPCs) leading to a rapid de-coppering without mobilization of free Cu that could cause tissue toxicity, including neurological deterioration. It is hoped that improved long-term compliance with ALXN1840 treatment through improved tolerability and the convenience of a simplified once daily dosing regimen compared with current therapeutic options (multiple daily dosing) could be achieved.

Additional information regarding ALXN1840 can be found in the Investigator's Brochure (IB; Alexion Pharmaceuticals, Inc 2020).

1.1.1 ALXN1840 Pharmacology

In the in vitro human ether a-go-go-related gene (hERG)-IKr Assay (Study A0889), results indicated that ALXN1840 is devoid of activity to block the delayed rectifying potassium currents responsible for cardiac repolarization at concentrations up to 1618 µM, which is several magnitudes above the expected total Mo plasma exposure in patients.

The PK of ALXN1840 were evaluated in 2 Phase 1 studies in healthy participants and in 1 Phase 1 study in patients with WD.

Study WTX101-101 assessed the relative exposure of an ALXN1840 uncoated capsule (UC) with and without co-administration of a long-acting proton-pump inhibitor (PPI) under fasted conditions, the former also under fed conditions. Study WTX101-102 assessed the PK of an ALXN1840 enteric-coated tablet under fed and fasting conditions compared with the UC administered with a PPI under fasted conditions.

Total plasma molybdenum (Mo) concentrations are used as a surrogate PK measure for TTM as direct quantification of TTM in biological matrices is not possible due to its rapid conversion to molybdate in aqueous solution and the almost immediate formation of a drug-protein TPC.

In Study WTX101-101, based on total plasma Mo, administration of the UC + PPI under fasted conditions resulted in a 30% increase in exposure compared with the UC alone. Administration of the UC + PPI fed results in a 22% decrease in exposure compared with the UC + PPI fasted. The mean terminal elimination half-life ($t_{1/2}$) for total Mo was essentially

the same for all 3 treatments, with an overall mean of approximately 51 hours or slightly over 2 days.

There was a decrease in the between-participant variability when the UC was administered with a PPI. The between-participant coefficients of variation for maximum observed concentration in plasma (C_{max}), area under the concentration in plasma versus time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t}), and AUC from time 0 extrapolated to infinity (AUC_{0-inf}) were approximately 50% lower after administration of the UC + PPI under fasted or fed conditions compared with the UC fasted and comparable for both PPI treatments.

Study WTX101-102 evaluated the relative exposure of ALXN1840 from an enteric-coated tablet under fed and fasting conditions compared with the non-coated capsule (also referred to as UC administered with a PPI) under fasting conditions to confirm the in vivo performance characteristics of the enteric-coated tablet in humans, including the absorption profile and food effect. There was a slight decrease in the plasma total Mo after administration of the enteric-coated tablet fasted, compared with the UC + PPI fasted. Similar trends were observed with respect to C_{max}, AUC_{0-t}, and AUC_{0-inf}. Nevertheless, examination of the individual participant data indicated that while a similar pattern was observed with some of the individual participants, the majority had a total Mo concentration-time profile that was comparable for the enteric-coated tablet and UC + PPI when both were administered under fasted conditions. However, administration of the enteric-coated tablet fed resulted in a 60% to 75% decrease in absorption, which was consistent among the majority of participants.

There were no apparent relationships between apparent total clearance from plasma after oral administration (CL/F) and body size (weight, body mass index) in either Study WTX101-101 or Study WTX101-102, suggesting that a fixed dose, rather than a dose based on body size, ie, mg/kg or mg/m², may be appropriate for ALXN1840.

In the Phase 2 Study WTX101-201, preliminary results showed that, based on total Mo measures, exposure in patients with WD at the 30 mg dose appeared consistent with previous healthy participant data, although half-life estimates in this study were shorter than estimated in previous studies. However, plasma concentration sample collection was restricted to 12 hours, so a full profile including the terminal decay portion was not collected as in the previous studies, which could lead to underestimation of half-life. Other parameters appeared consistent with previous data, allowing for the limited scope of the PK sample collections and small number of participants and variability. There was no evidence that sex, age, or

weight had a major impact on PK parameters of ALXN1840 (Alexion Pharmaceuticals, Inc. 2020).

Further dose-exposure information is provided in Section 1.3.

1.1.2 ALXN1840 Safety

ALXN1840 has been evaluated in 108 healthy participants in Phase 1 studies, 28 patients with WD in the Phase 2 Study WTX101-201, 108 patients with WD in the ongoing Phase 3 Study WTX101-301 as of the cut-off date for analysis, 29 Dec 2019, and 163 patients in 5 oncology studies. In addition, 5 patients received ALXN1840 in a named patient program in Canada and Sweden that closed in mid-2014.

A review of AEs that were reported in patients treated with ALXN1840 during the Phase 2 Study WTX101-201 and the ongoing Phase 3 Study WTX101-301 was performed to identify potential adverse drug reactions. In patients with WD who received multiple daily doses of ALXN1840, the most commonly experienced drug effects were increased alanine aminotransferase, aspartate aminotransferase, and gamma glutamyl transferase (without increased bilirubin). Increases occurred 4 to 10 weeks after daily dosing at 30 mg/day or higher. All were asymptomatic. Liver function tests normalized within 1 to 2 weeks of dose reduction or treatment interruption. Other side effects observed with ALXN1840 with potential significance for the participating healthy participants were thrombocytopenia, neutropenia, and anemia. In all cases, treated patients recovered after dose reduction.

Rash (location non-specific) was also commonly reported in patients during Phase 2 and 3 clinical studies. The majority of the events of rash were mild in severity and the patients recovered with no modification to study intervention.

ALXN1840 administered once daily or twice daily (total daily dose 120 mg to 300 mg) to patients in oncology studies had an acceptable safety profile and was effective in lowering Cu, as evidenced by decreased plasma concentrations of potentially toxic Cu, measured as labile bound Cu and/or non-ceruloplasmin-bound Cu/corrected non-ceruloplasmin-bound Cu. The maximum tolerated dose (MTD) was 300 mg in this patient population, in which total body Cu was expected to be within normal limits at Baseline. Overall, ALXN1840 was generally well tolerated in oncology studies, and the main drug-related AEs were changes in hematologic parameters, fatigue, sulfur burps, and other GI symptoms. Changes in hematology parameters, namely anemia, leukopenia and thrombocytopenia, are a consequence of myelosuppression from over-decoppering. Myelosuppression is monitorable and has been shown to be reversible with correction of Cu deficiency. Only occasional

reports of liver function test abnormalities were noted (Lin 2013; Lowndes 2008). These findings were similar to those reported by Askari et al (Askari 2010) in patients with primary biliary cirrhosis in whom the most common AEs were related to symptoms of over-decoppering with no reports of liver function test abnormalities (Alexion Pharmaceuticals, Inc. 2020).

Cardiac safety events as defined by ICH E14 guidance (DHHS 2005) that have occurred in previous ALXN1840 studies as of 28 Dec 2019 are described in Table 1. Cardiac safety events included 3 participants with syncope and 1 participant with seizure. All participants recovered completely from the events. Single ECGs were collected as part of the healthy participant study with no evidence of concern. Nevertheless, no intensive cardiac monitoring or ECG analyses have been performed to date as part of the program. The proposed thorough QT (TQT) study is to evaluate the impact of ALXN-1840 on QT prolongation and other ECG wave form or interval changes that may place the participant at risk for a cardiac safety event.

Table 1 Adverse Events That Can Signal Potential Proarrhythmic Effects per ICH E14 Guidance

	Phase 1 N=108	Phase 2 N=28	Phase 3 N=108	Total Phase 2-3 N=136
Adverse Events	**Participant/Event**	**Participant/Event**	**Participant/Event**	**Participant/Event**
Syncope	1/1	1/2	1/1	2/3
Seizures	0/0	0/0	1/1	1/1
Ventricular tachycardia	0/0	0/0	0/0	0/0
Ventricular fibrillation and flutter	0/0	0/0	0/0	0/0
Torsade de pointes	0/0	0/0	0/0	0/0
Sudden death	0/0	0/0	0/0	0/0

Phase 1 includes Studies WTX101-101, WTX101-102, WTX101-104, and WTX101-106; Phase 2 includes Study WTX101-201; Phase 3 includes Study WTX101-301. Phase 2-3 includes Studies WTX101-201 and WTX101-301. Participants originally enrolled in Study WTX101-201 who then entered the extension of Study WTX101-301 have all of their data, irrespective of which study it occurred in, presented as if it occurred in Study WTX101-201.

Data cut-off: 29 Dec 2019

Additional information regarding the safety of ALXN1840 can be found in the IB (Alexion Pharmaceuticals, Inc. 2020).

1.2 RATIONALE FOR THE STUDY

The International Council for Harmonisation (ICH) E14 guidance, as adopted in the US Food and Drug Administration (FDA) Guidance for Industry, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (DHHS 2005), emphasizes the need to obtain clear and robust data through "thorough" studies that assess the effect of new chemical entities on electrocardiogram (ECG) parameters. Specifically, "thorough" studies are defined as studies dedicated to evaluating a compound's effect on cardiac repolarization, as measured by the corrected QT interval (QTc). Although many Phase 1, 2, and 3 studies may be conducted with a new compound, they typically utilize insufficient sample sizes, infrequent sampling of ECG data, or inadequate controls to overcome the variance in cardiac repolarization due to spontaneous change.

Based on existing nonclinical and clinical data (Alexion Pharmaceuticals, Inc 2020), no QT interval effect is expected from treatment with ALXN1840, so only a single supratherapeutic dose will be tested in this 3-way crossover study. The study will consist of 3 periods with 1 single-dose treatment administration per period of ALXN1840 120 mg, matching ALXN1840 placebo, or moxifloxacin 400 mg.

