MEDPACE

Statistical Analysis Plan: C1973-204-01

Version 1.0, 13 June 2019

Study Title:	A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study Evaluating the Safety and Efficacy of Different Doses of IW-1973 over 12 Weeks in Patients with Heart Failure with Preserved Ejection Fraction (CAPACITY HFpEF)
Study Number:	C1973-204
Protocol Version:	Amendment 3, 27 June 2018
Product Name:	IW-1973 (Praliciguat) Tablet
Sponsor:	Cyclerion Therapeutics, Inc. (formerly part of Ironwood Pharmaceuticals, Inc.) 301 Binney Street Cambridge, MA 02142
SAP Version/Date:	1.0, 13 June 2019

SIGNATURE PAGE

A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 2 Study Evaluating the Safety and Efficacy of Different Doses of IW-1973 over 12 Weeks in Patients with Heart Failure with Preserved Ejection Fraction (CAPACITY HFpEF)

Study Number: C1973-204

We, the undersigned, have reviewed and approve this Statistical Analysis Plan.

Signature | Date

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Medpace, Inc.

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Cyclerion Therapeutics

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Cyclerion Therapeutics

VERSION HISTORY

Version	Date	Description
1.0	13JUN2019	Original signed version

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LIST OF ABBREVIATIONS

Abbreviation	Full Term
6MWT	6-minute walk test
AE	Adverse event
AECI	TEAEs of Clinical Interest
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
BLQ	Below limit of quantification
BMI	Body mass index
CDF	Cumulative distribution function
CMH	Cochran-Mantel-Haenszel
CPET	Cardiopulmonary exercise test
CSS	Clinical summary score
CV	Coefficient of variation
DMC	Data Monitoring Committee
EF	Ejection fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HOMA	Homeostatic Model Assessment
HRQOL	Health-related quality of life
ICF	Informed consent form
IWRS	Interactive web response system
ITT	Intent-to-Treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	Left ventricular
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
NYHA	New York Heart Association
OSS	Overall summary score
PT	Preferred term
[redacted]	[redacted]
QOL	Quality of life

Abbreviation	Full Term
RER	Respiratory exchange ratio
SAE	Serious adverse event
SAP	Statistical analysis plan
[redacted]	[redacted]
SOC	System organ class
TAPSE	Tricuspid annular place systolic excursion
TEAE	Treatment-emergent adverse event
TSS	Total symptom score

1. INTRODUCTION

Study C1973-204 is a Phase 2, randomized, double-blind, placebo-controlled, parallel-group study in approximately 184 patients with established heart failure and limited exercise capacity with ejection fraction (EF) of at least 40%, and who have at least 2 of 4 risk factors for HFpEF (diabetes/prediabetes, hypertension, obesity, advanced age) to assess the safety and efficacy of IW-1973 (praliciguat) administered daily for approximately 12 weeks compared with placebo.

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the data presentations and statistical analyses of the efficacy and safety data as outlined and/or specified in the final protocol for Study C1973-204 (C1973-204-Amendment 3, dated 27 June 2018). Specifications for selected tables, figures, and data listings are contained in a separate document.

2. STUDY OBJECTIVES

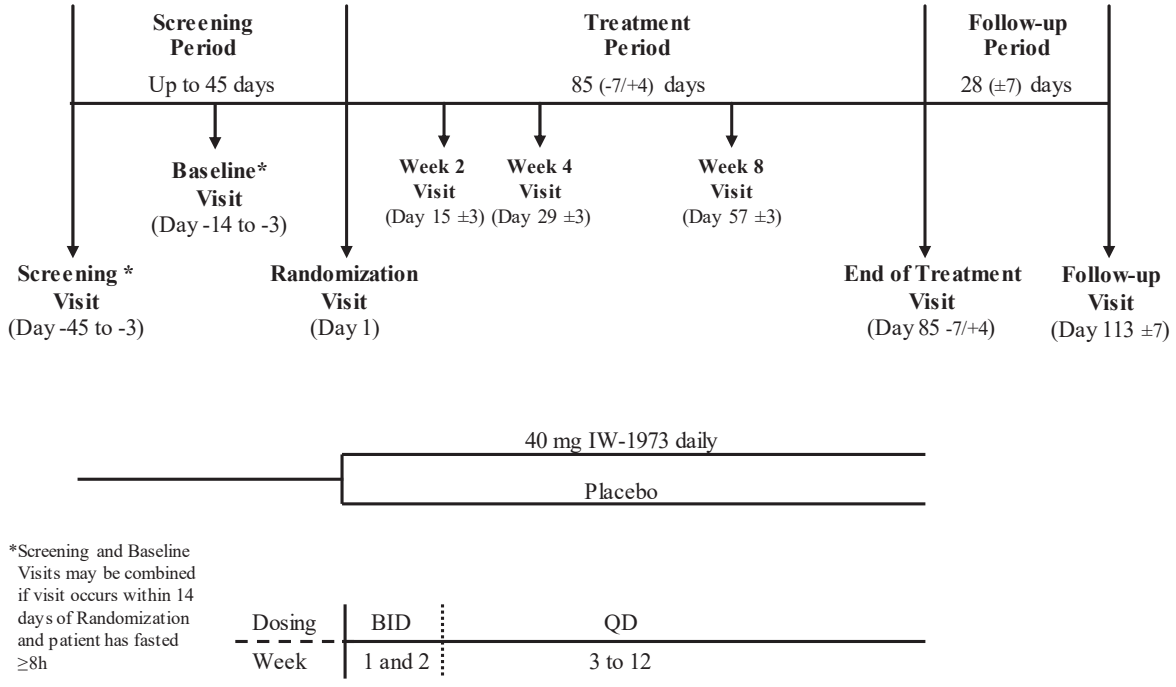
Primary Safety	To assess the safety of oral praliciguat when administered for approximately 12 weeks to patients with HFpEF
Primary Efficacy	To evaluate the effect of oral praliciguat on peak exercise capacity when administered for approximately 12 weeks to patients with HFpEF, both in all patients and in patients without permanent or persistent atrial fibrillation
Secondary Efficacy	To evaluate the effect of oral praliciguat on exercise and functional capacity when administered for approximately 12 weeks to patients with HFpEF
Exploratory Efficacy	[redacted]
Exploratory Pharmacokinetics (PK)	

3. STUDY DESIGN

3.1 GENERAL DESCRIPTION

Study C1973-204 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group 12-week study to evaluate the safety and efficacy of praliciguat compared with placebo. The study will enroll approximately 184 adult patients with established heart failure and limited exercise capacity with EF of at least 40% and who have at least 2 of 4 risk factors for HFpEF (diabetes/prediabetes, hypertension, obesity, advanced age). Patients will be stratified by atrial fibrillation status and by baseline peak VO_2 (<60% or ≥60% of age- and sex-adjusted normal values with respiratory exchange ratio [RER] ≥1.0 as determined by cardiopulmonary exercise test [CPET]), Starting with Amendment 3, patients will be randomized in a 1:1 ratio to daily 40 mg praliciguat or placebo for approximately 12 weeks. Patients randomized through Amendment 2 or earlier were randomized in a 1:1:1:1 ratio to 3 daily doses of praliciguat (10 mg, 20 mg, 40 mg) or placebo. Patients will receive daily oral study drug for up to 89 days. Total patient participation will be 109 to 165 days.

Figure 1: Overview of Study Design



3.2 TREATMENTS ADMINISTERED

The following dosage and dosing regimen will be administered during the 12-week double-blind treatment period for patients randomized (1:1 ratio) to either 40 mg praliciguat or placebo.

Table 1. Dose Regimen by Week

Dose	Weeks 1 and 2, BID Dosing	Weeks 3 through 12, QD Dosing
40 mg	one 20 mg praliciguat Tablet, orally twice daily	two 20 mg praliciguat Tablets, orally once daily
Placebo	one matching placebo tablet, orally twice daily	two matching placebo tablets, orally once daily

- BID=twice daily; QD=once daily

Per Investigator discretion and consultation with the Medical Monitor, patients will be allowed to reduce his or her daily dose by half, ie, from 2 tablets daily to 1 tablet daily. Each patient's dose may only be reduced once and will not be increased after reduction.

