NCT Number: NCT05906732

CLINICAL STUDY PROTOCOL

Title: A Phase 1b/2a, 2-Part Study; Part 1: Randomized, Double-Blind, Crossover, Dose-Escalation, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of SGK-1 Kinase Inhibition by LQT-1213 on Dofetilide-Induced QTc Prolongation in Healthy Adult Subjects. Part 2: Single-Blind, Multiple-Dose, Safety Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LQT-1213 in Patients Diagnosed With Type 2 or 3 Long QT Syndrome

Study Number: LQT-1213 061

CLINICAL STUDY PROTOCOL

A Phase 1b/2a, 2-Part Study; Part 1: Randomized, Double-Blind, Crossover, Dose-Escalation, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of SGK-1 Kinase Inhibition by LQT-1213 on Dofetilide-Induced QTc Prolongation in Healthy Adult Subjects. Part 2: Single-Blind, Multiple-Dose, Safety Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LQT-1213 in Patients Diagnosed With Type 2 or 3 Long QT Syndrome

PROTOCOL NO. LQT-1213-0061

Name of Drug:	LQT-1213
Sponsor:	Thryv Therapeutics Inc. 999 Blvd. De Maisonneuve West Suite 1250 Montreal, Québec
Medical Monitor:	[redacted] Thryv Therapeutics Inc. Telephone: [redacted] Email: [redacted]
Version:	7.0
Date:	05 December 2023

Good Clinical Practice Statement

This study will be conducted in compliance with the protocol, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice, and the applicable regulatory requirement(s).

Confidentiality Statement

Sponsor Signature Page

Protocol Title: A Phase 1b/2a, 2-Part Study; Part 1: Randomized, Double-Blind, Crossover, Dose-Escalation, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of SGK-1 Kinase Inhibition by LQT-1213 on Dofetilide-Induced QTc Prolongation in Healthy Adult Subjects. Part 2: Single-Blind, Multiple-Dose, Safety Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LQT-1213 in Patients Diagnosed With Type 2 or 3 Long QT Syndrome

Protocol Number: LQT-1213-0061

The undersigned have reviewed the format and content of this protocol and approve issuance of the document.

(signed)

[redacted]
Thryv Therapeutics Inc.

08-Dec-2023
Date

(signed)

[redacted]
Thryv Therapeutics Inc.

08-Dec-2023
Date

Investigator Signature Page

I agree to conduct the study as outlined in the protocol entitled "A Phase 1b/2a, 2-Part Study; Part 1: Randomized, Double-Blind, Crossover, Dose-Escalation, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of SGK-1 Kinase Inhibition by LQT-1213 on Dofetilide-Induced QTc Prolongation in Healthy Adult Subjects. Part 2: Single-Blind, Multiple-Dose, Safety Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LQT-1213 in Patients Diagnosed With Type 2 or 3 Long QT Syndrome" in accordance with the guidelines and all applicable government regulations including United States Title 21 of the Code of Federal Regulations Part 54. I have read and understand all sections of the protocol.

(signed)

08-Dec-2023

[redacted]
Principal Investigator

Date

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Protocol Amendment Summary of Changes Tables

Note: Only major changes to the protocol are presented in this summary of changes. Administrative changes have been made throughout the document to reflect changes in version number and date of issue. Corrections of minor typographical errors and inconsistencies, grammar, or formatting changes are not listed here.

DOCUMENT HISTORY	
Document	**Date**
Original	14 February 2023
Amendment 1, Version 2.0	02 March 2023
Amendment 2, Version 3.0	10 March 2023
Amendment 3, Version 4.0	17 March 2023
Amendment 4, Version 5.0	20 June 2023
Amendment 5, Version 6.0	29 September 2023
Amendment 6, Version 7.0	05 December 2023

Amendment 1, Version 2.0 (02 March 2023):

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1 (Synopsis), Section 3.4 (Dose Rationale), Section 5.1 (Study Design), Section 5.5.1 (Method of Assigning Subjects to Treatments), Section 5.5.2 (Treatments Administered), Section 5.5.3 (Identity of Study Drug), Section 5.5.4 (Management of Clinical Supplies)	Updated the wording in the body of the protocol for the low/mid/high dosing to match the details in Section 8.1 (Appendix A: Schedule of Events, footnote m)	To address inconsistencies in the original protocol
Section 1 (Synopsis), Section 3.6 (Study Rationale)	Revised the washout between doses to 5 times the half-life, which was shortened to at least 4 days	To clarify and take into account the half-life of LQT-1213
Section 1 (Synopsis), Section 5.1 (Study Design), Section 5.5.1 (Method of Assigning Subjects to Treatment Groups), Section 8.1 (Appendix A: Schedule of Events)	Revised randomization to take place before Day 3 of Period 1	To provide flexibility in the randomization language to clarify that randomization will take place before Day 3 of Period 1

Section 1 (Synopsis), Section 2 (List of Abbreviations), Section 4.3 (Exploratory Objectives), Section 5.1 (Study Design), Section 5.4.1.3 (Human Peripheral Blood Mononuclear Cell Collection), Section 5.7.4	Added the collection of samples for assessment of human peripheral blood mononuclear cells	To provide an exploratory endpoint of cell activation by LQT-1213

Section # and Name	Description of Change	Brief Rationale
(Pharmacokinetic/ Pharmacodynamic Analyses), Section 8.1 (Appendix A: Schedule of Events), Section 8.2 (Appendix B: Pharmacokinetic and Pharmacodynamic Time Points)		
Section 8.1 (Appendix A: Schedule of Events)	Updated footnote f to change Hour 6 to Hour 15	For consistency with changes made in Section 8.2
Section 8.2 (Appendix B: Pharmacokinetic and Pharmacodynamic Time Points)	• Day 1: Added electrocardiogram (ECG) extraction at 5 and 6 hours, removed the 6-hour safety ECG, and added a safety ECG at 15 hours • Day 2: Added safety ECGs at 3 and 15 hours and removed the 8.5-hour time point row • Day 3: Separated from Days 4-8 and added 15- and 24-hour time points for safety ECGs and ECG extractions • Days 4-8: Added 4- and 24-hour PK time points and removed the 6-hour pharmacokinetic time point Updated footnote c to change Hour 6 to Hour 15	To ensure subject safety and provide clarity

Amendment 2, Version 3.0 (10 March 2023):

Section # and Name	Description of Change	Brief Rationale
Section 1 (Synopsis), Section 5.2.2. (Exclusion Criteria)	Revised Exclusion Criterion #8 for 12-lead ECGs to occur at Screening and on Day –2, updated time from the onset of the P wave to the start of the QRS complex (PR) interval to >240 ms and QT interval corrected for heart rate by Fridericia's formula (QTcF) interval to <400 ms, and added if heart rate <50 or >85 bpm, then 2 more ECGs will be recorded and the mean values will be used	To clarify 12-lead ECG exclusion criterion

Section # and Name	Description of Change	Brief Rationale
Section 1 (Synopsis), Section 5.1 (Study Design), Section 5.2.2 (Exclusion Criteria), Table 5-1 (Clinical Laboratory Tests), Section 8.1 (Appendix A: Schedule of Events -footnote i)	Added that electrolyte supplementation is allowed at any time as long as it is >4 hours before dosing but preferred, especially on Days 1, 4, 6, and 8, that this be done in the evening (after the 12-hour time point)	To clarify the timing for when electrolyte supplementation is allowed
Section 1 (Synopsis), Section 5.1 (Study Design), Section 5.5.2 (Treatments Administered)	Clarified that the high dose should not exceed 0.747 mg/kg 3 times a day (TID)	To clarify the high dose frequency
Section 1 (Synopsis), Section 5.1 (Study Design), Figure 5-1 (Study Schematic – Part 1), Section 5.2.2 (Exclusion Criteria), Section 5.3.2 (Stopping Criteria or Dose Adjustment for Individual Subjects), Section 8.2 (Appendix B: Pharmacokinetic and Pharmacodynamic Time Points -footnote b)	Clarified that on Day 1 at 3 hours postdose the QTcF will be measured in the 3 ECGs and the mean value calculated in Period 1 only	To clarify QTcF will be measured on Day 1 at 3 hours postdose in Period 1 only
Section 1 (Synopsis), Section 5.1 (Study Design), Figure 5-1 (Study Schematic – Part 1), Section 5.2.2 (Exclusion Criteria), Section 5.3.1 (Reasons for Withdrawal), Section 5.3.2 (Stopping Criteria or Dose Adjustment for Individual Subjects), Section 5.3.3 (Stopping Criteria for the Study), Section 5.4.3.5 (Safety 12-Lead Electrocardiograms), Section 5.5.2 (Treatments Administered), Section 8.2 (Appendix B: Pharmacokinetic and Pharmacodynamic Time Points)	Revised ECG criteria, stopping criteria, and dose adjustments to remove semiautomatic measurements at baseline and on Day 1 at 3 hours and to further clarify these criteria in Period 1	To clarify ECG criteria in Period 1
Section 1 (Synopsis), Section 5.1 (Study Design)	Added that LQT-1213 or placebo matched to LQT-1213 dosing time points may be adjusted based upon emerging data	To allow for adjustment to dosing based on emerging data
Section 1 (Synopsis), Section 5.1 (Study Design)	Removed that dofetilide dosing will be consistent, including dose-down titration, with the label	To be consistent with revised stopping rules
Section 5.3.3 (Stopping Criteria for the Study)	Revised stopping criteria to include documented Torsade de Pointes	To provide additional detail for this criterion
Section 5.4.3.2.1 (Reporting of Serious Adverse Events)	Updated sponsor study physician contact information	To provide sponsor study physician text

Section # and Name	Description of Change	Brief Rationale
		number
Section 5.5.2 (Treatments Administered)	Added time points for first and second doses	To provide additional details for dosing
Section 5.7.1.1 (Categorical Analyses)	Added a categorical analysis criterion for change from baseline in QTc (ΔQTc) from dofetilide/placebo reduction and updated the ΔQTc categorical analysis criterion from ΔQTc to ΔQTc from baseline	To clarify the ΔQTc categorical analyses criteria
Section 8.1 (Appendix A: Schedule of Events)	Added continuous telemetry with corresponding footnote p and updated footnote e to change Hour 6 to Hour 15	For consistency with changes made in Section 8.2

Amendment 3, Version 4.0 (17 March 2023):

Section # and Name	Description of Change	Brief Rationale
Section 1 (Synopsis), Section 5.1 (Study Design), Section 5.3.2 (Stopping Criteria or Dose Adjustment for Individual Subjects), Section 8.2 (Appendix B: Pharmacokinetic and Pharmacodynamic Time Points-footnote b), Section 5.3.1 (Reasons for Withdrawal – Note)	Clarified that the 6 ECGs measurements on Day 1 at 3 hours postdose the QTcF will be captured as 3 (triplicate) repeated ECGs and the mean value calculated in Period 1	To clarify that 3 (triplicate) repeated ECG measurements will be taken
Section 1 (Synopsis), Section 5.1 (Study Design)	Removed the light meal start and stop times	To ensure consistent fasting times across subjects
Section 5.5.1 (Method of Assigning Subjects to Treatment Groups), Section 5.5.3 (Identity of Study Drug)	Specified that placebo will consist of the sugar-free Gatorade™ and cornstarch	Update the placebo treatment to align with the investigative product

Amendment 4, Version 5.0 (20 June 2023):

Section # and Name	Description of Change	Brief Rationale
All applicable sections	Global change to add Part 2, specify what was applicable for Part 1 only, and what was applicable for both Parts 1 and 2	Part 2 is a safety and PK study in subjects with Long QT Syndrome 2 or 3
Section 1 (Synopsis), Section 4 (Study Objectives), Section 5.4.1.3 (Human Peripheral Blood Mononuclear Cell Collection), Section 8.1 (Appendix A: Schedule of Events – Part 1), and Section 8.2 (Appendix B: Schedule of Events – Part 2)	Removed exploratory objective from Part 1 and moved it to Part 2	Samples were not collected in Part 1 and deemed more feasible for Part 2

All applicable sections	Global update of title and text to update multiple-dose escalation to multiple dose and patients diagnosed with LQT-2	To align with change in study design
Section 3.1 (Background)	Added preclinical data	Updated background information
Section 3.2 (Summary of LQT-1213 Nonclinical Development)	Revised cellular assay data; added blood pressure data	Updated nonclinical information
Section 5.3.5 (Replacement Subjects)	Specified that participants discontinued form the study due to drug-related hepatic AESIs will not be replaced	To provide clarity
Section 1 (Synopsis), Section 5.4.3 (Safety Assessments), Section 5.4.3.3 (Clinical Laboratory Tests-Part 2)	Coagulation added as a safety endpoint for Part 2	To ensure subject safety and provide clarity
Section 5.4.3 (Safety Assessments)	Added Continuous telemetry ECG monitoring for Part 2	To provide more stringent safety requirement
Section 5.4.3.1.3 (Adverse Events of Special Interest)	Added Adverse Events of Special Interest Section	To include Hepatic AEs as AEs of special interest for Part 2
Section 6.3 (Subject Consent)	Added that ICFs may be in paper or electronic forms and that original paper ICFs will be retained if used	To clarify ICF formats and handling of paper ICFs
Section 6.6 (Investigator Documentation)	Investigator documentation text added	Omitted from previous amendment in error

Amendment 5, Version 6.0 (29 September 2023):

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1 (Synopsis), Section 5.4.1.2 (Pharmacodynamic Assessments -Part 2), Section 5.6.2.2 (Analysis Populations), Section 5.7.1.2 (Pharmacodynamic Analyses - Part 2)	Text relevant to pharmacodynamic ECG endpoint, assessments and analyses, and population were removed and sections updated text relative to human PBMCs and SGK-1 protein target was added	SGK-1 data is more relevant to the target population
Section 1 (Synopsis), Section 5.2.1.2 (Inclusion Criteria – Part 2)	Removed upper age limit in Inclusion Criteria #1	To reflect the target population
Section 1 (Synopsis), Section 5.2.1.2 (Inclusion Criteria – Part 2)	Removed Criteria #2 that participant must not have previously been enrolled in the clinical study with LQT-1213	Requirement is more relevant to first-in-human studies

Section 1 (Synopsis), Section 5.2.1.2 (Inclusion Criteria – Part 2)	Removed BMI requirement in new Inclusion Criteria #2	Minimum weight of 45 kg is sufficient for this target population
Section 1 (Synopsis), Section 5.2.1.2 (Inclusion Criteria – Part 2)	Revised new Inclusion Criterion #7 to update QTcF values to have "or equal to" symbols (ie, QTcF interval ≥480 and ≤560 ms)	Correction from previous protocol versions
Section 1 (Synopsis), Section 5.2.1.2 (Inclusion Criteria – Part 2)	Revised new Inclusion Criterion #6 to stipulate that in addition to screening, historical documentation, if available may be used for consideration of LQTS2 or LQTS 3 pathology or likely pathology	To allow additional data for pathology or likely pathology consideration
Section 1 (Synopsis), Section 5.2.1.2 (Inclusion Criteria – Part 2)	Revised new Inclusion Criterion #8 to note that this stipulation may be altered upon agreement between the principal investigator and Sponsor based on emerging data	To allow flexibility based emerging data
All applicable sections in Part 2	Global change from BID (time points 0 and 11.5 hour) dosing to TID (0, 8, and 16 hour) dosing.	Change in study design
All applicable sections in Part 2	Global change to remove all ECG analysis until possibly after database lock	
Section 1 (Synopsis) and Section 5.2.2.2 (Exclusion Criteria – Part 2)	Updated Exclusion Criterion #7 to note blood volume donation greater than 300 mL should not occur within 30 days before dosing rather than before Screening	Correction from previous protocol versions
Section 1 (Synopsis) and Section 5.2.2.2 (Exclusion Criteria – Part 2)	Updated Exclusion Criterion #9 heart rate limits to <45 bpm and >95 bpm	Updated limits sufficient for study design and target population
Section 1 (Synopsis) and Section 5.2.2.2 (Exclusion Criteria – Part 2)	Updated Exclusion Criterion #9 to clarify that '2 or more ECGs' text should be updated to describe a second set of triplicate ECGs	Text updated for clarity
Section 1 (Synopsis) and Section 5.2.2.2 (Exclusion Criteria – Part 2)	Combined Exclusion Criteria #12 and 18 and renumbered list accordingly	Simplification purposes
Section 1 (Synopsis) and Section 5.2.2.2 (Exclusion Criteria – Part 2)	Added ECG electrodes to new Exclusion Criteria #18	To reflect adhesive items planned for use in the study
Section 1 (Synopsis) and Section 5.2.2.2 (Exclusion	Updated new Exclusion Criteria #21 to remove	Applicable to Part 1 objectives

Criteria – Part 2)	cruciferous vegetables and charbroiled meats restriction	not Part 2
Section 1 (Synopsis) and Section 5.2.2.2 (Exclusion Criteria – Part 2)	Updated new Exclusion Criteria #21 to restrict oranges, grapefruit and/or grapefruit juice consumption from within 14 days to 7 days before Check-in	Sufficient given the objectives for Part 2
Section 1 (Synopsis) and Section 5.2.2.2 (Exclusion Criteria – Part 2)	Removed Exclusion Criteria #27 to all smokers to be included in the study. The principal investigator will retain discretion to exclude based on judgement	To reflect LQT-1213 limited drug-drug interaction potential.
Section 1 (Synopsis), Section 5.5.2.2 (Treatments Administered – Part 2), and Section 5.5.8.2 (Diet, Fluid, Activity Control, and Subject Housing – Part 2)	Updated meal and fasting requirements and present requirements only in Section 5.5.8.2	To align with updated study design and correct duplicative text
Section 1 (Synopsis – ECG and QT/QTc Analyses), Section 5.1.2 (Study Design – Part 2), Section 5.4.3.5.2 (Safety 12-Lead ECG – Part 2), and Section 5.7.1.2 (Pharmacodynamic Analyses – Part 2)	Removed text specifying ECG analysis to be done by [redacted] at study conclusion and replaced with text specifying that all ECG data will be stored for potential future analysis by [redacted] and specify that all Thryv staff will be fully blinded to all Part 2 postdose ECG data until database lock	To allow flexibility on timing of [redacted] ECG analysis and reduce study bias.
Section 3.2 (Summary of LQT-1213 Nonclinical Development	Nonclinical text was updated	To reflect updated nonclinical data
Section 5.1.3 (Safety Review Committee)	Added chief medical officer to the individuals comprising the SRC at a minimum and updated text to specify data to include any available PK, PD, or safety data.	To ensure relevant stakeholders included in discussion
Table 5-2 Clinical Laboratory Tests – Part 2	Text updated to specify that serum pregnancy tests are to be conducted for females of childbearing potential instead of all female participants.	Serum pregnancy tests not necessary for postmenopausal female participants
Section 5.4.1.2 (Pharmacodynamic Assessments – Part 2)	Continuous 12-Lead ECG Acquisition heading was removed	To reflect that safety is the primary objective
Section 5.4.3.6.2 (Physical Examinations – Part 2)	Day −1 was removed for height measurement.	Not needed as height will be captured at Screening

Section 5.7.1.3.2 (Categorical Analyses – Part 2)	Removed categorical analysis	To align with updated study design
Appendix B (Schedule of Events – Part 2) and Appendix D (PK, PD, and Meal Time Points – Part 2)	Schedule of events, PK, PD, and meal assessments updated	To align with updated study design

Amendment 6, Version 7.0 (05 December 2023):

Section # and Name	Description of Change	Brief Rationale
Section 1 (Synopsis), Study Design Part 2, Section 5.4.3.5 Part 2, and Section 5.5.5.2 Part 2	Removed sentence requiring the study blind	Thryv staff will not be blinded to Part 2 postdose ECG data prior to database lock, which aligns with the single-blind study design.
Section 1 (Synopsis), Part 2 Exclusion criteria #9 and Section 5.2.2.2. Part 2 Exclusion criteria #9	Adding allowance for sponsor and investigator approval for PR interval in participants on beta blockade	Given beta blockade can confound PR interpretation, allowance made for sponsor and investigator to review PR.
Section 8.4: Appendix D: Pharmacokinetic and Pharmacodynamic, and Meal Time Points – Part 2:	For Part 2; updated start of mealtime and updated ECG and ECG extraction times	The start time of the mealtime period on Day 1 Part 2 was updated to begin after all ECG collections are complete. Timepoints for collection of 12-lead ECGs and ECG extractions in Part 2 were updated, primarily to capture ECG information during the placebo period on Day 1.

1. Protocol Synopsis

Title:	A Phase 1b/2a, 2-Part Study; Part 1: Randomized, Double-Blind, Crossover, Dose-Escalation, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of SGK-1 Kinase Inhibition by LQT-1213 on Dofetilide-Induced QTc Prolongation in Healthy Adult Subjects. Part 2: Single-Blind, Multiple-Dose, Safety Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LQT-1213 in Patients Diagnosed With Type 2 or 3 Long QT Syndrome
Phase of development:	1b/2a
Investigator:	[redacted]
Study site:	[redacted]
Objectives:	**Part 1** is a randomized, double-blind, crossover, dose-escalation, placebo-controlled study in 28 healthy adult subjects with the following objectives: • Primary: To evaluate the effect of oral LQT-1213 on dofetilide-induced QT interval corrected for heart rate (HR; QTc) prolongation in healthy adult subjects • Secondary: To evaluate the safety and tolerability of a combination of oral dofetilide and oral LQT-1213 in healthy adults • Secondary: To determine the pharmacokinetics (PK) of oral LQT-1213 and oral dofetilide in healthy adults **Part 2** is a single-blind, multiple-dose study in up to 12 adult participants with Long QT Syndrome Type 2 (LQT/LQTS 2) and in up to 12 adult participants with Long QT Syndrome Type 3 (LQT/LQTS 3) with the following objectives: • Primary: To evaluate the safety and tolerability of oral LQT-1213 in participants with LQT2 or LQT3 • Secondary: To determine the PK of oral LQT-1213 in participants with LQT2 or LQT3 • Exploratory: To evaluate the correlation between the PK of LQT-1213 and candidate serum- and glucocorticoid-regulated kinase-1 (SGK-1) protein targets in participant peripheral blood mononuclear cells (PBMCs) in order to derive PK/pharmacodynamic (PD) relationships between drug exposure and target engagement; additional exploratory PD endpoints may be assessed
Endpoints:	**Part 1:** **Pharmacodynamic:** The primary analysis will be the time-based comparison in the change from baseline (baseline defined as the Day 1 of Period 1 and Day 1 of Period 2 mean predose QTc) QTc by Fridericia's formula (QTcF) during approximate peak dofetilide exposure as detailed in the statistical analysis plan (SAP) between dofetilide and placebo treatment, and the dofetilide and LQT-1213 treatment on Day 8 of each period with secondary endpoints on Days 4 and 6 of each period. If a substantial HR effect is observed, other correction methods such as QTc with individual correction (QTcI) and QTc with population correction

	(QTcP) will be explored and compared, as will be detailed in the SAP. The primary correction method will be the one that removes the HR dependence of the QT interval most efficiently. Primary pharmacodynamic endpoints: • Dofetilide/placebo-corrected ΔQTcF (ΔΔQTcF) • Dofetilide/placebo-corrected ΔQTcI or ΔQTcP (ΔΔQTcI, ΔΔQTcP) if used as the primary correction method if a substantial HR effect is observed Secondary pharmacodynamic endpoints: • Change from baseline QTcF, HR, time from the onset of the P wave to the start of the QRS complex (PR), ventricular depolarization (QRS) intervals (ΔQTcF, ΔHR, ΔPR, and ΔQRS) • Dofetilide/placebo-corrected ΔHR, ΔPR, and ΔQRS (ΔΔHR, ΔΔPR, ΔΔQRS) • Exposure-response QTc analysis • Categorical outliers for QTcF (QTcI and QTcP if a substantial HR effect is observed), HR, PR, and QRS • Frequency of treatment-emergent changes of T-wave morphology and U-waves presence **Pharmacokinetic:** Plasma LQT-1213 and dofetilide PK endpoints will include the following: • AUC_{0-t}: Area under the concentration-time curve (AUC) from time 0 to the time of the last measurable concentration • AUC_{tau}: AUC from time 0 to the end of the dosing interval • C_{max}: Maximum observed plasma drug concentration • T_{max}: Time to the maximum observed plasma concentration • $t_{1/2}$: Terminal half-life • CL_{ss}/F: Apparent clearance at steady state • V_d/F: Apparent volume of distribution • λ_z: Apparent terminal rate constant Other PK parameters, as identified, agreed, and documented in the SAP. **Safety:** The safety and tolerability endpoints include: • Adverse events (AEs) monitoring, including clinically significant ECG abnormalities as determined by the investigator, recorded as AEs • Clinical laboratory tests results (hematology, serum chemistry, and urinalysis) • Vital sign measurements (including systolic and diastolic blood pressure, HR, respiratory rate, and oral temperature) • Physical examination findings **Part 2:** **Safety:** The safety and tolerability endpoints include: • Adverse events monitoring, including clinically significant ECG abnormalities as determined by the investigator, recorded as AEs • Clinical laboratory tests results (hematology, serum chemistry, coagulation, and urinalysis) • Vital sign measurements (including systolic and diastolic blood pressure, HR, respiratory rate, and oral temperature) • Physical examination findings