The study will employ moxifloxacin as the positive control, which has been shown to result in reproducible QT interval prolongation and can thus verify the sensitivity of the assay for the study. Following single-dose administration, moxifloxacin has a time to reach maximum observed concentration in plasma (T_{max}) between 1 and 3 hours postdose (Merck and Co. 2016). Holter monitoring for a period of 24 hours postdose is adequate to assess both the ALXN1840 (T_{max} approximately 4 to 8 hours based on total Mo and plasma ultrafiltrate Mo [PUF Mo]) and moxifloxacin. This is also in keeping with the ICH E14 guideline that the TQT monitoring is carried out during the entire dosing interval, which is daily dosing in the clinical setting. Time points were chosen to help ensure QT interval assessment at T_{max} for both drugs as well as additional time points to evaluate for hysteresis. A washout of 14 days between treatment administration is considered adequate given a half-life of the TPC of approximately 51 hours and a half-life of moxifloxacin of 12 hours (±1.3 hours).

Healthy participants are most appropriate to evaluate a QT/QTc interval effect of ALXN1840 as healthy participants are not anticipated to have underlying cardiac conduction abnormalities, cardiac comorbidities, concomitant medications, or other disease-specific abnormalities that may impact interpretation of the data.

1.3 RATIONALE FOR DOSE SELECTION

This study will be conducted as a single-dose study because the free and active ALXN1840 itself has an anticipated short half-life (as part of the PUF Mo) and the primary non-reactive product, the TPC which is composed of TTM-Cu-protein (where the protein is believed to be most commonly albumin), represents a stable protein complex and therefore is not anticipated to impact the QT interval. Based on crystal structure of TTM-Cu isolated from the lysosome of LEC rats treated with TTM, the Cu-S bonds of approximately 2.28 angstrom between TTM-Cu crystal may be consistent with a covalent bond (George 2003); a similar type bond may occur between TTM and Cu in the TPC. The dissociation constant of TTM-Cu has been measured at 2.32×10^{-20} M, making this a very high affinity complex (Smirnova 2018); this is supported by failure to dissociate TTM-Cu-albumin TPC with trichloroacetic acid precipitation (Mills 1981). Additionally, the stability of the TPC is supported clinically with an improvement in neurologic status as measured by the Unified Wilson Disease Rating Scale Parts 2 and 3 over time despite, in some cases such as WD, an initial overall increase in plasma total Cu with ALXN1840 treatment (Weiss 2017). Therefore, only the active, free ALXN1840 component in PUF Mo is relevant, while the TPC is expected to behave in a similar fashion to a protein adduct or biologic and is not considered relevant for TQT assessment.

Following ALXN1840 administration, the majority of the active drug moiety TTM rapidly binds Cu and protein to form the TPC of TTM-Cu-protein (where the protein is believed to be most commonly albumin) in the blood or target organ(s) and presents as such in the systemic circulation. If TPC is not rapidly formed, TTM spontaneously undergoes serial hydrolysis to form molybdate, the most common form of the nutrient Mo, and is excreted in the urine. Total Mo concentration has been measured as a surrogate of ALXN1840 pharmacokinetics (PK); however, total Mo concentration cannot distinguish whether the Mo is protein bound (mostly as TPC), free active drug as ALXN1840, intermediate hydrolysis products, or molybdate which is both a hydrolysis product of TTM and may be present from food intake as an essential micronutrient. To better characterize the amount of non-TPC-bound drug and its degradation products, PUF Mo has also been measured, which represents the free parent drug (TTM), short-lived intermediate hydrolysis products, and molybdate (which may have originated from the TTM or from food intake as a micronutrient). While it is not feasible to separate and quantify ALXN1840 directly in the plasma, total Mo and PUF Mo provide surrogate measures of total Mo PK and free Mo PK that can be used to inform study design and dose selection.

Single-dose administration of the enterically-coated ALXN1840 under fasting conditions in healthy participants resulted in a peak total Mo concentration at approximately 4.54 hours, with a half-life of approximately 51 hours. Data from the recently completed Study WTX101-HV-106 at the 60-mg dose have demonstrated a total Mo T_{max} of approximately 6 hours with only up to 14% of the total Mo represented as PUF Mo, which also peaked at approximately 6 hours postdose. By 24 hours, PUF Mo had declined to approximately 3% to 5% of the total Mo, near or within the range of endogenous Mo concentrations as measured in participants at Baseline in the ongoing Study WTX101-301 (mean: 1.9 ng/mL; range: 0 to 6.3 ng/mL), which suggests minimal to no accumulation of the free active ALXN1840 (or other free Mo hydrolysis products) when dosed daily in the clinical setting. ALXN1840 PK parameters in Study WTX101-HV-106 showed less than dose-proportional increases from 15 mg to 60 mg (4 × 15 mg) in both Japanese and non-Japanese subjects. These findings are consistent with the Phase 2 Study WTX101-201 in patients with WD. Because PUF Mo declined to approximately 3% to 5% of the total Mo by 24 hours with minimal to no accumulation and because total Mo and the PUF Mo peaked by 4 to 6 hours dominated largely by the TPC, a single dose is adequate for the conduct of this TQT study.

There were no apparent relationships between clearance and body size (weight, body mass index) in Study WTX101-101, Study WTX101-102, or Study WTX101-HV-106, suggesting that a fixed dose, rather than a dose based on body size, ie, mg/kg or mg/m², may be appropriate for ALXN1840. Additional information regarding ALXN1840 pharmacology can be found in the IB (Alexion Pharmaceuticals, Inc 2020).

A single dose of ALXN1840 120 mg is a reasonable dose to be tested in healthy participants based on existing safety data from healthy participants following a single-dose administration of ALXN1840 60 mg and existing patient experience to date in oncology with the MTD of bis-choline TTM at 300 mg/day.

Single dose administration of ALXN1840 60 mg has been shown to have an adequate safety profile and be well tolerated in healthy male and female participants in Phase 1 bioavailability studies, Study WTX101-101 and Study WTX101-102. In addition, preliminary data from Study WTX101-HV-106 have also shown ALXN1840 to be well tolerated in Japanese and non-Japanese healthy male and female participants at a single dose of 15 mg/day or 60 mg/day. No MTD has been identified in healthy participants.

In the Phase 2 Study WTX101-201 conducted in patients with WD, the ALXN1840 doses were 15 mg/day for 6 patients (21%), 30 mg/day for 13 patients (46%), and 60 mg/day for

9 patients (32%) at Week 24 when the primary endpoint assessment was conducted, or at the last dose received for patients with early discontinuation. The 15 mg/day to 60 mg/day dose range has been demonstrated to be efficacious with a favorable safety profile in treating patients with WD (Weiss 2017). Based on these Phase 2 study results, the ongoing Phase 3 Study WTX101-301 in patients with WD has been testing the efficacy and safety of ALXN1840 at a dose titration range from 15 mg/day to 60 mg/day.

As indicated in Section 1.1.2, ALXN1840 administered once daily or twice daily (total daily dose 120 mg to 300 mg) to patients in oncology studies had an acceptable safety profile, with an MTD of 300 mg/day.

In summary, ALXN1840 (bis-choline tetrathiomolybdate) has been well tolerated in repeat-dose studies up to 300 mg/day in oncology patients and has been well tolerated with an acceptable safety profile following single-dose administration up to 60 mg/day in healthy participants. Therefore, 120 mg is considered a reasonable single supratherapeutic dose to be tested in this TQT study in healthy participants. A single dose of 120 mg was chosen as it represents a 4-fold increase over the anticipated therapeutic dose of 30 mg and represents a 2-fold increase over the highest dose being tested in Study WTX101-301 in patients with WD. Given a lack of accumulation and approximate dose proportionality for PUF Mo following single-dose administration within the clinically relevant range of 15 mg to 60 mg (Study WTX101-HV-106), the dose of 120 mg is considered sufficient to test the effects of supratherapeutic doses of ALXN1840 on potential QT prolongation.

To mitigate risk against any safety concerns as this is the highest single dose tested in healthy participants to date, only participants with normal Cu and ceruloplasmin levels will be enrolled in the study. Additionally, the study will be conducted in a minimum of 2 groups with the first group (Group 1) including no more than 18 participants representing 6 participants per treatment. After review of first period (Period 1, Day 5) safety data from Group 1, the remaining group(s) will be initiated. Participants will also undergo safety assessments including safety laboratory tests at 24 and 96 hours postdose as well as vital sign and safety ECG assessments through Day 5. Participants will remain in-house until Day 5 safety assessments have been completed and reviewed by the Investigator to ensure participants can be safely discharged.

The positive-control group will receive moxifloxacin 400 mg, a commercially available fluoroquinolone antimicrobial indicated for the treatment of adults (≥18 years of age) with various infections caused by susceptible bacterial strains. Moxifloxacin at this dose is known to prolong the QT/QTc interval, with an expected change from Baseline in placebo-corrected

QTc of 5 to 10 ms using a time-averaged analysis, or 10 to 15 ms using a time-matched analysis (Merck and Co. 2016).

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the effect of a supratherapeutic dose of ALXN1840 on the heart rate (HR)-corrected QT interval with the intent to exclude a 10 ms effect.

2.2 SECONDARY OBJECTIVES

The secondary objectives of the study are:

- To demonstrate assay sensitivity of the study to detect an effect on the mean QT/QTc interval of approximately 5 ms using moxifloxacin as a positive control.
- To evaluate the safety and tolerability of a single oral supratherapeutic dose of ALXN1840 in healthy participants.
- To assess the PK of ALXN1840 following administration of a single oral supratherapeutic dose in healthy participants.
- To evaluate the effects of a single oral supratherapeutic dose of ALXN1840 on HR, PR and QRS intervals, treatment-emergent T-wave morphology abnormalities, and appearance of U-waves.

2.3 EXPLORATORY OBJECTIVE

The exploratory objective of this study is to evaluate the effects of plasma total Mo and PUF Mo (as surrogate measures of ALXN1840 PK) concentrations on QT/QTc.

3. STUDY DESIGN

This is a randomized, 3-treatment, 3-period, 6-sequence, crossover, placebo- and active-controlled, double-blind for ALXN1840, open-label for moxifloxacin, in healthy adult participants. Moxifloxacin will be used as the active control.