3.3 RANDOMIZATION AND BLINDING

Approximately 184 patients who meet all the inclusion criteria and none of the exclusion criteria will be stratified by permanent/persistent atrial fibrillation status (yes or no) and by baseline peak VO_2 (<60% or ≥60% of age- and sex-adjusted normal values and with RER ≥1.0 as determined by CPET) and randomized 1:1 to 40 mg praliciguat or placebo at the Randomization Visit on Day 1 through a centralized interactive web response system (IWRS). An upper limit of approximately 36 patients with permanent or persistent atrial fibrillation will be set in the IWRS. The randomization schedule was prepared by an independent statistician using SAS® PLAN procedure (PC SAS® Version 9.3 [1]) using a block size of 4. The lowest randomization number within a stratum will be assigned to the first patient that qualifies for randomization and subsequent assignments will proceed in increasing sequential order within a block as patients are qualified for the study.

This is a double-blind, placebo-controlled study in which the patients, investigators, study staff and the sponsor study team will remain blinded to the randomization scheme until the blind is formally broken for all subjects after all subjects have completed the study and the study database is locked.

Please refer to Section 5.5 for details on the external Data Monitoring Committee's (DMC) review of masked and potentially unblinded safety data to monitor trial safety.

Prior to database lock, a treatment assignment may be unblinded by the site only in emergency situations and/or by the Sponsor Safety group if the knowledge of the treatment received is essential for managing a serious adverse event (SAE).

3.4 STUDY SCHEMATIC AND SCHEDULE OF ASSESSMENTS

The schedule of evaluations for Study C1973-204 is presented in Table 2.

Table 2. Schedule of Events

Visit Days → Study Procedure ↓	Screening Period		Treatment Period					FU Period
	Screening Visit* (Day -45 to -3)	Baseline*Visit (Day -14 to -3)	Randomization Visit (Day 1)	Week 2 Visit (Day 15 ±3)	Week 4 Visit (Day 29 ±3)	Week 8 Visit (Day 57 ±3)	Week 12/ EOT Visit (Day 85 -7/+4)	FU Visit (Day 113 ±7)
ICF signed	X							
Demographics	X							
Medical history	X							
Inclusion/exclusion	X	X	X					
Prior & concomitant medications and procedures	X	X	X	X	X	X	X	X
Physical exam (a)	complete	pre CPET	predose	predose	predose	predose	predose	complete
Vital signs (BP, pulse, RR, & oral temperature) (b)	X	pre CPET	pre: 0 (≤1h) pd: 1,3,4h (±20m)	pre: 0 (≤1h) pd: 1,3,4h (±20m)	pre: 0 (≤1h)	pre: 0 (≤1h)	pre: 0 (≤1h)	X
Weight, height	W, H	W	W	W	W	W	W	W
NYHA classification	X		X				X	X
Hepatitis, HIV screen	X							
Urine drug screen	X							
Urine pregnancy (c)	X	pre CPET	predose	predose	predose	predose	predose	X
Urinalysis sample (d)	X		predose	predose	predose	predose	predose	X
Serum chemistry, CBC, coagulation (d)	X	pre CPET	predose	predose	predose	predose	predose	X
Hemoglobin A1c	X	pre CPET				predose	predose	X
12-lead ECG (e)	X	pre CPET	predose	predose	predose	predose	predose	
Adverse events	X	X	X	X	X	X	X	X
CPET (f)		X				postdose >1h (or ±3 days) (f)	postdose >1h	
6MWT (g)		post CPET >1h				post CPET >1h (g)	post CPET >1h	
NT-proBNP sample (d,h)	X (if needed)	pre CPET					predose	
Echocardiography (i)	X (if needed)	X (for baseline)					X	

Visit Days → Study Procedure ↓	Screening Period		Treatment Period					FU Period
	Screening Visit* (Day -45 to -3)	Baseline*Visit (Day -14 to -3)	Randomization Visit (Day 1)	Week 2 Visit (Day 15 ±3)	Week 4 Visit (Day 29 ±3)	Week 8 Visit (Day 57 ±3)	Week 12/ EOT Visit (Day 85 -7/+4)	FU Visit (Day 113 ±7)
Fasting plasma glucose & insulin (d)		pre CPET	predose			predose	predose	X
[redacted]								
UACR sample supplies dispensed		X				X		
First-void urine samples (j)			preVisit				preVisit	
[redacted]								
Pharmacokinetic blood samples			predose pd:1,2,4h (±20m)	predose pd:1,2,4h (±20m)	predose	predose	predose pd:1,2,4h (±20m)	X
[redacted]								
Orthostatic (sitting to standing) pulse, BP (k)			pre: 0 (≤1h) pd: 2,4h (±20m)	pre: 0 (≤1h) pd: 2,4h (±20m)			pre: 0 (≤1h)	
Randomization			X					
Study drug dispensed			X	X	X	X		
In-clinic study drug (l)			X	X	X	X	X	
Study drug return				X	X	X	X	
Study completion								X

6MWT=6-minute walk test; BP=blood pressure; CBC=complete blood count; CPET=cardiopulmonary exercise test; CV=cardiovascular; ECG=electrocardiogram; EOT=end of treatment; [redacted] FU=follow-up; h=hour; H=height; HIV=human immunodeficiency virus; ICF=informed consent form; [redacted] NT-proBNP=N-terminal pro B-type natriuretic peptide; NYHA=New York Heart Association; opt=optional; pd=postdose; pre=predose; QD=once daily; [redacted] RR=respiratory rate; [redacted] UACR=urine albumin creatinine ratio; W=weight

* Screening and Baseline Visits may be combined if the visit occurs within 14-day period before Randomization and if patient has fasted ≥8h. With prior approval from the Sponsor's Medical Monitor, the Screening and Baseline Visits can be combined and can occur 1 day prior to the Randomization Visit; in these instances, local laboratory values can be used to determine study eligibility, with duplicate samples sent to the Central laboratory for inclusion in the study database. Patients must have fasted for ≥8 hours prior to collection of the laboratory samples.

a. For Treatment Period visits, physical exam may be symptom directed or limited to cardiovascular system at the Investigator's discretion.
b. For eligibility at the Screening and Randomization Visits, BP will be the average of 3 measurements obtained at approximately 2-m intervals after the patient has been sitting quietly for ≥5 m; otherwise, 1 measurement after the patient has been sitting quietly for ≥5 m.
c. For female patients, a pregnancy test (by urine dipstick) must be documented at all visits and confirmed negative before dosing when applicable. Pregnancy tests are not required for female patients who are postmenopausal (no menses for ≥12 consecutive months) or surgically sterile (ie, bilateral oophorectomy, hysterectomy, or tubal sterilization [tie, clip, band, or burn]).
d. Pre CPET and predose samples require ≥8-h fast; fasting not required for the Screening Visit unless combined with Baseline Visit; blood collections after ECG or ≥10 m before ECG, when applicable. [redacted]
e. Patients must be supine for ≥5 minutes before the ECG recording. ECGs conducted before blood collections or ≥10 m after blood collections, when applicable.
f. CPETs should be performed at the same time of day (±2 h) and be timed to occur at ≥1 h postdose, when applicable. CPET will precede 6MWT by ≥1 h, when applicable. The Week 8 CPET can be conducted on a separate day (±3 days) from the other Week 8 assessments, as dictated by logistical considerations.
g. When applicable, 6MWT must be performed ≥1 h after CPET.
h. At Screening Visit only if needed for eligibility determination.
i. Echocardiography may be performed at the Screening Visit to confirm eligibility; if performed at the Screening Visit, it can be used for baseline and does not need to be repeated at the Baseline or Randomization Visit. If not performed at the Screening Visit, echocardiography for baseline may be performed at either the Baseline or Randomization Visit. Echocardiography performed at Baseline and EOT Visits must be before or ≥1 h after exercise (CPET, 6MWT).
j. One patient-collected, first-void urine sample from the morning before or the morning of the scheduled visit. Patients will be supplied with specimen collection supplies at the preceding study visit.
k. Patient must sit quietly for ≥5 m before sitting BP and pulse measurements are taken, and then assume standing position for 2 m (±1 m) before standing BP and pulse measurements are taken.
l. Study drug will be administered in the clinic on study visit days after predose assessments. On Day 1, only the morning dose will be administered in clinic. For at home dosing, patients will be instructed to take study drug with water at approximately the same time each day. Patients may take with or without food and, for QD dosing (Week 2 Visit onward), may swallow the 2 tablets together.