	Pharmacokinetic: Plasma LQT-1213 PK endpoints will include the following: • AUC_{0-t}, AUC_{tau}, C_{max}, C_{trough}, T_{max}, $t_{1/2}$, CL_{ss}/F, V_d/F, λ_z Other PK parameters as identified and documented in the SAP. **Pharmacodynamic:** The exploratory PD (SGK-1 protein targets) endpoints and analyses will be detailed in a separate analysis document. **Pharmacokinetic/Pharmacodynamic:** The exploratory PK (LQT-1213)/PD (SGK-1 protein targets) endpoints and analyses to derive PK/PD relationships between drug exposure and target engagement will be detailed in a separate analysis plan.
Number of subjects planned:	**Part 1:** Approximately 28 healthy subjects, with the attempt to balance for sexes, will be enrolled to complete approximately up to 20 subjects in Part 1. Additional subjects may be enrolled in Part 1 to compensate for subjects that do not complete both treatment periods, at the discretion of the sponsor. The exact number will be determined during the conduct of the study. **Part 2:** Up to 12 participants with LQT2 and up to 12 participants with LQT3 will be recruited.
Inclusion criteria:	**Part 1:** All subjects considered for study participation must meet the following criteria: 1. Male and female subjects between 18 and 60 years of age (inclusive) at Screening. 2. Not previously enrolled in a clinical study with LQT-1213. 3. Normal general health. 4. Body mass index within 18.0 to 32.0 kg/m^2, inclusively at Screening. 5. Female subjects of nonchildbearing potential must be either surgically sterile (hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before Screening) or postmenopausal, defined as spontaneous amenorrhea for at least 2 years, with follicle-stimulating hormone in the postmenopausal range at Screening, based on the central laboratory's ranges. 6. Female subjects of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) must use a highly effective contraceptive regimen during their participation in the study and for 30 days after the last administration of study drug. Highly effective contraceptive methods are defined as those with <1% failure rate per year. Acceptable methods of contraception for female subjects enrolled in the study include the following: • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable • Intrauterine device

	• Intrauterine hormone-releasing system • Bilateral tubal occlusion • Vasectomized partner • Heterosexual abstinence 7. Male subjects and their partners must use highly effective methods of contraception (ie, condom and spermicide) for the entire duration of the study. Male subjects must continue to use contraception and refrain from fathering a child and sperm donation for 90 days after the last administration of study drug. Acceptable methods of contraception for male subjects enrolled in the study include the following: • Condoms and spermicide • Surgical sterilization (vasectomy) of the subject at least 26 weeks before Screening • Heterosexual abstinence (subject must agree to use condom and spermicide if they become sexually active) 8. Understand the requirements of the study and voluntarily consent to participate in the study. **Part 2:** All participants with LQT2 or LQT3 considered for study participation must meet the following criteria: 1. Male and female participants 18 years of age or older at Screening. 2. Body weight of at least 45 kg at Screening. 3. Female participants of nonchildbearing potential must be either surgically sterile (hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before Screening) or postmenopausal, defined as spontaneous amenorrhea for at least 2 years, with follicle-stimulating hormone in the postmenopausal range (>40 mIU/mL) at Screening, based on the central laboratory's ranges. 4. Female participants of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) must use a highly effective contraceptive regimen during their participation in the study and for 30 days after the last administration of study drug. Highly effective contraceptive methods are defined as those with <1% failure rate per year. Acceptable methods of contraception for female participants enrolled in the study include the following: • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal • Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion • Vasectomized partner • Heterosexual abstinence 5. Male participants and their partners must use highly effective methods of contraception (ie, condom and spermicide) for the entire duration of the study.

	Male participants must continue to use contraception and refrain from fathering a child and sperm donation for 90 days after the last administration of study drug. Acceptable methods of contraception for male participants enrolled in the study include the following: • Condoms and spermicide • Surgical sterilization (vasectomy) of the participant at least 26 weeks before Screening • Heterosexual abstinence (participant must agree to use condom and spermicide if they become sexually active) 6. LQT2 or LQT3 mutation: • LQTS 2: Participants with potassium voltage-gated channel subfamily H member 2 (KCNH2) mutations that are dominant negative and considered to be pathologic or likely pathologic by the screening laboratory (or historical documentation, if available) can be included after approval from the sponsor. Participants with haploinsufficiency will not be eligible for this study. • LQTS 3: LQTS 3: Participants with a sodium voltage-gated channel alpha subunit 5 (SCN5A) gene chromosome 3 mutations that are considered to be pathologic or likely pathologic by the screening laboratory (or historical documentation, if available) can be included after approval from the sponsor. Participants with mutations associated with Brugada syndrome, overlap syndromes or where the effect of the mutations on the window current is the major effect without a substantial increase in the persistent 'late' Na current. 7. QTcF interval ≥480 and ≤560 ms determined at Screening and on Day −1 triplicate ECGS as assessed by a physician trained in complex ECG interpretation. 8. The first 2 participants with LQT2 require having an implantable cardioverter defibrillator (ICD) before further participants with LQT2 are enrolled and the first 2 participants with LQT3 require having an ICD before further participants with LQT3 are enrolled. This stipulation may be altered based on agreement between the principal investigator and Sponsor based on emerging data. The ICD implantation must have been at least 2 months before Screening. Note: Subsequent participants may or may not have had an ICD. The results of the ICD interrogation within the last 6 months should be available for review unless waived by the investigator and sponsor. 9. Understand the requirements of the study and voluntarily consent to participate in the study.

Exclusion criteria:	**Part 1:** Subjects will be excluded from the study if they meet any of the following criteria: 1. On Day 1 at 3 hours postdose in Period 1 only, of the first cycle of dofetilide, the QTcF on the triplicate ECGs will be manually confirmed by cardiologist experienced in ECG interval measurements. The ECG measurements at baseline and at the 3-hour time points will be performed by the same technician and cardiologist. If the mean QTcF increase from baseline is <25 ms on triplicate safety ECGs compared to the mean from baseline (all ECG QTcF measurements averaged), the subject will be disqualified from further study participation. 2. Clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease or any other condition, which, in the opinion of the investigator, would jeopardize the safety of the subject or impact the validity of the study results. No history of myocardial infarction or angina or ischemic heart disease, nonsustained or sustained ventricular tachycardia, atrial fibrillation, stroke, transient ischemic attack, syncope, congestive heart failure, family history of LQTS, Torsades de Pointes, or sudden cardiac death.

	3. Female subjects must not be pregnant, lactating, or breastfeeding, and must not be planning to become pregnant. 4. Female subjects of childbearing potential must have a negative result for the serum pregnancy test at Screening and Check-in. 5. Clinically significant abnormal findings on the physical examination or medical history during Screening as deemed by the investigator. 6. Participated in a previous clinical study in the previous 3 months before dosing. 7. Donation of blood volume greater than 300 mL within 30 days before Screening and agree to avoid donation from Screening and throughout the study. 8. At Screening and on Day –2, if the 12-lead ECG demonstrates any of the following: PR >240 ms; QRS >110 ms, or QTcF <400 ms and >440 ms; second- or third-degree atrioventricular block; bundle branch block, significant ST-T wave abnormalities or flat T waves that could interfere with QT analysis. If HR <50 or >85 bpm, then 2 more ECGs will be recorded, and the mean values will be used. 9. Known sensitivity to kinase inhibitors. 10. Abnormal renal function with an estimated glomerular filtration rate (eGFR) of <70 mL/min/1.73 m^2, with eGFR calculated by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula at Screening. One retest of the exclusionary eGFR value is allowed at the discretion of the investigator. 11. Subject has abnormal liver function tests (transaminases or total bilirubin) greater than 2.5 × the upper limit of normal at Screening or baseline. One retest of exclusionary abnormal liver function tests is allowed at the discretion of the investigator. 12. Subject has a positive serology test for HIV antibodies, hepatitis B surface antigen, or hepatitis C virus antibody at Screening. 13. Subject has a hemoglobin <11.0 g/dL, potassium <3.8 mg/dL, magnesium <1.9 mg/dL, or calcium <8.5 mg/dL at Screening or baseline. One retest of exclusionary hemoglobin, potassium, magnesium, and calcium is allowed at the discretion of the investigator. Electrolyte supplementation is allowed at any time as long as it is >4 hours before dosing. 14. Subject has a history of hypersensitivity to drugs with a clinically significant reaction or any clinically significant hypersensitivities. 15. Subject has an allergy to band aids, adhesive dressing, or medical tape. 16. Subject has a history within the past 2 months of strenuous exercise (eg, marathon running) and is unwilling to refrain from strenuous exercise from 7 days before Check-in and until the end of the study. Subject has abnormal creatine phosphokinase test greater than 3 × the upper limit of normal at Screening and baseline. One retest of exclusionary abnormal creatine phosphokinase tests is allowed at the discretion of the investigator. 17. Subject is unable to refrain from or anticipates the use of any drug, including prescription and nonprescription medications (with the exception of hormonal contraception), herbal preparations, or vitamin supplements beginning 14 days before the first dose and until the end of the study. After dosing, acetaminophen (up to 2 g per

	24 hours) may be administered at the discretion of the investigator or designee. a. Hepatic or renal clearance altering agents within 30 days before the first dose and until the end of the study. b. Avoid vaccinations from Screening until the end of the study. c. Has consumed cruciferous vegetables (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, and mustard greens) or charbroiled meats within 7 days before Check-in through the Follow-up Visit. d. Use of any drugs known to be significant strong inducers of cytochrome P450 (CYP) 3A enzymes, including St. John's Wort, for 28 days before Day –1 or 5 half-lives (whichever is longer) and through the Follow-up Visit. e. Has consumed Seville oranges, grapefruit and/or grapefruit juice within 14 days before Check-in and is unwilling to abstain from consuming these items until the end of the study. 18. Subject is considering or scheduled to undergo any surgical procedure during the study. 19. Subject has experienced an acute illness that has resolved in less than 14 days before the first study drug dose or has had a major illness or hospitalization within 1 month before the first study drug dose. 20. Subject is unwilling to abstain from ingestion of caffeine- or xanthine-containing products (eg, tea, coffee, chocolate, cola, etc.) beginning 96 hours before Check-in until the final PK sample of the study has been collected. 21. Subject is unwilling to abstain from alcohol beginning 48 hours before Check-in and until the final PK sample of the study has been collected. 22. Subject has a history of high alcohol consumption within 9 months before Screening, defined as an average weekly intake of >14 units for males or >10 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine, or 1 measure (25 mL) of spirits. 23. Subject has a history of drug abuse in the 3 years before Screening or positive screen for drugs of abuse or alcohol at Screening or baseline. Subjects may undergo a repeat urine drug screen at the discretion of the investigator. 24. Subject uses or has used tobacco-or nicotine-containing products (eg, cigarettes, cigars, chewing tobacco, snuff, etc.) within 6 months before Screening and is unwilling to abstain from tobacco-containing products until the end of the study, based on subject self-reporting. 25. Subject, who, for any reason, is deemed by the investigator to be inappropriate for this study or has any condition which would confound or interfere with the evaluation of the safety, tolerability, or PK of the investigational drug or prevent compliance with the study protocol.

	Part 2: Participants with LQT2 or LQT3 will be excluded from the study if they meet any of the following criteria: 1. Clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or significant structural cardiovascular disease or any other condition beyond LQT2 or LQT3, which, in the opinion of the investigator or sponsor, would jeopardize the safety of the participant or impact the validity of the study results. History of myocardial infarction or ongoing angina or active ischemic heart disease, atrial fibrillation, stroke, or transient ischemic attack within the past 12 months, greater than New York Heart Association Class II congestive heart failure, bundle branch block, hemodynamically significant ventricular tachycardia not due to Torsades de Pointes, or Brugada syndrome. 2. Participant has a history of an aborted cardiac arrest, ICD implantation, syncopal episode due to a ventricular arrhythmia or where confidence in the etiology cannot be established, or appropriate ICD therapy for ventricular tachycardia/ventricular fibrillation within 2 months before Screening. Participants with LQT2 or LQT3 can be enrolled after the 2-month time period has lapsed. 3. Female participants must not be pregnant, lactating, or breastfeeding, and must not be planning to become pregnant. 4. Female participants of childbearing potential must have a negative result for the serum pregnancy test at Screening and Check-in. 5. Clinically significant abnormal findings on the physical examination at Check-in or medical history during Screening as deemed by the principal investigator. 6. Currently participating in another interventional clinical study. 7. Donation of blood volume greater than 300 mL within 30 days before dosing and unwilling to avoid donation from Screening and throughout the study. 8. Screening diastolic blood pressure <45 or >95 mm Hg, systolic blood pressure <90 or >150 mm Hg, or with sponsor and investigator approval. 9. At Screening and on Day –1, if the triplicate 12-lead ECG demonstrates any of the following: mean PR >250 ms; QRS >110 ms, or QTcF >560 ms and <480 ms; bundle branch block or significant ST-T wave abnormalities or flat T waves that could interfere with QT analysis. Heart rate <45 bpm, unless receiving a beta-blocker in which case <40 bpm, or HR >95 bpm. If any of these exclusionary criteria are met, then a second set of triplicate ECGs may be acquired, and the mean values may be used. For participants on beta blockade, the PR interval may be higher than 250 ms with sponsor and investigator approval. 10. Atrial pacing rate set to ≥80 bpm in those with atrial pacing. 11. Participant has a pacemaker or ICD that is actively used for ventricular pacing. 12. Known sensitivity to kinase inhibitors or clinically significant drug allergies to any of the components of LQT-1213. 13. Abnormal renal function with an eGFR of <60 mL/min/1.73 m^2, with eGFR calculated by the CKD-EPI formula at Screening. One retest of the exclusionary eGFR value is allowed at Screening and Check-in at the discretion of the investigator. 14. Participant has abnormal liver function tests (transaminases greater

	than 2 × the upper limit of normal [ULN]) or total bilirubin > 1.5 × ULN. If the participant has documented Gilbert's Syndrome, participation is at the combined principal investigator and Sponsor's discretion after review of historical liver and bilirubin tests. 15. Participant has a positive serology test for HIV antibodies, hepatitis B surface antigen, or hepatitis C virus antibody at Screening. 16. Participant has a hemoglobin <11.0 g/dL, potassium <3.8 mg/dL, magnesium <1.8 mg/dL, or calcium <8.5 mg/dL at Screening or baseline. One retest of exclusionary hemoglobin, potassium, magnesium, and calcium is allowed at the discretion of the investigator. 17. Participant has a history of hypersensitivity to drugs with a clinically significant reaction or any clinically significant hypersensitivities. 18. Participant has a clinically significant allergy to band aids, adhesive dressing, ECG electrodes, or medical tape. 19. Participant has abnormal creatine phosphokinase test greater than 3 × ULN at Screening or baseline. One retest of exclusionary abnormal creatine phosphokinase tests is allowed at the discretion of the investigator. 20. Participant is currently taking, within the last 7 days before [redacted] admission or 5 half-lives (whichever is longer), or anticipates the use of any antiarrhythmic medications (including mexilitene except beta-blockers which are allowed,) or drugs known to affect the QT interval (including ranolazine; refer to drug lists for "Drugs with known, possible, or conditional risk of TdP" that are known to prolong the QT interval at https://crediblemeds.org), unless approved by the sponsor and principal investigator. 21. Participant is not permitted to use/consume the following: a. Any drugs known to be significant strong inducers of CYP 3A enzymes, including St. John's Wort, for 28 days before Day –1 or 5 half-lives (whichever is longer) and through the Follow-up Visit. b. Seville oranges, grapefruit and/or grapefruit juice within 7 days before Check-in and is unwilling to abstain from consuming these items until the end of the study. 22. Participant is considering or scheduled to undergo any surgical procedure during the study. 23. Participant has experienced an acute illness that has resolved in less than 14 days before the first study drug dose or has had a major illness or hospitalization within 1 month before the first study drug dose. 24. Participant is unwilling to abstain from ingestion of caffeine- or xanthine-containing products (eg, tea, coffee, chocolate, cola, etc.) beginning 96 hours before Check-in until the final PK sample of the study has been collected. 25. Participant is unwilling to abstain from alcohol beginning 48 hours before Check-in and until the final PK sample of the study has been collected. 26. Participant has a history of high alcohol consumption or substance abuse that would pose a risk for the participant's safety and compliance with the study protocol. Participant must not have positive screen for drugs of abuse at Screening or baseline and alcohol at baseline, except with sponsor permission. Participants may undergo a repeat urine drug screen at the discretion of the

	investigator. 27. Participant, who, for any reason, is deemed by the investigator to be inappropriate for this study or has any condition which would confound or interfere with the evaluation of the safety, tolerability, or PK of the investigational drug or prevent compliance with the study protocol.

Study design:	This is a Phase 1b/2a, 2-part study; Part 1: randomized, double-blind, crossover, dose-escalation, placebo-controlled study to evaluate the safety, tolerability, PK, and PD of SGK-1 kinase inhibition by LQT-1213 on dofetilide-induced QTc prolongation in healthy adult subjects. Part 2: single-blind, multiple-dose safety study to evaluate the safety, tolerability, and PK of LQT-1213 in patients diagnosed with LQT2 or LQT3. **Part 1:** This is a 2-treatment, 2-period crossover study. Approximately 28 healthy subjects, with the attempt to balance for sexes, will be enrolled to complete approximately up to 20 subjects in the study. Additional subjects may be enrolled to compensate for subjects that do not complete both treatment periods, at the discretion of the sponsor. The exact number will be determined during the conduct of the study. A sentinel group of up to 5 subjects may be enrolled first if warranted by the principal investigator. In both treatment periods, all subjects will receive dofetilide on Days 1 and 2 of each period. Randomization will take place before Day 3 of Period 1. Subjects will be randomly assigned to 1 of 2 treatment sequences (AB or BA), with treatment arms as follows: • Arm A: Dofetilide 500 µg twice daily (BID) (2 × 250 µg capsules), orally (Days 1-8) and LQT-1213 3 times a day (TID). LQT-1213 or matching placebo dosing: o Low dose: 3 doses on Day 3 and the first 2 doses on Day 4 o Mid dose: Last dose on Day 4, 3 doses on Day 5, and the first 2 doses on Day 6 o High dose (not to exceed 0.747 mg/kg TID, daily dose 2.24 mg/kg/day): Last dose on Day 6, 3 doses on Day 7, and the first dose on Day 8. The specific doses will be determined before administration of the first dose of LQT-1213. • Arm B: Dofetilide 500 µg BID (2 × 250 µg capsules), orally (Days 1-8) and placebo matched to LQT-1213 TID (Days 3-8) Note: Only 1 dose of dofetilide and LQT-1213 (or placebo) will be administered on Day 8. Screening will occur within 28 days of clinical research unit (CRU) admission. In both treatment periods, subjects will be domiciled starting 2 days before dofetilide dosing until after the last doses of dofetilide and LQT-1213 or placebo matched to LQT-1213 (Days –2 through 8). Days 1 and 2 are to establish near-steady state dofetilide plasma levels and observe the QTc response to dofetilide. On Day 1 at 3 hours postdose in Period 1 only, the QTcF will be measured in the 3 (triplicate) ECGs and the mean value calculated. Measurements will be manually confirmed by a cardiologist who is specifically trained and experienced in ECG interval measurements. The ECG measurements at baseline and at the 3-hour time points will be performed by the same technician and cardiologist. If the mean QTcF increase is <25 ms on the triplicate safety ECGs compared with the mean from baseline (triplicate –30 min and triplicate –15 min), the subject will be discontinued from the study. If on Day 1 at 3 hours postdose in Period 1 only, the mean QTcF on the triplicate ECGs, when repeated within 30 minutes and manually confirmed by a cardiologist

	specifically trained and experienced in ECG interval measurements, has a mean value on the 3 (triplicate) repeated ECGs >80 ms from the mean baseline QTcF, the dose of dofetilide will be reduced to 250 µg BID. If the mean QTcF is >500 ms on Day 1 in Period 1 only (repeated in triplicate within 30 minutes with a QTcF > 500 ms), the dose of dofetilide will be reduced to 250 µg BID. If the safety ECGs (repeated in triplicate within 30 minutes) shows a mean value on the 3 (triplicate) repeated ECGs of a QTcF of >500 ms on Day 2 or afterwards (or any time in Period 2), the subject will be discontinued from the study. All ECGs for these safety assessments must be manually confirmed by a cardiologist who is specifically trained and experienced in ECG interval measurements before actions are taken. If the dose is reduced to 250 µg BID, this will be the dose used in Period 2. Note: If the subject has a new QRS >110 ms or a new bundle branch block, then an adjusted QTcF will be utilized to account for the widened QRS interval (Adjusted QTcF = QTcF [ms] – [QRS interval [ms] – 90 [ms]). LQT-1213 or placebo matched to LQT-1213 will be administered at time 0, immediately after the 7.75-hour ECG extraction time point, and at 17 hours, though these time points may be adjusted based upon emerging data. Subjects will be discharged from the CRU on Day 9 or 10 (safety washout) in each period, if the QTcF is <460 ms and the increase from baseline is <40 ms. Day 10 evaluations will be performed if the subject is not discharged on Day 9. There will be a washout of at least 4 days (or at least 5 times the half-life) after the last dose of study drug. Subjects will return to the CRU on Day –2 and crossover to receive the alternate treatment in Period 2. Approximately 7 days after the end of treatment in Period 2, the Follow-up Visit will be conducted remotely via telephone call. Full PK sampling for dofetilide and LQT-1213 will be conducted on Days 4, 6, and 8 of each period. Continuous 12-lead 24-hour Holter data will be collected at the approximate 90-minute time point on Day –1 (corresponding to predose on Day 1) and stored, and on Day 1 starting 2 hours before dosing through Day 8. On each day, the Holter data card will be removed and a new one inserted 90 minutes before dosing. The ECGs will be extracted from the Holters on specific days and time points for core laboratory analysis, as detailed in the PK and PD time points table (Section 8.3, Appendix C). Subjects will have an overnight fast on Days –1 through Day 8 and will remain fasted until immediately after the 6-hour ECG extraction, when a light meal will immediately be provided, followed by a meal immediately after the 9.5- and 12-hour ECG extraction time points. Subjects will fast after the meals at 6 and 9.5 hours are completed, which must be within 20 minutes for these 2 time points. Subjects can eat at will after the 12-hour meal, a light meal will be provided, which must be completed to ensure the overnight fasting requirement is met (6-hour fast), (no food or fluid except water). Serum potassium and magnesium will be checked each day on Days –1, 1, and 2 and thereafter, beginning on Day 3, potassium and magnesium will be checked every other day. Potassium <3.8 mg/dL and magnesium <1.9 mg/dL will result in additional electrolyte supplementation. It is preferred, especially on Days 1, 4, 6, and 8, that this be done in the evening (after the 12-hour time point). Electrolyte supplementation is allowed at any time as long as it is >4 hours before dosing.