Approximately 54 participants will be randomized to ensure there will be 45 evaluable participants with data from all treatment periods. To ensure sequences are balanced within

sex, participant randomization will be stratified by sex. Study intervention will be given in randomized sequences: ABC, ACB, BAC, BCA, CAB, and CBA, with each intervention administered with 240 mL of water following an overnight fast of at least 10 hours. No food will be allowed for at least 4 hours postdose. Water can be allowed as desired except for 1 hour before and after drug administration:

- Treatment A: A single oral dose of ALXN1840 120 mg administered as 15-mg enteric-coated tablets (supratherapeutic dose)
- Treatment B: A single oral dose of enteric-coated placebo tablets matching ALXN1840
- Treatment C: A single oral dose of moxifloxacin 400 mg tablet

Cardiodynamic assessment will be performed for approximately 25 hours on Day –1 of Treatment Period 1 and Day 1 to Day 2 of each treatment period. Blood samples for PK will be collected predose and at specified times up to 96 hours after the Day 1 dose in each treatment period.

Twelve-lead ECGs will be extracted from a continuous (Holter) recording by the central laboratory. To support high quality data for extraction, participants will be resting in the supine position for at least 15 minutes prior to and 5 minutes after each nominal time point for ECG extraction. Blood for plasma PK will be collected as close as possible to nominal time but after completion of ECG extraction period with actual times for blood sample collections recorded.

Participants will be domiciled in the clinic for 7 days in Treatment Period 1 and for 6 days in Treatment Periods 2 and 3, starting on Day –2 for Treatment Period 1 and on the day before dosing (Day –1) for Treatment Periods 2 and 3, until safety procedures have been completed and reviewed on Day 5. There will be a washout of at least 14 days between dose administration in each period.

All participants (including participants who terminate the study early) will return to the study site 14 days (±2 days) after the last administration of study intervention for follow-up procedures and to determine if any AE has occurred since the last study visit.

Duration of participation for each participant from the Screening Visit to the End-of-Study (EOS) Visit will be approximately 70 days. This includes up to 29 days for the Screening Period, study intervention administration on Day 1 of each treatment period, a minimum of a 14-day washout between study intervention administration in each treatment period, and 14 days (±2 days) for the EOS Visit.

3.1 SCHEDULE OF EVENTS

Phase	Screening	Same Schedule for Treatment Periods 1, 2, and 3																				EOS
		Check-in (Day -2 for Period 1; Day -1 for Periods 2 and 3																				
Day	–29 to –2	–2	–1	1															2	3	4	5	15 ±2
Procedure[a] Hours	–	–	–	-0.75	-0.5	-0.25	0	0.5	1	2	3	4	5	6	7	8	10	12	24	48	72	96	–
Admission to clinic[b]		X	X																				
Discharge from clinic[c]																						X	
Outpatient visit[d]																							X
Informed consent	X																						
Inclusion/exclusion criteria	X	X	X																				
Medical history[e]	X																						
Demographics	X																						
Serology[f]	X																						
Serum FSH[g]	X																						
Serum copper and ceruloplasmin	X																						
Height, weight, and BMI[h]	X	X	X																				X
Physical examination[i]	X	X	X																				X
Vital sign measurements[j]	X	X	X	X						X									X	X	X	X	X
12-lead safety ECG[k]	X	X	X	X								X		X		X		X	X			X	X
Clinical laboratory testing[l]	X	X	X																X			X	X
Urinalysis	X	X	X																				X
Drug/alcohol/cotinine screen[m]	X	X	X																				
Serum pregnancy test[n]	X	X	X																				X
Randomization (Period 1 only)				X																			
Study intervention administration[o]							X																

12-lead Holter ECG[p]			X	X	X	X Error! Reference source not found.		X	X	X	X	X	X	X	X	X	X	X	X				
PK blood sample[r]				X				X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Fasting period[s]			X	X	X	X	X	X	X	X	X	X											
Non-fasting period[s]													X	X	X	X	X	X	X	X	X	X	X
Adverse events[t]	←									X													→
Nonpharmacologic therapies and procedures	←									X													→
Prior/concomitant medications	←									X													→

Abbreviations: AEs, adverse events; BMI, body mass index; ECG, electrocardiogram; EOS, end of study; FSH, follicle-stimulating hormone; PK, pharmacokinetic.

Notes:

[a] When procedures overlap or occur at the same time point, all blood draws should follow vital signs or ECGs, and PK sampling should be timed to occur last and as close to the scheduled time window as possible.

[b] Participants will be asked to arrive at the study site on Day –2 of Treatment Period 1 and on the day before the start of dosing (Day –1) of Treatment Periods 2 and 3. The assessments scheduled for Day –2 of Treatment Period 1 will not be repeated on Day –1 of Treatment Period 1.

[c] Discharge from the study site will occur after the 96-hour PK samples and after completion and review by the Investigator of all 96-hour safety assessments (including safety laboratory test results) on Day 5 of each study period. There will be a washout of at least 14 days between dose administration in each period.

[d] The EOS Visit will occur 14 days (±2 days) after the last dose of study intervention in Period 3 or upon early discontinuation.

[e] A full medical history will be performed at Screening only. Any subsequent changes to health status will be assessed at each Check-in.

[f] A complete list of serology assessments is provided in Section 6.3.2.

[g] Females only. Further details are provided in Section 6.3.2.

[h] Height and weight will be measured and BMI calculated at Screening only. Only weight will be measured at Check-in and EOS.

[i] A full physical examination will be performed at Screening. A brief physical examination will be performed at Check-in and EOS. Further details are provided in Section 6.3.5.

[j] Predose vital signs on Day 1 may be obtained up to 1.5 hours before dosing. Further details on vital sign measurements are provided in Section 6.3.3.

[k] Predose ECG on Day 1 may be obtained up to 1.5 hours before dosing. Further details on safety ECG recordings are provided in Section 6.3.4.

[l] Further details on clinical laboratory assessments, including a complete list of assessments, are provided in Section 6.3.2.

[m] Further details on drug/alcohol/cotinine screening are provided in Section 6.3.2.

[n] Women only.

[o] The time of study intervention (ALXN1840, placebo, or moxifloxacin) dosing will be called “0” hour in each period. Further dosing details are provided in Section 5.1.

(p) Continuous 12-lead Holter ECG will be performed on Day -1 of Treatment Period 1 only to record the baseline ECG, which will allow extraction of ECG recordings that match the time points of Day 1 of Periods 1, 2 and 3. Further details on Holter ECG monitoring are provided in Section 6.1.1. On Day -1, participants shall follow the Day 1 supine positioning schedule. Participants shall assume supine positioning starting at least 15 minutes before the Day 1 timepoints for ECG extraction and continue to remain in the supine position until 5 minutes after the timepoint.

(q) The –0.25-hour predose ECG time point of Day 1, Treatment Period 1 will be used as the 24-hour ECG time point of Day -1, Treatment Period 1.

(r) Predose samples on Day 1 may be obtained up to 1.5 hours before dosing. Further details on the collection of blood samples for PK analysis are provided in Section 6.2.1.

(s) Further details on fasting and nonfasting periods are provided in Section 5.1.

(t) Further details on collection and reporting of AEs are provided in Section 6.3.1 and Appendix 3.

4. STUDY POPULATION

Approximately 54 healthy male and female participants will be enrolled at 1 center in the United States.

4.1 INCLUSION CRITERIA

Each participant must meet all of the following criteria to be enrolled in this study:

1. Participant is a healthy adult male or female, 18 to 50 years of age, inclusive, at Screening.

2. Participant is a continuous nonsmoker and or an individual who has not used tobacco or nicotine-containing products (eg, electronic vapor cigarettes, cigarettes, cigars, chewing tobacco, snuff, nicotine gum, nicotine patches) for at least 3 months prior to the first dose of study intervention and for the duration of the study. A cotinine test performed during Screening and Check-in must be consistent with continuous nonsmoking status.

3. Participant must weigh at least 60 kg for males or 52 kg for females and have a body mass index ≥18.0 and ≤30.0 kg/m^2 at Screening.

4. Participant must have a medical assessment with no clinically significant or relevant abnormalities as determined by medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory evaluation (hematology, serum chemistry, coagulation, and urinalysis) that are reasonably likely to interfere with the participant's participation in or ability to complete the study, or to potentially confound interpretation of study results, as assessed by the Investigator.

5. Female participants of nonchildbearing potential must have undergone 1 of the following sterilization procedures and have official documentation of these occurring more than 6 weeks prior to the first dose of study intervention:

    a. Hysteroscopic sterilization;

    b. Bilateral tubal occlusion, including Essure®;

    c. Bilateral tubal ligation or bilateral salpingectomy;

    d. Hysterectomy;

    e. Bilateral oophorectomy;

or be postmenopausal with amenorrhea for at least 1 year prior to the first dose of study intervention and have serum follicle-stimulating hormone levels consistent with postmenopausal status.

6. Female participants or female partners of male participants of childbearing potential (including breastfeeding females), if heterosexually active, must use highly effective contraception starting at least 6 weeks before the first dose of study intervention and continuing for at least 3 months after the end of systemic exposure of the study intervention. Female participants must not donate ova for at least 3 months after the end of systemic exposure of the study intervention. Highly effective contraceptive methods for females are as follows:

    a. Progestogen-only hormonal contraception associated with inhibition of ovulation as follows:

        i. Oral

        ii. Injectable

        iii. Implantable

    b. Intrauterine device

    c. Intrauterine hormone-releasing system

    d. Male partner vasectomized (with documented evidence of azoospermia if possible)

    e. Abstinence (note: sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study interventions. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant).

7. Male participants, if heterosexually active and with a female spouse or partner of childbearing potential or a pregnant or breastfeeding spouse or partner, must agree to use barrier contraception (male condom) for the duration of the study and for at least 3 months after the end of systemic exposure of the study intervention. Male participants must not donate sperm for at least 3 months after the end of systemic exposure of the study intervention.

Female spouses or partners of male participants who are of childbearing potential must use highly effective contraception as previously defined, starting at least 6 weeks before (the male participant's) first dose of study intervention and continuing until at least 3 months after the end of their male partner's systemic exposure to the study intervention.

For male participants who have had a vasectomy (with documented evidence of azoospermia if possible) and agree to use a male condom for the stated time period, no additional contraceptive method is required by their female partner. Male condom is required even with documented medical assessment of surgical success of a vasectomy.