4. DETERMINATION OF SAMPLE SIZE

The study is not designed to formally test a single statistical hypothesis; however, approximately 184 subjects will provide approximately 90% power to detect a mean difference of 1.3 (mL O_2/kg/min) between the 40 mg praliciguat treatment arm and the placebo treatment arm in change from baseline at Week 12 peak VO_2. This estimate is based on the Evaluable Population (defined in Section 6.1), including patients with permanent or persistent atrial fibrillation at Screening, and using the follow assumptions:

- 5% Type I error for a 2-sided test
- Mean Peak VO_2 change from baseline at Week 12 for Placebo arm is 0.0 (mL O_2/kg/min)
- Mean Peak VO_2 change from baseline at Week 12 for 40 mg praliciguat is 1.3 (mL O_2/kg/min)
- Equal standard deviation for all treatment arms at 2.5 (mL O_2/kg/min) for change from baseline at Week 12
- 10% attrition prior to Week 12 CPET
- 10% of the total number of patients were randomized to either the 10 or 20 mg praliciguat dose groups under Amendment 2 of the protocol (or earlier)
- Reduced treatment effect for praliciguat in subjects with permanent or persistent atrial fibrillation at Screening

Additionally, under similar assumptions, this sample size will also provide 90% power to detect a mean difference of 1.5 (mL O_2/kg/min) on the same endpoint on the well-defined subgroup of a minimum of approximately 148 patients without permanent or persistent atrial fibrillation at Screening.

5. STATISTICAL METHODS

5.1 GENERAL METHODOLOGY

For descriptive summaries, the number of patients with non-missing values (n) for the summarized endpoint, mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum will be calculated for continuous variables. For summaries of continuous PK data, the geometric mean and the coefficient of variation (CV) will also be presented. For categorical variables, number and percentage of patients in each category will be presented. Percentages will be based on the total number of patients with non-missing values. If there are missing values, the number of missing values will be presented, but without a percentage.

All summary statistics will be presented by the treatment group (Placebo or Praliciguat 40 mg), unless otherwise specified. For subjects with dose reduction, the randomized treatment will be used for summary tables. Data for patients randomized to Praliciguat 10 mg or 20 mg under Amendment 2 or earlier will not be included in efficacy data analyses but will be included in disposition, demographic, adverse event and PK summaries by treatment group, as well as in subject data listings.

Data from screen failure subjects will be presented in subject data listings.

All hypothesis tests will be two-sided with a 5% significance level, and two-sided 95% confidence intervals will be used, unless otherwise specified.

All statistical analyses will be performed using SAS® Version 9.3 or later [1].

5.2 STUDY PERIODS

Table 3. Study Periods

Period	Start Date	End Date
Screening and Baseline	Date of Signed ICF	Up to Date/Time of First Dose (Exclusive)
Treatment	Date/Time of First Dose	Date of Last Dose
Follow-up	Date after Last Dose +1	Follow-up Visit Date

5.3 DEFINITION OF BASELINE

The following definition of baseline will be used, unless specified otherwise:

- Study baseline will be defined as the last non-missing assessment before first administration of study drug, usually the predose assessment on Day 1

5.4 HANDLING OF DROPOUTS OR MISSING DATA

All available data will be included.

For ANCOVA analyses, patients with missing change from baseline values will be excluded. No imputation will be performed for missing observations.

For responder analyses, all patients will be included. Patients with missing postdose data at an assessment timepoint will be treated as non-responders for that assessment timepoint

All safety and tolerability data will be summarized and analyzed when data values are available for a patient. Data handling for missing dates and other key safety data are described in Section 8.

5.5 INTERIM ANALYSIS AND DATA MONITORING

An independent DMC will be given the responsibility to review trial safety and provide guidance consistent with the objectives of the study and appropriate ethical requirements.

The DMC will comprise recognized experts in cardiovascular disease and one biostatistician who have experience in clinical trials and are not otherwise involved in the conduct of this trial. Their only role in this study will be as a member of the DMC, thus ensuring their independent review of safety data. The detail of DMC is documented in a separate DMC charter.

No additional unblinded interim analyses of efficacy (specified as optional in Protocol Section 5.14) will be performed.

5.6 MULTIPLE COMPARISONS/MULTIPLICITY

Due to the exploratory nature of this study, the analyses will focus primarily on estimation rather than inferential testing. No adjustment on the p-values for multiple testing is planned for this study. All reported p-values are considered nominal. A p-value ≤ 0.05 indicates that the 2 treatment samples are less likely to have been drawn from the same distribution by chance alone.

6. ANALYSIS METHODS

6.1 ANALYSIS POPULATIONS

The following populations will be defined for this study:

- **Screened Population:** All screened patients who have signed the informed consent form for the study and received a patient identification number.
- **ITT Population**: All randomized subjects. Patients in this population will be evaluated according to the treatment group they were assigned to at Randomization. However, all summary tables and efficacy analyses performed on this population will only include the treatment groups (placebo and 40 mg praliciguat) specified in the final amended protocol, unless specified otherwise.
- **Safety Population:** All randomized patients who take at least 1 dose of study drug. The Safety Population will be used for all safety assessments. In the event that a subject receives the wrong treatment, the actual treatment will be used. If a patient received more than 1 treatment, then the patient's data will be summarized according to the treatment they received for the longest duration. All summary tables performed on this population will only include the treatment groups (placebo and PRL 40 mg) included in the final amended protocol, unless otherwise specified.
- **Modified Intent-to-Treat (mITT) Population:** All patients in the ITT Population who take at least 1 dose of study drug and have at least 1 evaluable baseline measurement.
- **Evaluable Population**: All patients in the mITT who complete 8 weeks of dosing (±3 days) and have at least 1 evaluable postbaseline assessment and did not have a dose reduction. Other criteria, such as major protocol deviations that might have a potential impact on efficacy evaluations (see Section 6.2), may be established and reviewed before database lock and unblinding. The Evaluable Population will be the primary analysis population for the efficacy assessment.
- **PK Population:** All randomized patients who take at least 1 dose of praliciguat and have at least 1 postdose assessment with measurable PK concentration levels.

6.2 PROTOCOL DEVIATIONS

Major protocol deviations will be identified and documented for all randomized patients prior to unblinding through data reviews and programmatic checks of the study data, unless specified otherwise. Major protocol deviations will be determined based on review of all protocol deviations performed by members of the study team, including but not limited to the Sponsor

Medical Monitor and study biostatistician. The categories of major protocol deviations to be reviewed will include, but are not limited to, patients who:

- did not meet the following key inclusion/exclusion criteria
  - inclusion criterion #3 (patients with EF ≤ 35%)
  - inclusion criteria #4, 6, 9
  - exclusion criteria # 2, 4, 6, 8
- received disallowed medications postbaseline for ≥ 7 days prior to the Week 12 assessment, or received PDE5 inhibitors or nitroglycerine within 72 hours of the Week 12 assessment
- had overall study drug compliance rate ≤ 60% in the last 4 weeks of the treatment period or did not have measurable (non-BLQ) plasma concentration levels at the Week 8 and Week 12 predose assessments despite being randomized to praliciguat. The unblinded review of plasma concentration levels to identify such cases will be performed after database lock and study unblinding.
- dosing error likely to impact efficacy outcome measures

The number and percentage of subjects with major protocol deviations will be summarized by type of deviation and by treatment group for the ITT Population. All protocol deviations will be presented in a by-patient listing. Patients randomized to praliciguat 10 mg or 20 mg under Amendment 2 or earlier will not be included in the summary table but will be included in the listing.

6.3 DISPOSITION OF PATIENTS

The number of patients screened and screen-failed, along with the reason for screen failure will be presented for the Screened Population. Categorical summaries of patients randomized, included in each of the analysis populations, who completed the study, or who discontinued early (along with the reasons for discontinuation) will be presented by treatment group for the ITT Population. Subject disposition will also be summarized by investigational site within each geographical region. In addition, by-patient listings of patient disposition, including all patients who failed screening or terminated early, will be presented.

6.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Patient demographics [age, age category, sex, race, ethnicity, weight, height, BMI (defined as weight in kg divided by height in meters squared)], and baseline stratification factors (atrial fibrillation status, baseline peak VO_2 strata) will be summarized by treatment group and overall for the Safety (and ITT, if different), Evaluable, and mITT Populations.

6.5 MEDICAL HISTORY

Medical history, abnormalities and surgeries, reported and occurring prior to screening will be coded using MedDRA version 20.0 or newer. Categorical summaries will be presented by MedDRA system organ class (SOC) and preferred term (PT) by treatment arm and overall for the Safety Population. Patients will be counted once per SOC and PT.