	Safety assessments will include AEs, clinical laboratory test results, vital signs measurements, and safety 12-lead ECG findings. Bedside safety 12-lead ECGs will be collected by the CRU staff and reviewed by the investigator; 12-lead ECGs will be classified as normal or abnormal not clinically significant or abnormal clinically significant. The safety ECG data, including all time points, will be recorded on the electronic case report form, and be used for evaluating general safety of the subjects during study and for evaluation of an AE. The ECGs analyzed (the cardiodynamic evaluation) by [redacted] are the primary ECG data for the analysis of the ECG intervals for the study, once completed. The dosing, meal timing, and PK and ECG time points and extractions may be modified based on emerging data. Stopping rules will be predefined and evaluated after each successive dosing group. **Part 2:** A Phase 2a, single-blind, multiple-dose, safety study to evaluate the safety, tolerability, and PK of LQT-1213 in participants with LQT2 or LQT3. The study will utilize TID dosing of LQT-1213 for 3 days (the last dosing day will be a single dose). The actual dose may be modified based upon evolving data. After the second participant completes the end of study visit for each LQT subtype (LQT2 or LQT3), a safety review committee (SRC) will review all available data before enrolling additional participants. All participants with LQT2 or LQT3 will have a QTcF ≥480 and ≤560 ms. Up to 12 participants with LQT2 and up to 12 participants with LQT3 will be enrolled. The first 2 participants with LQT2 require having an ICD before further participants with LQT2 are enrolled and the first 2 participants with LQT3 require having an ICD before further participants with LQT3 are enrolled. The ICD implantation must have been performed at least 2 months before Screening. After initial screening, which may be conducted remotely by the CRU, individual participants with LQT2 or LQT3 will undergo a 1-day, single-blind placebo run-in period followed by 3 dosing days of LQT-1213 administered TID (the last dosing day will have a single dose). Screening (remote or in-person) will be conducted within 60 days of CRU admission. Participants with LQT2 or LQT3 will be domiciled starting on Day –1 until the end of treatment on Day 5. On Days –1 (CRU admission day) and 1, participants with LQT2 or LQT3 will undergo partial (Day –1) and baseline 24-hour 12-lead high fidelity Holter monitoring during placebo single-blind administration (Day 1 only). LQT-1213 will be administered TID (at time 0, 8, and 16 hours) on Days 2 and 3, with the final dose on Day 4 at time 0, though these time points may be adjusted based upon emerging data. Participants with LQT2 or LQT3 will be discharged from the CRU on Day 5. Approximately 7 days after discharge from the CRU, the Follow-up Visit will be conducted remotely via telephone call. The intensive PK sampling for LQT-1213 will be conducted on Days 2 and 4 and the morning of Day 5. Continuous 12-lead 24-hour Holter data will be collected on Days -1 through 5, as detailed in the PK and PD time points table (Section 8.4, Appendix D). All Holter data starting on Day -1 will be stored for potential future analysis. On each day, the Holter data card will be removed and a new one inserted approximately 90 minutes before first dosing on each Days and on Day 5. ECG extraction time points for potential future analysis are detailed in the PK and PD time points table (Section 8.4, Appendix D). On Day −1, there are no fasting requirements with the exception of an overnight 6-hour fast for clinical laboratory collections. On Days 1, 2,

	and 4, participants will begin fasting at midnight and will remain fasted until immediately after the 6-hour ECG extraction time point when a light low carbohydrate meal will be provided, which should be consumed within 30 minutes. Participants will then fast until after the 10-hour (Day 1) or 12-hour (Days 2 and 4) ECG extraction when food will be provided ad libitum until midnight. On Day 3, participants will begin fasting at midnight and will remain fasted until the 2- hour time point when food will be provided ad libitum until the 6- hour time point. Fasting will resume at the 6-hour time point until the 10- hour time point when food will be provided ad libitum until midnight. Food intake must be completed prior to the midnight fast to ensure the midnight fasting requirement is met (no food or fluid except water). On Day 5, normal food intake will begin ad libitum after the 29-hour ECG extraction. Serum potassium and magnesium will be checked each day while participants are housed (Days −1, 1, 2, 3, 4 and 5). In addition, serum potassium and magnesium may be repeated at the investigator's discretion. Potassium <3.8 mg/dL and magnesium <1.8 mg/dL will result in additional electrolyte supplementation. Electrolyte supplementation can be administered 12-18 hours after the morning dose of LQT-1213. Safety assessments will include AEs, clinical laboratory test results, vital signs measurements, continuous telemetry ECG monitoring, and safety 12-lead ECG findings. Bedside safety 12-lead ECGs will be collected by the CRU staff and reviewed by the investigator. The safety ECG data, including all time points, will be recorded on the eCRF, and be used for evaluating general safety of the participants with LQT2 or LQT3 during study and for evaluation of an AE. All ECG sent to [redacted] will be stored for possible future analysis. The dosing, meal timing, and PK and ECG time points and extractions may be modified based on emerging data.

Study drug, dosage, and route of administration:	**Part 1:** • LQT-1213 low, mid, and high (not to exceed 0.747 mg/kg TID, daily dose 2.24 mg/kg/day) doses TID (at time 0, immediately after the 7.75-hour ECG extraction time point, and at 17 hours) for oral suspension (Days 3-8; only 1 dose will be administered on Day 8) **Part 2:** • LQT-1213: TID (at time 0, 8, and 16 hours) on Days 2 and 3 and a single morning dose on Day 4 (last dose on Day 4 is the am dose). The dose will not exceed daily dose 2.24 mg/kg/day for oral suspension
Reference drug, dosage, and route of administration:	**Part 1:** • Dofetilide 500 µg BID for oral administration (for both treatment sequences, Days 1-2 alone and Days 3-8 with LQT-1213 or placebo matched to LQT-1213; only 1 dose will be administered on Day 8). Potential dose-down-titration to 250 µg BID for oral administration based on safety parameters. • Placebo matched to LQT-1213 (Days 3-8; only 1 dose will be administered on Day 8) **Part 2:** • Placebo matched to LQT-1213 (Day 1) TID
Study duration:	**Part 1:** The duration of treatment for each subject in the study will be approximately 34 days, from admission on Day –2 to the telephone follow-up call. This does not include the 28-day screening period. **Part 2:** The duration of the treatment for each participant with LQT2 or LQT3 in the study will be approximately 13 days, from admission on Day –1 to the telephone follow-up call. This does not include the 60-day screening period.
Criteria for evaluation:	**Part 1:** **Electrocardiogram and QT/QTc Analyses:** Pharmacodynamics will be evaluated using extracted ECG data obtained from continuous 12-lead Holter monitors placed on all subjects in Periods 1 and 2 at time points specified in the PK and PD time points table (Appendix C) and will be analyzed consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E14 guidance. **Pharmacokinetics:** Blood samples for dofetilide and LQT-1213 PK analysis will be collected in both treatment periods on Days 4, 6, and 8 at the following time points: predose (time 0 for dofetilide) and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7.75, 9.5, 12, and 24 hours postdose. **Safety:** Safety will be determined by monitoring AEs, clinical laboratory test results (hematology, serum chemistry, coagulation and urinalysis), vital sign measurements (blood pressure, HR, respiratory rate, and oral body temperature), 12-lead ECG results, and physical examination findings.

	Part 2: **Safety:** Safety will be determined by monitoring AEs, clinical laboratory test results (hematology, serum chemistry, coagulation, and urinalysis), vital sign measurements (blood pressure, HR, respiratory rate, and oral body temperature), continuous telemetry ECG monitoring, 12-lead ECG results, and physical examination findings. **Pharmacokinetics:** Blood samples for LQT-1213 PK analysis will be collected as detailed in Appendix D. **Pharmacodynamics:** Pharmacodynamics will be evaluated by analyzing SGK-1 targets obtained from Human PBMCs for potential biomarkers. **Pharmacodynamic Biomarkers:** Human PBMC and plasma samples will be isolated and stored for potential analysis of for potential PD biomarkers, including SGK-1 targets.
Analysis populations:	**Part 1:** Five analysis populations are defined, as follows: • The primary QT/QTc population will be those subjects in the total QT/QTc population meeting a threshold effect of dofetilide to prolong the QTc interval as will be defined in the SAP. • The total QT/QTc population will include all subjects in the safety population with measurements at baseline as well as on-treatment with at least 1 postdose time point with a valid change from baseline in QTc (ΔQTc) value. The QT/QTc population will be used for the by-time point and categorical analyses of cardiodynamic ECG parameters. • The PK population will include all subjects who received at least 1 dose of study drug and provided at least 1 evaluable PK concentration for LQT-1213 or dofetilide. • The primary PK/QTc population will include all subjects who are in both the PK and primary QT/QTc populations with at least 1 pair of postdose PK and QTc data from the same time point in each period. The PK/QTc population will be used for the concentration-QTc analysis. The safety population will include all subjects who received at least 1 dose of dofetilide and provide at least 1 postdose safety assessment. **Part 2:** Three analysis populations are defined, as follows: • The safety population will include all participants with LQT2 or LQT3 who received at least 1 dose of study drug (placebo or LQT-1213) and provide at least 1 postdose safety assessment. • The PK population will include all participants with LQT2 or LQT3 who received at least 1 dose of LQT-1213 and provided at least 1 evaluable PK concentration for LQT-1213. • The PD population (SGK-1 protein targets) will include all participants who received at least 1 dose of study drug (placebo or LQT-1213) and have at least 1 PD measurement.

Statistical methods:	**Part 1:** **Electrocardiogram and QT/QTc Analyses:** The analysis will be described in the SAP. All QTc data will represent the means of the extracted QTc intervals, based on ECGs extracted from the Holters at the defined time points. Each individual QT and time elapsed between 2 successive R waves of the QRS signal on the ECG (RR) interval will be used to calculate a QTc interval. The individual QTc intervals will then be averaged for analysis. Baseline will be defined as the mean of the triplicate ECG data collected predose for each period. Fridericia's formula will be the default correction method for QT intervals to remove HR dependence. If the QTcF is not an adequate correction, other methods will be reviewed. For each method tested (including Fridericia's correction), the relationship between the QTc and RR will be evaluated with a linear-regression model. Mean QTc and RR values at all nominal time points will be used. The model with the slope closest to zero will be selected as the primary QTc endpoint. The additional correction methods and definition of an adequate correction will be detailed in the SAP. A statistical analysis will be performed per ICH E14 guidance using the appropriate population and will be detailed in the SAP. The specifics of the concentration-QTc and categorical analyses will be detailed in the SAP. **Pharmacokinetics:** The analysis will be detailed in the SAP which will be finalized before database lock. Data will be listed and summarized, where applicable. Plasma concentrations of dofetilide and LQT-1213 will be listed and summarized by treatment for each sample time point using descriptive statistics. Mean and individual plasma dofetilide and LQT-1213 concentration-time profiles will be presented in figures on linear and semilogarithmic scales. Assessment of a drug interaction between dofetilide and LQT-1213 will be examined. **Safety:** Safety data including reported AEs, clinical laboratory assessments, vital signs measurements, and safety 12-lead ECGs will be summarized. Physical examination findings will be listed. **Part 2:** **Safety:** Safety data including reported AEs, clinical laboratory assessments, vital signs measurements, continuous telemetry ECG monitoring, and safety 12-lead ECGs will be summarized. Physical examination findings will be listed. **Pharmacokinetics:** The analysis will be detailed in the SAP which will be finalized before database lock. Data will be listed and summarized, where applicable. Plasma concentrations of LQT-1213 will be listed and summarized by LQT subtype for each sample time point using descriptive statistics. Mean and individual LQT-1213 concentration-time profiles will be presented in figures on linear and semilogarithmic scales. **Pharmacokinetics/Pharmacodynamics:** Details of the potential PD (SGK-1 protein targets) analyses to derive PK (LQT-1213)/PD relationships between drug exposure and target engagement will be provided in a separate analysis plan.

Sample size:	**Part 1:** Based on the calculation of the sample size for a Thorough QT study (Zhang and Machado, 2008), as the test is performed at 5 time points separately, a 1 sided 5% significance level (with adjusted 1-sided significance levels of 5%, 2.5%, 1.67%, 1.25%, and 1%) is used along with a within-subject SD of 8 ms for ΔQTcF for all treatment groups. A sample size of 20 evaluable subjects in a crossover design who complete the study will provide a power of 90% to detect 7 ms QTc effect, ie, the lower bound of all the 2 sided 90% CIs on ΔΔQTcF will exceed 7 ms at least 1 of the 5 prespecified time points. Multiplicity will be controlled by using a Hochberg procedure (Hochberg 1988). Twenty-eight subjects will be enrolled to account for dropouts. **Part 2:** In this exploratory safety study, up to 12 participants with LQT2 and up to 12 participants with LQT3 will be recruited. The sample size was not estimated based on statistical considerations but was considered sufficient to achieve the primary safety objectives of the study.
Date of protocol:	05 December 2023

2. List of Abbreviations

Abbreviation	Definition
ΔΔHR	time-matched, placebo-adjusted, change from baseline in HR
ΔΔQRS	time-matched, placebo-adjusted, change from baseline in QRS
ΔΔQTc	time-matched, placebo-adjusted, change from baseline in QTc
ΔΔQTcF	time-matched, placebo-adjusted, change from baseline in QTcF
ΔΔPR	time-matched, placebo-adjusted, change from baseline in PR
ΔHR	change from baseline in heart rate
ΔQRS	change from baseline in QRS
ΔQTc	change from baseline in QTc
ΔQTcF	change from baseline in QTcF
ΔQTcI	change from baseline in QTcI
ΔQTcP	change from baseline in QTcP
ΔPR	change from baseline in PR interval
λ_z	apparent terminal rate constant
ACLS	Advanced Cardiovascular Life Support
APD	action potential duration
AE	adverse event
AESI	adverse events of Special Interest
AUC	area under the plasma concentration-time curve5
AUC_{0-t}	area under the plasma concentration-time curve from time 0 to the time of the last measurable concentration
AUC_{tau}	area under the concentration-time curve from time 0 to the end of the dosing interval
BID	twice daily
CFR	Code of Federal Regulations
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL_{ss}/F	apparent clearance at steady state
C_{max}	maximum observed plasma concentration
CRU	clinical research unit
C_{trough}	concentration at the end of the dosing interval
CV%	percent coefficient of variation
CYP	cytochrome P450
DHHS	Department of Health and Human Services
ECG	electrocardiogram
eCRF	electronic case report form

eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hiPSC-CMs	human-induced pluripotent stem cell-derived cardiomyocytes
HR	heart rate
IC_{50}	half-maximal inhibitory concentration
ICD	Implantable cardioverter defibrillator
ICF	informed consent form
ICH	International Council for Harmonisation
Ikr	inward-rectifier potassium channels
IRB	institutional review board
KCNQ1	potassium voltage-gated channel subfamily Q member 1
KCNH2	potassium voltage-gated channel subfamily H member 2
LFT	liver function tests
LQT/LQTS	long QT syndrome
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse-effect-level
PBMCs	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PR	time from the onset of the P wave to the start of the QRS complex
QRS	ventricular depolarization
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate by Fridericia's formula
QTcI	QT interval corrected for heart rate with individual correction
QTcP	QT interval corrected for heart rate with population correction
RR	time elapsed between 2 successive R waves of the QRS signal on the ECG
SAE	serious adverse event
SAP	statistical analysis plan
SCN5A	sodium voltage-gated channel alpha subunit 5
SGK-1	serum- and glucocorticoid-regulated kinase 1
SRC	Safety Review Committee
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event

TID	3 times a day
T_{max}	time to the maximum observed plasma concentration
US	United States
ULN	upper limit of normal
V_d/F	apparent volume of distribution

3. Introduction

3.1. Background

Congenital Long QT syndrome (LQTS) is a rare cardiac disorder most commonly caused by mutations in 1 of 3 genes that encode for ion channels involved in ventricular repolarization. Changes in the function of these ion channels result in ventricular action potential duration (APD) prolongation and prolongation of the QT interval corrected for heart rate (HR; QTc) interval, which can precipitate the ventricular arrhythmia Torsades de Pointes, which can lead to fainting, seizures, ventricular fibrillation, and sudden death. LQTS can also occur as the result of adverse effects of drugs and/or electrolyte abnormalities that inhibit the hERG (referred to as acquired LQTS).

Serum- and glucocorticoid-regulated kinase 1 (SGK-1) is a serine-threonine kinase that is under acute transcriptional control by several stimuli, including serum and glucocorticoids. SGK-1 is activated both by insulin and growth factor signaling. Baseline SGK-1 activity is low in cardiomyocytes but is upregulated in pathological states. SGK-1 plays a critical role in the regulation of the voltage-gated sodium channel Nav1.5 in cardiomyocytes by direct phosphorylation as well as regulation of interacting proteins (Bezzerides et al 2017). Activation of SGK-1 in the heart causes an increase in the late sodium current leading to prolongation of the APD, while genetic inhibition of the gene coding for SGK-1 reduces the increase in APD seen with both cardiac stressors and in inherited arrhythmia syndromes in animal models (Das et al 2012, Bapat et al 2021) and cell culture models (Bezzerides et al 2017), respectively. SGK-1 inhibition has been shown to reduce the APD in human-induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) from patients with several types of inherited arrhythmia syndromes such as LQT1 (potassium voltage-gated channel subfamily Q member 1 [KCNQ1] potassium channel locus; loss of function), LQT2 (potassium voltage-gated channel subfamily H member 2 [KCNH2] potassium channel locus; loss of function), and LQT3 (sodium voltage-gated channel alpha subunit 5 [SCN5A] sodium channel locus; gain of function) (Bezzerides et al 2017), as well as acquired LQTS in hiPSC-CMs treated with anemonia viridis toxin II or dofetilide and a guinea pig Langendorff model treated with dofetilide (Kim et al 2023).

Beta-blockers are prescribed as first line therapy for congenital LQTS. This approach reduces autonomic triggers and the probability of Torsades de Pointes but does not address the underlying pathology of prolonged ventricular repolarization, and breakthrough episodes are not uncommon. Beta-blockers are prescribed most commonly to patients with LQT1 mutations and, less commonly, to patients with LQT2 mutations. However, beta-blockers have not been demonstrated to be effective in patients with LQT3 mutations (Han et al 2020). Compliance with beta-blocker therapy is limited by unpleasant side effects including lethargy, dizziness, weight gain, and nausea, and patients often do not comply with dosing recommendations. In certain patients, failure

of beta-blocker therapy is followed by the use of an implantable cardiac defibrillator (ICD).

Thryv Therapeutics Inc. is developing LQT-1213, a potent and selective small molecule drug that inhibits the activity of SGK-1, for the treatment of individuals with congenital or acquired LQTS. In a study of 44,496 Caucasian infants, the prevalence of LQTS was estimated to be 1:2,534 (Schwartz et al 2009). Of these patients, it is estimated that 60% have LQT1, 32% have LQT2, and 8% have LQT3 (Priori et al 2003). Inhibition of SGK-1 inhibition by LQT-1213 likely prevents SGK-1 activity on the late sodium channel current, modulating the late sodium current (including the mutant channel seen in LQT3) and possibly impacting cardiac calcium handling. Multiple preclinical data in hiPSC-CMs bearing LQT2 (KCNH2) and LQT3 (SCN5A) mutations, hiPSC-CMs sheets with KCNH2 mutations, a rabbit heart with a KCNH2 mutations, normal hiPSC-CMs treated with anemone toxin II (mimicking LQT3) and experiments using dofetilide, a hERG blocker, have shown that SGK-1 inhibition shortens or normalizes the prolonged APD. Thus, it is reasonable to evaluate the effects of LQT-1213 in patients with LQTS 2 or 3.

3.2. Summary of LQT-1213 Nonclinical Development

A comprehensive program of in vitro and in vivo nonclinical studies has been completed or is in progress to investigate the primary, secondary, and safety pharmacology, pharmacokinetics (PK), general toxicity, and genotoxicity of LQT-1213 in-line with current International Council on Harmonisation (ICH) and Good Laboratory Practice (GLP) regulatory guidance. Results from these studies are briefly described in this section; additional details can be found in the investigator's brochure.

In vitro studies were conducted to demonstrate the inhibitory effect of LQT-1213 on SGK-1, and the subsequent ability to inhibit APD. LQT-1213 was screened in biochemical and whole cell assays, where LQT-1213 inhibited SGK-1 with half-maximal inhibitory concentration (IC_{50}) values of 0.25 and 89 Nm, respectively. There was no effect of different concentrations of serum protein on LQT-1213 potency against SGK-1.

In cellular assays in hiPSC-CMs bearing LQT1 (V254M-KCNQ1), LQT2 (G604S-KCNH2), and LQT3 (P1332L-SCN5A) mutations, LQT-1213 markedly reduced the prolonged APD in all hiPSC-CMs cells. LQT-1213 additionally inhibited the prolongation of APD induced by treatment with anemonia viridis toxin II (a model for LQT3) or dofetilide (a specific hERG blocker and a model for LQT2) in both hiPSC-CMs (CRISPR/Cas-9 corrected P1332L isogenic line) and normal induced pluripotent stem cell-derived cardiomyocytes (unmodified by CRISPR/Cas-9). The in vivo efficacy of SGK-1 has not been evaluated in animal models of congenital LQTS (caused by ion channel mutations) as the available animal models are either not well-characterized, not translatable to human disease, or not accessible. Note that traditional models, such as heterologous systems, are considered to be incapable of completely recapitulating genetic and phenotypic

features of LQTS, while animal models, particularly in rodents, have electrophysiological characteristics that are often species-specific and different from humans (Sala et al 2019). This hampers the possibility of promptly translating results obtained in vitro directly to the clinics, with significant delays occurring between the discovery of promising treatments and their clinical application. However, the sponsor has shown that LQT-1213 reduced dofetilide-induced QTc prolongation (a model for LQT 2) in Langendorff-perfused guinea pigs and in vivo in dogs.

In secondary pharmacology studies, at presumed supratherapeutic exposures, LQT-1213 demonstrated antagonistic activity toward adrenergic receptors α1A, α1B, α1D, and α2B; AKT3; the calcium channel L-type; nicotinic acetylcholine receptor α3β4; and serotonin receptor 5HT2B, and had agonistic activity toward serotonin receptor 5HT1A. Half-maximal inhibitory concentration/half-maximal inhibitory effective concentration for these receptors were greater than 400 times the IC_{50} of free LQT-1213 against its target, SGK-1. Clinically significant central tendency effects on blood pressure or orthostatic blood pressure were not observed in the healthy volunteer single-ascending dose/ multiple-ascending dose study.

In vitro safety pharmacology findings indicated that LQT-1213 was found to be a weak inhibitor of hERG channel (IC_{50} 3.38 μM; given 99% human protein binding the margin between the hERG IC_{50} and the LQT-1213 free fraction at the inhibitory exposure of the SGK-1 IC_{50} (89 nM is >3500 times). No significant inhibitory effects were observed against the other cardiac ion channels evaluated (hCav1.2, hKir6.2/SUR2A, hKv1.5, hKv4.3/KchiP2.2, and hNav1.5), with the exception of a mild potentiating effect on Nav1.5 channel currents at high supratherapeutic exposures.

In PK studies in mouse, rat, dog, and monkey, LQT-1213 was rapidly absorbed following oral administration with the fastest absorption in rodents (mouse and rat) followed by dog and monkey (time to the maximum observed plasma concentration [T_{max}] <1 h).

Bioavailability was low to moderate in mouse, rat, and dog (22.2%, 17.9-24.0%, and 14.0%, respectively) and lower in monkey (2.88 to 3.01%), consistent with findings of low permeability in Caco-2 and Madin-Darby canine kidney II cells. Volume of distribution at steady state values was slightly greater than total body water (0.91-1.57 L/kg), suggesting distribution to tissues. LQT-1213 partitioned primarily into plasma (blood:plasma ratio of 0.74). LQT-1213 demonstrated high plasma protein binding in human and variable, moderate-to-high binding in nonclinical species.

LQT-1213 demonstrated very high metabolic stability in hepatocytes, liver and intestinal microsomes, S9 liver fractions, plasma, and whole blood. No unique human metabolites were identified in studies in liver microsomes or hepatocytes. Based on cytochrome P450 (CYP) induction and inhibition studies as well as transporter studies, there appears to be limited potential for LQT-1213 to be involved in drug-drug interactions.