8. Participant has no clinically significant history or presence of ECG findings as judged by the Investigator at Screening and Check-in, including each criterion as follows:

   a. Normal sinus rhythm (HR between 45 beats per minute [bpm] and 100 bpm inclusive)

   b. QT interval corrected for HR using Fridericia's formula (QTcF) ≤ 450 ms

   c. QRS interval ≤ 110 ms; and confirmed by manual over read if > 110 ms

   d. 120 ms ≤ PR interval ≤ 220 ms

4.2 EXCLUSION CRITERIA

Participants meeting any of the following criteria will be excluded from the study:

1. Participant has a significant history of or current cardiovascular, respiratory, hepatic, renal, GI, endocrine, hematological, psychiatric, or neurologic disorders.

2. Participant has a history of gastric bypass, other surgical procedure, or medical condition that may significantly alter absorption, metabolism, or excretion of drugs.

3. Participant has had lymphoma, leukemia, or any malignancy within the past 5 years, except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years; or has a history of breast cancer within the past 10 years.

4. Participant has abnormal blood pressure, defined as a supine blood pressure <90/50 mm Hg or >140/90 mm Hg at Screening and predose vital signs; if either systolic or diastolic components of blood pressure meet these criteria, then the participant must be

excluded. Blood pressure should be taken after a minimum of 5 minutes in the supine position.

5. Participant has serum potassium, calcium, or magnesium levels outside the normal range at Screening and/or Check-in, confirmed by repeat.

6. Participant has serum Cu and/or ceruloplasmin values below the lower limit of normal at Screening.

7. Female participant has hemoglobin <10.8 g/dL and male participant has hemoglobin <12.5 g/dL at Screening or Check-in.

8. Participant has history of alcoholism or history of regular alcohol consumption within 24 months prior to the study, defined as an average weekly intake of >7 units. One unit is equivalent to 1 pint of beer, 1 glass of wine, or 1 measure (single shot) of spirits.

9. Participant has clinically significant multiple or severe drug allergies, food allergies, or allergies to study intervention, this class of drug, its derivatives, or to medical products that may be used in the study (eg, allergy to ALXN1840, any sulfur containing drugs, moxifloxacin, fluoroquinolone antibiotics, latex, band-aids, adhesive dressing, medical tape).

10. Participant has alanine aminotransferase, aspartate aminotransferase, serum creatinine, or total bilirubin greater than upper limit of normal (ULN) for the testing laboratory. Participant's with confirmed Gilbert's syndrome may be included with total bilirubin >ULN if the participant has a measured direct bilirubin <ULN.

11. Participant has used any prescribed or over-the-counter medication (including dietary supplements, herbal remedies, and medications known to prolong the QTc interval) without the approval of the Investigator or Alexion within 14 days (or 5 half-lives, whichever is longer) before the first dose of study intervention and during the study.

12. Female participant is pregnant, as evidenced by a positive serum pregnancy test at screening or check-in, or lactating.

13. Participant has positive urine drug or alcohol results at Screening or Check-in.

14. Participant has presence of hepatitis B surface antigen or positive hepatitis C antibody or ribonucleic acid (RNA) test result at Screening or within 3 months prior to first dose of study intervention. NOTE: Participants with positive hepatitis C antibody due to prior

resolved disease can be enrolled if a confirmatory negative hepatitis C RNA test is obtained. NOTE: The RNA test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.

15. Participant has positive syphilis or human immunodeficiency virus (HIV)-1 and HIV-2 antigen/antibody immunoassay at Screening.

16. Participant has been on a diet incompatible with the on-study diet (including an extreme diet which resulted in a significant weight change for any reason), in the opinion of the Investigator, within the 29 days prior to the first dose of study intervention, and throughout the study.

17. Participant has donated blood or has had a significant blood loss of more than 500 mL within 56 days prior to the first dose of study intervention.

18. Participant has donated plasma within 7 days prior to the first dose of study intervention.

19. Participant is currently enrolled or has had past participation (within the last 30 days before signing of consent, 5 half-lives of the study intervention, or twice the duration of the biological effect of the study intervention [whichever is longer]) in this or any other clinical study involving an investigational study intervention or any other type of medical research.

20. Participant has participated in a previous clinical study where the participant received ALXN1840.

21. Participant has history or presence of:

    a. Hypokalemia, in the opinion of the Investigator

    b. Risk factors for torsades de pointes (eg, heart failure, cardiomyopathy, or family history of long QT syndrome)

    c. Sick sinus syndrome, second- or third-degree atrioventricular block, myocardial infarction, pulmonary congestion, cardiac arrhythmia, prolonged QT interval, or conduction abnormalities

    d. Repeated or frequent syncope or vasovagal episodes

    e. Hypertension, angina, bradycardia (if assessed as clinically significant by the Investigator), or severe peripheral arterial circulatory disorders

4.3 OTHER SCREENING CONSIDERATIONS

- Participants must be willing to remain at the study site from Day –2 through Day 5 of Treatment Period 1 and Day –1 through Day 5 in Treatment Periods 2 and 3.
- Participants must refrain from strenuous activity or contact sports from 24 hours before the first dose of study intervention through the end of the study.
- Participant must refrain from ingesting grapefruit or grapefruit juice, pomegranate or pomegranate juice, pomelo fruit or pomelo juice, alcohol, or xanthine-containing products (eg, tea, coffee, chocolate, cola) within 72 hours before the first dose of study intervention through the end of the study.

4.4 WITHDRAWAL OF PARTICIPANTS FROM THE STUDY

4.4.1 Reasons for Withdrawal

Participants can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment.

The Investigator may withdraw a participant from the study if the participant:

1. Is noncompliant with the protocol;
2. Experiences a serious AE (SAE) or intolerable AE(s) that in the investigator's opinion requires withdrawal from the study;
3. Has laboratory safety assessments that reveal clinically significant hematological or biochemical changes from Baseline values;
4. Has postdose safety ECG result (confirmed by repeat within 1 hour) that reveals a new QTc duration >500 ms or an increase from Baseline of >60 ms;
5. Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria;
6. Requires a medication prohibited by the protocol; or
7. Requests an early discontinuation for any reason.

The Investigator can also withdraw a participant upon the request of Alexion, or if Alexion terminates the study. Upon occurrence of an SAE or intolerable AE, the Investigator will

confer with Alexion. If a participant is discontinued because of an AE, the event will be followed until it is resolved, stable, or judged by the Investigator to be not clinically significant.

4.4.2 Handling of Withdrawals

Participants are free to withdraw from the study at any time upon request. Participation in the study may be stopped at any time at the discretion of the Investigator or at the request of Alexion.

When a participant withdraws from the study, the reason(s) for withdrawal shall be recorded by the Investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, any participant who withdraws from the study prematurely will undergo all EOS assessments. Any participant who fails to return for final assessments will be contacted by the study site in an attempt to have them comply with the protocol. The status of participants who fail to complete final assessments will be documented in the eCRF.

4.4.3 Replacements

At the discretion of Alexion, and in consultation with the Investigator, any participant who withdraws before completing the study may be replaced to retain the target of 45 evaluable participants. Any replacement participant will be assigned to receive the same treatment as the participant he or she is replacing.

5. STUDY INTERVENTION

5.1 STUDY INTERVENTION ADMINISTERED

On Day 1 of each period, participants will receive 1 of the following study interventions according to the randomization schedule:

- Treatment A: A single oral dose of ALXN1840 120 mg administered as eight 15-mg enteric-coated tablets (supratherapeutic dose)
- Treatment B: A single oral dose of 8 enteric-coated placebo matching tablets of ALXN1840
- Treatment C: A single oral dose of moxifloxacin 400 mg tablet

The possible sequences are as follows:

	Period 1	Period 2	Period 3
Sequence 1	A	B	C
Sequence 2	A	C	B
Sequence 3	B	A	C
Sequence 4	B	C	A
Sequence 5	C	A	B
Sequence 6	C	B	A

All doses of study intervention will be administered with 240 mL of room temperature water under fasting conditions. Water is permitted as desired except for the period 1 hour before and 1 hour after administration of study intervention. During fasting periods, participants will fast overnight (nothing to eat or drink except water) for at least 10 hours before each study intervention administration. Participants will remain fasting and will maintain an upright (seated or standing) position for 4 hours after dosing with study intervention (not including the time when the participant is required to be supine for Holter ECG extractions). During nonfasting periods, participants should receive standardized meals scheduled at the same time in each period of the study.

5.2 STUDY INTERVENTION

The study interventions that will be used are as follows:

Product	Supplied Formulation
ALXN1840	15-mg enteric-coated tablet
Placebo	Enteric-coated tablet
Moxifloxacin (positive control)	400-mg tablet

ALXN1840 tablets will be supplied by Alexion. The ALXN1840 tablet contains the following inactive excipients: tribasic calcium phosphate, National Formulary (NF), anhydrous sodium carbonate NF, sodium starch glycolate NF, magnesium stearate NF, Opadry 03K19229 clear, and acryl-EZE.

Placebo tablets will be supplied by Alexion. The placebo tablet contains only inactive excipients.

Moxifloxacin (generic formulation, Torrent Pharmaceuticals Limited) will be sourced by the PPD pharmacy.

Further information on ALXN1840 can be found in the IB (Alexion Pharmaceuticals, Inc. 2020).

5.2.1 Study Intervention Packaging and Storage

Alexion Pharmaceuticals, Inc. will provide the Investigator and study site with adequate quantities of ALXN1840. The study site will provide moxifloxacin in its commercially-available form. An unblinded study site pharmacist will prepare the study interventions for each participant according to the schedule of events (Section 3.1). Detailed instructions for the preparation of study interventions will be provided in a separate pharmacy manual.

All study interventions must be stored according to the labeled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. The study site will be required to keep a temperature log to establish a record of compliance with storage conditions.

5.2.2 Study Intervention Accountability

The Investigator will maintain accurate records of receipt of all study interventions, including dates of receipt. Accurate records will be kept regarding when and how much study intervention is dispensed and used by each participant in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, and to satisfy regulatory requirements regarding drug accountability, all study interventions will be reconciled and retained or destroyed according to applicable regulations.

5.3 METHOD OF ASSIGNING PARTICIPANTS TO TREATMENT GROUPS

A randomization schedule will be generated containing randomization numbers (in sequential order), which will be assigned before the first dose of study intervention is administered on Day 1 of Treatment Period 1.

After meeting all of the inclusion criteria and none of the exclusion criteria, participants will be randomized to 1 of the 6 pre-specified treatment sequences. To ensure that the sequences are balanced within sex, randomization will be stratified by sex.