6.6 PRIOR AND CONCOMITANT MEDICATIONS AND PROCEDURES

Prior medications will be defined as medicines taken or procedures performed on the patient prior to the date of first dose of study drug. Concomitant medications and procedures will be defined as medications taken or procedures performed on or after the date of first dose of study drug. Any medication taken or procedures performed after the date of last dose of study drug will not be considered concomitant for the purposes of analysis.

Reported medication will be coded using the World Health Organization (WHO) Drug Dictionary (WHO-DDE B2, Mar 2017 or newer) to their Anatomical Therapeutic Chemical (ATC) class and PT. Categorical summaries for both prior and concomitant medication use for each treatment group will be presented by ATC and PT for the ITT Population. Patients will be counted once per ATC and PT.

6.7 EXPOSURE AND DRUG COMPLIANCE

Exposure to study drug, calculated as the number of days from the first dose taken to the date of the last dose taken, inclusive, will be summarized by treatment group for the ITT Population. The total number of doses taken during the entire study will be calculated for each patient. Patient-years, defined as exposure to the study drug in years, will be summarized by treatment for the ITT Population.

In addition, a frequency table will be provided to display the number and percentage of subjects with exposure in the following categories:

- 1 to ≤2 weeks (1-14 days),
- >2 to ≤4 weeks (15-28 days),
- >4 to ≤8 weeks (29-56 days),
- >8 to ≤12 weeks (57-84 days), and
- >12 weeks (85 days or more).

Dosing compliance for the treatment period will be defined as the number of doses actually taken by a patient divided by the number of doses that were expected to be taken, multiplied by 100. The total number of doses actually taken will be calculated by subtracting the total number of tablets returned from the total number of tablets dispensed, divided by 2. For patients who had a dose reduction, the total number of actual doses taken from the date of dose reduction will be calculated as the difference between the total number of tablets dispensed and returned. The total number of doses expected to be taken is the number of days between the date of first dose taken and the date of end of treatment visit, inclusive. In addition, drug compliance for the intervals Randomization Visit up to Week 4 Visit, Week 4 Visit up to Week 8 Visit, and Week 8 Visit to Week 12 Visit will be presented. Patients will only be included in the intervals that they were on study (that is, the intervals that are prior to or contain the last dose date). Summaries will be presented by treatment arm and overall for the ITT Population.

Compliance rates will also be categorized as missing, <60%, ≥60% and <80%, ≥80% and ≤120%, and >120% and summarized by treatment group.

6.8 EFFICACY ANALYSES

6.8.1 Baseline Summaries for Efficacy Endpoints

Baseline efficacy parameters including peak VO_2 strata, atrial fibrillation strata, peak VO_2, 6-minute walk test (6MWT), NT-pro BNP, and KCCQ-physical limitations score (PLS), overall summary score (OSS) and clinical summary scores (CSS) will be summarized descriptively by treatment group for the Evaluable Population.

6.8.2 Primary Efficacy Endpoint

6.8.2.1 Definition of Endpoint

The primary efficacy endpoint, change from baseline in peak VO_2, as obtained from CPET at Week 12, will be used to evaluate the effect of praliciguat on peak exercise capacity. CPET measurements will be provided by an independent central CPET Core Lab.

6.8.2.2 Main Analytical Approach

Corresponding with the primary efficacy objective of the trial, the primary inference for hypothesis testing is the treatment difference between the placebo group and the 40 mg praliciguat group on the change from baseline in peak VO_2 at Week 12. The primary efficacy analysis will be conducted using the Evaluable Population using an analysis of covariance (ANCOVA) model with treatment group and atrial fibrillation stratification factor as categorical variable terms and baseline peak VO_2 value as a covariate. The null hypothesis of the test will be interpreted as equality between the placebo and 40 mg praliciguat groups, and rejection of the null hypothesis as evidence that the 40 mg praliciguat group has a greater effect on change from baseline in peak VO_2 than the placebo group. Data for patients randomized to 10 mg praliciguat or 20 mg praliciguat under Amendment 2 or earlier will not be included in the analysis.

Least squares means (LSMs) and 95% confidence intervals for each treatment group as well as LSM difference between the 40 mg praliciguat group and the placebo group will be presented, along with the corresponding confidence intervals and p-values.

Distribution assumptions of the models will be evaluated for evident departure from normality and non-constant variances by examining the model residuals. Upon examination of the model residuals, a suitable data transformation may be applied, and if the results of these analyses show consistency with those obtained from the original analyses, only results from the original analysis will be reported.

6.8.2.3 Additional Analysis of the Primary Efficacy Endpoint

Analysis of the primary efficacy endpoint will also be performed on a subset of the Evaluable Population, excluding patients who had permanent or persistent atrial fibrillation at baseline.

6.8.2.4 Sensitivity/Supportive Analysis

Table 4. Sensitivity/Supportive Analyses of Primary Efficacy Endpoint

Endpoint/Method	Description	Summary Method
mITT Population - LOCF	Repeat primary efficacy analysis using the mITT Population. A last-observation-carried-forward (LOCF) approach will be used to impute missing Week 12 assessments of change from baseline in peak VO2. Under the LOCF approach, the patient's previous value during the Treatment Period from Week 8 or earlier postbaseline assessments will be used in case of missing Week 12 assessments. In the case of premature discontinuation from the trial, the patient's last available value during the Treatment Period will be used. If no previous postdose value exists, a change-from-baseline value of "0" will be imputed.	Continuous Summary ANCOVA results for Week 12
Subset of mITT-LOCF	Repeat the mITT LOCF analysis on a subset of the mITT Population, excluding patients who had permanent or persistent atrial fibrillation at baseline	Continuous Summary ANCOVA results for Week 12
Evaluable Population With other covariates	If baseline imbalances are apparent for other parameters, include them in the model to adjust for variability	ANCOVA results for Week 12
Evaluable Population including geographic region	Repeat primary efficacy analysis including geographic region, as defined in Appendix 4 - Table 10, in the ANCOVA model.	Continuous Summary ANCOVA results for Week 12
Evaluable Population - Rank Transform	Performed only if there is evidence of non-normality. Change and baseline values will be ranked based on the normalization method of Blom with ties set to the mean. If the results of the sensitivity analysis show consistency with those obtained from the original analysis, only results from the original analysis will be reported.	
MMRM – Evaluable Population	Perform a mixed-effects model repeated measures (MMRM) analysis with change from baseline in peak VO_2 as the response variable, treatment, visit, treatment-by-visit interaction, and baseline atrial fibrillation status as fixed effects and baseline peak VO_2 as the covariate with unstructured as the variance-covariance structure. All available data will be included in the analysis. Please see code in Appendix 5.	Continuous Summary MMRM results

6.8.2.5 Graphical Presentation of Primary Efficacy Data

Least squares mean plots of change from baseline in peak VO_2 assessments over time, along with the corresponding 95% confidence intervals will be presented by treatment group.

In addition, cumulative distribution function (CDF) plots of the percent change from baseline values at Week 12 will be plotted by treatment group. To aid in the interpretation of the graphical representation of the CDF across treatments, a two-sample Kolmogorov-Smirnov test will be conducted.

6.8.3 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be used to evaluate the effect of praliciguat on exercise and functional capacity.