Repeat-dose studies were conducted to evaluate the potential toxicity of LQT-1213 in Sprague Dawley rats and Beagle dogs in studies of up to 14-day durations. LQT-1213

was well tolerated in 7-day studies in rats and dogs at doses up to 300 mg/kg/day and 100 mg/kg/day, respectively, which were the highest doses administered and considered to be the no-observed-adverse-effect levels (NOAELs) for each study. Fourteen-day GLP studies in both rats and dogs were conducted using twice daily (BID) administration. LQT-1213 was well tolerated over 14 days of BID dosing in both rats and dogs at doses up to 300 mg/kg/day and 100 mg/kg/day, respectively. At the high dose of 100 mg/kg/day in dogs, sporadic emesis was observed in both male and female animals. Decreases in body weight and food consumption as well as slight changes in clinical pathology parameters (increases in white blood cell parameters [neutrophils, monocytes], bilirubin [rat], urea nitrogen and urine volume and decreases in total protein and albumin [rat] and urine specific gravity [dog]) were observed in both rats and dogs; however, these findings were typically minimal in severity, were reversible following the recovery period, and were not considered adverse.

The 3-month repeat dose GLP toxicology studies in dogs and rats is underway. The total daily doses in these studies are 10, 30 and 100mg/kg in dogs (BID) and 30mg, 100mg and 300mg/kg in rats (BID). The dosing and recovery phases have been completed. Elevations in liver enzymes (ALT, AST, ALP and GGT) and total bilirubin were observed at the end of the dosing phase (Day 92) in the preliminary and unaudited results for the study in dogs at the highest dose of 100mg/kg/day with smaller elevations in ALT at the 30mg/kg/day dose in one dog, compared to control animals. These elevations were reversible in the recovery phase (Day 119). Preliminary results from the study in rats did not show elevations in these enzymes or total bilirubin.

No evidence of genotoxicity has been observed with LQT-1213 in non-GLP and GLP bacterial reverse mutation studies in Salmonella typhimurium or Escherichia coli strains, in a non-GLP in vitro micronucleus assay in Chinese hamster ovary cells, or in a GLP in vivo rat micronucleus assay.

3.3. Summary of LQT-1213 Preclinical Cardiovascular Safety

The potential for LQT-1213 to adversely affect cardiovascular system function was evaluated via in vivo GLP safety pharmacology assessments in male Sprague Dawley rats and telemetered male Beagle dogs. Single-doses of LQT-1213 at 0 (vehicle), 30, 100, and 300 mg/kg by oral gavage showed no adverse effects on the central nervous system, as measured by Functional Observational Battery assessments, or respiratory functions in Sprague Dawley rats. In telemetered Beagle dogs, single-doses of LQT-1213 administered at 0 (vehicle), 10, 30, or 100 mg/kg/day (5, 15, and 50 mg/kg/dose BID) by oral gavage showed limited to slight-to-moderate material in the cage pan at ≥30 mg/kg/day, indicative of vomiting. LQT-1213 related cardiovascular effects were observed and included dose-dependent and transient decreases in blood pressure (by 12 and 20 mm Hg, at the 5 mg/kg BID and 50 mg/kg BID doses; the maximal reductions [maximum change relative to baseline adjusted controls] were 17 and 27 mm Hg,

respectively) and presumed compensatory increases in HR beginning at 0.5 hours postdose and continuing until 5 hours postdose. No other meaningful cardiovascular effects or changes in temperature were observed. However, clinically meaningful blood pressure reductions have not been observed to date in the first-in-human single dose study (completed) and the multiple-ascending dose study (completed). No other meaningful cardiovascular effects or changes in temperature were observed.

3.4. Dose Rationale

3.4.1. Part 1

The 3 times a day (TID) dosing regimen and dose selection is based on PK modeling using data from the ongoing single-ascending dose/multiple-ascending dose study LQT-1213-0059 to achieve similar concentration at the end of the dosing interval (C_{trough}) levels in the general range of 250 to 620 ng/mL while slightly reducing the maximum observed plasma concentration (C_{max}). These levels were chosen to provide multiples of the whole cell SGK-1 IC_{50} for inhibition of 89 ng/mL. The model is based on the single-and multiple-dose study with BID dosing in healthy subjects. The high dose of LQT-1213 used in this study will be equal to or lower than the maximum dose that has been evaluated in the multiple-ascending dose study (daily dose of 2.24 mg/kg/day). The LQT-1213-0059 study is ongoing at the time of finalization of this protocol, so the actual low, mid, and high doses of LQT-1213 to be used in this study will be determined before dosing with LQT-1213 but will not exceed 2.24 mg/kg/day.

3.4.2. Part 2

The TID dosing regimen and dose selection is based on the PK data obtained from the ongoing single-ascending dose/multiple-ascending dose study LQT-1213-0059. LQT-1213 dose used in Part 2 will be equal to or lower than the maximum dose that has been evaluated in the multiple-ascending dose study (daily dose of 2.24 mg/kg/day). The actual dose of LQT-1213 to be used in Part 2 will be determined before dosing with LQT-1213 but will not exceed 2.24 mg/kg/day.

3.5. Dofetilide

Dofetilide is a potent, pure inward-rectifier potassium channels (I_{Kr}) blocker with current indications for the conversion of atrial fibrillation/flutter, and for maintenance of normal sinus rhythm in patients with atrial fibrillation/flutter of greater than 1 week duration who have been converted to normal sinus rhythm. The PK, pharmacodynamic (PD), and safety profile of the commercially available formulation of dofetilide has been well characterized in prior studies, making it a good candidate for characterization of the

interplay between I_{kr} and late sodium current in cardiac repolarization.

The dose selection for dofetilide reflects the maximum dose approved in the United States (US) product label. The safety of this dose, in addition to its PK, PD, and safety profile, has been demonstrated in several cohorts of healthy subjects (Allen et al 2000; Johannesen et al 2014; Le Coz et al 1995; Tham et al 1993). Dofetilide was shown to be well absorbed with a systemic bioavailability >90%, to reach mean C_{max} in 2.6 hours, and to have a terminal elimination half-life of about 8 hours (Allen et al 2000; Tham et al 1993).

3.6. Study Rationale

This is a Phase 1b/2a, 2-part study.

3.6.1. Part 1

This is a Phase 1b, randomized, double-blind, crossover, dose-escalation, placebo-controlled study to evaluate the safety, tolerability, PK, and PD of SGK-1 kinase inhibition by LQT-1213 on dofetilide-induced QTc prolongation in healthy adult subjects. To avoid any issues with carryover, a washout period of at least 4 days between doses or at least 5 times the half-life of LQT-1213 will be utilized.

3.6.2. Part 2

This will be a Phase 2a, single-blind, multiple-dose safety study to evaluate the safety, tolerability, and PK of LQT-1213 in participants diagnosed with LQT2 or LQT3. The ability to attenuate QT prolongation in LQT2 and LQT3 is the basis for the anticipated effect of LQT-1213 in this proposed study. All participants with LQT2 or LQT3 will have a QTc by Fridericia's formula (QTcF) ≥480 and ≤560 ms. Up to 12 participants with LQT2 and up to 12 participants with LQT3 will be enrolled, of which the first 2 participants for each LQT subtype require having an ICD, which must have had ICD implantation at least 2 months before Screening. After initial screening which may be conducted remotely by the clinical research unit (CRU), individual participants with LQT2 or LQT3 will undergo a 1-day, single-blind placebo run-in period followed by LQT-1213 administered TID.

This study has been designed to minimize potential risk to participants. The short dosing duration was chosen to reduce any potential long term exposure risk to participants while maintaining the ability to assess the objectives of this study. Given the inpatient setting of this study, participants will be closely monitored clinically, electrographically, and by laboratory assessments during the treatment period. Furthermore, safety data obtained in Part 1 of this protocol did not suggest any safety signals or trend and is considered

supportive of this current design.

4. Study Objectives

4.1. Part 1

Part 1 is a randomized, double-blind, crossover, dose-escalation, placebo-controlled study in 28 healthy adult subjects with the following objectives:

- Primary: To evaluate the effect of oral LQT-1213 on dofetilide-induced QTc prolongation in healthy adult subjects
- Secondary: To evaluate the safety and tolerability of a combination of oral dofetilide and oral LQT-1213 in healthy adults
- Secondary: To determine the PK of oral LQT-1213 and oral dofetilide in healthy adults

4.2. Part 2

Part 2 is a single-blind, multiple-dose study in up to 12 adult participants with LQT2 and in up to 12 participants with LQT3 with the following objectives:

- Primary: To evaluate the safety and tolerability of oral LQT-1213 in participants with LQT2 or LQT3
- Secondary: To determine the PK of oral LQT-1213 in participants with LQT2 or LQT3
- Exploratory: To evaluate the correlation between the PK of LQT-1213 and candidate SGK-1 protein targets in participant peripheral blood mononuclear cells (PBMCs) in order to derive PK/PD relationships between drug exposure and target engagement; additional exploratory PD endpoints may be assessed

5. Investigational Plan

5.1. Study Design

This is a Phase 1b/2a, 2-part study; Part 1: randomized, double-blind, crossover, dose-escalation, placebo-controlled study to evaluate the safety, tolerability, PK, and PD of SGK-1 kinase inhibition by LQT-1213 on dofetilide-induced QTc prolongation in healthy adult subjects. Part 2: single-blind, multiple-dose safety study to evaluate the safety, tolerability, and PK of LQT-1213 in patients diagnosed with LQT2 or LQT3.

5.1.1. Part 1

This is a 2-treatment, 2-period crossover study. Approximately 28 healthy subjects, with the attempt to balance for sexes, will be enrolled to complete approximately up to 20 subjects in the study. Additional subjects may be enrolled to compensate for subjects that do not complete both treatment periods, at the discretion of the sponsor. The exact number will be determined during the conduct of the study. A sentinel group of up to 5 subjects may be enrolled first if warranted by the principal investigator.

In both treatment periods, all subjects will receive dofetilide on Days 1 and 2 of each period. Randomization will take place before Day 3 of Period 1. Subjects will be randomly assigned to 1 of 2 treatment sequences (AB or BA), with treatment arms as follows:

- Arm A: Dofetilide 500 µg BID (2 × 250 µg capsules), orally (Days 1-8) and LQT-1213 3 times a day (TID). LQT-1213 or matching placebo dosing:
  - Low dose: 3 doses on Day 3 and the first 2 doses on Day 4
  - Mid dose: Last dose on Day 4, 3 doses on Day 5, and the first 2 doses on Day 6
  - High dose (not to exceed 0.747 mg/kg TID, daily dose 2.24 mg/kg/day): Last dose on Day 6, 3 doses on Day 7, and the first dose on Day 8. The specific doses will be determined before administration of the first dose of LQT-1213.
- Arm B: Dofetilide 500 µg BID (2 × 250 µg capsules), orally (Days 1-8) and placebo matched to LQT-1213 TID (Days 3-8)

Note: Only 1 dose of dofetilide and LQT-1213 (or placebo) will be administered on Day 8.

Screening will occur within 28 days of CRU admission. In both treatment periods, subjects will be domiciled starting 2 days before dofetilide dosing until after the last doses of dofetilide and LQT-1213 or placebo matched to LQT-1213 (Days –2 through 8). Days 1 and 2 are to establish near-steady state dofetilide plasma

levels and observe the QTc response to dofetilide. On Day 1 at 3 hours postdose in Period 1 only, the QTcF will be measured in the 3 (triplicate) ECGs and the mean value calculated. Measurements will be manually confirmed by a cardiologist who is specifically trained and experienced in ECG interval measurements. The ECG measurements at baseline and at the 3-hour time points will be performed by the same technician and cardiologist. If the mean QTcF increase is <25 ms on the triplicate safety ECGs compared with the mean from baseline (triplicate –30 min and triplicate –15 min), the subject will be discontinued from the study. If on Day 1 at 3 hours postdose in Period 1 only, the mean QTcF on the triplicate ECGs, when repeated within 30 minutes and manually confirmed by a cardiologist specifically trained and experienced in ECG interval measurements, has a mean value on the 3 (triplicate) repeated ECGs >80 ms from the mean baseline QTcF, the dose of dofetilide will be reduced to 250 µg BID. If the mean QTcF is >500 ms on Day 1 in Period 1 only (repeated in triplicate within 30 minutes with a QTcF > 500 ms), the dose of dofetilide will be reduced to 250 µg BID. If the safety ECGs (repeated in triplicate within 30 minutes) shows a mean value on the 3 (triplicate) repeated ECGs of a QTcF of >500 ms on Day 2 or afterwards (or any time in Period 2), the subject will be discontinued from the study. All ECGs for these safety assessments must be manually confirmed by a cardiologist who is specifically trained and experienced in ECG interval measurements before actions are taken. If the dose is reduced to 250 µg BID, this will be the dose used in Period 2. Note: If the subject has a new QRS >110 ms or a new bundle branch block, then an adjusted QTcF will be utilized to account for the widened QRS interval (Adjusted QTcF = QTcF [ms] – [QRS interval [ms] – 90 [ms]).

LQT-1213 or placebo matched to LQT-1213 will be administered at time 0, immediately after the 7.75-hour ECG extraction time point, and at 17 hours, though these time points may be adjusted based upon emerging data. Subjects will be discharged from the CRU on Day 9 or 10 (safety washout) in each period, if the QTcF is <460 ms and the increase from baseline is <40 ms. Day 10 evaluations will be performed if the subject is not discharged on Day 9. There will be a washout of at least 4 days (or at least 5 times the half-life) after the last dose of study drug. Subjects will return to the CRU on Day –2 and crossover to receive the alternate treatment in Period 2.

Approximately 7 days after the end of treatment in Period 2, the Follow-up Visit will be conducted remotely via telephone call.

Full PK sampling for dofetilide and LQT-1213 will be conducted on Days 4, 6, and 8 of each period. Continuous 12-lead 24-hour Holter data will be collected at the approximate 90-minute time point on Day –1 (corresponding to predose on Day 1) and stored, and on Day 1 starting 2 hours before dosing through Day 8. On each day, the Holter data card will be removed and a new one inserted 90 minutes before dosing. The ECGs will be extracted from the Holters on specific days and time points for core laboratory analysis, as detailed in the Part 1 PK and PD time points table (Section 8.3, Appendix C).

Subjects will have an overnight fast on Days –1 through Day 8 and will remain fasted until immediately after the 6-hour ECG extraction, when a light meal will immediately be provided, followed by a meal immediately after the 9.5- and 12-hour ECG extraction time points.

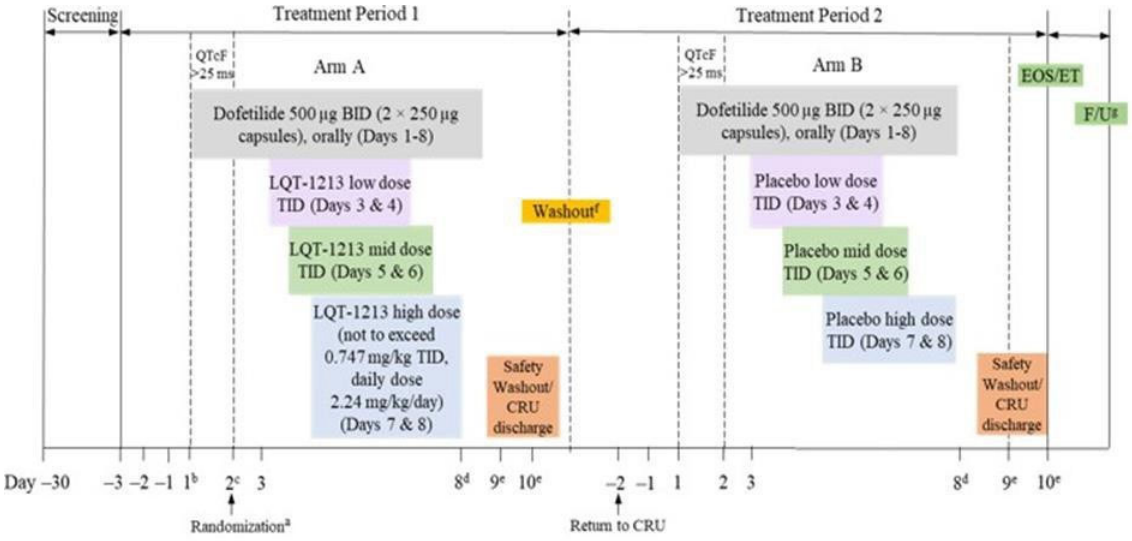
Subjects will fast after the meals at 6 and 9.5 hours are completed, which must be within 20 minutes for these 2 time points. Subjects can eat at will after the 12-hour meal, a light meal will be provided, which must be completed to ensure the overnight fasting requirement is met (6-hour fast), (no food or fluid except water). Serum potassium and magnesium will be checked each day on Days –1, 1, and 2 and thereafter, beginning on Day 3, potassium and magnesium will be checked every other day. Potassium <3.8 mg/dL and magnesium <1.9 mg/dL will result in additional electrolyte supplementation. It is preferred, especially on Days 1, 4, 6, and 8, that this be done in the evening (after the 12-hour time point). Electrolyte supplementation is allowed at any time as long as it is >4 hours before dosing.

Safety assessments will include AEs, clinical laboratory test results, vital signs measurements, and safety 12-lead ECG findings. Bedside safety 12-lead ECGs will be collected by the CRU staff and reviewed by the investigator; 12-lead ECGs will be classified as normal or abnormal not clinically significant or abnormal clinically significant. The safety ECG data, including all time points, will be recorded on the electronic case report form, and be used for evaluating general safety of the subjects during study and for evaluation of an AE. The ECGs extracted from Holters and analyzed by [redacted] are the primary ECG data for the analysis of the ECG intervals of the study, once completed.

The dosing, meal timing, and PK and ECG time points and extractions may be modified based on emerging data.

Stopping rules will be predefined and evaluated after each successive dosing group.

Figure 5-1 Study Schematic - Part 1



Abbreviations: BID, twice daily; CRU, clinical research unit; ECG, electrocardiogram; EOS, end of study; ET, early termination; F/U, follow-up; QTcF, QT interval corrected for heart rate by Fridericia's formula; TID, 3 times a day.

a Randomization will take place before Day 3 of Period 1.

b On Day 1 at 3 h in Period 1 only, the QTcF will be measured in the 3 ECGs and the mean value calculated. Measurements will be manually confirmed by a cardiologist who is specifically trained and experienced in ECG interval measurements. The ECG measurements at baseline and at the 3-h time points will be performed by the same technician and cardiologist. If the mean QTcF increase is <25 ms on the triplicate safety ECGs compared with the mean from baseline (triplicate −30 min and triplicate −15 min), the subject will be discontinued from the study. If on Day 1 in Period 1 only at 3 h postdose, the mean QTcF on the triplicate ECGs, when repeated within 30 min and manually confirmed by a cardiologist specifically trained and experienced in ECG interval measurements, is >80 ms from the mean baseline QTcF, the dose will be reduced to 250 µg BID. If the mean QTcF is >500 ms on Day 1 (repeated in triplicate within 30 min), the dose will be reduced to 250 µg BID.

c If the safety ECGs (repeated in triplicate within 30 min) shows a mean QTcF of >500 ms on Day 2 or afterwards, the subject will be discontinued from the study. Subjects can be discharged from the CRU once the QTcF is <500 ms or the increase from baseline is <40 ms. All ECGs for these safety assessments must be manually confirmed by a cardiologist who is specifically trained and experienced in ECG interval measurements before actions are taken. If the dose is reduced to 250 µg BID, this will be the dose used during Period 2 of the study. Note: If the subject has a new QRS >110 ms or a new bundle branch block, then an adjusted QTcF will be utilized to account for the widened QRS interval (Adjusted QTcF = QTcF [ms] – [QRS interval [ms] – 90 ms]).

d Only 1 dose of dofetilide, LQT-1213, and placebo matched to LQT-1213 will be administered on Day 8.

e Subjects will be discharged from the CRU on Day 9 or 10 (safety washout) in each period if the QTcF is <460 ms and the increase from baseline is <40 ms. Day 10 evaluations will be performed if the subject is not discharged on Day 9.

f There will be a washout of at least 4 days (or at least 5 times the half-life) after the last dose of study drug. Subjects will return to the CRU on Day −2 and crossover to receive the alternate treatment in Period 2.

g Approximately 7 days after the end of treatment in Period 2, the Follow-up Visit will be conducted remotely via telephone call.

5.1.2. Part 2

This is a Phase 2a, single-blind, multiple-dose, safety study to evaluate the safety, tolerability, and PK of LQT-1213 in participants with LQT2 or LQT3. The study will utilize TID dosing of LQT-1213 for 3 days (the last dosing day will be a single dose). The actual dose may be modified based upon evolving data. After the second participant completes the end of study visit for each LQT subtype (LQT2 or LQT3), a safety review committee (SRC) will review all available data before enrolling additional participants. All participants with LQT2 or LQT3 will have a QTcF ≥480 and ≤560 ms. Up to 12 participants with LQT2 and up to 12 participants with LQT3 will be enrolled. The first 2 participants with LQT2 require having an ICD before further participants with LQT2 are enrolled and the first 2 participants with LQT3 require having an ICD before further participants with LQT3 are enrolled. The ICD implantation must have been

performed at least 2 months before Screening. After initial screening, which may be conducted remotely by the CRU, individual participants with LQT2 or LQT3 will undergo a 1-day, single-blind placebo run-in period followed by 3 dosing days of LQT-1213 administered TID (the last dosing day will have a single dose).

Screening (remote or in-person) will be conducted within 60 days of CRU admission. Participants with LQT2 or LQT3 will be domiciled starting on Day –1 until the end of treatment on Day 5. On Day 1, participants with LQT2 or LQT3 will undergo baseline 24-hour 12-lead high fidelity Holter monitoring during placebo single-blind administration.

LQT-1213 will be administered TID (at time 0, 8, and 16 hours) on Days 2 and 3, with the final dose on Day 4 at time 0, though these time points may be adjusted based upon emerging data. Participants with LQT2 or LQT3 will be discharged from the CRU on Day 5. Approximately 7 days after discharge from the CRU, the Follow-up Visit will be conducted remotely via telephone call.

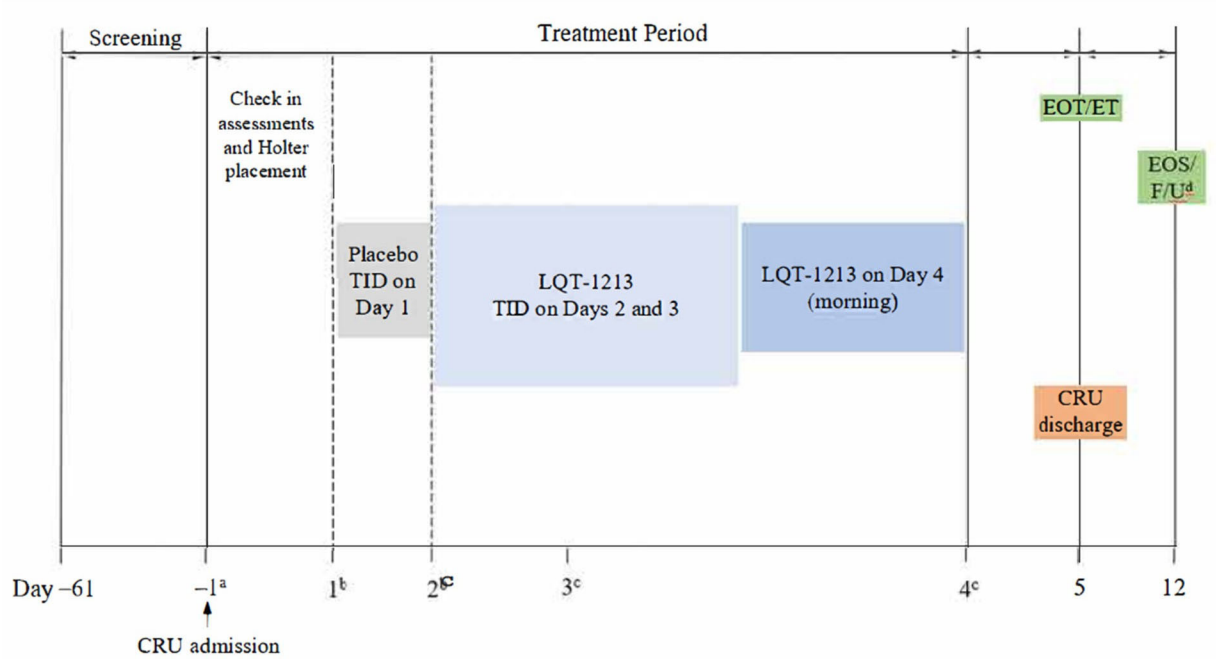
The intensive PK sampling for LQT-1213 will be conducted on Days 2 and 4, and the morning of Day 5. Continuous 12-lead 24-hour Holter data will be collected on Days −1 through 5, as detailed in the PK and PD time points table (Section 8.4 Appendix D). All Holter data starting on Day -1 will be stored for potential future analysis. On each day, the Holter data card will be removed and a new one inserted approximately 90 minutes before first dosing on each Days and on Day 5. ECG extraction time points for potential future analysis are detailed in the PK and PD time points table (Section 8.4, Appendix D).