5.4 BLINDING

5.4.1 Blinding Procedures

This study will employ a double-blind study design. The ALXN1840 and matching placebo will be identical in appearance and will be administered in a double-blind manner.

Moxifloxacin, as the positive control, will not be blinded. The unblinded pharmacist will be responsible for dispensing the study intervention in a manner consistent with maintaining the blind; moxifloxacin doses will be prepared in an open-label manner.

Access to the randomization code will be strictly controlled according to the standard operating procedures of PPD. The ECG core laboratory will be blinded to all study interventions.

5.4.2 Breaking the Blind

The Medical Monitor will be responsible for maintaining the blind throughout the study. If a participant becomes seriously ill or pregnant during the study, the blind will be broken only if knowledge of the administered study intervention will affect that participant's available treatment options. In the event of a medical emergency requiring identification of the study intervention administered to an individual participant, the Investigator will make every attempt to contact the Medical Monitor to explain the need for opening the code within 24 hours of opening the code. The Investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

5.5 TREATMENT COMPLIANCE

All doses of the study intervention will be administered in the study site under direct observation of study site personnel and recorded in the eCRF. Study site personnel will confirm that the participant has received the entire dose of study intervention.

The date and time of study intervention dosing will be recorded on the appropriate page of the eCRF. If a participant is not administered study intervention, the reason for the missed dose will be recorded.

5.5.1 Prior and Concomitant Medications

Restrictions for prior and concomitant medications and therapies are provided in Sections 4.1 and 4.2. Prior and concomitant medications and therapies will be coded using the World Health Organization Drug Dictionary.

5.5.1.1 Prior Medications

Information regarding prior medications taken by the participant within the 30 days before signing the informed consent form (ICF) will be recorded in the participant's eCRF.

5.5.1.2 Concomitant Medications

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, or other specific categories of interest) that the participant receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

If a concomitant medication is taken, except for those specified in the protocol, a joint decision will be made by the Investigator and Alexion to continue or discontinue the participant based on the time the medication was administered, its pharmacology and PK, and whether the use of the medication will compromise the safety of the participant or the interpretation of the data. The Investigator is responsible for ensuring that details regarding the medication are adequately recorded in the eCRF.

6. STUDY PROCEDURES

Before performing any study procedures, all potential participants will sign an ICF as outlined in Section 9.2.2.3. Participants will undergo study procedures at the time points specified in the schedule of events (Section 3.1).

The total amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

6.1 CARDIODYNAMIC ASSESSMENTS AND ENDPOINTS

6.1.1 Continuous Holter Electrocardiograms

Twelve-lead ECGs will be extracted from approximately 25-hour continuous (Holter) recordings on Day –1 of Treatment Period 1 and Days 1 and 2 in each treatment period. Participants should be resting supinely for at least 15 minutes before and 5 minutes after each time point for ECG extraction, which should precede blood samples. The actual times of dosing, supine rest, and PK sampling will be communicated to the central ECG laboratory (ERT, Rochester, NY) by the site.

Electrocardiograms will be extracted by a central ECG laboratory (ERT, Rochester, NY) from the continuous Holter recording of Day 1 of the Treatment Periods 1, 2, and 3 at the following 15 (3 predose and 12 postdose) time points: predose at –45, –30, and –15 minutes; and postdose at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 (Day 2) hours. For HR-corrected QTc calculation in case of a substantial HR-effect due to ALXN1840, ECG extraction from the Holter recording of Day -1 of Treatment Period 1 will include continuous ECG extraction for optimized QT interval (QTcI) calculation, and if needed, ECG extraction at the 15 timepoints that precisely match the extraction timepoints for Day 1 of Periods 1, 2 and 3 for individual QT interval (QTcS) calculation. The following ECG parameters will be measured and calculated: HR, PR interval, QTcF, QRS interval, treatment-emergent T-wave morphology abnormalities, and appearance of U-waves.

All ECG data will be collected using Welch Allyn (Mortara) Surveyor Central. The raw data from the Surveyor system will be saved to the archive database (hScribe). The data will be burned onto a hard drive and sent to ERT. The ECGs to be used in the analyses will be selected by pre-determined time points, as defined in the schedule of events (Section 3.1), and will be read centrally by ERT.

The following principles will be followed in ERT's core laboratory:

- ECG analysts will be blinded to the participant, visit, and treatment allocation.
- Baseline and on-treatment ECGs for a particular participant will be over-read on the same lead and will be analyzed by the same reader.
- The primary analysis lead will be lead II. If lead II is not analyzable, then the primary lead of analysis will be changed to another lead for the entire participant data set.

6.1.1.1 Thorough QT Plus Electrocardiogram Technique

Ten 14-second digital 12-lead ECG tracings will be extracted from the continuous Holter recordings using the "TQT Plus method", a computer-assisted and statistical process utilized by ERT. The method enables the extraction of ECGs with the lowest HR variability and noise within the protocol-specified extraction time window (eg, the HR and QT changes from beat to beat in the range of <10%). At each protocol-specified time point, 10 ECG replicates will be extracted from a 5-minute ECG window (typically, the last 5 minutes of the 15-minute period when the participant is maintained in a supine or semi-recumbent quiet position).

6.1.1.2 Expert-Precision QT Analysis

Expert-precision QT analysis will be performed on all analyzable (non-artifact) beats in the 10 ECG replicates. Statistical quality control procedures are used to review and assess all beats and identify "high" and "low" confidence beats using several criteria, including:

- QT or QTc values exceeding or below certain thresholds (biologically unlikely)
- RR values exceeding or below certain thresholds (biologically unlikely)
- Rapid changes in QT, QTc, or RR from beat to beat

Measurements of all primary ECG parameters (QT, QTc, RR) in all recorded beats of all replicates that are deemed "high confidence" will be performed using the COMPAS software. All low-confidence beats will be reviewed manually and adjudicated using pass-fail criteria. The final quality control assessment will be performed by a cardiologist. The beats found acceptable by manual review will be included in the analysis. The median QT, QTc, and RR value from each extracted replicate will be calculated, and the mean of all available medians from a nominal time point will be used as the participant's reportable value at that time point.

Categorical T-wave morphology analysis and the measurement of PR and QRS intervals will be performed manually in 3 of the 10 ECG replicates at each time point. Each fiducial point (onset of P-wave, onset of Q-wave, offset of S-wave, and offset of T-wave) will be electronically marked.

For T-wave morphology and U-wave presence, treatment-emergent changes will be assessed, ie, changes not present at Baseline. For each category of T-wave morphology and of U-waves, the category will be deemed as present if it is observed in any replicates at the time point. For Baseline, the category will be deemed as present if it is observed in any replicates from all time points that constitute Baseline. The T-wave morphology categories are described in Table 2.

Table 2: Categories for T-Wave Morphology and U-Wave Presence (Assessed Manually)

Category	Description
Normal T-wave	Any positive T-wave not meeting any criterion below
Flat T-wave	T amplitude <1 mm (either positive or negative), including a flat isoelectric line
Notched T-wave (+)	Presence of notch(es) of at least 0.05 mV amplitude on ascending or descending arm of the positive T-wave

Category	Description
Biphasic	T-wave that contains a second component with an opposite phase that is at least 0.1 mV deep (both positive/negative and negative/positive and polyphasic T-waves included)
Normal T-wave (-)	T amplitude that is negative, without biphasic T-wave or notches
Notched T-wave (-)	Presence of notch(es) of at least 0.05 mV amplitude on descending or ascending arm of the negative T-wave
U-waves	Presence of abnormal U-waves

6.1.2 Cardiodynamic Electrocardiogram Analysis

The primary endpoint is placebo-corrected change from Baseline QTcF (ΔΔQTcF) for ALXN1840 using the by-time point analysis. The secondary endpoints are the ΔΔQTcF for moxifloxacin; the change from Baseline in HR, QTcF, PR, QRS (ΔHR, ΔQTcF, ΔPR and ΔQRS); the placebo-corrected change from Baseline HR, PR, and QRS (ΔΔHR, ΔΔPR and ΔΔQRS); categorical outliers for QTcF, HR, PR, and QRS; and the frequency of treatment-emergent changes of T-wave morphology and U-wave presence. The exploratory endpoint is the ΔΔQTcF for ALXN1840 using the concentration-QTc analysis by concentrations of total Mo or PUF Mo (as surrogate measures of ALXN1840 PK) in plasma.

For all continuous ECG parameters from each period, Baseline is defined as the average of the measured ECG intervals from the 3 predose time points (−45, −30, and −15 minutes before dosing) on Day 1 for the respective period. For T-wave morphology and U-wave presence, Baseline includes findings observed in any replicates from the 3 predose time points (−45, −30, and −15 minutes) on Day 1 in each period.

To enable HR-corrected evaluation of QTc via methods such as QTcI and/or QTcS calculation, if justified by a substantial change in HR due to ALXN1840, participants will undergo 12-lead Holter ECG monitoring on Day -1 of Treatment Period 1.

6.2 PHARMACOKINETIC ASSESSMENTS AND ENDPOINTS

Blood samples for PK analysis of total Mo and PUF Mo (as surrogate measures of ALXN1840 PK) will be collected at the following time points: within 1.5 hour before dosing and postdose at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, and 96 hours in each period. Only samples collected predose and after ALXN1840 administration will be analyzed for plasma total Mo and PUF Mo. Samples collected predose and after placebo or moxifloxacin administration will be saved for analysis, if needed.

The following plasma PK parameters will be calculated as endpoints for total Mo and PUF Mo, using noncompartmental methods with Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) Version 8.0 or higher or SAS® (SAS® Institute Inc., Cary, North Carolina) Version 9.4 or higher, as applicable. Calculations will be based on the actual sampling times elapsed from the reference dosing time in the period as recorded during the study.

- Time delay between the time of dosing and time of appearance of Mo concentration in plasma (T_{lag})
- Maximum observed concentration in plasma (C_{max})
- Time to reach maximum observed concentration in plasma (T_{max})
- Area under the concentration in plasma versus time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t})
- AUC from time 0 to 96 hours postdose (AUC_{0-96})
- AUC from time 0 extrapolated to infinity (AUC_{0-inf})
- Apparent terminal-phase elimination rate constant (λ_z)
- Terminal elimination half-life ($t_{1/2}$)
- Apparent total clearance from plasma after oral administration of ALXN1840 (CL/F)
- Apparent volume of distribution during the terminal phase (V_z/F)

Additional PK parameters may be calculated if deemed appropriate.

