STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of GS-6615 on Exercise Capacity in Subjects with Symptomatic Hypertrophic Cardiomyopathy	
Name of Test Drug:	GS-6615/Eleclazine	
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BLQ	below the limit of quantitation
BMI	body mass index
BSA	body surface area
eCRF	electronic case report form
CANVAS	Cerebellar Ataxia, Neuropathy and Vestibular Areflexia
CCS	Canadian Cardiovascular Society
CPET	cardiopulmonary exercise testing
DMC	Data Monitoring Committee
EDBT	end of double-blind treatment
ECG	Electrocardiogram
ECHO	Echocardiography
FAS	full analysis set
HCM	hypertrophic cardiomyopathy
HLT	high level term
HLGT	high level group term
ICD	implantable cardioverter-defibrillator
ICH	International Conference on Harmonisation
ITT	intention-to-treat
hsTnT	high-sensitivity Troponin T
ICD	implantable cardioverter-defibrillator
IXRS	Interactive Voice/Web Response System
LLOQ	lower limit of quantitation
LLT	lower level term
LV	left ventricular
LVOT	left ventricular outflow tract
MedDRA	Medical Dictionary for Regulatory Activities
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MMRM	mixed models repeated measurement
NYHA	New York Heart Association
OLE	open-label extension
PE	physical examination
PK	pharmacokinetics
PP	per protocol
PR	electrocardiographic interval occurring between the onset of the P wave and the QRS complex representing time for atrial and ventricular depolarization, respectively

PT	preferred term
Q1	first quartile
Q3	third quartile
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	corrected QT
QTcB	corrected QT (Bazett's formula)
RR	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
SAE	serious adverse event
SAP	statistical analysis plan
SMQ	Standardized MedDRA queries
SOC	system organ class
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used during the final reporting and analysis of data collected under Gilead Sciences, Inc. Protocol GS-US-361-1157 "A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of GS-6615 on Exercise Capacity in Subjects with Symptomatic Hypertrophic Cardiomyopathy."

This SAP was updated to reflect a synoptic CSR. All planned listings will be produced, however summaries will only be provided for primary and secondary endpoints, relevant exploratory endpoints, and relevant safety measures.

1.1. Study Objectives

Primary Study Objective	• Evaluate the effect of eleclazine on exercise capacity, as measured by Peak VO_2 achieved during cardiopulmonary exercise testing (CPET), in subjects with symptomatic hypertrophic cardiomyopathy (HCM)
Secondary Study Objectives	• Evaluate the safety and tolerability of eleclazine in subjects with symptomatic HCM • Evaluate the effect of eleclazine on quality of life as measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) • Evaluate the effect of eleclazine on treadmill exercise time during CPET
Exploratory Objectives	PPD

1.2. Study Design

Design Configuration and Subject Population	This is a randomized, double-blind, placebo-controlled, global, multicenter study to evaluate the effect of eleclazine on exercise capacity in subjects with symptomatic HCM. Eligible subjects will be enrolled and randomized 1:1 to receive either eleclazine or matching placebo for a minimum treatment duration of 24 weeks. Randomization will be stratified by sex and by age (≥ 50 years and < 50 years).
Treatment Groups	**Eleclazine** Day 1 through End of Double-Blind Treatment (EDBT) Oral single loading dose of 30 mg eleclazine (5 × 6 mg tablets) on Day 1, followed by maintenance dose of 3 mg eleclazine (1 × 3 mg eleclazine tablets) once daily until Week 12 then daily maintenance dose of 6 mg (2 × 3 mg eleclazine tablets) from Week 12 to at least Week 24 visit Day of EDBT Oral single, double-blind loading dose of placebo (5 tablets) on day of EDBT visit (to maintain retrospective blinding to double-blind study treatment assignment). **Placebo** Day 1 through EDBT Oral single loading dose of placebo to match eleclazine (5 × placebo tablets) on Day 1, followed by daily maintenance dose of matching placebo (1 × placebo tablet) until Week 12 then daily maintenance dose of matching placebo (2 × placebo tablets) from Week 12 to at least Week 24 visit Day of EDBT Oral single, double-blind loading dose of eleclazine (5 x 6 mg tablets) on day of EDBT visit (to maintain retrospective blinding to double-blind study treatment assignment). **Open-label Extension (OLE) Period** Maintenance dose of 6 mg open-label eleclazine (2 × 3 mg eleclazine tablets) once daily through the end of the open-label extension period

Key Eligibility Criteria	Subjects with symptoms (New York Heart Association [NYHA] Class ≥ II dyspnea or Canadian Cardiovascular Society [CCS] Class ≥ II angina) due to HCM (defined as a maximal LV wall thickness of ≥ 15 mm in the absence of other causative loading abnormalities capable of producing the magnitude of hypertrophy observed) will be randomized. Subjects with and without left ventricular outflow tract obstruction will be eligible. Medications commonly used in the treatment of HCM are permitted, unless specifically excluded, and may be continued throughout the study, including beta-blockers, calcium channel blockers, and Class III antiarrhythmics (eg, amidoarone and sotalol). It is recommended that the doses of such medications remain stable after screening through the end of the double-blind treatment period, unless clinically warranted at the discretion of the investigator. **Inclusion Criteria** Subjects must meet all of the following inclusion criteria to be eligible for participation in this study. 1) Have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures 2) Males and females 18 to 65 years old, inclusive 3) Established diagnosis of HCM defined by standard criteria as a maximal LV wall thickness ≥ 15 mm at initial diagnosis in the absence of other causative loading abnormalities capable of producing the magnitude of hypertrophy observed 4) Exertional symptoms including at least one of the following: a) NYHA Class ≥ II Dyspnea b) CCS Class ≥ II Angina 5) Screening (baseline) Peak VO_2 < 80% of predicted based on age, sex, and weight-adjusted equations (see Appendix 4 of the protocol), as confirmed by the investigator 6) Ability to perform an upright treadmill CPET