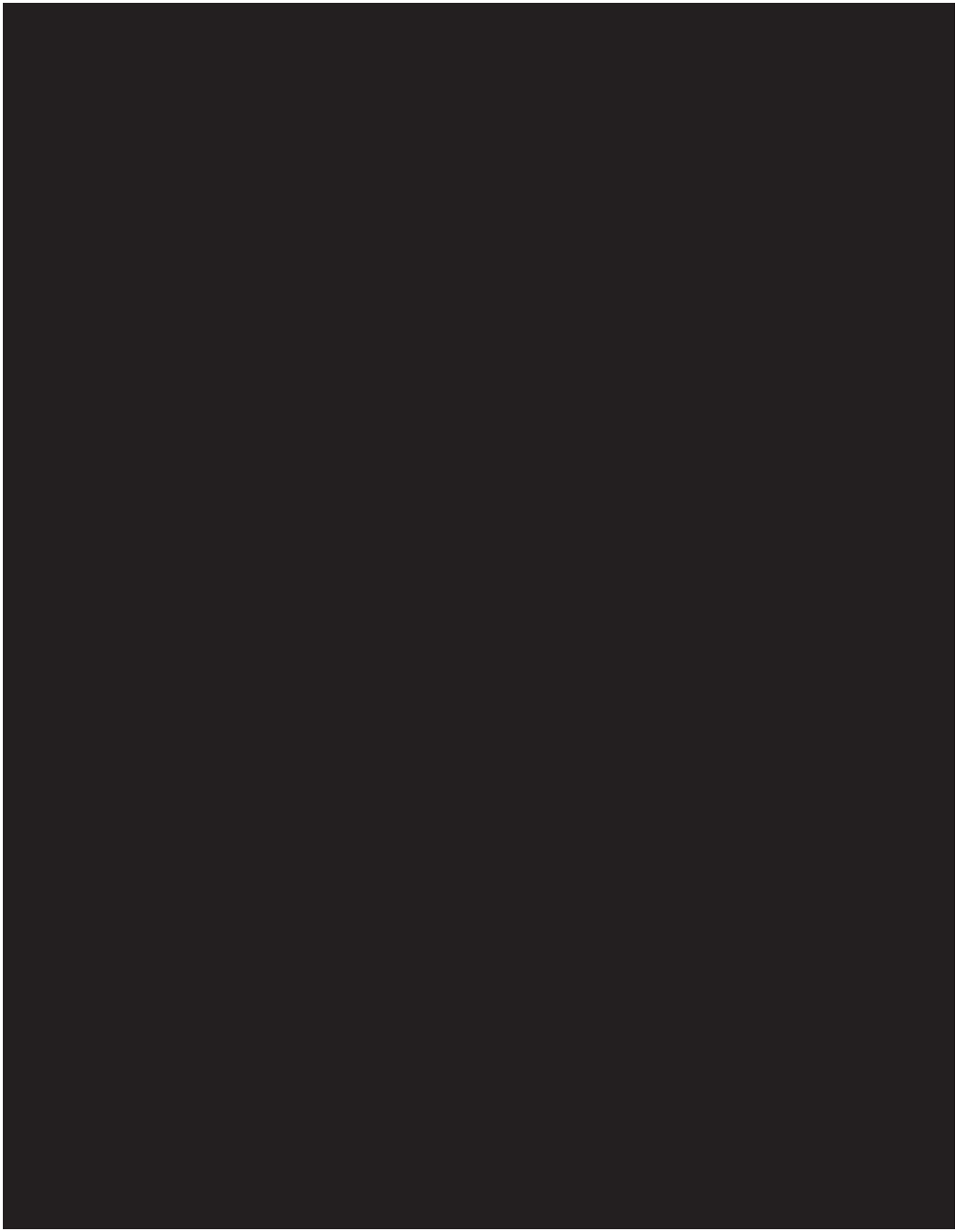
- Change from baseline in 6MWT distance at Week 12. 6MWT is a simple assessment of everyday functional capacity and provides a global evaluation of the organ/physiologic systems involved in exercise. The distance, in meters, travelled in 6 minutes, measured at approximately the same time of day will define the endpoint.

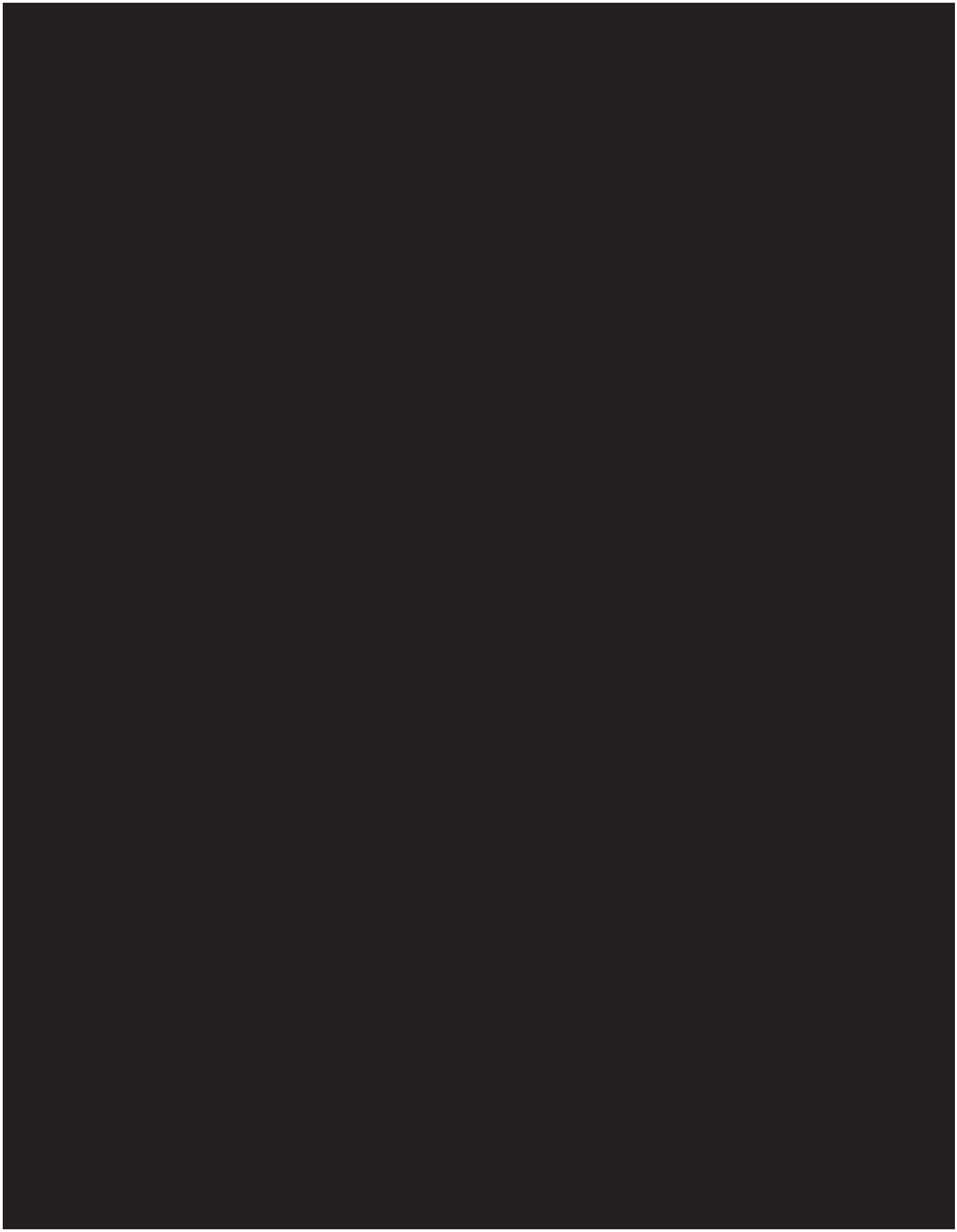
- Change in ventilatory efficiency as defined by VE/VCO_2 slope (minute ventilation/carbon dioxide production) obtained from CPET at Week 12. These values will be provided by an independent central CPET Core Lab