6.2.1 Pharmacokinetic and Pharmacodynamic Sample Collection

Collection of samples for PK evaluation should occur as close as possible to the scheduled time and actual time of collection should be documented on the eCRF. Samples collected within ± 10% of the scheduled time, or 30 minutes whichever is less, will not be considered a protocol deviation. Details for the collection, processing, storage, and shipping of PK samples will be provided to the study site separately.

6.2.2 Pharmacokinetic and Pharmacodynamic Sample Analyses

Pharmacokinetic samples will be analyzed using validated inductively coupled plasma-mass spectrometry (ICP-MS) methods for total Mo and PUF Mo in human plasma. Assay results and validation details will be provided in a separate bioanalytical report.

Pharmacokinetic samples may be used for the quantification of pharmacodynamic (PD) endpoints such as total Cu, PUF Cu, labile bound Cu, ceruloplasmin, and ceruloplasmin-bound Cu.

6.3 SAFETY ASSESSMENTS AND ENDPOINTS

Safety and tolerability will be assessed by the following endpoints: monitoring and recording of AEs, clinical laboratory test results (hematology, serum chemistry, and urinalysis), vital sign measurements, 12-lead safety ECG results, and physical examination findings.

For all safety assessments, the Investigator will determine whether results are clinically significant, which is defined as any variation in a result that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If clinical significance is noted, the result and reason for significance will be documented and an AE will be reported on the AE page of the participant's eCRF. The Investigator will monitor the participant until the result has reached the reference range or the result at Screening, or until the Investigator determines that follow-up is no longer medically necessary.

6.3.1 Adverse Events and Serious Adverse Events

The definitions of AEs and SAEs can be found in Section 9.3. Adverse events will be reported to the Investigator or qualified designee by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention(s) (see Section 4.4). Procedures for recording, evaluating, follow-up, and reporting AEs and SAEs are outlined in Appendix 3.

6.3.1.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be assessed from the time of signing the informed consent until EOS and should be followed until they are resolved, stable, or judged by the Investigator to be not clinically significant.

All SAEs will be recorded and reported to Alexion or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to Alexion within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify Alexion.

6.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

6.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the Investigator is required to proactively follow each participant at subsequent visits or contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is provided in Appendix 3.

6.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the Investigator to Alexion of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs), and Investigators.

- Suspected unexpected serious adverse reactions (SUSARs) must be reported according to local regulatory requirements and Alexion policy and forwarded to Investigators as necessary.

- An Investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

6.3.1.5 Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female participants and female spouses/partners of male participants. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure. If a female participant or a male participant's female partner becomes pregnant from the first dose of study drug up to 3 months post the last dose of study drug, the Investigator must submit the Pregnancy/Breastfeeding Reporting and Outcome Form to Alexion Global Drug Safety (GDS) via facsimile or email within 24 hours of awareness of the pregnancy: PPD or Fax: PPD When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow-up is required, the Investigator will be requested to provide the information.

Exposure of an infant to an Alexion product during breastfeeding must also be reported (via the Pregnancy/Breastfeeding Reporting and Outcome Form) and any AEs experienced by the infant must be reported to Alexion GDS or designee via email or facsimile.

Pregnancy is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

For all Alexion products, both in development or post-approval, exposure during pregnancy must be recorded and the pregnancy followed until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the participant discontinues the study intervention or withdraws from the study. The corresponding infant must be followed for 3 months postpartum.

Any female participant who becomes pregnant while participating in the study will be discontinued from study intervention.

6.3.1.5.1 Male Participants with Partners who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate Pregnancy/Breastfeeding Reporting and Outcome Form and submit it to Alexion within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Alexion. Generally, the follow-up will be no longer than 3 months following the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

6.3.1.5.2 Female Participants who Become Pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to Alexion within 24 hours of learning of a participant's pregnancy.

- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to Alexion. Generally, follow-up will not be required for longer than 3 months beyond the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at less than 22 weeks gestational age) or stillbirth (occurring at greater than 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to Alexion as described in Section 6.3.1.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

6.3.2 Clinical Laboratory Testing

Clinical laboratory testing will occur at Screening; at Check-in (Day –2 of Treatment Period 1 and Day –1 of Treatment Periods 2 and 3), Day 2, and Day 5 of each period; and at the EOS Visit. Clinical laboratory tests will be performed by the PPD Central Laboratory. Blood and urine samples will be collected under fasting conditions and will be prepared using standard procedures.

Repeat clinical laboratory tests may be performed at the discretion of the Investigator, if necessary, to evaluate inclusion and exclusion criteria or clinical laboratory abnormalities. The clinical laboratory that will perform the tests will provide the reference ranges for all clinical laboratory parameters. Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter.

The following clinical laboratory assessments will be performed:

Hematology	Absolute neutrophil count, total leukocytes, and leukocyte differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, and red cell distribution width
Coagulation	Activated partial thromboplastin time, prothrombin time, and international normalized ratio (Screening only)

Serum Chemistry	Alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin (total and direct), blood urea nitrogen, calcium, bicarbonate, chloride, cholesterol (total, high-density lipoprotein, and calculated low-density lipoprotein), creatinine, gamma-glutamyltransferase, globulin, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total protein, triglycerides, and creatine kinase Screening only: serum Cu and ceruloplasmin
Urinalysis	Appearance, bilirubin, color, glucose, ketones, leukocytes, reflex microscopy (performed if dipstick is positive for protein or the blood value is 1+ or greater; and includes bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells), nitrites, occult blood, pH, protein, specific gravity, turbidity, and urobilinogen
Serology	Hepatitis B surface antigen, hepatitis C virus antibody; HIV-1 and HIV-2 antigen/antibody immunoassay; and syphilis (Screening only) NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C RNA test is obtained. NOTE: The RNA test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.
Other analyses	• All participants: Urine drug screen (alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, cotinine, methamphetamines, methylenedioxymethamphetamine, and opiates [including heroin, codeine, and oxycodone]) • Female participants: Follicle-stimulating hormone, serum pregnancy test (human chorionic gonadotropin)

6.3.3 Vital Sign Measurements

Vital signs will be measured at Screening and at the following time points in each period: Day –1; on Day 1 within 1.5 hours prior to study intervention; and at 2, 24, 48, 72, and 96 hours postdose; and at EOS after the participant has been in the supine position for at least 5 minutes.

Vital signs will include systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

If vital signs are abnormal, 2 additional repeats should be performed with an average of the 3 reported in the eCRF and to support eligibility.

6.3.4 Safety Electrocardiograms

Since an ECG recorder that stores all digital ECGs on a digital flash card performs the recording of ECGs for the endpoint analysis, no ECG is available for immediate assessment of safety at the site. Therefore, after the participant has been in the supine position for at least 5 minutes, standard digital 12-lead safety ECGs will be recorded on site at Screening, Day -2 of Treatment Period 1, and at the following time points in each period: Day –1; on Day 1 within 1.5 hours before dosing (in triplicate, approximately 1 minute apart); at 4, 6, 8, 12, 24, and 96 hours postdose; and at EOS (single ECGs) to detect any immediate ECG effects on participant safety. A single repeat measurement is permitted at Screening for eligibility determination.

The Mortara Eli 250c machine will be used for safety ECG collection. Measurements of the following intervals will be automatically measured and reported by the Mortara Eli 250c: RR interval, PR interval, QRS width, QT interval, and QTcF. The safety ECGs will be evaluated on site by the Investigator. The Investigator will document his or her assessment on the ECG; assessments will include comments on whether the tracings are normal or abnormal, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST-segment, T-wave, and U-wave abnormalities.

Any postdose ECG with a QTc >500 ms or an increase from Baseline of >60 ms (as defined by automatically measured intervals) should be confirmed by a second ECG within 1 hour. If results are confirmed by repeat measurement, the participant will be discontinued from the study (Section 4.4.1).

6.3.5 Physical Examinations

A full physical examination will be performed at Screening. A brief physical examination will be performed at Day –1 in each period and at EOS. A full physical examination will include, at minimum, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities. A brief physical examination will include, at minimum, assessment of skin, lungs, cardiovascular system, and abdomen (liver and spleen). Interim physical examinations may be performed at the discretion of the Investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

7. STATISTICAL ANALYSIS PLANS

7.1 SAMPLE SIZE CALCULATIONS

A sample size of approximately 54 participants was chosen to obtain 45 evaluable participants to complete the study. Assuming a 1-sided 5% significance level and a within-participant standard deviation of 8 ms for ΔQTcF for all treatment groups and a true mean difference of 3 ms in ΔQTcF between ALXN1840 and placebo, based on the calculation of the sample size for a TQT study (Zhang 2008), a sample size of 45 evaluable participants will provide a power of 90% to demonstrate that the upper bound of all the 2-sided 90% CIs on ΔΔQTcF will fall below 10 ms for up to 12 postdose time points. To account for a drop-out rate of approximately 16%, 54 participants will be enrolled.

Based on the calculation of the sample size for a TQT study (Zhang 2008), as the test is performed at 3 time points separately (1, 2, and 3 hours), a 1-sided 5% significance level (with adjusted 1-sided significance levels of 5%, 2.5%, and 1.67%) is used along with a within-participant standard deviation of 8 ms for ΔQTcF and a true effect of moxifloxacin of 10 ms, a sample size of 45 evaluable participants will provide greater than 98% power to demonstrate assay sensitivity of excluding a mean difference of 5 ms in ΔQTcF between moxifloxacin and placebo groups.

7.2 ANALYSIS SETS

The analysis populations are as follows:

- The Safety Set will include all participants who receive at least 1 dose of study intervention (ALXN1840, moxifloxacin, or placebo) and for whom any safety data are available.
- The QT/QTc Set will include all participants in the Safety Set with measurements at Baseline as well as on-treatment with at least 1 postdose time point with a valid ΔQTcF value. The QT/QTc Set will be used for the by-time point, assay sensitivity, and categorical analyses of the cardiodynamic ECG parameters.
- The PK Set will include all participants who receive at least 1 dose of ALXN1840 and have evaluable PK data for total Mo and PUF Mo (as surrogate measures of ALXN1840 PK) in plasma. The PK Set will be used for PK analysis.
- The PK/QTc Set will include all participants who are in both the QT/QTc and PK Sets with at least 1 pair of postdose PK and QTcF data from the same time point as well as

participants in the QT/QTc Set who received placebo. The PK/QTc Set will be used for the exploratory concentration-QTc analysis.