Serum potassium and magnesium will be checked daily while participants are housed (Days −1, 1, 2, 3, 4, and 5) and may be repeated at any time at the investigator's discretion. Potassium <3.8 mg/dL and magnesium <1.8 mg/dL will result in additional electrolyte supplementation. Electrolyte supplementation can be administered 12-18 hours after the morning dose of LQT-1213.

Safety assessments will include AEs, clinical laboratory test results, vital signs measurements, continuous telemetry ECG monitoring, and safety 12 lead ECG findings. Bedside safety 12-lead ECGs will be collected by the CRU staff and reviewed by the investigator. The safety ECG data, including all time points, will be recorded on the electronic case report form, and be used for evaluating general safety of the participants with LQT2 or LQT3 during the study and for evaluation of an AE.

The dosing, meal timing, and PK and ECG time points and extractions may be modified based on emerging data.

Figure 5-2 Study Schematic - Part 2



Abbreviations: TID, 3 times a day; CRU, clinical research unit; EOS, end of study; EOT, end of treatment; ET, early termination; F/U, Follow-Up; QTcF, QT interval corrected for heart rate by Fridericia's formula.

a Up to 12 participants with LQT2 and up to 12 participants with LQT3 will be enrolled, of which the first 2 participants for each LQT subtype require having an implantable cardioverter defibrillator (ICD), which must have had ICD implantation at least 2 months before Screening. All participants with LQT2 or LQT3 will have a QTcF ≥480 and ≤560 ms.

b On Day 1, participants with LQT2 or LQT3 will undergo baseline 24-hour 12-lead high fidelity Holter monitoring during placebo single-blind administration.

c LQT-1213: LQT-1213 will be administered TID (at time 0, 8, and 16 hours) on Day 2 and 3, with the final dose on Day 4 at time 0, though these time points may be adjusted based upon emerging data.

d Approximately 7 days after discharge from the CRU, the Follow-up Visit will be conducted remotely via telephone call.

5.1.3. Safety Review Committee

In **Part 2**, after the second participant completes the end of study visit for each LQT subtype (LQT2 or LQT3), a SRC, will at a minimum, be comprised of the investigator and sponsor's chief medical officer and medical monitor. Other consultants may be added to the SRC as needed. The data reviewed will include any available PK, PD, and safety data as well as any other findings that the investigator or sponsor finds clinically significant. One primary responsibility of the SRC is to review accumulated safety and PK (as available) and make recommendations for continued participant enrollment. The SRC may recommend changes to the planned dosing scheme, adding dose groups, stopping dosing, and potential replacement of participants. The final outcome/decision from the SRC will be documented. Additional details may be found in the SRC Charter.

5.2. Selection of Study Population

The investigator or designee will be responsible for confirming subject eligibility by documenting in the electronic case report form (eCRF) that each subject meets all of the inclusion criteria in Section 5.2.1 and does not meet any of the exclusion criteria in Section 5.2.2.

5.2.1. Inclusion Criteria

5.2.1.1. Part 1

All subjects considered for study participation must meet the following criteria:

1. Male and female subjects between 18 and 60 years of age (inclusive) at Screening.
2. Not previously enrolled in a clinical study with LQT-1213.
3. Normal general health.
4. Body mass index within 18.0 to 32.0 kg/m^2, inclusively at Screening.
5. Female subjects of nonchildbearing potential must be either surgically sterile (hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before Screening) or postmenopausal, defined as spontaneous amenorrhea for at least 2 years, with follicle-stimulating hormone in the postmenopausal range at Screening, based on the central laboratory's ranges.
6. Female subjects of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) must use a highly effective contraceptive regimen during their participation in the study and for 30 days after the last administration of study drug. Highly effective contraceptive methods are defined as those with <1% failure rate per year. Acceptable methods of contraception for female subjects enrolled in the study include the following:

    - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable
    - Intrauterine device
    - Intrauterine hormone-releasing system
    - Bilateral tubal occlusion
    - Vasectomized partner
    - Heterosexual abstinence

7. Male subjects and their partners must use highly effective methods of contraception (ie, condom and spermicide) for the entire duration of the study. Male subjects must continue to use contraception and refrain from fathering a child and sperm donation for 90 days after the last administration of study drug. Acceptable methods of contraception for male subjects enrolled in the study include the following:
   - Condoms and spermicide
   - Surgical sterilization (vasectomy) of the subject at least 26 weeks before Screening
   - Heterosexual abstinence (subject must agree to use condom and spermicide if they become sexually active)
8. Understand the requirements of the study and voluntarily consent to participate in the study.

5.2.1.2. Part 2

All participants with LQT2 or LQT3 considered for study participation must meet the following criteria:

1. Male and female participants 18 years of age or older at Screening.
2. Body weight of at least 45 kg at Screening.
3. Female participants of nonchildbearing potential must be either surgically sterile (hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before Screening) or postmenopausal, defined as spontaneous amenorrhea for at least 2 years, with follicle-stimulating hormone in the postmenopausal range (>40 mIU/mL) at Screening, based on the central laboratory's ranges.
4. Female participants of childbearing potential (ie, ovulating, premenopausal, and not surgically sterile) must use a highly effective contraceptive regimen during their participation in the study and for 30 days after the last administration of study drug. Highly effective contraceptive methods are defined as those with <1% failure rate per year. Acceptable methods of contraception for female participants enrolled in the study include the following:
   - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal
   - Progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable, implantable
   - Intrauterine device
   - Intrauterine hormone-releasing system

- Bilateral tubal occlusion
- Vasectomized partner
- Heterosexual abstinence

5. Male participants and their partners must use highly effective methods of contraception (ie, condom and spermicide) for the entire duration of the study. Male participants must continue to use contraception and refrain from fathering a child and sperm donation for 90 days after the last administration of study drug. Acceptable methods of contraception for male participants enrolled in the study include the following:
   - Condoms and spermicide
   - Surgical sterilization (vasectomy) of the participant at least 26 weeks before Screening
   - Heterosexual abstinence (participant must agree to use condom and spermicide if they become sexually active)
6. LQT2 or LQT3 mutation:
   - LQTS 2: Participants with potassium voltage-gated channel subfamily H member 2 (KCNH2) mutations that are dominant negative and considered to be pathologic or likely pathologic by the screening laboratory can be included after approval from the sponsor. Participants with haploinsufficiency will not be eligible for this study.
   - LQTS 3: Participants with a sodium voltage-gated channel alpha subunit 5 (SCN5A) gene chromosome 3 mutations that are mutations and considered to be pathologic or likely pathologic by the screening laboratory can be included after approval from the sponsor. Participants with mutations not associated with Brugada syndrome or overlap syndromes or where mutations affect the window current or the persistent 'late' Na current to exert a primary or major role in the phenotype, will be eligible for this study.
7. QTcF interval ≥480 and ≤560 ms determined at Screening and on Day −1 triplicate ECGs as assessed by a physician trained in complex ECG interpretation.
8. The first 2 participants with LQT2 require having an ICD before further participants with LQT2 are enrolled and the first 2 participants with LQT3 require having an ICD before further participants with LQT3 are enrolled. This stipulation may be altered based on agreement between the principal investigator and Sponsor based on emerging data. The ICD implantation must have been at least 2 months before Screening.

   Note: Subsequent participants may or may not have had an ICD. The results of the ICD interrogation within the last 6 months should be available for review unless

waived by the investigator and sponsor.

9. Understand the requirements of the study and voluntarily consent to participate in the study.

5.2.2. Exclusion Criteria

5.2.2.1. Part 1

Subjects will be excluded from the study if they meet any of the following criteria:

1. On Day 1 at 3 hours postdose in Period 1 only, of the first cycle of dofetilide, the QTcF on the triplicate ECGs will be manually confirmed by cardiologist experienced in ECG interval measurements. The ECG measurements at baseline and at the 3-hour time points will be performed by the same technician and cardiologist. If the mean QTcF increase from baseline is <25 ms on triplicate safety ECGs compared to the mean from baseline (all ECG QTcF measurements averaged), the subject will be disqualified from further study participation.
2. Clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease or any other condition, which, in the opinion of the investigator, would jeopardize the safety of the subject or impact the validity of the study results. No history of myocardial infarction or angina or ischemic heart disease, nonsustained or sustained ventricular tachycardia, atrial fibrillation, stroke, transient ischemic attack, syncope, congestive heart failure, family history of LQTS, Torsades de Pointes, or sudden cardiac death.
3. Female subjects must not be pregnant, lactating, or breastfeeding, and must not be planning to become pregnant.
4. Female subjects of childbearing potential must have a negative result for the serum pregnancy test at Screening and Check-in.
5. Clinically significant abnormal findings on the physical examination or medical history during Screening as deemed by the investigator.
6. Participated in a previous clinical study in the previous 3 months before dosing.
7. Donation of blood volume greater than 300 mL within 30 days before Screening and agree to avoid donation from Screening and throughout the study.
8. At Screening and on Day –2, if the 12-lead ECG demonstrates any of the following: PR >240 ms; QRS >110 ms, or QTcF <400 ms and >440 ms; second- or third-degree atrioventricular block; bundle branch block, significant ST-T wave abnormalities or

flat T waves that could interfere with QT analysis. If HR <50 or >85 bpm, then 2 more ECGs will be recorded, and the mean values will be used.

9. Known sensitivity to kinase inhibitors.
10. Abnormal renal function with an estimated glomerular filtration rate (eGFR) of <70 mL/min/1.73 m^2, with eGFR calculated by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula at Screening. One retest of the exclusionary eGFR value is allowed at the discretion of the investigator.
11. Subject has abnormal liver function tests (transaminases or total bilirubin) greater than 2.5 × the upper limit of normal at Screening or baseline. One retest of exclusionary abnormal liver function tests is allowed at the discretion of the investigator.
12. Subject has a positive serology test for HIV antibodies, hepatitis B surface antigen, or hepatitis C virus antibody at Screening.
13. Subject has a hemoglobin <11.0 g/dL, potassium <3.8 mg/dL, magnesium <1.9 mg/dL, or calcium <8.5 mg/dL at Screening or baseline. One retest of exclusionary hemoglobin, potassium, magnesium, and calcium is allowed at the discretion of the investigator. Electrolyte supplementation is allowed at any time as long as it is >4 hours before dosing.
14. Subject has a history of hypersensitivity to drugs with a clinically significant reaction or any clinically significant hypersensitivities.
15. Subject has an allergy to band aids, adhesive dressing, or medical tape.
16. Subject has a history within the past 2 months of strenuous exercise (eg, marathon running) and is unwilling to refrain from strenuous exercise from 7 days before Check-in and until the end of the study. Subject has abnormal creatine phosphokinase test greater than 3 × the upper limit of normal at Screening and baseline. One retest of exclusionary abnormal creatine phosphokinase tests is allowed at the discretion of the investigator.
17. Subject is unable to refrain from or anticipates the use of any drug, including prescription and nonprescription medications (with the exception of hormonal contraception), herbal preparations, or vitamin supplements beginning 14 days before the first dose and until the end of the study. After dosing, acetaminophen (up to 2 g per 24 hours) may be administered at the discretion of the investigator or designee.
    a. Hepatic or renal clearance altering agents within 30 days before the first dose and until the end of the study.
    b. Avoid vaccinations from Screening until the end of the study.

c. Has consumed cruciferous vegetables (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, and mustard greens) or charbroiled meats within 7 days before Check-in through the Follow-up Visit.

d. Use of any drugs known to be significant strong inducers of cytochrome P450 (CYP) 3A enzymes, including St. John's Wort, for 28 days before Day –1 or 5 half-lives (whichever is longer) and through the Follow-up Visit.

e. Has consumed Seville oranges, grapefruit and/or grapefruit juice within 14 days before Check-in and is unwilling to abstain from consuming these items until the end of the study.

18. Subject is considering or scheduled to undergo any surgical procedure during the study.

19. Subject has experienced an acute illness that has resolved in less than 14 days before the first study drug dose or has had a major illness or hospitalization within 1 month before the first study drug dose.

20. Subject is unwilling to abstain from ingestion of caffeine- or xanthine-containing products (eg, tea, coffee, chocolate, cola, etc.) beginning 96 hours before Check-in until the final PK sample of the study has been collected.

21. Subject is unwilling to abstain from alcohol beginning 48 hours before Check-in and until the final PK sample of the study has been collected.

22. Subject has a history of high alcohol consumption within 9 months before Screening, defined as an average weekly intake of >14 units for males or >10 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine, or 1 measure (25 mL) of spirits.

23. Subject has a history of drug abuse in the 3 years before Screening or positive screen for drugs of abuse or alcohol at Screening or baseline. Subjects may undergo a repeat urine drug screen at the discretion of the investigator.

24. Subject uses or has used tobacco-or nicotine-containing products (eg, cigarettes, cigars, chewing tobacco, snuff, etc.) within 6 months before Screening and is unwilling to abstain from tobacco-containing products until the end of the study, based on subject self-reporting.

25. Subject, who, for any reason, is deemed by the investigator to be inappropriate for this study or has any condition which would confound or interfere with the evaluation of the safety, tolerability, or PK of the investigational drug or prevent compliance with the study protocol.

5.2.2.2. Part 2

Participants with LQT2 or LQT3 will be excluded from the study if they meet any of the following criteria:

1. Clinically significant gastrointestinal, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or significant structural cardiovascular disease or any other condition beyond LQT2 or LQT3, which, in the opinion of the investigator or sponsor, would jeopardize the safety of the participant or impact the validity of the study results. History of myocardial infarction or ongoing angina or active ischemic heart disease, atrial fibrillation, stroke, or transient ischemic attack within the past 12 months, greater than New York Heart Association Class II congestive heart failure, bundle branch block, hemodynamically significant ventricular tachycardia not due to Torsades de Pointes, or Brugada syndrome.
2. Participant has a history of an aborted cardiac arrest, ICD implantation, syncopal episode due to a ventricular arrhythmia or where confidence in the etiology cannot be established, or appropriate ICD therapy for ventricular tachycardia/ventricular fibrillation within 2 months before Screening. Participants with LQT2 or LQT3 can be enrolled after the 2-month time period has lapsed.
3. Female participants must not be pregnant, lactating, or breastfeeding, and must not be planning to become pregnant.
4. Female participants of childbearing potential must have a negative result for the serum pregnancy test at Screening and Check-in.
5. Clinically significant abnormal findings on the physical examination at Check-in or medical history during Screening as deemed by the principal investigator.
6. Currently participating in another interventional clinical study.
7. Donation of blood volume greater than 300 mL within 30 days before dosing and unwilling to avoid donation from Screening and throughout the study.
8. Screening diastolic blood pressure <45 or >95 mm Hg, systolic blood pressure <90 or >150 mm Hg, or with sponsor and investigator approval.
9. At Screening and on Day –1, if the triplicate 12-lead ECG demonstrates any of the following: mean PR >250ms; QRS >110 ms, or QTcF >560 ms and <480 ms; bundle branch block or significant ST-T wave abnormalities or flat T waves that could interfere with QT analysis. Heart rate <45 bpm, unless receiving a beta-blocker in which case <40 bpm, or HR >95 bpm. If any of these exclusionary criteria are met, then a second set of triplicate ECGs may be acquired, and the mean values may be used. For participants on beta blockade, the PR interval may be higher than 250 ms with sponsor and investigator approval.
10. Atrial pacing rate set to ≥80 bpm in those with atrial pacing.

11. Participant has a pacemaker or ICD that is actively used for ventricular pacing.
12. Known sensitivity to kinase inhibitors or clinically significant drug allergies to any of the components of LQT-1213.
13. Abnormal renal function with an eGFR of <60 mL/min/1.73 m^2, with eGFR calculated by the CKD-EPI formula at Screening. One retest of the exclusionary eGFR value is allowed at Screening and Check-in at the discretion of the investigator.
14. Participant has abnormal liver function tests (transaminases greater than 2 × the upper limit of normal [ULN] or total bilirubin > 1.5 × ULN. If the participant has documented Gilbert's Syndrome, participation is at the combined principal investigator and Sponsor's discretion after review of historical liver and bilirubin tests.
15. Participant has a positive serology test for HIV antibodies, hepatitis B surface antigen, or hepatitis C virus antibody at Screening.
16. Participant has a hemoglobin <11.0 g/dL, potassium <3.8 mg/dL, magnesium <1.8 mg/dL, or calcium <8.5 mg/dL at Screening or baseline. One retest of exclusionary hemoglobin, potassium, magnesium, and calcium is allowed at the discretion of the investigator.
17. Participant has a history of hypersensitivity to drugs with a clinically significant reaction or any clinically significant hypersensitivities.
18. Participant has a clinically significant allergy to band aids, adhesive dressing, ECG electrodes, or medical tape.
19. Participant has abnormal creatine phosphokinase test greater than 3 × the ULN at Screening or baseline. One retest of exclusionary abnormal creatine phosphokinase tests is allowed at the discretion of the investigator.
20. Participant is currently taking, within the last 7 days before [redacted] admission or 5 half-lives (whichever is longer), or anticipates the use of any antiarrhythmic medications (including mexilitene except beta-blockers which are allowed,) or drugs known to affect the QT interval (including ranolazine; refer to drug lists for "Drugs with known, possible, or conditional risk of TdP" that are known to prolong the QT interval at https://crediblemeds.org), unless approved by the sponsor and principal investigator.
21. Participant is not permitted to use/consume the following:
    a. Any drugs known to be significant strong inducers of CYP 3A enzymes, including St. John's Wort, for 28 days before Day –1 or 5 half-lives (whichever is longer) and through the Follow-up Visit.
    b. Seville oranges, grapefruit and/or grapefruit juice within 7 days before Check-in and is unwilling to abstain from consuming these items until the end of the study.
22. Participant is considering or scheduled to undergo any surgical procedure during

the study.

23. Participant has experienced an acute illness that has resolved in less than 14 days before the first study drug dose or has had a major illness or hospitalization within 1 month before the first study drug dose.
24. Participant is unwilling to abstain from ingestion of caffeine- or xanthine-containing products (eg, tea, coffee, chocolate, cola, etc.) beginning 96 hours before Check-in until the final PK sample of the study has been collected.
25. Participant is unwilling to abstain from alcohol beginning 48 hours before Check-in and until the final PK sample of the study has been collected.
26. Participant has a history of high alcohol consumption or substance abuse that would pose a risk for the participant's safety and compliance with the study protocol. Participant must not have positive screen for drugs of abuse at Screening or baseline and alcohol at baseline, except with sponsor permission. Participants may undergo a repeat urine drug screen at the discretion of the investigator.
27. Participant, who, for any reason, is deemed by the investigator to be inappropriate for this study or has any condition which would confound or interfere with the evaluation of the safety, tolerability, or PK of the investigational drug or prevent compliance with the study protocol.

5.3. Withdrawal of Subjects from the Study

5.3.1. Reasons for Withdrawal

Parts 1 and 2: The primary reason for treatment discontinuation will be noted using the following categories:

1. Adverse event: The subject experiences an AE that, in the opinion of the investigator, requires early termination. If a subject is discontinued from the study due to an AE, the investigator or designee will be required to follow-up with the subject until the event resolves or becomes stable. If a subject dies during the study, the cause of death will be reported as a serious AE (SAE), with an outcome of death noted on the eCRF.

   Additionally, refer to Section 5.4.3.5 for safety 12-lead ECG discontinuation criteria.
2. Stopping criterion: The subject meets one of the stopping criteria for individual subjects (Section 5.3.3).
3. Protocol deviation/violation: The subject fails to meet protocol entry criteria or does not adhere to protocol requirements, and continued participation poses an unnecessary risk to the subject's health.

   Note: For **Part 1** only, if the safety ECGs (repeated in triplicate within 30 minutes)

shows a mean QTcF of >500 ms on the repeated (triplicate) ECGs on Day 2 or afterwards, which will be manually confirmed by a cardiologist who is specifically trained and experienced in ECG interval measurements, the subject will be discontinued from the study. Details for subject discontinuation from the study and QTcF adjustment for a new QRS >110 ms or a new bundle branch block are provided in Section 5.3.3.

4. Voluntary withdrawal of consent: The subject wishes to withdraw from the study for any reason.

   Note: Withdrawal due to an AE will not be recorded in the voluntary withdrawal category.

5. Study termination: The sponsor, institutional review board (IRB), Food and Drug Administration (FDA), or other regulatory agency terminates the study.

6. Pregnancy: The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject is to be withdrawn immediately. The pregnancy will be followed to term, and the outcome, including premature termination, will be recorded. A second follow-up will be performed after 30 calendar days of pregnancy outcome.

7. Other.

   Note: This category includes withdrawals caused by an accidental or a medical emergency, unblinding, or other rare cases. The specific reasons will be recorded on the eCRF.

5.3.2. Handling of Withdrawals

Parts 1 and 2: The investigator may terminate a subject's study participation at any time during the study if the subject meets any of the withdrawal criteria described in Section 5.3.1. Should a subject's participation be discontinued, the primary reason for termination must be recorded. In addition, efforts will be made to perform all early termination procedures specified in the schedule of events (Section 8.1, Appendix A and Section 8.2, Appendix B). The AE eCRF will be completed for each AE.

5.3.3. Stopping Criteria for Individual Subjects

5.3.3.1. Part 1

A subject will be withdrawn from the study if he or she meets any of the following criteria:

- Alanine aminotransferase ≥5 × ULN, confirmed on a repeat measurement,

not due to an obvious nondrug etiology.

- ECG criteria

  Note: The QTcF is always used, regardless of the HR.

  IMPORTANT: When evaluating the safety signals below, the QTcF or arrhythmia must be confirmed by a cardiologist who is specifically trained and experienced in ECG interval measurements or a cardiac electrophysiologist.

  - Torsades de Pointes associated with a QTcF >500 ms
  - Repetitive pause-dependent ventricular ectopy associated with at least a 35% increase in the QTc interval.
  - Potential dose-down titration. Note: These measurements will be manually confirmed by a cardiologist specifically trained and experienced in ECG interval measurements. The ECG measurements at baseline and at 3 hours postdose on Day 1 of Period 1 will only be evaluated by the same technician and cardiologist. If on Day 1 at 3 hours postdose in Period 1 only, the mean QTcF on the triplicate ECGs, when repeated within 30 minutes, show a mean increase >80 ms from the mean baseline QTcF on the 3 (triplicate) repeated ECGs, the dose of dofetilide will be reduced to 250 µg BID.
  - If at any time after the first dose of dofetilide, a subject develops a QTcF >500 ms, 2 additional ECGs will be immediately performed, and then the ECG will be repeated approximately 30 minutes later, in triplicate. Note: If the subject has a new QRS >110 ms or a new bundle branch block, then an adjusted QTcF will be utilized to account for the widened QRS interval (Adjusted QTcF = QTcF [ms] – [QRS interval [ms] – 90 ms]). If the mean QTcF increase of the triplicate ECGs is confirmed (mean QTcF of the 3 (triplicate) repeated ECGs is >500 ms):
    - If this occurs on Day 1, the dose of dofetilide will be reduced to 250 µg BID.
    - If this occurs on Day 2 or afterwards (or any time in Period 2), the subject will be discontinued from the study.

Findings that meet any of these criteria should be reported to the sponsor immediately.

5.3.3.2. Part 2

A participant with LQT2 or LQT3 will be withdrawn from the study if he or she meets any of the following criteria:

- Alanine aminotransferase (ALT) or aspartate transaminase (AST) ≥8 × upper limit of normal, confirmed on a repeat measurement, not due to an obvious nondrug etiology.