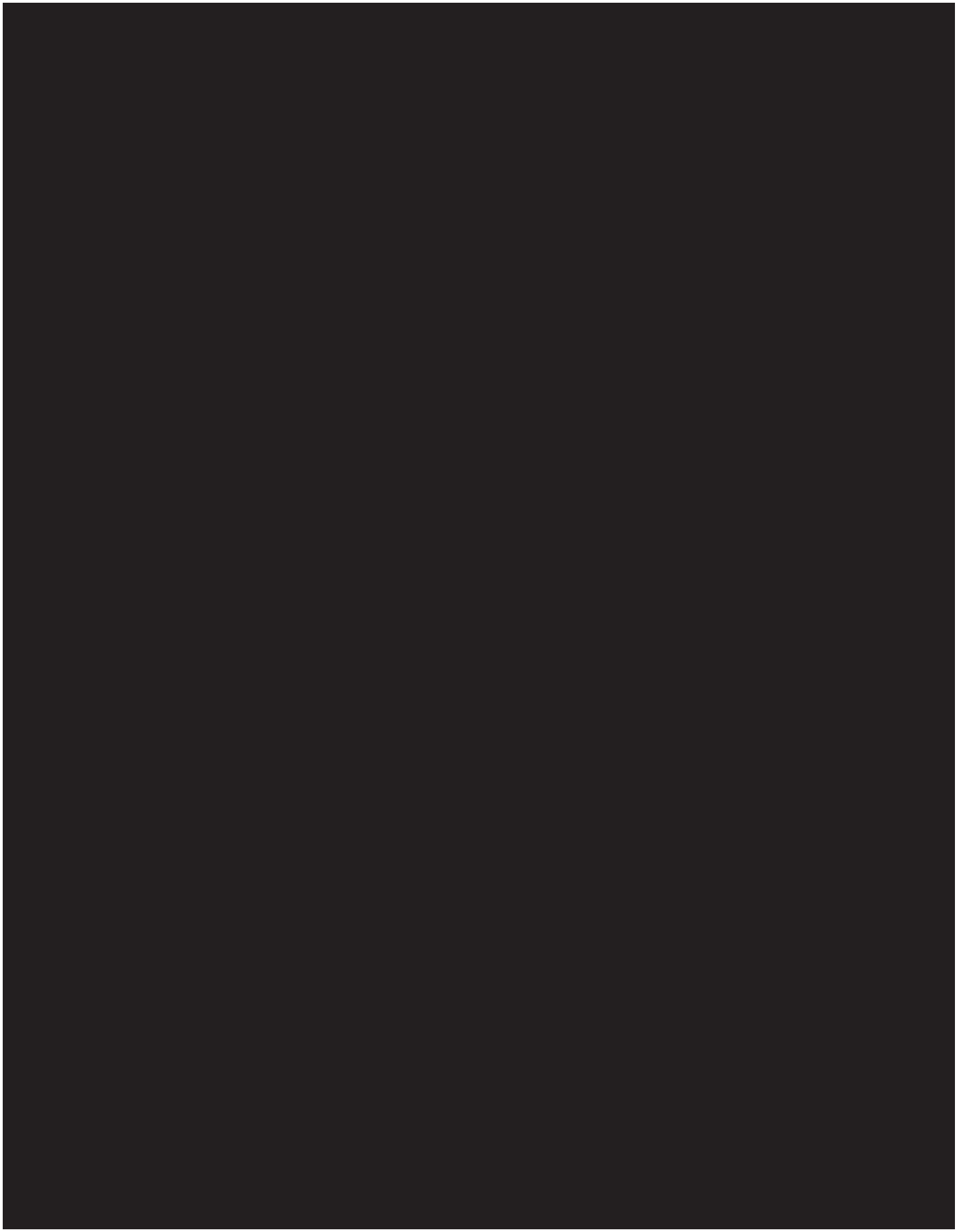
- CPET Responders, defined as patients who improve by at least 1.5 mL O_2/kg/min in peak VO_2 from baseline to Week 12. Patients who are hospitalized or who die due to heart failure during the study treatment period or who are missing Week 12 postdose values will be considered non-responders.

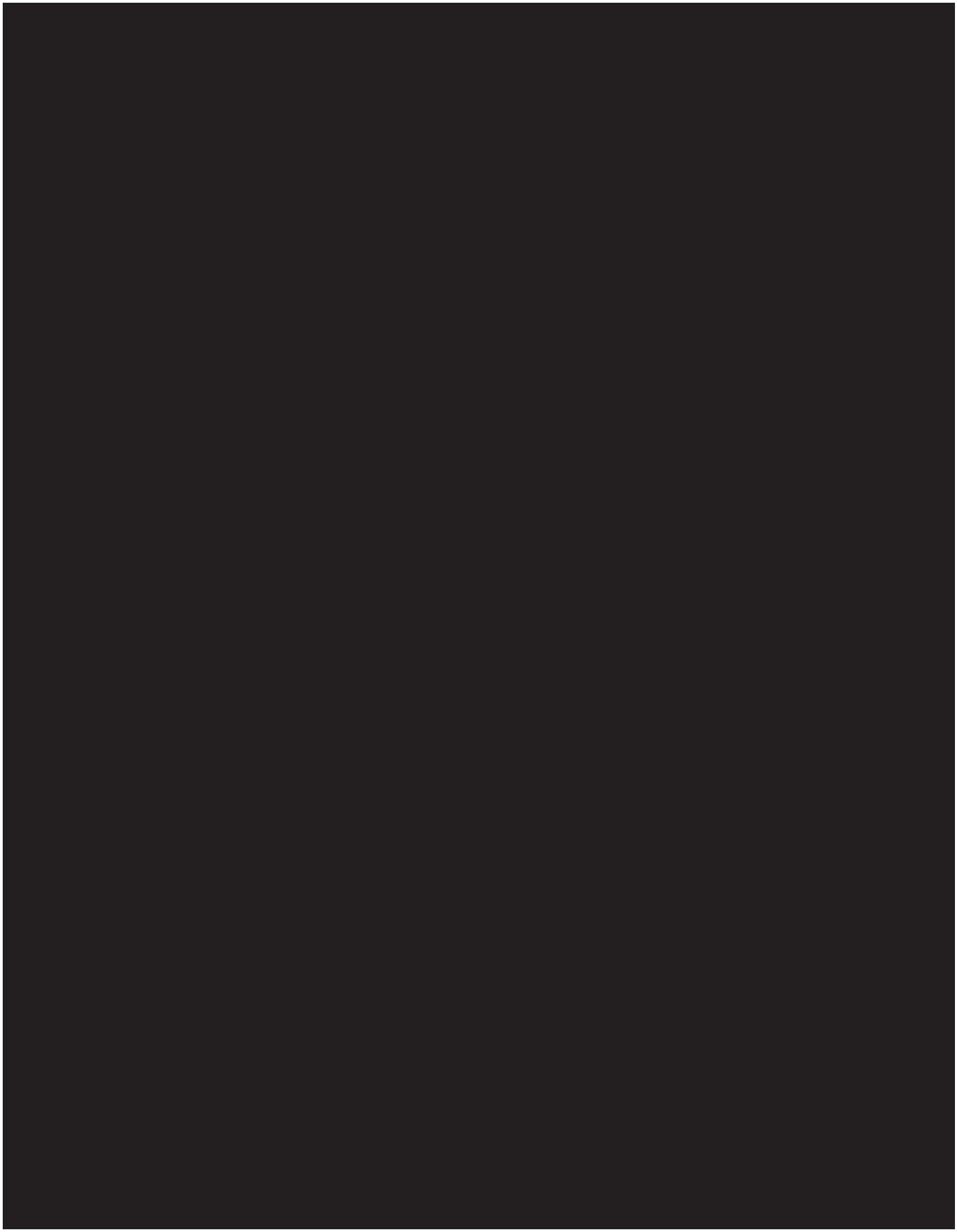
6.8.4 Exploratory Efficacy Endpoints

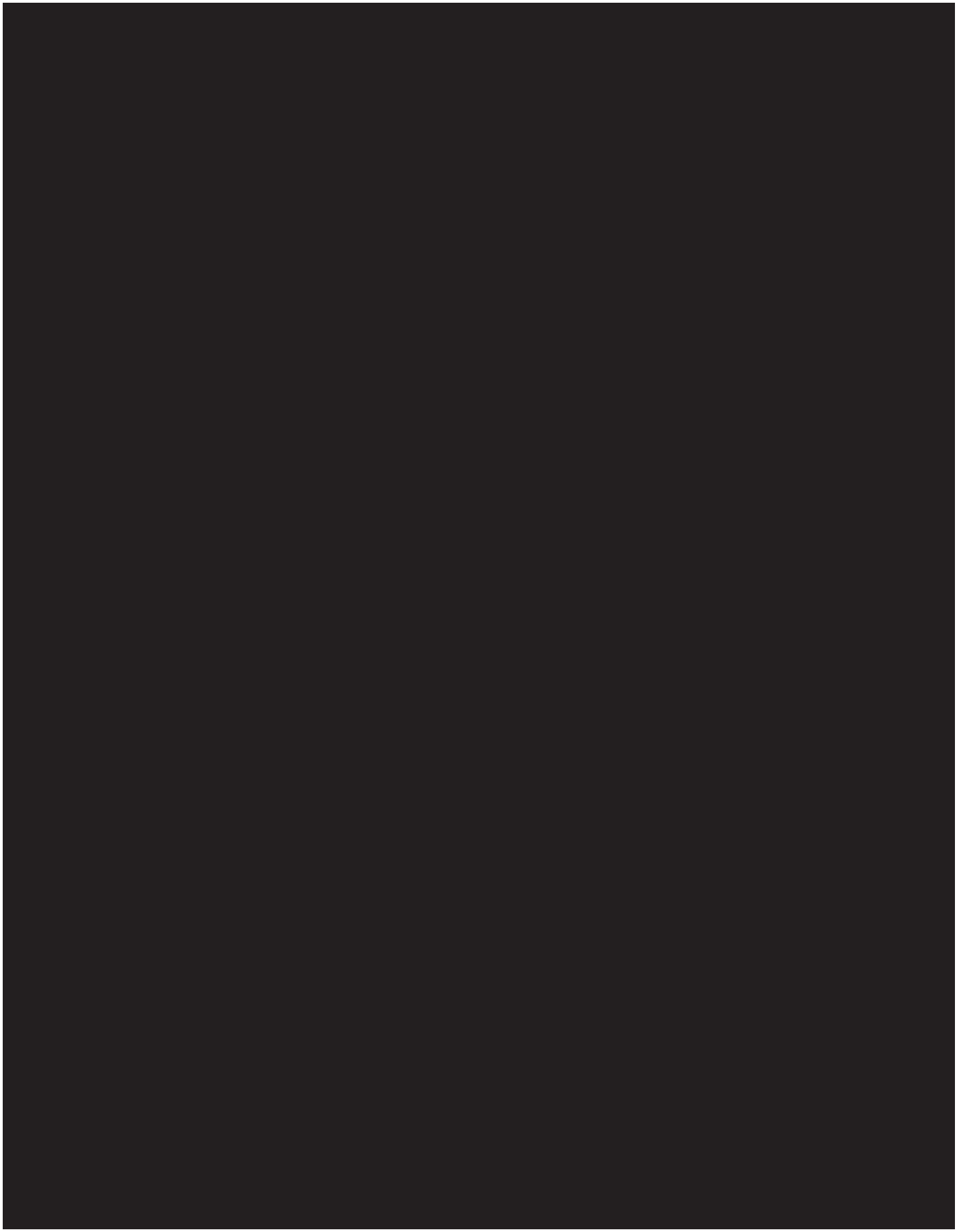
[redacted]