7.3 STATISTICAL ANALYSIS

Details of all statistical analyses will be described in a statistical analysis plan. All data collected will be presented in data listings. Data from participants excluded from an analysis population will be presented in the data listings, but not included in the calculation of summary statistics.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of participants, mean, median, standard deviation, minimum, and maximum).

Baseline demographic and background variables will be summarized for all participants. The number of participants who enroll in the study, the number and percentage of participants in each analysis set, and the number and percentage of participants who complete the study will be presented. Frequency and percentage of participants who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

7.3.1 Cardiodynamic Analyses

7.3.1.1 By-Time Point Analysis (Primary Analysis)

Cardiodynamic analyses will be based on the QT/QTc Set. The primary analysis will be based on by-time point analysis to evaluate the effect of ALXN1840 on the ΔΔQTcF at each postdosing time point ("by-time point" analysis) using the intersection union test (IUT). The effect of ALXN1840 on placebo-corrected change from Baseline in HR, PR, and QRS (ΔΔHR, ΔΔPR, and ΔΔQRS) will also be evaluated using the IUT.

The statistical hypothesis to be tested for the primary assessment of QT prolongation for the ALXN1840 treatment is:

H_0: $\cup \{\mu_{D(i)} - \mu_{P(i)}\} \geq 10$, $i = 1,2,\ldots,12$

H_1: $\cap \{\mu_{D(i)} - \mu_{P(i)}\} < 10$, $i = 1,2,\ldots,12$

where $\mu_{D(i)}$ and $\mu_{P(i)}$ are the least squares (LS) mean of ΔQTcF for ALXN1840 and placebo at postdose time point i, respectively.

The by-time point analysis for QTcF will be based on a mixed-effects model for repeated measures (MMRM) with change from Baseline QTcF (ΔQTcF) as the dependent variable; period, sequence, time (ie, postdose time point: categorical), treatment (supratherapeutic dose of ALXN1840, moxifloxacin, and placebo), and time-by-treatment interaction as fixed effects and Baseline QTcF and sex as a covariates. An unstructured covariance matrix will be used to model within-participant errors. If the model with unstructured covariance matrix fails to converge, other covariance structure such as Toeplitz with heterogeneity (TOEPH), auto-regressive with heterogeneity (ARH), compound symmetry with heterogeneity (CSH), TOEP, AR, and CS will be considered in decreasing complexity in parameterization. The final model selection will be based on Akaike information criterion (AIC). The degrees of freedom estimates will be determined by the Kenward-Roger method. The model will also include a participant-specific random effect. Least squares mean difference and 2-sided 90% CI will be calculated for the contrast ALXN1840 versus placebo at each postdose time point, separately. If the upper bound of the 2-sided 90% CI of LS mean ΔΔQTcF lies below 10 ms at all 12 postdose time points, ALXN1840 will be concluded not to have a significant effect on QT interval prolongation.

For HR, PR, and QRS, the analysis will be based on the change from Baseline postdosing (ΔHR, ΔPR, and ΔQRS). The same (by-time point analysis) model will be used as described for QTcF. The LS mean, SE, and 2-sided 90% CI from the statistical modeling for both change from Baseline and placebo-corrected change from Baseline values will be listed in the tables and graphically displayed.

Other QT interval corrections such as QTcI may be performed, if justified, with details to be included in the Statistical Analysis Plan.

7.3.1.2 Categorical Analyses

An analysis of categorical outliers will be performed for changes in HR, PR, QRS, QTcF, T-wave morphology, and U-wave presence. The results for categorical outliers, T-wave morphology, and U-wave presence will be summarized in frequency tables with counts (percentages) for both number of participants and number of time points. For categorical outliers, the number (percentage) of participants as well as time points who had absolute QTcF values >450 and ≤480 ms, >480 and ≤500 ms, or >500 ms, and changes from predose Baseline (ΔQTcF) of >30 and ≤60 ms, or >60 ms; increase in PR from predose Baseline >25% to a PR >200 ms; increase in QRS from predose Baseline >25% to a QRS >120 ms; decrease in HR from predose Baseline >25% to a HR <50 bpm; and increase in HR from predose Baseline >25% to a HR >100 bpm will be determined. For T-wave morphology and

U-wave presence, treatment-emergent changes will be assessed; ie, changes not present at Baseline. For each category of T-wave morphology and of U-waves, the category will be deemed as present if observed in any replicates at the time point.

7.3.1.3 Assay Sensitivity

Assay sensitivity will also be evaluated using by-time point analysis of the effect on ΔΔQTcF of moxifloxacin using a similar model as for the primary analysis. The analysis to show assay sensitivity will be based on the change from Baseline postdosing QTcF of moxifloxacin. For the 3 predefined time points (1, 2, and 3 hours postdose), the contrast in treatment ΔΔQTcF = moxifloxacin versus placebo will be tested against the 1-sided null hypothesis ΔΔQTcF ≤5 ms on the 5% level. Multiplicity will be controlled by using a Hochberg procedure (Hochberg 1998). If after this procedure the LS mean of ΔΔQTcF is significantly larger than 5 ms for at least 1 time point of these 3 time points, assay sensitivity will be considered to have been demonstrated. In addition, 2-sided 90% CIs will be obtained for the contrast at all time points and used in the figures.

7.3.2 Pharmacokinetic Analyses

Pharmacokinetic analyses will be based on the PK Set. Plasma total Mo and PUF Mo (as surrogate measures of ALXN1840 PK) and time deviation data will be presented in a data listing by participant. Concentration data will be summarized separately by analyte and time point for each treatment using the following descriptive statistics: number of participants, arithmetic mean, SD, coefficient of variation (CV), geometric mean, geometric CV, median, minimum, and maximum. Mean concentration versus scheduled time profiles will be presented in figures on both linear and semilogarithmic scales. Individual concentration versus actual time profiles will be presented similarly.

Pharmacokinetic parameters derived from plasma total Mo and PUF Mo using noncompartmental methods will be presented in data listings and summarized separately using the following descriptive statistics: number of participants, arithmetic mean, standard deviation, arithmetic CV, geometric mean, geometric CV, median, minimum, and maximum. Geometric mean and geometric CV will be presented for C_{max} and AUCs only.

7.3.3 Pharmacokinetic Concentration/QTc Analysis (Exploratory Analysis)

Pharmacokinetic concentration/QTc analysis will be based on the PK/QTc Set. The relationship between total Mo or PUF Mo (as surrogate measures of ALXN1840 PK)

concentrations in plasma and ΔΔQTcF will be explored graphically and using a linear mixed-effects modeling approach with ΔΔQTcF as the dependent variable, total Mo or PUF Mo concentration in plasma as the exploratory variate (0 for placebo), centered Baseline QTcF (ie, Baseline QTcF for individual participant minus the population mean Baseline QTcF for all participants in the same treatment period) as an additional covariate, treatment (active = 1 or placebo = 0) and time (ie, postdose time point) as fixed effects, and a random intercept and slope per participant (Garnett 2018). The degrees of freedom estimates will be determined by the Kenward-Roger method. From the model, the slope (ie, the regression parameter for the total Mo or PUF Mo concentration in plasma) and the treatment effect-specific intercept (defined as the difference between active and placebo) will be estimated together with 2-sided 90% CI. The estimates for the time effect will be reported with degrees of freedom and SE.

The geometric mean of the individual C_{max} values for total Mo or PUF Mo (as surrogate measures of ALXN1840 PK) concentrations in plasma for participants in the active drug group will be determined. The predicted effect and its 2-sided 90% CI for ΔΔQTcF (ie, slope estimate × concentration + treatment effect-specific intercept) at this geometric mean C_{max} will be obtained.

7.3.4 Safety Analyses

Safety analyses will be based on the Safety Set. Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) Version 22 or higher. All AE data will be presented in a data listing. Treatment-emergent AEs will be summarized by treatment and overall, as well as by severity and relationship to study intervention. Serious AEs and AEs leading to early discontinuation will also be presented in data listings.

Actual values and changes from Baseline for clinical laboratory test results, vital sign measurements, and 12-lead safety ECG results will be summarized by treatment at each time point using descriptive statistics (number of participants, mean, SD, median, minimum, and maximum). Laboratory parameter values will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). Shift tables by treatment will be produced for these laboratory parameters. These tables will summarize the number of participants with each Baseline grade relative to the reference ranges and changes to the worst highest grade assessed postdose during the study. Clinical laboratory test results, vital sign measurements, 12-lead safety ECG results, and physical examination findings will be presented in data listings.

7.4 HANDLING OF MISSING DATA

For descriptive statistics of safety and PD laboratory data values that are below the lower limit of quantification (LLOQ) will be treated as LLOQ and those above the upper limit of quantification (ULOQ) will be treated as ULOQ. Missing concentrations will be excluded from the calculations.

For the PK analysis, results below the LLOQ values will be treated as zero with the exception that a value below the LLOQ between 2 quantifiable concentrations will be set as missing. Missing concentrations will be treated as missing from the PK parameter calculations. If consecutive concentrations below the LLOQ are followed by quantifiable concentrations in the terminal phase, those concentrations after the concentrations that are below the LLOQ will be treated as missing.

7.5 INTERIM ANALYSES

No formal interim analyses will be performed in this study.