	7) Hemodynamically stable at both Screening and Randomization visits defined as: systolic blood pressure ≥ 90mmHg, heart rate ≤ 100 beats/min, and not requiring mechanical circulatory support or intravenous treatment with diuretics or vasoactive drugs 8) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to utilize protocol-specified method(s) of contraception as described in Appendix 8 of the protocol. See protocol for exclusion criteria.
Study Periods/Phases	Subjects will be seen in the clinic for a Screening visit (within 14 to 28 days prior to Randomization; within 14 to 60 days for those enrolled under Protocol Amendment 1), a Randomization visit, and during the treatment period at Week 2, 6, 12, 18, and 24 visits. Subjects will be contacted between study visits for assessment of adverse events and concomitant medications. In order to accumulate additional long-term safety data in this population, subjects will continue double-blind treatment (and 12-weekly assessments) until the last subject has been followed up for approximately 24 weeks. As that date approaches, all remaining subjects (including subjects who have already discontinued treatment but are continuing the study) will be contacted to return for the EDBT Period visit. At the end of the double-blind, placebo-controlled treatment period, all subjects who complete the treatment period (including study drug dosing) may continue in the study, at the discretion of the investigator, and receive eleclazine in an OLE. During the OLE period, subjects will continue to undergo periodic required assessments. A safety follow-up visit will occur 30 days after the last dose of study drug. The schedule of follow-up and OLE visits may vary according to country specific requirements.

Schedule of Assessments

The study includes 4 periods: Screening, Double-Blind Placebo-Controlled Treatment (minimum of 24 weeks), Open-Label Extension (OLE), and Follow-up (30 days after last dose). During the Screening phase, baseline CPET as well as implantable cardioverter-defibrillator (ICD) interrogation, where applicable, will be performed and subjects will wear the ZIO® XT Patch which will be collected on Day 1. Demographic, medical history, adverse events (AE), concomitant medications, physical examination (PE), ECG, ECHO, and vital signs results will be recorded and samples will be collected for laboratory results.

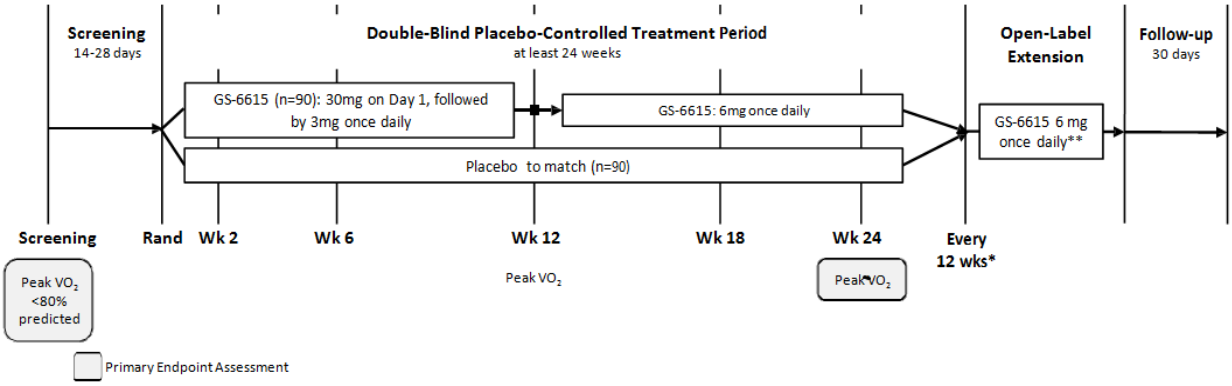
Eligible subjects will be randomized on Day 1. Pharmacokinetic (PK), NT-proBNP and hsTnT samples will be collected, and ECG, ECHO, MLHFQ, and PE including vitals will be performed. Study drug will be dispensed on Day 1 and all subsequent study visits during the double-blind placebo-controlled treatment and the OLE periods.

During the double-blind placebo-controlled period, subjects will be contacted on Weeks 1, 9, 15, and 21 to review AEs and concomitant medications and have visits on Weeks 2, 6, 12, 18, 24, and every 12 weeks after Week 24 through EDBT. During these visits, samples for PK and laboratory results, unused study drug and the ZIO® XT Patch will be collected and PE, including vitals, and ECG will be performed. Additionally, at the Week 12 and 24 visits, ECHO, CPET, MLHFQ, and samples for NT-proBNP and hsTnT will be collected and ICD interrogation, where applicable, will be performed.

During the OLE period, subject will be contacted at OLE Week 1 and have visits at OLE Weeks 12 and 24 and every 24 weeks thereafter and include PK (through OLE Week 24) and lab sample collection, PE including vitals, ECG, and returning and dispensing study drug.

The follow-up period consists of a visit 30 days after the last dose of study drug with the same assessments that were performed during the OLE period. The schedule of follow-up and OLE visits may vary according to country specific requirements.

A schematic of the study is presented below.



* Subjects will continue double-blind treatment until the last subject has been followed up for approximately 24 weeks. As that date approaches, all remaining subjects (including subjects who have already discontinued treatment but who are continuing the study) will be contacted to return for the End of Double-Blind Treatment Period visit.

** Subjects who complete double-blind treatment period at a down-titrated dose of 1 tablet of blinded study drug once daily are eligible to continue into the open-label extension period. It is encouraged that these subjects attempt the target dose of eleclazine 6 mg once daily (2 x 3 mg eleclazine tablets), if appropriate in the opinion of the investigator.

See Appendix 1 for the complete study procedures table.

Randomization	Eligible subjects will be randomized in a 1:1 ratio to one of the following groups: 1) 30 mg single loading dose of eleclazine on Day 1 followed by 3 mg daily dose of eleclazine until Week 12 and 6 mg daily dose of eleclazine from Week 12 to at least Week 24 2) Matching placebo single loading dose on Day 1 followed by matching placebo until Week 12 and matching placebo from Week 12 to at least Week 24 Randomization will be stratified by sex and by age (≥ 50 years and < 50 years). There will be up to 60 sites.
Site and/or Stratum Enrollment Limits	There were no site enrollment limits.
Study Duration	The enrollment period is expected to be 12 months. The maximum double-blind treatment period is approximately 20 months. The OLE period will be up to a maximum of approximately 32 months. The OLE period will continue until eleclazine is commercially available for the treatment of patients with HCM, or the investigator deems it no longer in the subject's best interest, or until Gilead terminates development of the study drug for the treatment of patients with HCM. The maximum length of participation in the OLE varies as applicable by local country requirements.