[redacted]

6.8.5 Analytical Approach for Secondary and Exploratory Efficacy Data

All secondary and exploratory efficacy analyses will be conducted using the Evaluable Population.

Analyses of change-from-baseline efficacy endpoints will be conducted using the same methods as the primary efficacy analysis. Analyses of percent-change-from-baseline will be performed on rank-transformed data. [redacted]

All responder and remitter efficacy endpoints will be analyzed using Cochran-Mantel-Haenszel (CMH) test controlling for the baseline stratification factors, atrial fibrillation status, and baseline peak VO_2 (< 60% or ≥ 60%). The number and percentage of responders for each treatment group

along with exact (Clopper-Pearson) 95% confidence intervals will be presented for responder rates. Difference in the proportion of responders between the 40 mg praliciguat dose group and the placebo group, controlling for the stratification factors, as well as the CMH estimates of odds ratios and p-values will be presented along with the corresponding 95% CIs for differences in responder rates using the normal approximation to the binomial distribution. P-values associated with the CMH test will also be presented.

6.8.6 Graphical Presentation of Secondary and Exploratory Efficacy Data

Least squares mean plots of change from baseline in 6MWT, [redacted] assessments over time, along with the corresponding 95% confidence intervals will be presented by treatment group. [redacted]

In addition, cumulative distribution function plots of the percent change from baseline values at Week 12 will be plotted by treatment group.

6.8.7 Subgroup Analyses

Analysis for change from baseline in peak VO2, 6MWT, [redacted] will be performed for the each of the following subgroups:

- Gender [Male/Female]
- Baseline atrial-fibrillation strata (yes/no)
- Baseline peak VO_2 (mL O_2/kg/min) strata [≤ 60%, > 60%]
- Baseline NT-pro BNP (pg/mL) [≤ 300, > 300]
- Baseline LVEF (≤ 50%, > 50%)
- Presence of diabetes versus non-diabetes (diagnosis made by currently treated and/or hemoglobin A1c > 6.5)

Subgroup analyses will be performed only if the total number of subjects in each treatment group within a subgroup category is ≥10. ANCOVA models will be used with change from baseline as the response variable, treatment, visit, subgroup, treatment-by-subgroup interaction, treatment-by-visit interaction and baseline stratification factors as fixed effects, and the respective baseline

value as covariate. Appropriate contrasts will be specified to obtain parameter estimates for each subgroup.

6.9 SAFETY ANALYSIS

All safety analyses will be performed using the Safety Population. Data for patients randomized to 10 mg praliciguat or 20 mg praliciguat under Amendment 2 or earlier will be included in adverse event summaries by treatment group, as well as in subject data listings, but will not be included in other safety summary tables. The following safety analyses will be performed to assess the safety of praliciguat when administered for approximately 12 weeks to patients with HFpEF.

6.9.1 Primary Safety Endpoints

The primary safety endpoints are the incidence of patients with TEAEs and study drug-related TEAEs. The summary and frequency tables for safety data will be by treatment group unless otherwise specified.

All adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 or newer and will be classified by MedDRA system organ class (SOC), and preferred term (PT).

Treatment-emergent adverse events (TEAEs) are those AEs that started or worsened in severity after the administration of study drug.

6.9.2 Adverse Events

An overall summary table of all adverse events will be presented and include the following:

- Patients with any TEAEs,
- Patients with any TEAEs by maximum severity,
- Patients with any TEAEs related to the Investigational Medicinal Product (IMP),
- Patients with any TEAEs leading to drug withdrawn,
- Patients with any SAEs,
- Patients with any TEAEs of Clinical Interest (AECIs; see Section 6.9.2.2).

All TEAEs will be summarized for each treatment group with the number and percentage of subjects by SOC and PT; by relationship to study drug, by maximum severity. If a patient has more than 1 TEAE coded to the same preferred term, the patient will be counted only once for that preferred term by identifying those TEAEs with the highest severity (severe > moderate > mild) and the strongest causality relationship (related > not related) to study drug per investigator.

AEs will also be summarized by study period, where AEs that started during the Screening Period, Treatment Period or Follow-up Period will be presented by treatment group (placebo and 40 mg praliciguat only) for the respective period.

For presentation of AE incidence, AEs will be sorted alphabetically by SOC, and within each SOC, by decreasing incidence of PT in the praliciguat 40 mg group. An additional presentation will include a summary of TEAEs for each treatment group by PTs only, sorted by decreasing incidence of PT in the praliciguat 40 mg group.

Summary tables will also be presented for SAEs in decreasing overall PT frequency.

Listings of AEs in screen failure patients, pretreatment AEs in randomized patients, TEAEs, severe TEAEs, study drug-related TEAEs, SAEs, TEAEs leading to study discontinuation and AEs leading to death (if any) will be provided. The listings will include the dose levels that the patients are using when AEs occur.

6.9.2.1 Subgroup Analyses

TEAEs will also be summarized by atrial fibrillation status and by baseline peak VO_2 (<60% or ≥60%), respectively, with the number and percentage of subjects by SOC and PT. Subgroup analyses will be performed only if the total number of subjects in each treatment group within a subgroup category is >10.

6.9.2.2 TEAEs of Clinical Interest (AECI)

Although not collected as such in the protocol, based on a possible class effect with sGC stimulators, TEAEs related to bleeding, hypotension, and elevated heart rate will be categorized as AECI. These will be summarized by treatment group, by severity and by PT and presented in

a by-patient listing. See Appendix 1 for details on the determination of the events for each category of interest.

6.9.3 Clinical Laboratory Endpoints

For each quantitative clinical laboratory endpoint, descriptive statistics of the observed values (in standard units) as well as change from study baseline will be presented overall for each assessment timepoint for the Safety Population. 95% confidence intervals for the change from baseline endpoints will also be presented.

Laboratory test values will also be categorized as low, normal, or high based on reference ranges provided by the lab. Shifts from study baseline to each later timepoint will be tabulated. If there is more than 1 measurement for a lab parameter at a postbaseline timepoint, only the last measurement will be used. Listings of laboratory endpoints with reference ranges and the above categorizations will be provided.

Clinical laboratory test values will also be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 5. The number and percentage of patients who have PCS post-baseline clinical laboratory values will be tabulated by treatment group. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 assessment in the corresponding postbaseline period. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS value in the corresponding postbaseline period. A supportive listing of patients with PCS postbaseline values will be provided, including the baseline and all postbaseline (including non-PCS) values. A listing of all TEAEs for patients with postbaseline PCS laboratory values will also be provided.