8. REFERENCE LIST

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9. APPENDICES

9.1 APPENDIX 1: LIST OF ABBREVIATIONS

Abbreviation	Term
ΔHR	change from Baseline in heart rate
ΔPR	change from Baseline in PR interval
ΔQRS	change from Baseline in QRS interval
ΔQTcF	change from Baseline in the QT interval corrected for heart rate using Fridericia's formula
ΔΔHR	placebo-corrected change from Baseline in heart rate
ΔΔPR	placebo-corrected change from Baseline in PR interval
ΔΔQRS	placebo-corrected change from Baseline in QRS interval
ΔΔQTcF	placebo-corrected change from Baseline in the QT interval corrected for heart rate using Fridericia's formula
AE	adverse event
ATP	adenosine triphosphatase
ATPase2	adenosine triphosphatase 2
AUC	area under the concentration in plasma versus time curve
AUC_{0-96}	area under the concentration in plasma versus time curve from time 0 to 96 hours postdose
AUC_{0-inf}	area under the concentration in plasma versus time curve from time 0 extrapolated to infinity
AUC_{0-t}	area under the concentration in plasma versus time curve from time 0 to the last quantifiable concentration
bpm	beats per minute
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration in plasma
Cu	copper
CV	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end of study
FDA	Food and Drug Administration
GDS	Global Drug Safety
GI	gastrointestinal
HR	heart rate
IB	Investigator's brochure

Abbreviation	Term
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
IUT	intersection union test
LLOQ	lower limit of quantification
LS	least squares
MMRM	mixed-effects model for repeated measures
Mo	molybdenum
ms	millisecond
MTD	maximum tolerated dose
NF	National Formulary
PD	pharmacodynamic
PK	pharmacokinetic(s)
PPI	proton-pump inhibitor
PUF Mo	plasma ultrafiltrate molybdenum
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTcI	optimized HR-corrected QT interval
QTcS	individual HR-corrected QT interval
SAE	serious adverse event
T_{max}	time to maximum observed concentration in plasma
TPC	tripartite complex
TQT	thorough QT
TTM	tetrathiomolybdate
UC	uncoated capsule
ULN	upper limit of normal
ULOQ	upper limit of quantification
WD	Wilson disease

9.2 APPENDIX 2: STUDY GOVERNANCE

9.2.1 Data Quality Assurance

This study will be conducted using the quality processes described in applicable procedural documents. The quality management approach to be implemented will be documented and will comply with current ICH guidance on quality and risk management. All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current Good Clinical Practice, the protocol, and standard operating procedures. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff. Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with US Title 21 Code of Federal Regulations (CFR) Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability.

Important protocol deviations, should they occur during the study, will be presented in Section 10.2 of the clinical study report.

9.2.2 Investigator Obligations

The following administrative items are meant to guide the Investigator in the conduct of the study and may be participant to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

9.2.2.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant (or the participant's legal guardian), except as necessary for monitoring and auditing by Alexion, its designee, the FDA, or the IRB.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from Alexion or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2.2.2 Institutional Review

Federal regulations and ICH guidelines require that approval be obtained from an IRB before participation of human participants in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study participants, and any other written information regarding this study that is to be provided to the participant or the participant's legal guardian must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH harmonised tripartite guideline E6(R2): Good Clinical Practice will be maintained by the study site and will be available for review by Alexion or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

9.2.2.3 Participant Consent

Written informed consent in compliance with US Title 21 CFR Part 50 shall be obtained from each participant before he or she enters the study or before performing any unusual or nonroutine procedure that involves risk to the participant. If any institution-specific modifications to study-related procedures are proposed or made by the study site, the consent should be reviewed by Alexion or its designee or both before IRB submission. Once reviewed, the Investigator will submit the ICF to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating participants must sign the revised form.

Before recruitment and enrollment, each prospective participant or his or her legal guardian will be given a full explanation of the study and will be allowed to read the approved ICF. Once the Investigator is assured that the participant/legal guardian understands the implications of participating in the study, the participant/legal guardian will be asked to give his or her consent to participate in the study by signing the ICF. A copy of the ICF will be provided to the participant/legal guardian.

9.2.2.4 Financial Disclosure and Obligations

The Investigator is required to provide financial disclosure information to allow Alexion to submit the complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the Investigator must provide to Alexion a commitment to

promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

Neither Alexion nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither Alexion nor PPD is financially responsible for further treatment of the disease under study.

9.2.2.5 Investigator Documentation

Prior to beginning the study, the Investigator will be asked to comply with ICH E6(R2) Section 8.2 and US Title 21 of the CFR by providing essential documents, including but not limited to, the following:

- IRB approval
- An original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the Principal Investigator and each Subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. Curriculum vitae will be signed and dated by the Principal Investigators and Subinvestigators at study start-up, indicating that they are accurate and current.
- Financial disclosure information to allow Alexion to submit complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the Investigators must provide to Alexion a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- An IRB-approved ICF, samples of study site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the participant or legal guardians
- Laboratory certifications and reference ranges for any local laboratories used by the study site, in accordance with US Title 42 CFR Part 493

9.2.2.6 Study Conduct

The Investigator agrees to perform all aspects of this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH E6(R2): Good Clinical Practice; the protocol; and all national, state, and local laws or regulations.

9.2.2.7 Case Report Forms and Source Documents

Site personnel will maintain source documentation, enter participant data into the eCRF as accurately as possible, and will rapidly respond to any reported discrepancies.

Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and any subsequent investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by study site personnel, who can add and edit data, add new participants, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of some discrepancies, enabling study site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed and signed by the Investigator. This system provides study site personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and investigator comment information.

9.2.2.8 Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol, in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.2.2.9 Reporting Adverse Events

By participating in this study, the Investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the Investigator agrees to submit annual reports to his or her IRB as appropriate. The Investigator also agrees to

provide Alexion with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

9.2.2.10 Investigator's Final Report

Upon completion of the study, the Investigator, where applicable, should inform the institution; the Investigator/institution should provide the IRB with a summary of the study's outcome and Alexion and regulatory authorities with any reports required.

9.2.2.11 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with Alexion. Alexion is responsible for informing the Investigator/institution when these documents no longer need to be retained.

9.2.2.12 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, Alexion will be responsible for these activities and will work with the Investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and any other related issues. Alexion has final approval authority over all such issues.

Data are the property of Alexion and cannot be published without their prior authorization, but data and any publication thereof will not be unduly withheld.

9.2.3 Study Management

9.2.3.1 Monitoring

9.2.3.1.1 Monitoring of the Study

The clinical monitor, as a representative of Alexion, is obligated to follow the study closely. In doing so, the monitor will visit the Investigator and study site at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain

current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and staff.

All aspects of the study will be carefully monitored by Alexion or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and standard operating procedures.

9.2.3.1.2 Inspection of Records

The Investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow Alexion, their representatives, the FDA, or other regulatory agencies access to all study records.

The Investigator should promptly notify Alexion and study site(s) of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to Alexion.

9.2.3.2 Management of Protocol Amendments and Deviations

9.2.3.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the participant, must be reviewed and approved by Alexion or designee. Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before participants are enrolled into an amended protocol.

9.2.3.2.2 Protocol Deviations

The Investigator or designee must document and explain in the participant's source documentation any deviation from the approved protocol. The Investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study participants without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to Alexion for agreement, and to the regulatory authorities, if required.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important deviation (sometimes referred to as a major

or significant deviation) is a subset of protocol deviations that leads to a participant being discontinued from the study, or significantly affects the participant's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH E6(R2) guidelines.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The Investigator will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations, if appropriate, in a timely manner.

9.2.3.3 Study Termination

Although Alexion has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last participant completes the last visit (including the EOS Visit and any additional long-term follow-up). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report.

9.2.3.4 Final Report

Regardless of whether the study is completed or prematurely terminated, Alexion will ensure that clinical study reports are prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s). Alexion will also ensure that clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results.

Upon completion of the clinical study report, the Investigator(s) will be provided with the final approved clinical study report, as appropriate.

9.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

9.3.1 Definition of Adverse Event

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment . • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, serum chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error. • Cases of pregnancy that occur during maternal or paternal exposure to study intervention are to be reported within 24 hours of investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

9.3.2 Definition of Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

A suspected unexpected serious adverse reaction (SUSAR) is defined as:
A serious event that is not listed in the IB and that the Investigator identifies as related to investigational product or procedure. United States Title 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Alexion has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with

A suspected unexpected serious adverse reaction (SUSAR) is defined as:
global regulations and the associated detailed guidances. Suspected unexpected serious adverse reactions will be reported to the national competent authority and IRBs/IECs where applicable.

9.3.3 Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to Alexion in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Alexion. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Alexion.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories from National Cancer Institute CTCAE v 5.0, published 27 Nov 2017:

- Grade 1: Mild (awareness of sign or symptom, but easily tolerated)
- Grade 2: Moderate (discomfort sufficient to cause interference with normal activities)
- Grade 3: Severe (incapacitating, with inability to perform normal activities)
- Grade 4: Life-threatening
- Grade 5: Fatal

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study intervention and each occurrence of each AE or SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - **Not related:** There is no reasonable possibility the study intervention caused the AE.
    - The AE has a more likely alternative etiology; it may be due to underlying or concurrent illness, complications, concurrent treatments, or effects of another concurrent drug.

Assessment of Causality

- The event does not follow a reasonable temporal relationship to administration of the study intervention.

- **Related:** There is a reasonable possibility the study intervention caused the AE.
  - The AE has a temporal relationship to the administration of the study intervention.
  - The event does not have a likely alternative etiology.
  - The event corresponds with the known pharmaceutical profile of the study intervention.
  - There is improvement on discontinuation and/or reappearance on rechallenge.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he or she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Alexion. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Alexion.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information.

9.3.4 Reporting of Serious Adverse Events

SAE Reporting to Alexion via Paper Safety Reporting Form

- All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours awareness.

SAE Reporting to Alexion via Paper Safety Reporting Form

- SAEs will be reported using the Safety Reporting Form and submitted to Alexion GDS. The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via email or facsimile to the contact information provided below:
  Email: PPD or Fax: PPD
- Additional follow-up information, if required or available, should be entered into the CRF and sent to Alexion GDS within 24 hours of the Investigator or study site staff becoming aware of this additional information via the reporting process outlined above.
- For all SAEs, the Investigator must provide the following:
  - Appropriate and requested follow-up information in the time frame detailed above
  - Causality of the serious event(s)
  - Treatment of/intervention for the SAE(s)
  - Outcome of the serious event(s)
  - Medical records and laboratory/diagnostic information
- All paper forms and follow-up information submitted to Alexion GDS MUST be accompanied by a cover page signed by the Investigator.
- Paper source documents and/or reports should be kept in the appropriate section of the study file.

9.4 APPENDIX 4: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	12 Jun 2020
Amendment 1	01 Sep 2020