1.3. Sample Size and Power

Planned Sample Size	The planned sample size is 180 (90 per arm).
Power Statement	Based on a 2-sided, 2-sample t-test ($\alpha = 0.01$), and a standard deviation of 4 mL/kg/min, a sample size of 90 subjects per arm provides greater than 95% power assuming a treatment difference of 3 mL/kg/min in the primary endpoint (Peak VO_2) given a null hypothesis of no treatment effect. This treatment difference is clinically significant and similar to that seen with alcohol septal ablation {Firoozi 2002}. The program nQuery Advisor® version 6.0 (Statistical Solutions, Cork, Ireland) was used for sample size and power calculations.

2. TYPE OF PLANNED ANALYSIS

The Data Monitoring Committee (DMC) periodically reviewed safety data as specified in its charter.

This study was terminated by the Sponsor prior to the end of the double-blind phase, and therefore no subjects entered the OLE period. After all subjects have terminated the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the study blind will be broken and then the final analysis of the data will be performed.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

3.1. Analysis Sets

Analysis sets define which subjects are included in an analysis.

The assignment of subjects to analysis sets will be done before database lock and the study blind is broken for analysis. A summary of the number and percentage of subjects in each analysis set will be provided by treatment group and in total.

3.1.1. Randomized

The randomized analysis set includes subjects who were randomized into the study.

3.1.2. Full Analysis Set

The "full analysis set (FAS)" identifies the analysis set that is both relevant for analysis of efficacy data from this study and as close as possible to the intention-to-treat (ITT) principle per International Conference on Harmonisation (ICH) E9 guidance. The full analysis set (FAS) is defined as all randomized subjects who received at least one dose of study drug. This will be the primary analysis set for evaluation of efficacy. For FAS, consistent with ITT, subjects will be categorized according to the assigned treatment.

3.1.3. Safety Analysis Set

The primary analysis set for safety analyses is defined as all randomized subjects who receive at least one dose of study drug. Subjects will be grouped according to the treatment received.

3.1.4. Pharmacokinetic Analysis Set

The primary analysis set for the PK analyses is defined as all randomized subjects who received at least one dose of active study drug and have any post-baseline plasma concentrations.

3.1.5. Biomarker Analysis Set

The primary analysis set for the biomarker (NT-proBNP, hsTnT) analyses is defined as all randomized subjects who received at least one dose of study drug and who have an NT-proBNP or hsTnT measurement both prior to study drug administration and after study drug administration. For the biomarker analysis set, subjects will be grouped based on the treatment received.

3.2. Subject Groups

Subjects will be grouped for analyses according to randomized treatment for efficacy analysis using FAS, where appropriate. Subjects will be grouped for analyses according to treatment received for efficacy analysis using biomarker analysis set, where appropriate. Subjects will be grouped according to actual treatment received for safety analysis using safety analysis set. The actual treatment received will differ from the randomized treatment only when the subject's actual treatment differs from randomized treatment for the entire treatment duration.

Treatment groups are Eleclazine 30/3/6 mg and Placebo.

3.3. Strata and Covariates

Sex and age will be used as covariates in analyses of efficacy data. Age will be included in the model as a continuous covariate for analysis of continuous response variable and as a dichotomized (≥ 50 years and < 50 years) covariate for analysis of categorical or ordinal response if applicable. Strata will be included in the analyses if at least 10 subjects per treatment group are in each stratum.

3.4. Examination of Subject Subsets

No subgroup analyses are planned.

3.5. Multiple Comparisons

All endpoints will be tested at a 2-sided nominal significance level of 0.05, with no adjustment for multiple testing.

3.6. Missing Data

A missing data point for a given study visit may be due to any of the following reasons:

- A visit occurred in the window but data were not collected or were unusable
- A visit did not occur in the window
- A subject permanently discontinued from the study before reaching the window.

Missing values will not be imputed with the following exceptions:

- Missing day and month will be imputed for birth date in order to compute age as specified in Section 3.7
- If individual items are missing in the MLHFQ, the score will be computed as specified in Section 6.4.1.

The determination of treatment-emergence for AEs with incomplete dates is specified in Section 7.1.5.2.

3.7. Data Handling Conventions and Transformations

Baseline is defined as the last available record on or prior to the date of the first dose of study drug.

QT interval is affected by heart rate. Bazett's correction formula will be used to correct for heart rate.

Bazett's QT (QTcB) correction formula:

$$QT_cB = \frac{QT}{\sqrt{RR}}$$

QT, RR, and other ECG parameters will be collected and adjudicated by the core ECG laboratory.

Pressure gradient for ECHO LV outflow tract will be computed using the modified Bernoulli equation:

$$\text{Pressure gradient (mmHg)} = 4 \times \text{Velocity (m/s)}^2$$

LA volume index will be computed as LA volume (mL) / body surface area (m^2), where body surface area is computed using baseline height weight at the time of ECHO.
Body surface area (BSA) is computed as follows:

$$BSA = \sqrt{\frac{(height\ (cm) * weight\ (kg)}{3600}}$$

Age will be calculated as (Day 1 date − birth date) / 365.25, truncated to a whole number. If day for birth date is missing, set to the 1st day of the month. If both day and month are missing for birth date, set to January 1st. The randomization date will be used in lieu of Day 1 if the subject does not receive study drug. The informed consent date will be used if the subject is not enrolled.

Body mass index (BMI) is calculated as baseline weight (kg) / [height (m)]^2. BMI will be displayed to 1 decimal place in listings and summary statistics will be rounded to 1 decimal place, with the exception of standard deviation which will be rounded to 2 decimal places.

PK concentration values below the limit of quantitation (BLQ) will be treated as 0 at predose time points, and one-half the value of the lower limit of quantitation (LLOQ) at postbaseline time points for the determination of summary and order statistics. Individual values that are BLQ will be presented as "BLQ" in the concentration data listing. For the presentation of summary and order statistics, if at least one subject has a concentration value BLQ for the time point, then the minimum value will be displayed as "BLQ". If more than 25% of subjects have a concentration data value of BLQ for a given time point, then the minimum and first quartile [Q1] will be displayed as "BLQ." If more than 50% of the subjects have a concentration data value BLQ for

the time point, then the minimum, Q1, and median values will be displayed as "BLQ". If more than 75% of the subjects have a concentration data value of BLQ for a given time point, then the minimum, Q1, median, and third quartile [Q3] values will be displayed as "BLQ". If all subjects have concentration data values BLQ for the time point, then all order statistics (minimum, Q1, median, Q3, maximum) will be displayed as "BLQ".