- ALT or AST >3 times the ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (treatment emergent >5% with at least a 75% increase from baseline)

- ALT or AST ≥3 × ULN in conjunction with total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase) confirmed on a repeat measurement, not due to an obvious nondrug etiology.

- ECG criteria

  Note: The QTcF is always used, regardless of the HR.

  IMPORTANT: When evaluating the safety signals below, the QTcF or arrhythmia must be confirmed by a cardiologist who is specifically trained and experienced in ECG interval measurements or a cardiac electrophysiologist.

  If at any time after the first dose of LQT-1213, a participant develops a QTcF >600 ms with an increase from baseline >50 ms; or an increase from baseline >70 ms, 2 additional ECGs will immediately be performed, and then the ECG will be repeated approximately 30 minutes later, in triplicate. If the criteria are met (participant develops a QTcF >600 ms with an increase from baseline >50 ms; or an increase from baseline >70 ms) on the second triplicate ECG, the participant will be withdrawn from the study.

  - Episodes of Torsades de Pointes will be evaluated by the sponsor's medical monitor and principal investigator. Further dosing will be held until a decision regarding participant disposition is made.

5.3.4. Stopping Criteria for the Study

5.3.4.1. Part 1

The study may be terminated if any of the following stopping criteria are met:

- 2 or more subjects experience documented Torsade de Pointes ventricular tachycardia with a QTcF >500 ms (which are not associated with hypokalemia or hypomagnesemia) confirmed by a cardiac electrophysiologist.
- 2 subjects with confirmed alanine aminotransferase ≥10 × upper limit of normal, confirmed on a repeat measurement, not due to an obvious nondrug etiology.

5.3.4.2. Part 2

The study may be terminated upon the following:

- 2 participants with confirmed ALT or AST ≥10 × ULN, confirmed on a repeat measurement, not due to an obvious nondrug etiology.
- 2 participants with confirmed ALT or AST ≥3 × ULN in conjunction with total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase) confirmed on a repeat measurement, not due to an obvious nondrug etiology
- Potentially significant QTc prolongations or clinically significant cardiac arrhythmias will be promptly reviewed by the SRC and it will be decided if a new participant can receive study drug or if the study will be stopped or modified.

Any potentially clinically significant QTc prolongations or clinically significant cardiac arrhythmias must be reported to the sponsor's medical monitor.

5.3.5. Replacement Subjects

Parts 1 and 2: Any subject who is withdrawn or discontinued from the study may be replaced after mutual agreement between the sponsor and the investigator, except for drug-related hepatic adverse events of special interest (AESI) leading to study discontinuation.

5.4. Study Procedures

Note: When assessment time points coincide, the order of assessments will be ECGs/ECG extraction window, PK blood sample collection followed by vital sign

measurements. When a PK blood sample collection time point coincides with study drug dosing, the PK sample will be collected before study drug dosing. Extractions and ECG analysis will not be performed on all Holter data collected.

5.4.1. Pharmacodynamic Assessments

5.4.1.1. Part 1

Pharmacodynamics will be evaluated using extracted ECG data obtained from continuous 12-lead Holter monitors placed on all subjects in Periods 1 and 2 at time points specified in the PK and PD time points table (Section 8.3, Appendix C) and will be analyzed based on accumulating safety and PK data, which may result in changes in the PK and ECG extraction time points. In both treatment periods, Holter recordings on Day 1 (predose time points only) and Days 4, 6, and 8 may be analyzed. The Holter recordings from Day –1, the other time points on Day 1, and Days 2, 3, 5, and 7 will be stored at the CRU for possible future analysis. Up to 10 replicate 12-lead ECG recordings will be extracted from the Holter monitor data within a 5-minute window with time points scheduled before the PK blood sample collections. Holter and PK data and extractions may be modified based on the evolving data. Holter recordings will be collected for 2 hours predose on Day 1 and 3 ECG extractions will be performed. Continuous 12-Lead ECG acquisition for Part 1 will be described in the statistical analysis plan (SAP).

5.4.1.2. Part 2

Pharmacodynamic endpoint data will be evaluated using SGK-1 protein targets. Central ECG analysis is not planned at this time but may be performed after database lock.

Part 2 only: Human PBMC and plasma samples will be harvested and isolated from the blood samples and stored for potential analysis of PD biomarkers, including SGK protein targets. Details for PD sample collection are specified in Section 8.2, Appendix B.

5.4.2. Pharmacokinetic Assessments

Parts 1 and 2: Where PK sampling time points coincide with the triplicate ECG time points, the extraction window will end before each PK collection nominal time point. Details for PK blood sample collection are specified in Section 8.3, Appendix C and Section 8.4, Appendix D.

Detailed instructions for the handling and shipping of PK samples will be outlined in the laboratory manual.

5.4.2.1. Part 1

Blood samples for dofetilide and LQT-1213 PK analysis will be collected in both treatment periods on Days 4, 6, and 8 at the following time points: predose (time 0 for dofetilide) and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7.75, 9.5, 12, and 24 hours postdose.

5.4.2.2. Part 2

Blood samples for LQT-1213 PK analysis will be collected as detailed in Section 8.4, Appendix D.

5.4.3. Safety Assessments

Safety will be determined by monitoring AEs, clinical laboratory test results (hematology, serum chemistry, coagulation, and urinalysis), vital sign measurements (blood pressure, HR, respiratory rate, and oral body temperature), continuous telemetry ECG monitoring (Part 2 only), 12-lead ECG results, and physical examination findings.

Part 1: An emergency physician will be present for at least the first 6 hours for initial dosing of dofetilide. Advanced Cardiovascular Life Support (ACLS)-experienced nurses or paramedics will be present for at least 72 hours for initial dofetilide dosing, and ACLS-trained physicians, physicians assistants, nurse practitioners, paramedics, or registered nurses will be present on Days 1 through 9. The CRU is equipped with appropriate emergency equipment and medications, including a defibrillator and ACLS medications. The staff will be trained in the management of ventricular arrythmias and Torsades de Pointes.

Part 2: An emergency physician will be present for at least the first 6 hours for initial dosing of LQT-1213 on Day 2. Advanced Cardiovascular Life Support-experienced nurses or paramedics will be present for at least 48 hours for initial LQT-1213 dosing, and ACLS-trained physicians, physicians assistants, nurse practitioners, paramedics, or registered nurses will be present on Days 1 through 5. The CRU is equipped with appropriate emergency equipment and medications, including a defibrillator and ACLS medications. The staff will be trained in the management of ventricular arrythmias and Torsades de Pointes.

At the discretion of the investigator, additional safety assessments may be performed as needed to ensure participant safety.

5.4.3.1. Adverse Events

An AE is defined (per ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use E2A) as any untoward medical occurrence in a patient

or clinical investigation subject administered a pharmaceutical product whether there was a causal relationship with this treatment.

An AE can, therefore, be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease that is temporally associated with the use of a medicinal (investigational) product, whether it is related to the medicinal (investigational) product or not related to the medicinal (investigational) product.

For **Part 1**, a treatment-emergent AE (TEAE) is defined as an AE with onset date/time after LQT-1213 or placebo matched to LQT-1213 administration or a continuing AE with an onset date/time before LQT-1213 or placebo matched to LQT-1213 administration.

For **Part 2**, a TEAE is defined as an AE with onset date/time after LQT-1213 administration.

All AEs occurring before LQT-1213 administration will be provided in a data listing.

An adverse reaction is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there are reasons to conclude that the drug caused the event.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the study drug caused the AE. For the purposes of investigational new drug safety reporting, “reasonable possibility” means that there is evidence to suggest a causal relationship between the study drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a study drug.

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator’s brochure or at the specificity or severity that has been observed with the study drug being tested; or, if an investigator’s brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator’s brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator’s brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator’s brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events will be recorded from the time of provision of written informed consent through Follow-up (Section 8.1, Appendix A and Section 8.2, Appendix B). At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question such as, “How have you been feeling since your last visit?” will be asked. Participant may report AEs that occur at any other time during the study.

All participants experiencing AEs, whether considered associated with the use of the study drug or not, will be followed until resolution or until the investigator judges that further follow-up is not necessary. All AEs will be documented on the AE page of the eCRF, whether or not the investigator concludes the event is related to the study drug. The event term, start and stop date, and severity will be documented, along with the investigator's opinion of the causal relationship between the event and study drug administration (not, unlikely, possibly, or probably related).

Severity of Adverse Events

An AE may occur during or following the administration of the investigational compound or control agent. Each AE will be graded according to severity using the following criteria as appropriate:

- Mild: The experience does not cause substantial discomfort; symptoms are well tolerated and do not interrupt or hinder the subject's daily activities; the experience resolves spontaneously, and no treatment is required beyond administration of nonprescription medication.
- Moderate: The experience causes some discomfort and the symptoms experienced interfere with but do not interrupt the subject's daily activities; the experience may require treatment with prescription medication.
- Severe: The experience substantially hinders or interrupts the subject's daily activities; the subject may be incapacitated and may require prolonged treatment with prescription medication.

Causality of Adverse Events

The investigator must attempt to explain each AE and its relationship to study drug (eg, possibly or unlikely). Criteria for determining the relationship of clinical adverse reactions to test drug administration are as follows:

- Not Related: Onset of the AE has no reasonable temporal relationship to administration of the study drug, a causal relationship to administration of the study drug is biologically implausible, or the event is attributed to an alternative etiology.
- Unlikely Related: Onset of the AE has a reasonable temporal relationship to study drug administration and, although a causal relationship is unlikely, it is biologically plausible.
- Possibly Related: Onset of the AE has a strong temporal relationship to administration of the study drug, cannot be explained by the subject's clinical state or other factors, and a causal relationship is biologically plausible.
- Probably Related: Onset of the AE shows a distinct temporal relationship to administration of the study drug that cannot be explained by the subject's clinical

state or other factors, and the AE is a known reaction to the product or chemical group or can be predicted by the product's pharmacology.

Adverse Events of Special Interest (Part 2)

The following events are considered to be AESIs:

- Hepatic AEs, including liver function tests (LFT) abnormalities considered clinically significant by the Investigator.

For AEs that are considered AESIs, additional clinical information may be collected based upon the severity or nature of the event. If a patient has a hepatic AESI meeting any of the above criteria, the Investigator, or designee, should contact the Medical Monitor. A detailed narrative of the event should be reported to the Sponsor within 24 hours of the event. All AESIs must be reported for the duration of the study regardless of causality. For participants with hepatic AEs, additional information, including clinical history, course of events, and unscheduled laboratory results to monitor LFT levels or other laboratory parameters, may be collected.

Serious Adverse Events

An SAE is an AE that results in any of the following:

- Death
- Is life threatening (ie, the subject was at risk of death from the event. "Life threatening" in the definition of "serious" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- An important medical event that does not result in death, is not life threatening, or does not require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

If an SAE occurs, appropriate therapy will be administered based on the investigator's judgment. Subjects will then be monitored closely as appropriate.

5.4.3.2. Additional Points to Consider for Adverse Events

Diagnoses versus signs and symptoms:

- Each AE will be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms will NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) will be recorded as an AE(s).

Clinical laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiological fluctuation).
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), then only the diagnosis will be reported as an AE, not the abnormal laboratory values or ECG findings.

Pre-existing conditions:

- Pre-existing conditions (present before the start of the AE collection period) are considered concurrent medical conditions and will NOT be recorded as AEs. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication will be recorded as an AE. Investigator will ensure that the AE term recorded captures the change in the condition (eg, “worsening of…”).

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled before the start of AE collection are not considered AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition will be captured as an AE.

Elective surgeries or procedures:

- Preplanned or performed elective procedures (surgeries or therapies) where there is no change in the subject’s medical condition will not be recorded as AEs but will be documented in the subject’s source documents.

Overdose:

- Cases of study drug overdose without manifested side effects are NOT considered AEs.

Reporting of Serious Adverse Events

Serious AEs require immediate reporting to the sponsor and the medical monitor (contact details provided below), within 24 hours of the investigator's knowledge of the event, whether or not the investigator believes that the experience is related to study drug.

An SAE form must be completed, signed by the investigator, and include at a minimum: the event term(s), a short description of the AE, the reason why the AE is categorized as serious, the investigator's current opinion of the relationship between the experience and the study drug (causality assessment), as well as the subject's identification number, sex, age, and relevant medical history.

Additional information, as appropriate, can be sent to the sponsor and medical monitor when it becomes available (eg, copies of relevant subject records, autopsy reports, and other documents). A corresponding AE eCRF must also be completed.

The investigator is responsible for notifying the IRB in writing of any SAE. All SAEs are to be documented in the eCRF with the date of onset and resolution, determination of seriousness, severity, action taken, outcome, and relationship to study drug.

Any SAE, including death, occurring while the subject is receiving study drug irrespective of the investigator's opinion regarding study drug relationship, will be reported. Within 24 hours, 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 by fax or email.

Serious AEs that occur within 30 days after study drug administration that come to the attention of the investigator, and are thought to be related to study drug, will be reported to the sponsor and the medical monitor.

Regulatory Group Name: [redacted]

Information and updates related to the medical monitoring of SAEs will be presented and shared via a shared drive folder hosted by [redacted].

Sponsor Study Physician Contact Information:

Name: [redacted]

Title: Medical Monitor

Telephone: [redacted]

Email: [redacted]

Follow-Up of Serious Adverse Events

All SAEs will be followed until the outcome is known or the subject's condition has stabilized.

All follow-up information for SAEs is to be reported within 24 hours of receipt by the investigator in the manner described previously.

The FDA requires that all SAEs that are unexpected and potentially related to the study drug must be reported to the FDA in writing within 15 calendar days of notification to the sponsor. Serious AEs that result in death or are immediately life threatening require the sponsor to notify the FDA as soon as possible but no later than 7 calendar days after the first knowledge that the case qualifies, followed by a complete report within 8 additional calendar days.

[redacted] will prepare the expedited report for the FDA, and [redacted] will be responsible for submitting the expedited report to the FDA. Copies will be distributed to the investigator.

Expedited reports, as addenda to the investigator's brochure, will be placed in the back pocket of the brochure by the investigator upon receipt. The investigator will also forward a copy of all expedited reports to his or her IRB.

Subject Deaths

All subject deaths, regardless of cause, occurring within 30 days after subject termination from the study, and which are known to the investigator, will be reported on the appropriate page of the eCRF. Documentation of the subject's cause of death and a copy of the autopsy report, if any, will also be provided. [redacted] must be notified by fax and the sponsor's study physician must be notified by telephone of all subject deaths immediately (contact details provided in Section 5.4.3.2.1). Fax/email modes of communication must be utilized in case of any difficulty with telephone lines; written follow-up must be received within 3 working days of initial notification.

Death should not be reported as an SAE term, but rather as a clinical outcome. The cause of death on a source document, such as the death certificate or autopsy report, will be used as the event term for the SAE. The SAE that is the cause of death will be marked as fatal with the date of death as the end date. If concurrent AEs or SAEs are present at the time of death, but are not the cause of death, those AEs or SAEs will be marked as not recovered/not resolved and ongoing.

Adverse Event Collection Period

Collection of AEs will commence from the time that the subject signs the informed consent form (ICF). Any AE that occurs between the time the subject signs the ICF to

before the first dose of study drug will be documented as medical history, unless the AE is related to a protocol-required procedure, in which case the event will be documented as an AE unrelated to study drug. Routine collection of AEs will continue until the End of Study Visit or Early Termination.

Reporting of Pregnancy

An exposure during pregnancy (also referred to as exposure in-utero) will be reported as follows:

- Pregnancies occurring up to 30 days after study drug administration must be reported to the investigator. The investigator will make arrangements for the subject to be counseled by a specialist, to discuss the risks of continuing with the pregnancy, and the possible effects on the fetus. Monitoring of the subject should continue until the outcome of the pregnancy is known.
- The investigator should report all pregnancies in female subjects to the sponsor within 1 working day of becoming aware of them.
- If the investigator becomes aware of a pregnancy occurring in the partner of a male subject participating in the study up to 90 days after the completion of the study drug, the pregnancy should be reported to the sponsor within 1 working day of obtaining written consent from the pregnant partner. The investigator will make arrangements for the partner to be counseled by a specialist, to discuss the risks of continuing with the pregnancy, and the possible effects on the fetus. Monitoring of the partner should continue until the outcome of the pregnancy is known.

During the conduct of the study, if pregnancy is reported in a female subject, the investigator will withdraw the subject immediately from the study and inform [redacted] and the sponsor's medical monitor within 24 hours of knowledge of the event using the information provided in Section 0. The investigator will complete and send the signed Exposure in Pregnancy Form to [redacted] using the information provided in Section 0. Any other maternal SAE in the course of pregnancy will be reported on a separate SAE form. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live birth, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator will follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs are as follows:

- Spontaneous abortion includes miscarriage and missed abortion; neonatal deaths that occur within 1 month of birth will be reported, without regard to causality, as SAEs. In addition, infant death after 1 month will be reported as an SAE when the investigator assesses the neonatal death as related or possibly related to exposure to investigational product.

- In the case of paternal exposure, the study subject will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document on the Exposure in Pregnancy Form that the subject was given this letter to provide to his partner. If the pregnancy outcome fulfills the criteria for an SAE, it will be reported to the respective regulatory authorities in an expedited manner.
- Pregnant female subjects will be contacted within 15 calendar days after the expected date of delivery for the pregnancy outcome. A second follow-up will be performed after 30 calendar days of pregnancy outcome.
- Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays).

5.4.3.3. Clinical Laboratory Tests

5.4.3.3.1 Part 1

Clinical laboratory samples and samples for diagnostic screening tests will be collected at the time points specified in the schedule of events (Section 8.1, Appendix A). All subjects will fast overnight for a minimum of 6 hours (no food or fluid except water) before blood collection for clinical laboratory testing. All samples will be collected in accordance with acceptable laboratory procedures. The tests that will be performed are presented in Table 5-1.

Hematology, serum chemistry, urinalysis, and diagnostic screening tests will be performed at [redacted]. The results of laboratory tests will be returned to the investigator or medically qualified designee, who will review the results together with the data in the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges used by the laboratory.

The investigator will review the clinical laboratory test results and any values outside the reference range will be evaluated for clinical significance. The investigator may repeat the clinical laboratory tests if deemed appropriate.

Table 5-1 Clinical Laboratory Tests – Part 1

Hematology	Serum Chemistry	Urinalysis
Complete Blood Count Hematocrit Hemoglobin Platelet count Red blood cell count White blood cell count (with automated differential)	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Creatine Phosphokinase Creatinine Direct bilirubin Estimated glomerular filtration rate (eGFR)[a] Glucose Lactic dehydrogenase Magnesium[b] Phosphorus Potassium[b] Sodium Total bilirubin Total protein Uric acid	Appearance Bilirubin Blood Color Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination: red blood cells; white blood cells; epithelial cells; bacteria, crystals, casts, etc. (if present)

Diagnostic Screening Tests:	
Blood	**Urine**
Serology: hepatitis panel (hepatitis B surface antigen and hepatitis C virus antibody) and HIV antibody Serum pregnancy test (all female subjects)	Urine drug screen: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, opiates, phencyclidine, propoxyphene, cotinine, and methadone

Abbreviation: eGFR, estimated glomerular filtration rate.

a eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

b Serum potassium and magnesium will be checked each day on Days –1, 1, and 2 and thereafter, beginning on Day 3, potassium and magnesium will be checked every other day. Potassium <3.8 mg/dL and magnesium <1.9 mg/dL will result in additional electrolyte supplementation. It is preferred, especially on Days 1, 4, 6, and 8, that this be done in the evening (after the 12-hour time point). Electrolyte supplementation is allowed at any time as long as it is >4 hours before dosing.

5.4.3.3.2 Part 2

Clinical laboratory samples and samples for diagnostic screening tests will be collected at the time points specified in the schedule of events (Section 8.2, Appendix B). All participants will fast overnight for a minimum of 6 hours (no food or fluid except water) before blood collection for clinical laboratory testing. All samples will be collected in accordance with acceptable laboratory procedures. The tests that will be performed are presented in Table 5-2.

Note: An intravenous catheter will be placed, at the investigator's discretion, as needed to facilitate study procedures or for participant safety reasons.

Hematology, serum chemistry, coagulation, urinalysis, and diagnostic screening tests will be performed at [redacted] or a local laboratory. The results of laboratory tests will be returned to the investigator or medically qualified designee, who will review the results together with the data in the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges used by the laboratory.

The investigator will review the clinical laboratory test results and any values outside the reference range will be evaluated for clinical significance. The investigator may repeat the clinical laboratory tests if deemed appropriate.

Table 5-2 Clinical Laboratory Tests – Part 2

Hematology	Serum Chemistry	Urinalysis
Complete Blood Count Hematocrit Hemoglobin Platelet count Red blood cell count White blood cell count (with automated differential)	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Blood urea nitrogen Calcium Chloride Creatine Phosphokinase Creatinine Direct bilirubin Estimated glomerular filtration rate (eGFR) Gamma-glutamyl transpeptidase (GGT) Glucose Lactic dehydrogenase Magnesium Phosphorus Potassium Sodium Total bilirubin Direct bilirubin Total protein Uric acid Coagulation (PT/PTT)	Appearance Bilirubin Blood Color Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination: red blood cells; white blood cells; epithelial cells; bacteria, crystals, casts, etc. (if present)

Diagnostic Screening Tests:	
Blood	**Urine**
Serology: hepatitis panel (hepatitis B surface antigen and hepatitis C virus antibody) and HIV antibody Serum pregnancy test (females of childbearing potential)	Urine drug screen: amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol (Day -1 only), opiates, phencyclidine, propoxyphene, cotinine, and methadone

5.4.3.4. Vital Sign Measurements

Vital signs (blood pressure, HR, respiratory rate, and oral body temperature [°C]) will be measured at the time points specified in the schedule of events (Section 8.1, Appendix A and Section 8.2, Appendix B) using a calibrated digital device and a cuff size that is matched to the subject. This must be verified. Vital signs will be measured daily during confinement. Subjects will be in a supine position, if possible, for no less than 5 minutes before vital signs are measured. A window of ±30 minutes for each time point will be utilized for vital sign measurements.

5.4.3.5. Safety 12-Lead Electrocardiograms

Part 1

Standard digital safety 12-lead ECGs will be recorded as specified in the schedule of events (Section 8.1, Appendix A). Subjects will be in a supine position for no less than 5 minutes before the safety 12-lead ECG is performed. Triplicate ECGs, when collected, will be 30 seconds to 1 minute apart. The safety 12-lead ECG may be collected using the Holter devices, when applicable. If a safety 12-lead ECG is scheduled at the same time point as blood sample collection, the ECG will be performed first.

Clinically significant, abnormal 12-lead safety ECGs should be repeated so that an investigator can determine if an AE has occurred. The final ECG interval read will be manually confirmed by a cardiologist experienced in ECG interval measurements.

Part 2

Standard digital safety 12-lead ECGs will be recorded as specified in the schedule of events (Section 8.2, Appendix B). Participants will be in a supine position for no less than 5 minutes before the safety 12-lead ECG is performed. Triplicate ECGs, when collected, will be approximately 30 seconds to 1 minute apart. The safety 12-lead ECG may be collected using the Holter devices, when applicable. If a safety 12-lead ECG is scheduled at the same time point as blood sample collection or vital sign, the ECG will be performed first.

Triplicate ECGs will also be collected as described Section 8.4, Appendix D and sent to [redacted] for storage.

Clinically significant, abnormal 12-lead safety ECGs should be repeated so that an investigator can determine if an AE has occurred. The final ECG interval read will be manually confirmed by a cardiologist experienced in ECG interval measurements. In general, ECG changes will only be reported as AEs if they are clinically significant or as at the investigator's discretion.

5.4.3.6. Physical Examinations

Part 1

Physical examinations will be performed at the time points specified in the schedule of events (Section 8.1, Appendix A). The complete physical examination will consist of the following body systems: head, eyes, ears, nose, throat; cardiovascular, respiratory, gastrointestinal, dermatologic, musculoskeletal, and nervous systems; extremities; lymph nodes; and other. The abbreviated physical examination will consist of the following body systems: dermatologic, cardiovascular, respiratory, and gastrointestinal. Additional body systems may be evaluated at the investigator's discretion.