NT-proBNP and hsTnT results will be log-transformed.

3.8. Visit Windows

3.8.1. Definition of Study Day

Study Day 1 is defined as the day of first dose of study drug which is also the Randomization visit.

Study day is the day relative to the first dose of study drug, calculated as:

Visit Date – Dose Date + 1, if Visit Date is on or after the First Dose Date

Visit Date – Dose Date, if Visit Date is prior to the First Dose Date

3.8.2. Analysis Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to visits based on the windows presented in Table 3-1. Day 1 is the day of first dose of study drug.

Table 3-1. Visit Windows for Peak VO_2, MLHFQ, Treadmill Exercise Time, Biomarker Data, CPET 12-Lead ECG, and ICD Interrogation

Visit	Target Day	Visit Window in Day(s)
Baseline		≤ 1
Week 12	84	2–126
Week 24	168	> 126

Table 3-2. Visit Windows for ECHO

Visit	Target Day	Visit Window in Day(s)
Baseline		≤ 1
Week 2	14	2-49
Week 12	84	50–126
Week 24	168	> 126

Table 3-3. Visit Windows for Arrhythmia Burden

Visit	Target Day	Visit Window in Day(s)
Baseline		< 1
Days 1–14	1	1–21
Weeks 6–8	42	22–84
Weeks 18–20	126	> 84

The target and window are based on the start date of the 14-day ZIO® XT Patch period.

Table 3-4. Visit Windows for 12-Lead ECG, Vital Signs, and Clinical Laboratory Data

Visit	Target Day	Visit Window in Day(s)
Baseline		≤ 1
Week 2	14	2–28
Week 6	42	29–63
Week 12	84	64–105
Week 18	126	106–147
Week 24	168	148–210
Week 36	252	211–294
Week 48	336	295–378
Week 60	420	379–462
Week 72	504	463–546
Week 84	588	> 546 – last dose date + 30 days

All visits, including Unscheduled, Early Termination, and Follow-up visits, will be eligible for inclusion in table summaries based on the windows presented in Table 3-1, Table 3-2, and Table 3-3.

In the efficacy summary tables, Peak VO_2, treadmill exercise time, MLHFQ, ECHO, QTc interval at rest and at Peak from the exercise ECG, and biomarker results will be summarized based on values obtained at the visit using the windows in Table 3-1 or Table 3-2.

For the safety summaries, all visits other than the Follow-up visit, including Unscheduled and Early Termination visits, will be eligible for inclusion in table summaries based on the windows presented in Table 3-4.

In the safety summary tables for 12-lead ECG and vital signs, data obtained after the last dose date plus 30 days will be excluded from the summaries, but will be included in the listings.

3.8.3. Selection of Data in the Event of Multiple Records in a Window

Depending on the statistical analysis method, single values may be required for each analysis window. A single value will be chosen based on the rules below.

If multiple nonmissing numeric observations exist in a window, a record will be chosen based on the following rules:

- For baseline, the last available record on or prior to the date of the first dose of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, average (arithmetic or geometric mean, as appropriate) will be used for the baseline value.

- For post baseline assessments:

  — The record closest to the target day for that visit will be selected.

  — If there are 2 records equidistant from the target, the later record will be selected.

  — If there is more than 1 record on the selected day, the average will be taken, unless otherwise specified.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment

Subjects randomized will be summarized by number and percentage in each country and by each investigator within a country and by treatment group. The denominator for percentage calculation will be the number of randomized subjects. Similarly, the number and percentage of subjects enrolled in each randomization strata will be presented. If there is a discrepancy between the interactive voice/web response system (IXRS) and the electronic case report form (eCRF) regarding age or sex, the value calculated from the eCRF will be used and discrepancies between the IXRS and eCRF will be listed.

The number and percentage of subjects included in each analysis set (randomized, safety, FAS, PK analysis set and biomarker analysis set) will be presented. If applicable, the reasons for exclusion from the analysis sets will be summarized. The denominator for this calculation will be the number of randomized subjects.

4.2. Disposition of Subjects

A summary of subject disposition will be provided by treatment group. This summary will present the number of subjects screened, randomized, included in the safety analysis set, and the number and percentage of subjects meeting the following criteria:

- Completed Week 24
- Completed study drug through the double-blind period
- Did not complete study drug through the double-blind period, (with summary of reasons for discontinuation)
- Completed the double-blind study period
- Did not complete the double-blind study period (with summary of reasons for not completing the study period)

The denominator for the percentages of subjects in each category will be the number of subjects in the safety analysis set. In addition, a flowchart will be provided to depict the disposition.

Summaries will be provided by treatment group for the safety analysis set. No inferential statistics will be generated. A data listing of reasons for premature study treatment and study discontinuation will be provided.

4.3. Extent of Exposure

4.3.1. Duration of Exposure to Study Drug

Duration of exposure to study drug will be defined as (last dose date – first dose date + 1), regardless of temporary interruptions in study drug administration, and will be expressed in days. Duration of exposure to study drug will be summarized using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) and as the number and percentage of subjects exposed for specific periods (eg, ≥ 1 day, ≥ 4 weeks, ≥ 8 weeks, ≥ 12 weeks, ≥ 16 weeks, ≥ 20 weeks, ≥ 24 weeks, ≥ 28 weeks, ≥ 32 weeks, ≥ 36 weeks, ≥ 40 weeks, ≥ 44 weeks, ≥ 48 weeks, ≥ 52 weeks, ≥ 56 weeks, ≥ 60 weeks, ≥ 64 weeks, ≥ 68 weeks, ≥ 72 weeks, ≥ 76 weeks, ≥ 80 weeks, and ≥ 84 weeks). First and last dose dates are determined from the Study Drug Administration eCRF page. In addition, the number and percentage of subjects with study drug reduced from 6 mg daily to 3 mg, temporarily interrupted, and drug permanently discontinued due to AE (based on the Study Drug Administration and Adverse Event eCRF pages) will be summarized.

Summaries will be provided by treatment group for the safety analysis set. No inferential statistics will be provided.

A by-subject listing of study drug administration will be provided separately by subject ID number (in ascending order) and visit (in chronological order).

4.4. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry, but were enrolled in the study will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria by treatment group based on the Safety Analysis Set. A listing will be provided for subjects in the randomized analysis set who violated at least one inclusion or exclusion criteria. The listing will include the criteria not met and related comments.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by treatment group for the safety analysis set. A by-subject listing will be provided for those subjects with important protocol deviations.

5. BASELINE DATA

5.1. Demographics and Baseline Characteristics

Subject demographic data (age, sex, race, and ethnicity) and baseline characteristics (body weight, height, BMI, LVOT gradient, maximal LV wall thickness, baseline LV ejection fraction, presence of known sarcomeric mutation, Peak VO_2, QTcB, CCS class, NYHA class of dyspnea, use of beta-blockers, and use of calcium channel blockers) will be summarized by treatment group and overall using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) for continuous data and by the number and percent of subjects for categorical data. CCS Class is captured on the exertional symptoms eCRF page, presence of sarcomeric mutation is captured on the cardiovascular medical history eCRF page, use of beta-blockers and calcium channel blockers is captured on the prior and concomitant medications eCRF page, and adjudicated ECHO data (maximal LV wall thickness and baseline LV ejection fraction) will be provided by the core imaging laboratory. The summaries of demographic data and baseline characteristics will be provided for the safety analysis set. No inferential statistics will be provided.

5.2. Medical History

Cardiovascular history and risk factors (diabetes mellitus, dyslipidemia, smoking status) will be collected on the eCRF and will be summarized by treatment group and overall by the number and percentage of subjects with each condition. Summaries of cardiovascular history and risk factors will be provided for the safety analysis set. No inferential statistics will be generated.

Other medical history (ie, conditions not specific to the disease being studied) data will be listed only. General medical history data will not be coded.

6. EFFICACY ANALYSES

6.1. Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint is the change in Peak VO_2 from baseline to Week 24. Data will be sent to the core exercise physiology laboratory from the sites and the core exercise physiology laboratory will provide adjudicated results to Gilead. The adjudication process at the core exercise physiology laboratory will be blinded to treatment assignment.

6.2. Statistical Hypothesis for the Primary Efficacy Endpoint

H_0: $\mu_{Eleclazine} = \mu_{Placebo}$

(ie, the difference between the mean change from baseline in Peak VO_2 in eleclazine and placebo groups is zero)

H_a: $\mu_{Eleclazine} \neq \mu_{Placebo}$

(ie, the difference between the mean change from baseline in Peak VO_2 in eleclazine and placebo groups is not zero)

6.3. Analysis of the Primary Efficacy Endpoint

Peak VO_2 at baseline, Week 24, and change from baseline at Week 24 will be summarized by treatment group (eleclazine or placebo) for the FAS with the following descriptive statistics: sample size, mean, standard deviation, median, minimum, maximum, Q1 and Q3. The change in Peak VO_2 from baseline to Week 24 for the eleclazine treatment group will be compared to that of the placebo treatment group using analysis of covariance (ANCOVA) including terms for baseline Peak VO_2, sex, and age (continuous). This analysis will be performed on the FAS. Missing data will not be imputed.

The assumption of normality for the ANCOVA analyses will be assessed with the Shapiro-Wilk statistic and residuals will be visually examined for heterogeneity via scatter plots. If the normality assumption is violated, treatment differences will be assessed using an ANCOVA model on the rank-transformed change from baseline values.

6.4. Secondary Efficacy Endpoints

6.4.1. Definition of Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Change in MLHFQ between baseline and Week 24.
  - If there are no missing items, the MLHFQ score is computed by adding the values for all 21 items. Each item is measured on a 6-point Likert scale (0 to 5) with higher values being worse. If more than half of the items are missing, the score is missing. If less than half of the items are missing, the score is computed as follows: $(\sum nonmissing\ items\ /\ number\ of\ nonmissing\ items) * 21$

- Change in treadmill exercise time between baseline and Week 24
- Change in Peak VO_2 between baseline and Week 12
- Change in MLHFQ between baseline and Week 12
- Change in treadmill exercise time between baseline and Week 12

6.4.2. Analysis Methods for Secondary Efficacy Endpoints

The secondary efficacy endpoints will be summarized and analyzed in a manner similar to the primary efficacy endpoint.

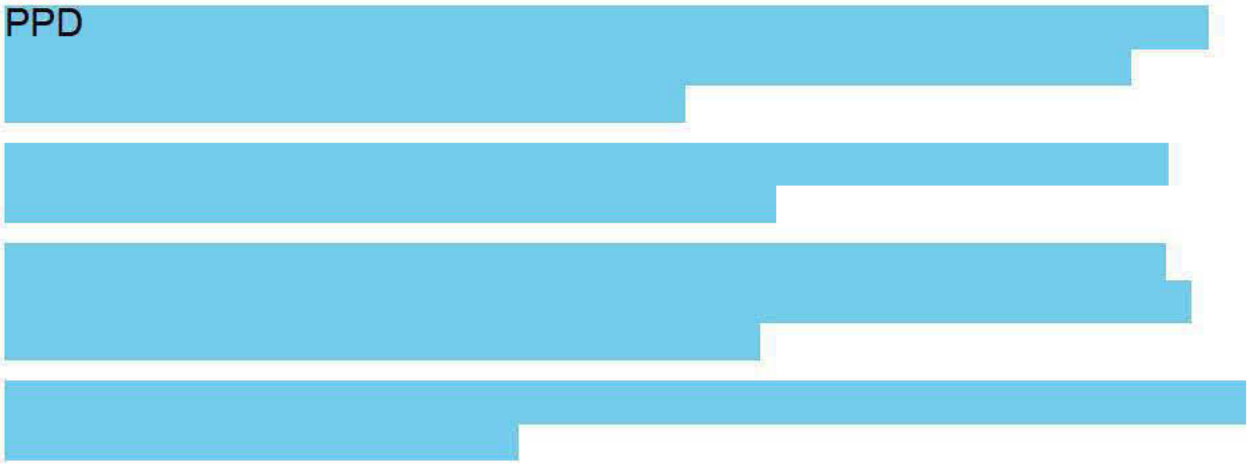
The FAS will be used for the analysis of all secondary efficacy endpoints.