At Screening, the complete physical examination will include height and body weight for calculation of body mass index. The subject's weight (kg) and height (cm) will be measured using a calibrated scale while the subject is wearing light street clothing and no shoes.

The subject's body mass index will be calculated using metric units and rounded to the nearest tenth according to the following formula:

$$\text{Body mass index} = \text{weight (kg)}/\text{height (m)}^2$$

Any abnormal treatment-emergent physical examination finding during the study that represents a change from baseline (ie, a change from the examination at Screening) will be documented as an AE, with causality assigned by the investigator as described in Section 5.4.3.1.2.

Part 2

Physical examinations will be performed at the time points specified in the schedule of events (Section 8.2, Appendix B). The complete physical examination will consist of the following body systems: head, eyes, ears, nose, throat; cardiovascular, respiratory, gastrointestinal, dermatologic, musculoskeletal, and nervous systems; extremities; lymph nodes; and other. The abbreviated physical examination will consist of the following body systems: dermatologic, cardiovascular, respiratory, and gastrointestinal. Additional body systems may be evaluated at the investigator's discretion.

At Screening height and body weight will be measured. On Day −1 body weight will be measured. Height and weight measurement will be used to calculate body mass index. The participant's weight (kg) and height (cm) will be measured using a calibrated scale while the participant is wearing light street clothing and no shoes.

The participant's body mass index will be calculated using metric units and rounded to the nearest tenth according to the following formula:

$$\text{Body mass index} = \text{weight (kg)}/\text{height (m)}^2$$

Any abnormal treatment-emergent physical examination finding during the study that represents a change from baseline (ie, a change from the examination at Day-1) will be documented as an AE, with causality assigned by the investigator as described in Section 0.

5.4.4. Demographics, Medical History, and Other Baseline Assessments

Demographics will include date of birth, sex (at birth), ethnicity, and race as provided by the subject.

The complete medical history will include a review of all major body systems, reproductive status, and menstrual history (ie, regularity), if applicable. Any conditions and diseases that arise after Screening (ie, after the ICF is signed) are to be reported as AEs.

Smoking, ethanol, and caffeine use will also be recorded, as will any medications taken during the 30 days before study drug administration.

5.4.5. Documentation of Concomitant Medications

Prior and concomitant medication information will be recorded beginning 30 days before study drug administration through Follow-up. Any therapy administered before informed consent is obtained will be recorded as a prior medication and medication ongoing at the time of signing the ICF or administered after informed consent will be recorded as a concomitant medication. Relevant information (ie, name of medication, dose, unit, frequency of administration, dates, and reasons for use) will be recorded in the source documents and in the eCRF. All changes in medication will be noted. If the reason for medication use meets the definition of an AE, the AE will be recorded on the appropriate page of the eCRF and in the source documents for that subject.

At the discretion of the principal investigator and/or medical monitor, additional potassium and/or magnesium can be administered to increase the electrolyte serum concentrations.

5.4.6. Total Blood Volume

The total blood volume to be collected during the study will be specified in the ICF.

5.5. Study Treatments

5.5.1. Method of Assigning Subjects to Treatment Groups

5.5.1.1. Part 1

The randomization schedule will be generated by the unblinded randomization statistician. Randomized subjects will be assigned unique subject numbers in sequential order based on their order of qualification. An attempt will be made to achieve an equal balance between sexes.

A sentinel group of up to 5 subjects may be enrolled first if warranted by the principal investigator.

The subject number assigns a randomized treatment to each subject and determines the study drug that the subject will receive. In both treatment periods, all subjects will receive dofetilide on Days 1 and 2 of each period. Randomization will take place before Day 3 of Period 1. Subjects will be randomly assigned to 1 of 2 treatment sequences: AB or BA.

At the end of the washout period following Period 1, subjects who meet a satisfactory review of safety and PK data from Period 1 will be brought back for treatment in Period 2. Subjects randomized to LQT-1213 in Period 1 will start receiving placebo in Period 2. Subjects randomized to placebo matched to LQT-1213 in Period 1 will start receiving LQT-1213 in Period 2.

In order to maintain the blind, a suspension of LQT-1213 in sugar-free Gatorade™ will be prepared before dosing. Placebo will consist of the sugar-free Gatorade™ and cornstarch.

The following LQT-1213 doses will be evaluated:

- Low dose: 3 doses on Day 3 and the first 2 doses on Day 4
- Mid dose: Last dose on Day 4, 3 doses on Day 5, and the first 2 doses on Day 6
- High dose or 0.747 mg/kg: Last dose on Day 6, 3 doses on Day 7, and the first dose on Day 8

Note: Only 1 dose of dofetilide and LQT-1213 (or placebo) will be administered on Day 8.

Blinding information is provided in Section 5.5.5.

5.5.1.2. Part 2

Participants will be assigned unique participant numbers in sequential order based on their order of qualification.

Participants will undergo a 1 day, single-blind placebo run-in period followed by LQT-1213. Placebo will consist of sugar-free Gatorade™ and cornstarch.

The following doses will be administered:

- Placebo: Day 1 TID
- LQT-1213 dose: 3 doses on Day 2 and 3, and 1 dose on Day 4

Blinding information is provided in Section 5.5.5.

5.5.2. Treatments Administered

5.5.2.1. Part 1

All eligible subjects will be administered dofetilide 500 µg BID (2 × 250 µg capsules), orally for approximately 8 days (Days 1 to 8; only 1 dose will be administered on Day 8) in both treatment periods. The first dose will be administered at time 0 and the second dose at 12 hours after the first dose (± 10 minutes).

All subjects will fast overnight for a minimum of 6 hours (no food or fluid except water) before study drug administration. LQT-1213 will be dispensed based on the body weight of the subject. Randomized subjects will receive LQT-1213 or matching placebo as follows:

- Low dose: 3 doses on Day 3 and the first 2 doses on Day 4
- Mid dose: Last dose on Day 4, 3 doses on Day 5, and the first 2 doses on Day 6
- High dose or 0.747 mg/kg: Last dose on Day 6, 3 doses on Day 7, and the first dose on Day 8

Note: Only 1 dose of dofetilide and LQT-1213 (or placebo) will be administered on Day 8.

LQT-1213 will be administered orally and diluted in sugar-free Gatorade™. The high dose is not to exceed 0.747 mg/kg TID (daily dose 2.24 mg/kg).

Dose-down titration will occur if the mean QTcF increase of the triplicate ECGs after assessment by a cardiac electrophysiologist is confirmed on Day 1, and the dose of

dofetilide will be reduced to 250 µg BID. If the mean QTcF increase of the triplicate ECGs occurs on Day 2 or afterwards (or any time in Period 2), the subject will be discontinued from the study as described in Section 5.3.2.

After dosing, water will be available ad libitum and meals (lunch, dinner, and light meal) will be served as regularly scheduled. Meal timing and components, activity levels, and general conditions in the CRU will be as similar as possible on each dosing day.

5.5.2.2. Part 2

All participants with LQT2 or LQT3 will fast overnight for a minimum of 6 hours (no food or fluid except water) before study drug administration. Participants will receive study drug as follows:

The following doses will be administered:

- Placebo: TID on Day 1
- LQT-1213 dose: 3 doses on Day 2 and 3, and 1 dose on Day 4

LQT-1213 will be administered orally and diluted in sugar-free Gatorade™. The dose is not to exceed daily dose 2.24 mg/kg.

5.5.3. Identity of Study Drug

5.5.3.1. Part 1

LQT-1213 for suspension will be provided as powder. LQT-1213 will be diluted in sugar-free Gatorade™ for oral administration. The placebo matched to LQT-1213 will consist of sugar-free Gatorade™ and cornstarch.

Dofetilide is a sulfonamide class of antiarrhythmic agents and will be utilized in this study in its 250 and 500 µg capsule formulation.

5.5.3.2. Part 2

LQT-1213 for suspension will be provided as powder. LQT-1213 will be diluted in sugar-free Gatorade™ for oral administration.

5.5.4. Management of Clinical Supplies

5.5.4.1. Study Drug Packaging and Storage

Study drug must be kept in a secure cabinet or room with access restricted to necessary study site personnel.

LQT-1213 will be stored at 20°C to 25°C (68°F to 77°F) and protected from light. Dofetilide will be stored at 15°C to 30°C (59°F to 86°F) and protected from moisture and humidity. Placebo matched to LQT-1213 will be stored at 25ºC (77ºF) with excursions permitted to 15°C to 30°C (59°F to 86°F).

All study drugs will be dispensed by the investigator or a person under the investigator's supervision. The investigational products will be dispensed based on the body weight of the subject. The calculated amount will be weighed, recorded, and transferred to the dispensing container. For the oral suspension, sugar-free Gatorade™ will be added to the drug substance and mixed until the drug is dissolved or evenly dispersed according to the pharmacy manual.

Additional study drug packaging, storage, and dispensing information will be detailed in the pharmacy manual.

5.5.4.2. Study Drug Accountability

In accordance with Code of Federal Regulations (CFR) (21 CFR 312.62), the investigator is required to keep accurate records showing final disposition of all investigational drugs.

THE INVESTIGATOR MUST NOT USE MATERIAL PROVIDED FOR THIS PARTICULAR STUDY IN ANOTHER STUDY WITHOUT PRIOR WRITTEN APPROVAL FROM THE SPONSOR.

The investigator or his or her designee will record:

- Person Responsible: On the Distribution Log, if the same individual signs the forms from day to day, his or her title need not be recorded after the first time.
- Lot Number: The lot number is indicated on the label applied to each container of study drug.
- Manufacture/Expiration Date: The manufacture and expiration date may be listed on the study drug.
- Date Used: Date administered or dispensed to the subject.

- Disposition of Material: Indicate if administered, destroyed, damaged in transit and destroyed, or other final disposition of material. Material cannot be transferred for preclinical or other use without prior written approval from the sponsor.
- Date Returned to the Sponsor/Designee or Destroyed: At the termination of the study, unused and opened and partially used containers may be returned to the sponsor or designee. However, the investigator or designee will not destroy the supplies without immediate prior consultation with the sponsor. Indicate the date when unused containers are returned (mo/day/yr-Ret.) or destroyed (mo/day/yr-Des.).

Ultimate accountability for receiving, dispensing, and inventory of the test material lies with the investigator or designee. Federal regulation requires that storage of the substance be in a secure enclosure, access to which is limited, to prevent theft or diversion, and in accordance with the labeling and storage guidelines.

Material that is not outdated at the completion of the study will be returned to the sponsor or will be handled otherwise according to written instructions from the sponsor.

5.5.5. Blinding

5.5.5.1. Part 1

This is a double-blind study. For study drug dosing, study drug administration will be double blinded only on Days 3 through 8. The randomization schedule will be generated by the unblinded randomization statistician. The sponsor, study participants, and site personnel performing study evaluations will be blinded to random treatment assignments. The blinded dose information may only be received by the investigator (or designee) in an emergency when the information may have an impact on further treatment decisions or aid in the emergency treatment of the subject. Every effort will be made to contact the sponsor before unblinding.

The study blind will be maintained for all personnel through the end of the study until the database is locked. Once the database is locked, a blind-break approval form will be signed by the sponsor, study statistician, and data manager, after which the randomization schedule will be provided to unblind the study.

The laboratory performing the PK analysis will not be blinded.

5.5.5.1.1 Breaking the Blind

The study blind will not be broken by the sponsor or the investigator or designee unless information concerning the study drug is necessary for the medical treatment of a subject. For unblinding a subject, the randomization information can be obtained by contacting the dispensing pharmacist. The sponsor or medical monitor must be notified immediately if the study blind is broken. The date, time, and reason that the blind was broken will be

recorded in the source documents. The study drug must be stopped immediately, and the subject must be withdrawn from the study. Data or specimens already collected from subjects who discontinue prematurely and for whom the blind is broken may be made available for analysis.

5.5.5.2. Part 2

This is a single-blind study, with the participants with LQT2 or LQT3 blinded to the treatment they are receiving.

5.5.6. Treatment Compliance

All doses of study drug will be administered in the CRU under direct observation of study personnel and recorded in the eCRF. Clinic personnel will confirm that the participant has received and ingested the entire dose of study drug.

5.5.7. Prior and Concomitant Medications

5.5.7.1. Part 1

Subjects will be instructed not to take any medications, including over-the-counter and herbal products, without first consulting the investigator (excluding oral and other contraceptives [eg, depot formulations, transdermals, intrauterine devices]). After dosing, acetaminophen (up to 2 g per 24 hours) will also be allowed with investigator approval. If needed, appropriate management and treatment of any AEs or clinically relevant abnormal laboratory values will be permitted during the study.

The study site will notify the sponsor immediately if a subject receives a prohibited medication/therapy while on study.

The following is prohibited within 6 months before Screening and throughout the course of study:

- Tobacco- or nicotine-containing products (eg, cigarettes, cigars, chewing tobacco, snuff, etc.)

The following is prohibited within 30 days before study drug administration and throughout the course of study:

- Hepatic or renal clearance altering agents

The following are prohibited within 14 days before study drug administration and throughout the course of study:

- Prescription and nonprescription medications (with the exception of hormonal contraception)

- Herbal preparations (including ginseng, kava kava, ginkgo biloba)
- Vitamin supplements

The following is prohibited within 14 days before Check-in (Day –2) and throughout the course of study:

- Seville oranges (sour), grapefruit, grapefruit juice

The following are prohibited within 28 days before Day 1 or 5 half-lives (whichever is longer) and throughout the course of study:

- Use of any drugs known to be significant strong inducers of CYP 3A enzymes, including St. John's Wort

The following are prohibited within 7 days before Check-in (Day –2) and throughout the course of study:

- Consumption of cruciferous vegetables (eg, kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, and mustard greens) or charbroiled meats

The following are prohibited for 96 hours before Check-in (Day –2) until the final PK sample of the study has been collected:

- Caffeine- or xanthine-containing products

The following are prohibited for 48 hours before Check-in (Day –2) until the final PK sample of the study has been collected:

- Alcohol-containing products

5.5.7.2. Part 2

Participants with LQT2 or LQT3 will be instructed not to take any antiarrhythmic medications (including mexilitene), other than beta-blockers or drugs known to affect the QT interval (including ranolazine; refer to drug lists for "Drugs with known, possible, or conditional risk of TdP" that are known to prolong the QT interval at https://crediblemeds.org), and antacids, proton pump inhibitors, or histamine H2 receptor antagonists, unless approved by the sponsor and principal investigator. If needed, appropriate management and treatment of any AEs or clinically relevant abnormal laboratory values will be permitted during the study. The study site will notify the sponsor immediately if a participant receives a prohibited medication/therapy while on study.

The following are prohibited within 28 days before Day 1 or 5 half-lives (whichever is longer) and throughout the course of study:

- Use of any drugs known to be significant strong inducers of CYP 3A enzymes, including St. John's Wort

The following is prohibited within 14 days before Check-in (Day –1) and throughout the course of study:

- Seville oranges (sour), grapefruit, grapefruit juice

The following are prohibited for 96 hours before Check-in (Day –1) until the final PK sample of the study has been collected:

- Caffeine- or xanthine-containing products

The following are prohibited for 48 hours before Check-in (Day –1) until the final PK sample of the study has been collected:

- Alcohol-containing products
- Antacids, proton pump inhibitors, or histamine H2 receptor are prohibited from time of admission to time of discharge.

5.5.8. Diet, Fluid, Activity Control, and Subject Housing

5.5.8.1. Part 1

Subjects will be confined in the CRU in Periods 1 and 2 on the day of Check-in (Day –2) until after all study procedures are completed on Day 9 or Day 10 for a total of up to 11 nights of confinement.

All subjects will fast overnight for a minimum of 6 hours (no food or fluid except water) on Days –1 through 8 and will remain fasted until immediately after the 6-hour ECG extraction, when a light meal will be provided, followed by a meal right after the 9.5- and 12-hour ECG extraction time points. No food or fluids will be served containing caffeine. Strenuous exercise (eg, marathon running) is not allowed from 7 days before Check-in and throughout the study. Subjects will not be allowed to sleep during the ECG resting or collection times. Subjects will be supine, with legs uncrossed, arms at the side, remain quiet, and refrain from laughing and talking for 10 minutes before, during, and approximately 5 minutes after each scheduled ECG extraction time point for motion-free recordings. Staff will work quietly during this same period, keeping conversation to a minimum.

5.5.8.2. Part 2

Participants will be confined in the CRU on the day of Check-in (Day –1) until after all study procedures are completed on Day 5 for a total of up to 5 nights of confinement.

On Day −1, there are no fasting requirements with the exception of an overnight 6-hour fast for clinical laboratory collections. On Days 1, 2, and 4, participants will begin fasting at midnight and will remain fasted until immediately after the 6-hour ECG extraction time point when a light low carbohydrate meal will be provided, which should be consumed within 30 minutes. Participants will then fast until after the 10-hour (Day 1) or 12-hour (Days 2 and 4) ECG extraction when food will be provided ad libitum until midnight. On Day 3, participants will begin fasting at midnight and will remain fasted until the 2- hour time point when food will be provided ad libitum until the 6- hour time point. Fasting will resume at the 6-hour time point until the 10- hour time point when food will be provided ad libitum until midnight. Food intake must be completed prior to the midnight fast to ensure the midnight fasting requirement is met (no food or fluid except water). On Day 5, normal food intake will begin ad libitum after the 29-hour ECG extraction. Participants will not be allowed to sleep during the ECG resting or collection times. Participants will be supine, with legs uncrossed, arms at the side, remain quiet, and refrain from laughing and talking for 10 minutes before, during, and approximately 5 minutes after each scheduled ECG extraction time point for motion-free recordings. Staff will work quietly during this same period, keeping conversation to a minimum.

5.6. Statistical Analysis Plan

Details of all statistical analyses will be described in a separate SAP.

All data collected will be presented in data listings. Data from subjects excluded from an analysis population will be presented in the data listings, but not included in the calculation of summary statistics. For categorical variables, number of subjects/participants/number of observations, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects/participants/number of observations, mean, SD, median, minimum, and maximum, unless otherwise specified). In addition, for PK concentrations and parameters, the percent coefficient of variation (CV%) for arithmetic mean, geometric mean, and geometric CV% will be included.

The number of subjects/participants who enroll in the study and the number and percentage of subjects/participants who discontinue and reasons for discontinuation will be presented. Demographic and baseline characteristics will be summarized by sequence and overall for Part 1 and by LQT subtype and overall for Part 2 participants.

Missing data will not be imputed. Measurements that are excluded from the descriptive and inferential analyses will be included in the subject data listings. This will include

those measurements from excluded subjects/participants, or measurements from unscheduled collections.

All summary tables and figures will be generated using SAS® version 9.4 or above.

5.6.1. Sample Size Considerations

5.6.1.1. Part 1

[redacted]

5.6.1.2. Part 2

[redacted]

5.6.2. Analysis Populations

5.6.2.1. Part 1

Seven analysis populations are defined, as follows:

- The primary QT/QTc population will be those subjects in the total QT/QTc population meeting a threshold effect of dofetilide to prolong the QTc interval as will be defined in the SAP.
- The total QT/QTc population will include all subjects in the safety population with measurements at baseline as well as on-treatment with at least 1 postdose time point with a valid change from baseline in QTc (ΔQTc) value. The QT/QTc population will be used for the by-time point and categorical analyses of cardiodynamic ECG parameters.
- The PK population will include all subjects who received at least 1 dose of study drug and provided at least 1 evaluable PK concentration for LQT-1213 or dofetilide.
- The primary PK/QTc population will include all subjects who are in both the PK and primary QT/QTc populations with at least 1 pair of postdose PK and QTc data from the same time point in each period. The PK/QTc population will be used for the concentration-QTc analysis.
- The safety population will include all subjects who received at least 1 dose of study

dofetilide and provide at least 1 postdose safety assessment.

5.6.2.2. Part 2

Three analysis populations are defined, as follows:

- The safety population will include all participants with LQT2 or LQT3 who received at least 1 dose of study drug (placebo or LQT-1213) and provide at least 1 postdose safety assessment.
- The PK population will include all participants with LQT2 or LQT3 who received at least 1 dose of LQT-1213 and provided at least 1 evaluable PK concentration for LQT-1213.
- The PD population (SGK-1 protein targets) will include all participants who received at least 1 dose of study drug (placebo or LQT-1213) and have at least 1 PD measurement.

5.7. Statistical Analyses

Data from **Parts 1 and 2** will be collected in separate databases. Analysis of each part will be described in independent SAPs and reported in independent clinical study reports.

5.7.1. Pharmacodynamic Analyses

5.7.1.1. Part 1

The analysis will be described in the SAP. All QTc data will represent the means of the extracted QTc intervals, based on ECGs extracted from the Holters at the defined time points. Each individual QT and RR interval will be used to calculate a QTc interval. The individual QTc intervals will then be averaged for analysis. Baseline will be defined as the mean of the triplicate ECG data collected predose for each period.

Fridericia's formula will be the default correction method for QT intervals to remove HR dependence.

If the QTcF is not an adequate correction, other methods will be reviewed. For each method tested (including Fridericia's correction), the relationship between the QTc and RR will be evaluated with a linear-regression model. Mean QTc and RR values at all nominal time points will be used. The model with the slope closest to zero will be selected as the primary QTc endpoint. The additional correction methods and definition of an adequate correction will be detailed in the SAP.

A statistical analysis will be performed per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E14 guidance using the appropriate population and will be detailed in the SAP. The specifics of the concentration-QTc and categorical analyses will be detailed in the SAP.

5.7.1.2. Part 2

Human PBMCs and plasma samples will be isolated and stored for potential analysis of potential PD biomarkers, including SGK-1 targets.

5.7.1.3. Categorical Analyses

5.7.1.3.1 Part 1

Categorical analyses of QTc, PR, QRS, and HR will be provided to determine the number and percentage of subjects, by treatment, who meet the following criteria overall and at each time point:

- QTc results >450 and ≤480, >480 and ≤500, and >500 ms
- ΔQTc from baseline >30 and ≤60, and >60 ms
- ΔQTc from dofetilide/placebo reduction of >10, >15, >20, >25, >30, and >40 ms
- PR outliers (PR >200 ms and a 25% or greater increase from baseline)
- QRS outliers (QRS >120 ms and a 25% or greater increase from baseline)
- HR outliers (HR <50 bpm and a 25% or greater decrease from baseline)
- HR outliers (HR >100 bpm and a 25% or greater increase from baseline)

5.7.1.3.2 Part 2

None planned.

5.7.2. Pharmacokinetic Analyses

5.7.2.1. Concentrations in Plasma

5.7.2.1.1 Part 1

The analysis will be detailed in the SAP, which will be finalized before database lock. Data will be listed and summarized, where applicable. Plasma concentrations of dofetilide and LQT-1213 will be listed and summarized by treatment for each sample time point using descriptive statistics. Mean and individual plasma dofetilide and LQT-1213 concentration-time profiles will be presented in figures on linear and semilogarithmic scales. Assessment of drug interaction between dofetilide and LQT-1213 will be performed.

5.7.2.1.2 Part 2

The analysis will be detailed in the SAP which will be finalized before database lock. Data will be listed and summarized, where applicable. Plasma concentrations of LQT-1213 will be listed and summarized by LQT subtype for each sample time point using descriptive statistics. Mean and individual LQT-1213 concentration-time profiles will be presented in figures on linear and semilogarithmic scales.

5.7.2.2. Pharmacokinetic Parameters

5.7.2.2.1 Part 1

The PK parameters of dofetilide and LQT-1213 will be determined from the concentration-time profiles for all evaluable subjects. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

The following plasma PK parameters will be calculated for LQT-1213 using noncompartmental methods with Phoenix® WinNonlin® (version 8.3 or later):

- AUC_{0-t}: Area under the concentration-time curve (AUC) from time 0 to the time of the last measurable concentration
- AUC_{tau}: AUC from time 0 to the end of the dosing interval
- C_{max}: Maximum observed plasma drug concentration
- T_{max}: Time to the maximum observed plasma concentration
- $t_{1/2}$: Terminal half-life

- CL_{ss}/F: Apparent clearance at steady state
- V_d/F: Volume of distribution
- λ_z: apparent terminal rate constant

Dofetilide and LQT-1213 PK parameters will be summarized using descriptive statistics. Additional statistical analysis may be performed.