6.5. Exploratory Efficacy Endpoints

6.5.1. Definition of Exploratory Efficacy Endpoints

PPD

6.5.2. Analysis Methods for Exploratory Efficacy Endpoints



6.6. Changes From Protocol-Specified Efficacy Analyses

The primary and secondary endpoints will be tested at a 2-sided nominal significance level of 0.05, with no adjustment for multiple testing. No inferential statistics will be provided for exploratory endpoints. The sensitivity analyses of secondary efficacy endpoints using Mixed Models Repeated Measures (MMRM) will not be performed. Missing values will not be imputed. Correlations between efficacy endpoints will not be explored, and subgroup analyses will not be performed. The following ECHO efficacy endpoints specified in the protocol will not be summarized: mitral E velocity, mitral a velocity, mitral deceleration time, mitral regurgitation severity, LA volume index, Tei myocardial performance index, and maximal LV wall thickness.

6.7. Summary of Efficacy Analyses

The analyses of the efficacy endpoints are summarized in the following table:

Table 6-1. Summary of Efficacy Analyses

Endpoint Description	Analysis Set	Analysis Method
Primary: Δ Peak VO_2 at Week 24	FAS	ANCOVA
1st Secondary: Δ MLHFQ at Week 24	FAS	ANCOVA
2nd Secondary: Δ treadmill exercise time at Week 24	FAS	ANCOVA
3rd Secondary: Peak VO_2 at Week 12	FAS	ANCOVA
4th Secondary: Δ MLHFQ at Week 12	FAS	ANCOVA
5th Secondary: Δ treadmill exercise time at Week 12	FAS	ANCOVA
Exploratory Endpoints		
PPD		

Δ is the change from baseline.
The ANCOVA model will include terms for age, sex, baseline value, and treatment.

7. SAFETY ANALYSES

Formal statistical comparisons between treatment groups are not planned for safety analyses.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high level group term (HLGT), high level term (HLT), preferred term (PT), and lower level term (LLT) will be attached to the clinical database.

7.1.2. Adverse Event Severity

AEs are graded by the investigator as mild, moderate, or severe according to guidelines specified in the study protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings, and will be considered the least severe for the purposes of sorting for data presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE CRF to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor Events for which the investigator did not record relationship to study drug will be considered related to study drug. Data listings will show relationship as missing.

Adverse events related to study procedures are those for which there are facts/arguments to suggest a reasonable possibility that there is a causal relationship of the AE to one or more study procedures.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those identified as serious in the clinical database.
The clinical database will be reconciled with the SAE database from the
Drug Safety and Public Health Department before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent

Treatment-emergent AEs are events that meet one of the following criteria:

- Any AEs with onset date of on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug.

7.1.5.2. Incomplete Dates

If the date of onset is incomplete, then the month and year (or year alone if month is not recorded) of onset determine treatment emergent as follows. The event is treatment emergent if the month and year of onset (or year of onset) of the event meets both of the following criteria:

- The same as or after the month and year (or year) of the first dose of study drug
- The same as or before the month and year (or year) of 30th day after the date of the last dose of study drug

If the start date is missing and the stop date is on or before the date of the last dose of study drug plus 30 days, then the event is considered treatment-emergent.

7.1.6. Summaries of Adverse Events and Deaths

A brief summary of AEs will show, by treatment group, the number and percentage of subjects who (1) had any treatment-emergent AE, (2) had any treatment-emergent moderate or severe AE, (3) had any treatment-emergent severe AE, (4) had any treatment-emergent treatment-related AE, (5) had any treatment-emergent treatment-related moderate or severe AE, (6) had any treatment-emergent treatment-related severe AE, (7) had any treatment-emergent SAE, (8) had any treatment-emergent treatment-related SAE, (9) permanently discontinued from study drug due to an AE, (10) had dose reduced or temporarily interrupted due to an AE, and (11) died during study.

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, HLT and PT. For other AEs described below, summaries will be provided by SOC and PT, and/or by PT as indicated:

- All treatment-emergent AEs by severity
- All treatment-emergent AEs (by PT)
- All treatment-emergent treatment-related AEs (and by PT)
- All treatment-emergent serious AEs (and by PT)
- All treatment-emergent treatment-related SAEs (and by PT)
- All treatment-emergent AEs that caused permanent discontinuation from study drug
- All treatment-emergent AEs that caused temporary interruption of study drug
- All treatment-emergent AEs that caused dose reduction of study drug
- All treatment-emergent AEs that caused permanent discontinuation from study
- All treatment-emergent AEs leading to death

Multiple events will be counted once only per subject in each summary. For data presentation, SOC and HLT will be ordered alphabetically, with PT sorted by decreasing total frequency. For summaries by severity grade, the most severe event will be selected. In addition to the presentation by SOC and HLT, all treatment-emergent AEs will also be presented by preferred term only, ordered by decreasing total frequency.

In addition to the by-treatment summaries, data listings will be provided for the following:

- All AEs (with a flag indicating whether the event is treatment-emergent)
- SAEs (including deaths)
- Subjects who became pregnant during the study
- AEs leading to discontinuation of study or study drug
- Severe AEs
- AEs leading to temporary interruption of study drug
- AEs leading to dose reduction
- AEs leading to death

7.1.7. Additional Analysis of Adverse Events

The following treatment-emergent adverse events of special interest will be summarized by preferred term:

- Cardiac failure (narrow standardized MedDRA queries [SMQ])
- Cardiac failure (broad SMQ)
- Syncope, dizziness, or vertigo. MedDRA Version 19.1 PTs include dizziness, dizziness exertional, dizziness postural, fall, loss of consciousness, presyncope, vertigo, and CANVAS syndrome.
- Convulsions (narrow SMQ)

7.2. Laboratory Evaluations

Laboratory data will be listed.

7.2.1. Graded Laboratory Values

There are no plans to assign toxicity grade to clinical laboratory results in this study. A separate listing of treatment-emergent laboratory abnormalities will be provided. Treatment-emergent laboratory abnormalities are defined as values that are normal at baseline (on or within the reference range bounds) and abnormal post-baseline (outside of the reference range bounds).

If the baseline value is missing and the post-baseline value is abnormal, the abnormality will be considered treatment-emergent. Laboratory abnormalities during the screening visit will be included in the laboratory data listings only.

Laboratory abnormalities may be reported as AEs, and as such the investigator will assign severity grade to each, and the events will be included in the AE summaries.

7.3. Body Weight and Vital Signs

Vital signs and body weight at each visit and their change from baseline values will be summarized for the safety analysis set using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum, and maximum) by treatment group for each post-baseline analysis visit. Baseline body weight and height will be summarized in the baseline and demographics table. The vital signs listing will include body weight, height, BMI, blood pressure, respiratory rate, and pulse.

7.4. Vital Signs from CPET

Vital signs are collected as part of the CPET. The vital sign values from the CPET (resting, peak, and 2-minute recovery) will be presented in the listings.

7.5. Prior Medications

Prior medications are defined as any medications taken before a subject took the first study drug. Prior medications will be coded using the World Health Organization (WHO) Drug Dictionary. The WHO preferred name and Anatomical Therapeutic Chemical (ATC) code and classes will be attached to the clinical database.

Any medication with a start date prior to the first dosing date of study drug will be classified as a prior medication regardless of when the stop date is. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be classified as prior medications.

7.6. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Concomitant medications will be coded using the WHO Drug Dictionary. The WHO preferred name and drug code will be attached to the clinical database.

Any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug will not be considered concomitant medications. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will not be classified as concomitant medications. Medications with completely missing start and stop dates will be considered concomitant medications.

Prior and concomitant medications will not be summarized. All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.7. Electrocardiogram Results

The following analyses of 12-lead ECG results are intended to identify gross changes in QT interval and other ECG characteristics. If potential abnormalities of interest are identified, further analyses may be conducted. Summaries of continuous ECG results (RR, PR, QRS, QT, and QTcB) will be provided for the safety analysis set using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum, and maximum) by treatment group for each post-baseline analysis visit.

7.7.1. Corrected QT Intervals

The QT interval (measured in msec) will be corrected for heart rate as indicated in Section 3.7 using Bazett's formula.

QTcB, and uncorrected QT values at each visit and change from baseline at each visit will be summarized for the safety analysis set by treatment group using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum, and maximum).

7.7.2. Prolonged QT Intervals and QT, PR and QRS Intervals

The number (%) of subjects with core laboratory ECG values, and change from baseline in the ranges shown in the table below will be summarized by treatment group at each visit.

PR Interval (msec)	QRS Interval (msec)	QT_cB (msec)	QT_cB Change from Baseline (msec)
< 200	< 120	> 450	< -60
≥ 200	≥ 120	≥ 480	≥ -30
≥ 220		≥ 500	≥ 0
			≥ 30
			≥ 60

Categorical ECG abnormalities (borderline and prolonged QTcB, PR ≥ 200, PR ≥ 220, QRS ≥ 120, QTcB > 450, QTcB ≥ 480, QTcB ≥ 500, QTcB change from baseline ≥ 30, QTcB change from baseline ≥ 60) will be flagged in the corresponding listing.

7.7.3. Investigator Assessment of ECG Readings

A by-subject listing for ECG assessment results will be provided by subject ID number and visit in chronological order.

7.8. Continuous ECG Results from ZIO® XT Patch

Continuous ECG monitoring results from ZIO® XT Patch worn during the 14-day baseline period (prior to randomization), Days 1 to 14, Weeks 6 to 8, and Weeks 18 to 20 will be analyzed as indicated in Section 6.5.1.

7.9. Other Safety Measures

The number of subjects who died or who experienced at least 1 adjudicated appropriate ICD intervention (shock or anti tachycardia pacing) will be summarized by treatment group for subjects with an ICD. A data listing will be provided for adjudicated ICD interventions (shocks or anti-tachycardia pacing).

A data listing will be provided for subjects experiencing pregnancy during the study.

7.10. Changes From Protocol-Specified Safety Analyses

Laboratory data, concomitant medication data, vital signs from CPET, and ECG overall assessments will not be summarized.

8. PHARMACOKINETIC ANALYSES

Plasma and urine concentrations of eleclazine and metabolite GS-623134 will be listed.

8.1. Changes From Protocol-Specified PK Analyses

Concentrations will not be summarized. Correlations between plasma concentrations and primary and secondary endpoints will not be explored.

9. REFERENCES

Firoozi S, Elliott PM, Sharma S, Murday A, Brecker SJ, Hamid MS, et al. Septal myotomy-myectomy and transcoronary septal alcohol ablation in hypertrophic obstructive cardiomyopathy. A comparison of clinical, haemodynamic and exercise outcomes. Eur Heart J 2002;23 (20):1617-24.

10. SOFTWARE

SAS® Software Version 9.1. SAS Institute Inc., Cary, NC, USA.

nQuery Advisor(R) Version 6.0. Statistical Solutions, Cork, Ireland.

11. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision
10 May 2017	All	Changed GS-6615 to eleclazine	Consistency with other eleclazine studies
	1	Updated introduction to indicate that synoptic report will be written.	Synoptic Report
	2, 3, 7	Removed reference to 2 database freezes	Synoptic Report
	3.1.3, 4.1	Removed reference to Per Protocol (PP) Analysis	Synoptic Report
	3.4, 6.3, 6.4.2	Removed subset analyses	Synoptic Report
	3.5, 6.5.2, 6.7	Removed references to sequential step-down testing; removed significance testing for exploratory endpoints	Synoptic Report
	3.7.6.4.1	Added details on calculation of MLHFQ if items are missing	Clarification
	3.7, 3.8.2, 7.2	Removed reference to laboratory data summaries	Synoptic Report
	4.3.2	Removed adherence to study drug summaries	Synoptic Report
	4.2	Removed reference to OLE; added week 24	Study stopped prior to OLE period
	3.1.3, 3.1.4, 3.8.2, 4.4, 7.1.3	Updated for consistency with new SAP template	Consistency with other studies
	6.3	Interaction term removed	FDA feedback
	6.3, 6.7	Removed reference to imputation methods	Synoptic Report
	6.3, 6.4.2, 6.7, 8	Removed reference to sensitivity analyses	Synoptic Report
	6.5.1	Removed some exploratory endpoint analyses	Synoptic Report
	6.6, 7.10	Updated	Synoptic Report
	7.1.7	Added summaries for AEs of special interest	Consistency with other eleclazine studies
	7.5, 7.6	Updated definition of prior medications to medications taken prior to first dose and specified how to handle partial or missing start dates	Consistency with other eleclazine studies and clarification
	7.4	Removed CPET vital signs summary table	Synoptic Report