5.7.2.2.2 Part 2

The PK parameters of LQT-1213 will be determined from the concentration-time profiles for all evaluable participants. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times.

The following plasma PK parameters will be calculated for LQT-1213 using noncompartmental methods with Phoenix® WinNonlin® (version 8.3 or later):

- AUC_{0-t}: AUC from time 0 to the time of the last measurable concentration
- AUC_{tau}: AUC from time 0 to the end of the dosing interval
- C_{max}: Maximum observed plasma drug concentration
- C_{trough}: Concentration at the end of the dosing interval
- T_{max}: Time to the maximum observed plasma concentration
- $t_{1/2}$: Terminal half-life
- CL_{ss}/F: Apparent clearance at steady state
- V_d/F: Volume of distribution
- λ_z: apparent terminal rate constant

Other PK parameters as identified and documented in the SAP.

LQT-1213 PK parameters will be summarized using descriptive statistics. Additional statistical analysis may be performed.

5.7.3. Safety Analyses

The safety analyses will be based on the safety population. Safety data, including AEs, clinical laboratory test results, vital sign measurements, and 12-lead safety ECG results will be summarized by treatment, if appropriate.

5.7.3.1. Adverse Events

All AEs captured in the database will be presented in by-subject/participant data listings; however, only TEAEs will be summarized. All answers will be interpreted by the investigator using the Medical Dictionary for Regulatory Activities (MedDRA, most recent version) for AEs and will be recorded in the eCRF. Each verbatim term will be

mapped to a system organ class and preferred term.

An overall summary of TEAEs will be provided summarizing subjects/participants with at least 1: TEAE, related TEAE, serious TEAE, related serious TEAE, TEAE leading to study withdrawal, or related TEAE leading to study withdrawal, as well as the number of events within each of the previously mentioned categories by treatment and overall for Part 1 and by LQT subtype, and overall for Part 2. In addition, summaries of unique TEAEs will be presented by system organ class, preferred term, and by treatment and overall for Part 1 and by LQT subtype, and overall for Part 2, and will include the number and percentage of subjects/participants who experience the unique event for: all TEAEs, all TEAEs by relationship, all TEAEs by severity grade, and all TEAEs leading to study withdrawal.

Data listings will be provided for all AEs, AEs leading to study withdrawal, and SAEs.

5.7.3.2. Clinical Laboratory Tests

All continuous clinical laboratory test results and change from baseline will be summarized for each treatment (**Part 1**) or LQT subtype (**Part 2**) using descriptive statistics (number of subjects/participants/ observations, mean, SD, minimum, median, and maximum) at each scheduled time point, as appropriate. All categorical laboratory parameters (ie, urinalysis) will be summarized at baseline and at each planned postbaseline visit by treatment. All clinical laboratory data will be presented in data listings.

5.7.3.3. Vital Sign Measurements

Descriptive statistics (number of subjects/participants, mean, SD, median, minimum, and maximum) of each vital sign measurement and changes from baseline will be tabulated for each treatment (**Part 1**) or LQT subtype (**Part 2**). All vital sign data will be listed in the data listings.

5.7.3.4. Safety 12-Lead Electrocardiograms

Descriptive statistics (number of subjects/participants, mean, SD, median, minimum, and maximum) of each safety 12-lead ECG measurement and changes from baseline will be tabulated for each treatment (**Part 1**) or LQT subtype (**Part 2**). All safety 12-lead ECG data will be presented in the data listings.

5.7.3.5. Physical Examination

Physical examination findings will be presented in the data listings.

5.7.3.6. Interim Analyses

No interim analysis is planned.

5.7.4. Pharmacodynamic Biomarker Analyses

Part 2 only: Details of the potential analysis of PD biomarkers will be provided in a separate analysis plan.

5.7.5. Pharmacokinetic/Pharmacodynamic Analyses

Part 2 only: Details of the potential exploratory PK (LQT-1213)/PD (SGK-1 protein targets) endpoints and analyses to derive PK/PD relationships between drug exposure and target engagement will be provided in a separate analysis plan.

5.8. Data Quality Assurance

The sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the sponsor lies with the investigator generating the data.

Before study initiation, the sponsor or designee will explain the protocol, investigator's brochure, and eCRFs to the investigator. In addition, the monitor will be available to explain applicable regulations and to answer any questions regarding the conduct of the study.

At its discretion, the sponsor may conduct audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the ICH harmonised tripartite guideline E6(R2): Good Clinical Practice (GCP; Department of Health and Human Services [DHHS] 2018), the protocol, standard operating procedures, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. The clinic may also be compelled to undergo an inspection by a regulatory authority.

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

The investigator will permit study-related monitoring, audit(s), IRB review(s), and regulatory inspection(s), with direct access to all of the required source documents and associated records. Source documents and records need to be preserved for at least 15 years after the completion, discontinuation of, or withdrawal from the study or 2 years after the last approval of a marketing application of the sponsor in an ICH region, whichever is longest. Refer to Section 8.5, Appendix E for details of the responsibilities of the investigator.

6. Investigator's Obligations

The following administrative items are meant to guide the investigator or subinvestigator in the conduct of the study but may be subject to change based on industry and

government standard operating procedures or working practice documents or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

The investigator will permit study-related monitoring, audit(s), IRB review(s), and regulatory inspection(s), with direct access to all of the required source documents and associated records. Source documents and records need to be preserved for at least 15 years after the completion, discontinuation of, or withdrawal from the study or for 2 years after the last approval of a marketing application of the sponsor in an ICH region, whichever is longest. Refer to Section 8.5, Appendix E for details of the responsibilities of the investigator.

6.1. Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes such as sex, age or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH guidelines for GCP and to verify compliance with this protocol, the sponsor requires that the investigator permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization by the subject as part of the informed consent process (Section 6.3).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected in the subject's eCRF).

6.2. Institutional Review

The IRB must be constituted according to the applicable state and federal requirements of the participating region. The sponsor or designee will require documentation noting all names and titles of members who comprise the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. If the US center is unwilling to provide names and titles of all members due to privacy and conflict of interest concerns, the center will instead provide a Federal Wide Assurance Number or comparable number assigned by the DHHS.

The sponsor or designee will supply relevant documents for submission to the IRB for the protocol's review and approval. This protocol, the investigator's brochure or package insert, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to the local IRB for approval. Written approval by the IRB of the protocol and subject ICF must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the study drug). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date.

The site must adhere to all requirements stipulated by the IRB. This may include notification to the IRB regarding: protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. The IRB approval and relevant documentation for these items must be provided to the sponsor or designee.

6.3. Subject Consent

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki, the ICH guidelines for GCP, and in accordance with all applicable laws and regulations. The ICF may be in paper or electronic form. The ICF describes the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the ICF. The ICF must be approved by both the IRB and the sponsor before use.

The ICF must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF to the subject. Information will be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB.

The subject, or subject's legally acceptable representative, must be given ample opportunity to: 1) inquire about details of the study and 2) decide whether to participate in the study. If the subject, or subject's legally acceptable representative, determines that he or she will participate in the study, then the ICF must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject enters into the study. Subjects will be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink (if paper ICF). The person

obtaining consent must also sign and date the ICF at the time of consent and before the subject enters into the study.

Once signed, the ICF will be stored in the investigator's site file; the original version will be retained if a paper ICF was used. The investigator must document the date that the subject signs the ICF in the subject's medical record. A copy of the signed ICF will be given to the subject.

All revised ICFs must be reviewed and signed in the same manner as the original ICF. The date the revised consent was obtained will be recorded in the subject's medical record and the subject will receive a copy of the revised ICF.

6.4. Study Reporting Requirements

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to the study investigators or to regulatory agencies, except as required by law or regulation.

6.5. Financial Disclosure and Obligations

The investigator or subinvestigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator or subinvestigators must provide to the sponsor a commitment to update this information promptly if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

Neither the sponsor nor [redacted] 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 the sponsor nor [redacted] is financially responsible for further treatment of the subject's disease.

6.6. Investigator Documentation

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subjects' health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR Parts 160 and 164 (the Health Insurance Portability and Accountability Act of 1996 privacy regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with the privacy regulations of the Health Insurance Portability and Accountability Act and in a form satisfactory to the sponsor.

6.7. Study Conduct

The investigator will conduct all aspects of this study in accordance with US FDA regulations, the ICH E6(R2), and applicable local, state, and federal laws.

6.8. Data Management

The full details of procedures for data handling will be documented in the Data Management Plan. Adverse events, medical history, and concurrent conditions will be coded using MedDRA.

6.8.1. Case Report Forms and Source Documents

Completed eCRFs are required for each subject randomly assigned to study drug. Electronic data entry is accomplished through [redacted], which allows for onsite data entry and data management. This provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, will be able to identify coordinators, investigators, and individuals who have entered or modified records. Furthermore, the investigator retains full responsibility for the accuracy and authenticity of all data entered into the electronic data capture system. The completed dataset and associated files are the sole property of the sponsor and will not be made available in any form to third parties, except for authorized business representatives or appropriate governmental health or regulatory authorities, without written permission of the sponsor.

Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or designee and by the IRB.

6.9. Adherence to the Protocol

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

6.10. Reporting Adverse Events

By participating in this study, the investigator or subinvestigator agrees to submit reports of SAEs according to the timeline and method outlined in the protocol.

6.11. Investigator's Final Report

Upon completion of the study, the investigator, where applicable, will inform the institution; the investigator or institution will provide the IRB with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any required reports.

6.12. Records Retention

The investigator agrees to keep the records stipulated in Section 6.8.1 and those documents that include (but are not limited to) the study-specific documents, identification log of all participating subjects, medical records, source worksheets, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition, to enable evaluations or audits from regulatory authorities, the sponsor, or its designees. Furthermore, ICH 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH 4.9.5 states that the study records will be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the clinical study site agreement between the investigator and sponsor.

Refer to the clinical study site agreement for the sponsor's requirements on record retention. The investigator will contact and receive written approval from the sponsor before disposing of any such documents.

6.13. Publications

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. Publication of study results will be in-line with the agreement executed by [redacted] and the sponsor for the conduct of the study.

7. Study Management

7.1. Monitoring

7.1.1. Monitoring of the Study

Study site monitoring visits will be performed by the sponsor or designee periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded in the eCRFs. Additionally, all aspects of the study and its documentation will be subject to review, including but not limited to, the investigator's binder, study drug, subject medical records, informed consent documentation, eCRFs, and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

7.1.2. Inspection of Records

The investigator involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspection(s). In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, the competent authority, or other regulatory agency access to all study records. The investigator will promptly notify the sponsor of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

7.2. Management of Protocol Amendments and Deviations

7.2.1. Modification of the Protocol

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

7.2.2. Protocol Deviations

The investigator will conduct the study in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority and that was given approval/favorable opinion by the IRB.

The investigator, or designee, will document and explain any deviation from the approved protocol.

The investigator will notify the IRB of any deviations from the protocol in accordance with local procedures.

7.3. Study Termination

The study will be completed as planned unless the following criteria are satisfied that require early termination of the study:

1. New information regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the investigational product, such that the risk/benefit is no longer acceptable for subjects participating in the study.
2. Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

The sponsor reserves the right to suspend or terminate the study at any time.

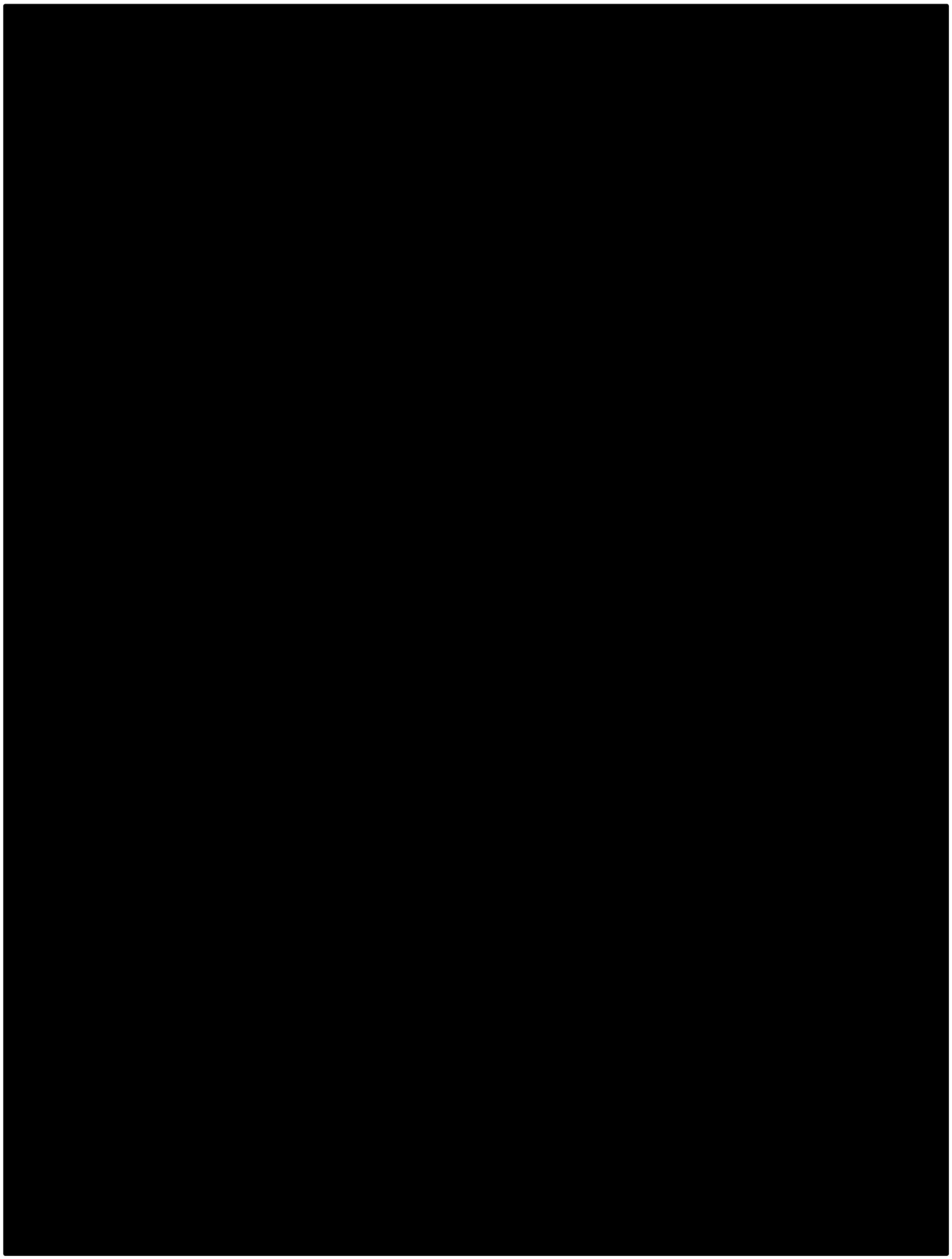
The study site may be terminated if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, or is unable to ensure adequate performance of the study.

7.4. Final Report

Whether the study is completed or prematurely terminated, the sponsor's designee will ensure preparation of the clinical study report and provision of it to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The clinical study report will be structured in accordance with the FDA guideline document entitled, "ICH E3 Structure and Content of Clinical Study Reports" (DHHS 1996).

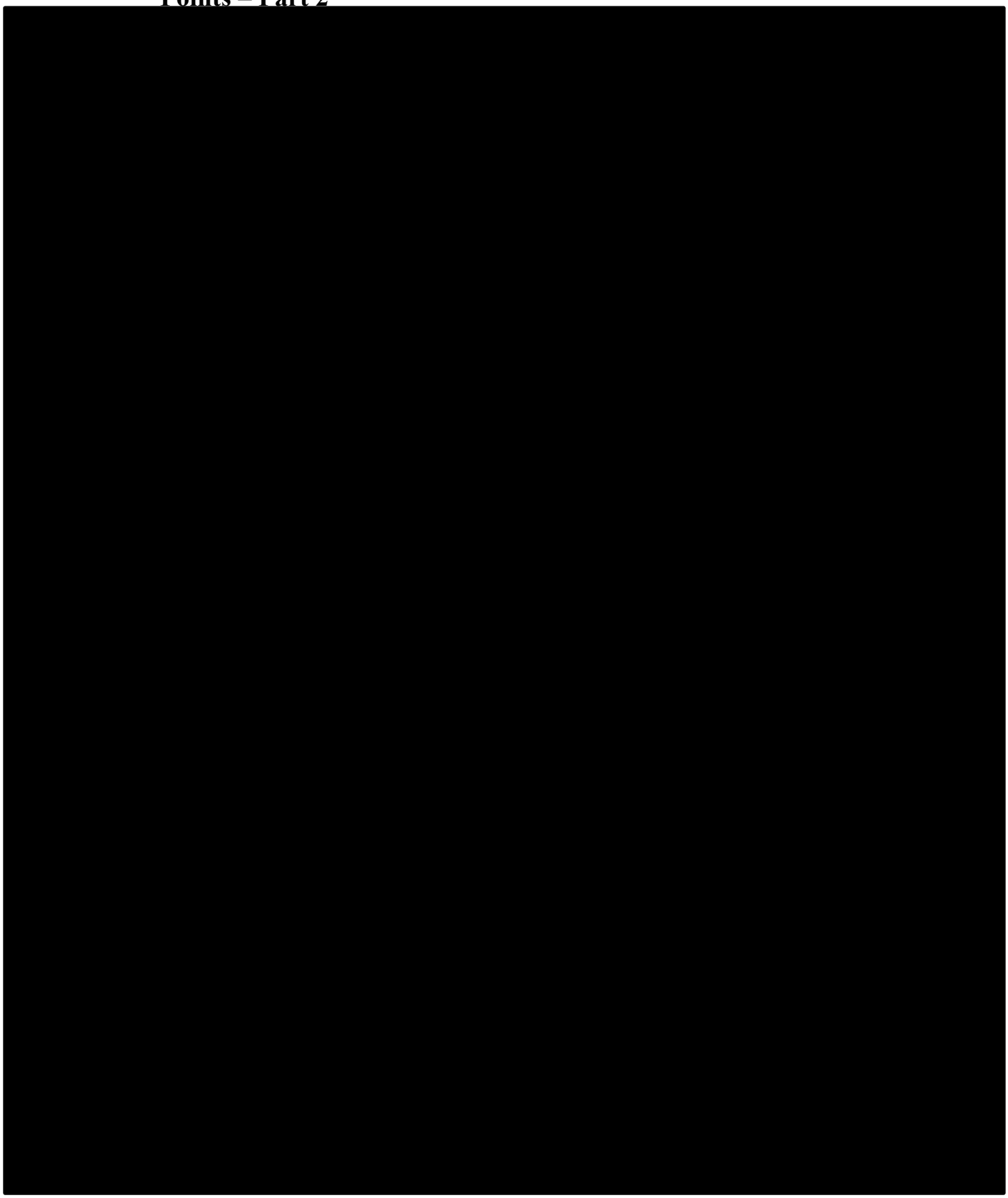
8. Appendices

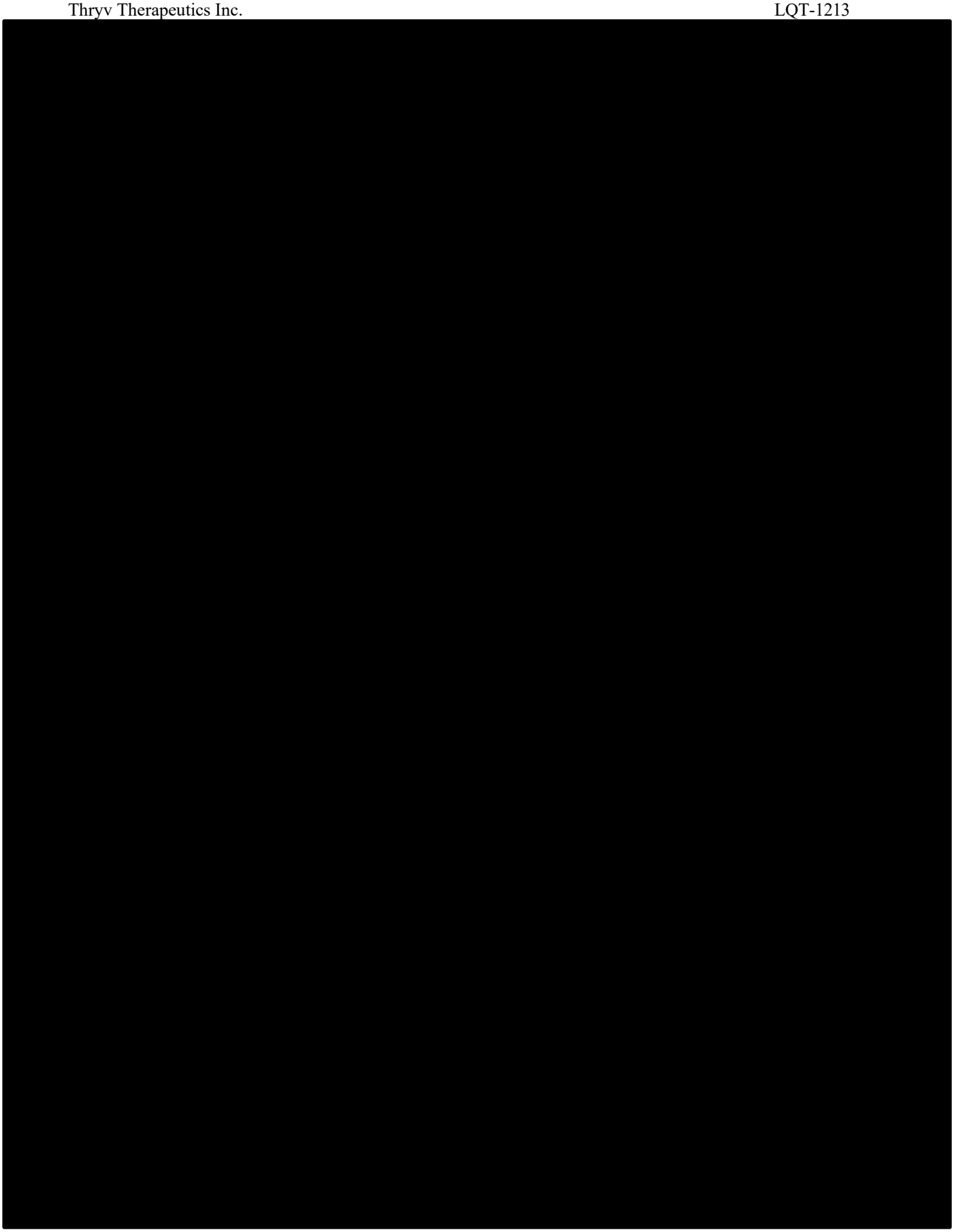
[redacted]



[redacted]

8.4. Appendix D: Pharmacokinetic, Pharmacodynamic, and Meal Time Points – Part 2





8.5. Appendix E: Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to the regulations of the FDA. The responsibilities imposed on the investigator by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

In signing a Form FDA 1572, the investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the conduct of the study.
3. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
4. Secure prior approval of the study and any changes by an appropriate IRB that conforms to FDA requirements.
5. Ensure that the IRB will be responsible for initial, continuing review, and approval of the protocol. Promptly report to the IRB all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB and issue a final report within 3 months of study completion.
6. Ensure that requirements for informed consent as outlined in 21 CFR Part 50 are met.
7. Obtain valid informed consent from each subject who participates in the study and document the date of consent in the subject's medical chart. Each ICF will contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study.
8. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain this data for a minimum of 2 years after notification by the sponsor that all investigations have been discontinued or that the FDA has approved the New Drug Application. Before disposing of any records, the sponsor must be contacted.
9. Allow possible inspection and copying by the FDA of eCRFs and records of drug distribution.
10. Maintain current records of the receipt, administration, and disposition of study medication, and return all unused study medication to the sponsor.
11. Report adverse reactions to the sponsor promptly. In the event of an SAE, immediately notify the sponsor and medical monitor within 24 hours of knowledge of the event.

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