	7.5, 7.6	Removed reference to medication summaries	Synoptic Report
	7.7.3	Removed ECG summary table	Synoptic Report
	7.9	Removed time to event summary table	Very few events
	8	Removed reference to summary tables	Synoptic Report
	Appendix 1, Appendix 2	Removed appendix with list of tables, figures, and listings and appendix with SAS code	Per current SAP template, appendices part of separate document

12. APPENDICES

Appendix 1. Study Procedures Table

Appendix 1. Study Procedures Table

	Screening Period		Double-Blind Treatment Period						OLE	Follow-up
	Screening Visit	Randomization Visit	Week 2 Visit	Week 6 Visit	Week 12 Visit[a]	Week 18 Visit	Week 24 Visit[a]	Every 12 Weeks after Week 24 through EDBT Visit	Visits at OLE Weeks 12, 24, & Then Every 24 Weeks	30-day Follow-up Visit or ET Visit[b]
	Day -28 to Day -14	Day 1	Day 14 ± 3 days	Day 42 ± 7 days	Day 84 ± 7 days	Day 126 ± 7 days	Day 168 ± 7 days			
Written Informed Consent	X									ET only[b]
Inclusion/Exclusion Criteria Review	X	X								
Medical History	X									
Physical Exam[c]	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X
Study Drug Dosing During Visit[d]		X	X	X	X	X	X	X	OLE Wk 12 & OLE Wk 24 only	
MLHFQ[e]		X			X		X			ET only[g]
Perception of Treatment Assignment Questionnaire[f]							X			ET only[g]
12-Lead resting ECG	X	X	X	X	X	X	X	X	X	X
CPET/Peak VO_2 Measurement	X				X		X			ET only[g]
Echocardiogram	X		X		X		X			ET only
ICD Interrogation		X			X		X			ET only[g]
Clinical Laboratory Assessments[h]	X		X	X	X	X	X	X	X	X
Pregnancy Test[i]	X	X	X	X	X	X	X	X	X	X
PK Sample Collection		X[j]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X[k,l]	X[l]
NT-proBNP & hsTnT	X				X		X			
Optional PG Sample Collection[m]		X								
Start ZIO® XT Patch (14 Day Wear)	X	X		X		X				
Collect ZIO® XT Patch		X	X		X		X			

	Screening Period		Double-Blind Treatment Period						OLE	Follow-up
	Screening Visit	Randomization Visit	Week 2 Visit	Week 6 Visit	Week 12 Visit[a]	Week 18 Visit	Week 24 Visit[a]	Every 12 Weeks after Week 24 through EDBT Visit	Visits at OLE Weeks 12, 24, & Then Every 24 Weeks	30-day Follow-up Visit or ET Visit[b]
	Day -28 to Day -14	Day 1	Day 14 ± 3 days	Day 42 ± 7 days	Day 84 ± 7 days	Day 126 ± 7 days	Day 168 ± 7 days			
Dispense Study Drug		X	X	X	X	X	X	X	X	
Study Drug Accountability & Compliance			X	X	X	X	X	X	X	X[n]
Contact Subject[o]									X[p]	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X

a Recommended order of assessments at Week 12 and Week 24 visits: (1) predose PK sample collection, (2) witnessed study drug dosing, (3) MLHFQ, (4) ECG, (5) CPET, (6) ECHO, and (7) all other blood sample collection including postdose PK sample. All other required visit assessments may occur at any point during the study visit. For Week 24 visit only: For some subjects, Week 24 visit is the same as the End of Double-Blind Treatment Period Visit

b If a subject prematurely discontinues study participation before completing the 24 Week treatment period, the subject will be asked to return to the study center for the Early Termination (ET) Visit. The ET Visit should be performed as soon as possible. Informed consent for future contact and collection of vital status will be obtained.

c Complete PE including body weight and height measurements, and BMI calculation at Screening, abbreviated PE at all other visits.

d At visits where study drug dosing occurs on site, the first PK sample should be collected before the subject has taken the daily dose of study drug.

e It is very important that MLHFQ administration occurs prior to CPET.

f The Perception of Treatment Assignment Questionnaire will be administered only after completion of MLHFQ. Subjects should complete the questionnaire after all other assessments and interactions that may bias their responses.

g Complete at Early Termination visit for subjects who prematurely discontinued prior to Week 24 visit

h Hematology, Serum Chemistry and Urinalysis will be assessed at all visits where clinical laboratory assessments are performed. eGFR (and upon request FSH, estradiol, and progesterone) will be assessed at Screening only.

i Females of Child-Bearing Potential only. Serum pregnancy test at Screening and urine pregnancy test at all other visits.

j Day 1 PK samples collected predose and 2-3 hours postdose, if 2-3 hours postdose is not possible postdose sample should be collected as late as possible before subject leaves the site.

k At all post randomization visits through OLE Week 24, plasma and urine PK samples are collected predose and plasma PK sample is 3 hours postdose, if 3 hours postdose is not possible postdose plasma PK sample should be collected as late as possible before subject leaves the site.

l Single PK sample collected at each open-label extension visit starting at OLE Week 48 and at the 30-day Follow-up visit or ET visit, if applicable.

m Optional pharmacogenomic sample should be drawn at Randomization visit, but may be collected at any time during the study or at a separate post study visit, if necessary.

n ET visit only, when applicable

o Contact subject at Week 1 (Day 7 ± 3), Week 9 (Day 63 ± 3), Week 15 (Day 105 ± 3 days), Week 21 (Day 147 ± 3 days) to review, adverse events and concomitant medications and to remind the subject to hold study drug dose on the day of the next visit so subject can take the study drug while on site. During Week 1 contact, also review ongoing ZIO® XT Patch wear. During Week 9 and Week 21 contacts, also review ZIO® XT Patch use/removal and remind the subject of the CPET restrictions on the day of the next visit.

p Contact subject at OLE Week 1 to review adverse events and concomitant medications. Additional subject contacts between OLE visits are at investigator discretion.