Table 5. Criteria for Potentially Clinically Significant Laboratory Results

Parameter	*SI Unit*	*Lower Limit*	*Higher Limit*
CHEMISTRY			
Albumin	g/L	< 0.75 × LLN	> 1.1 × ULN

Table 5. Criteria for Potentially Clinically Significant Laboratory Results

Alanine aminotransferase	U/L	—	≥ 3 × ULN
Alkaline phosphatase	U/L	—	≥ 3 × ULN
Aspartate aminotransferase	U/L	—	≥ 3 × ULN
Bicarbonate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Bilirubin, total	µmol/L	—	> 1.5 × ULN
Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Cholesterol, total	mmol/L	—	> 1.6 × ULN
Creatinine	µmol/L	—	> 1.3 × ULN
Glucose	mmol/L	< 0.8 × LLN	> 1.4 × ULN
Phosphate	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Protein, total	g/L	< 0.9 × LLN	> 1.1 × ULN
Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Uric acid	µmol/L	< 0.9 × LLN	> 1.1 × ULN
HEMATOLOGY			
Hematocrit	Ratio	< 0.8 × LLN	> 1.1 × ULN
Hemoglobin	g/L	< 0.8 × LLN	> 1.1 × ULN
Neutrophils, absolute cell count	10^9/L	< 0.8 × LLN	> 1.5 × ULN
Platelet count	10^9/L	< 0.5 × LLN	> 1.5 × ULN
Red blood cell count	10^{12}/L	< 0.8 × LLN	> 1.1 × ULN
White blood cell count	10^9/L	< 0.7 × LLN	> 1.5 × ULN

LLN = lower limit of normal value provided by the laboratory; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal value provided by the laboratory.

6.9.4 Vital Signs Endpoints

Descriptive statistics of the observed values as well as change from study baseline will be presented for seated BP and pulse at each assessment timepoint for the Safety Population. 95%

confidence intervals for the change from baseline endpoints will also be presented. Vital signs evaluations at each assessment timepoint will be presented in a by-patient listing.

The number and percentage of patients who had a PCS change from study baseline in BP and pulse (based on the criteria in Table 6), will be presented by treatment group. Percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 assessment in the corresponding postbaseline period. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS value in the corresponding postbaseline period.

Table 6. Criteria for Potentially Clinically Significant Vital Signs Results

Vital Sign Parameter	***Flag***	***Criteria****	
		Observed Value	*Change from Study Baseline*
Seated Systolic Blood Pressure (mmHg)	High	≥ 180	Increase of ≥ 30
	Low	≤ 90	Decrease of ≥ 30
Seated Diastolic Blood Pressure (mmHg)	High	≥ 105	Increase of ≥ 20
Seated Pulse Rate (bpm)	High	≥ 110	Increase of ≥ 20
	Low	≤ 50	Decrease of ≥ 20
Weight, kg	High	—	Increase of > 5 kg and ≥ 5%
	Low	—	Decrease of > 5 kg and ≥ 5%

*A postbaseline value is considered potentially clinically significant if it meets both the criteria for observed value and change from baseline.

Orthostatic changes in systolic BP, diastolic BP, and pulse will be summarized for each treatment group. An orthostatic measurement is obtained by subtracting the seated measurement from the standing measurement.

The number and percentage of patients who meet the following notable orthostatic criteria at any postdose timepoint during a visit, as well as over the overall treatment period will also be summarized by treatment group:

- Orthostatic decrease in systolic BP of > 20 mmHg from seated to standing
- Orthostatic increase in pulse of > 30 bpm from seated to standing

A supportive listing of patients with PCS postbaseline values or notable orthostatic values will be provided, including the baseline and all postbaseline (including non-PCS) values. A listing of all TEAEs for patients with postbaseline PCS vital signs values will also be provided.

6.9.5 ECG Endpoints

For each ECG endpoint, descriptive statistics of the observed values as well as change from study baseline will be presented by treatment group and overall for each assessment timepoint for the Safety Population. 95% confidence intervals for the change from baseline endpoints will also be presented. Shift tables from study baseline to the end of treatment visit for the overall ECG interpretation (normal, abnormal not clinically significant, or abnormal clinically significant) will be provided for each treatment group in the Safety Population. The number and percentage of patients who had PCS ECG values (based on the criteria in Table 7), will be presented by treatment group. Percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 assessment in the corresponding postbaseline period. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS value in the corresponding postbaseline period.

Table 7. Criteria for Potentially Clinically Significant ECG Results

ECG Parameter (unit)	Higher Limit
QRS duration (msec)	≥150
PR interval (msec)	≥250
QTc interval (msec)	>480

ECG endpoints will also be presented in a by-patient listing.

6.9.6 Physical Examination

Physical examination will be listed at each visit sorted by subject ID. Summary tables of abnormalities will be provided by visit for each treatment group and overall for the Safety Population.

6.10 EXPLORATORY PHARMACOKINETIC (PK) ANALYSIS

7. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

The following changes will be made to the analyses described in the study protocol.

- The primary ANCOVA analyses described in Protocol Section 5.9.2 notes the treatment group and the two stratification factors (atrial fibrillation status and baseline peak VO_2 [< 60% or ≥ 60%]) as categorical variable terms and the baseline CPET value (baseline peak VO_2) as the covariate. Instead, the primary ANCOVA model will include treatment group and atrial fibrillation status as categorical variable terms and the continuous baseline peak VO_2 as a covariate.

- [redacted]

- Descriptive statistics for continuous safety laboratory, vital signs and ECG change-from-baseline endpoints will include 95% confidence intervals.

Statistical analyses of the following endpoints, using the same methods as the primary efficacy endpoint, will be performed in addition to those described in the study protocol.

- [redacted]

- [redacted]

- [redacted]

8. DATA HANDLING CONVENTIONS

8.1 END OF TREATMENT ASSESSMENT

Assessments performed at the end of treatment visit will be included in Week 8 and Week 12 evaluations as follows:

- If a patient has a missing Week 8 assessment, but has a non-missing EOT assessment, then the EOT assessment will be used as the Week 8 assessment if the EOT assessment was conducted on or after study day 50.
- If a patient has a non-missing Week 8 assessment and has a non-missing EOT assessment, then the EOT assessment will be used at the Week 12 assessment if the EOT assessment was performed on or after study day 77.

8.2 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a patient has repeated safety assessments (e.g., for a lab endpoint) prior to initial dosing of study drug, then the results from the final non-missing assessment made prior to the start of study drug will be used as baseline. If there is more than 1 safety measurement (e.g., for a lab endpoint) at a postbaseline timepoint, only the last measurement will be used. All postbaseline assessments including unscheduled assessments, if any, will be used for PCS value determination, and all assessments will be presented in by-patient listings.

8.3 CONVENTIONS FOR SUMMARIZING ADVERSE EVENTS

The following conventions will be followed in summarizing TEAEs within a treatment group:

- For patient incidence summaries, each patient will be counted only once within each SOC, PT, or the overall AE summary

- If a patient reported more than 1 AE within an SOC or PT, then the AE with the highest severity or strongest causality relationship to study drug per investigator within each SOC and each PT will be included in the respective summaries by severity or relationship, respectively.

8.4 MISSING DATE INFORMATION FOR ADVERSE EVENTS

If the onset date of an AE is missing / incomplete, it is assumed to have occurred during the study (i.e., a TEAE) except if the partial onset date or other data, such as stop date, indicates differently.

8.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started prior to initiation of study drug dosing, all efforts should be made to obtain the severity from the Investigator. If it is still missing after all efforts, then a severity of "Mild" will be assigned. If the severity is missing for a TEAE, then a severity of "Severe" will be assigned. The imputed values for the missing severity assessment will be used for the incidence summary, while the actual missing values will be presented in by-patient listings.

8.6 MISSING RELATIONSHIP TO STUDY DRUG FOR ADVERSE EVENTS

If the relationship to study drug is missing for a TEAE, all efforts should be made to obtain the relationship from the Investigator. If it is still missing after all efforts, a study drug causality of "Related" will be assigned in the corresponding analysis-derived data set for non-serious and non-AECI treatment-emergent adverse events. The imputed values for the missing relationship to study drug will be used only for incidence summary, while the actual missing values will be presented in by-patient data listings. For SAEs and AECIs, if causality from investigators is missing after all efforts to obtain it, then the causality determination from the sponsor will apply.

8.7 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

If the onset date of a medication is missing / incomplete, it is assumed to have occurred during the study (i.e., concomitant) except if the partial onset date or other data, such as stop date, indicates differently).

9. REFERENCES

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4. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28(7):412-9.

5. EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy. 1990;16:199-208.

10. APPENDIX 1 – ADVERSE EVENTS OF CLINICAL INTEREST

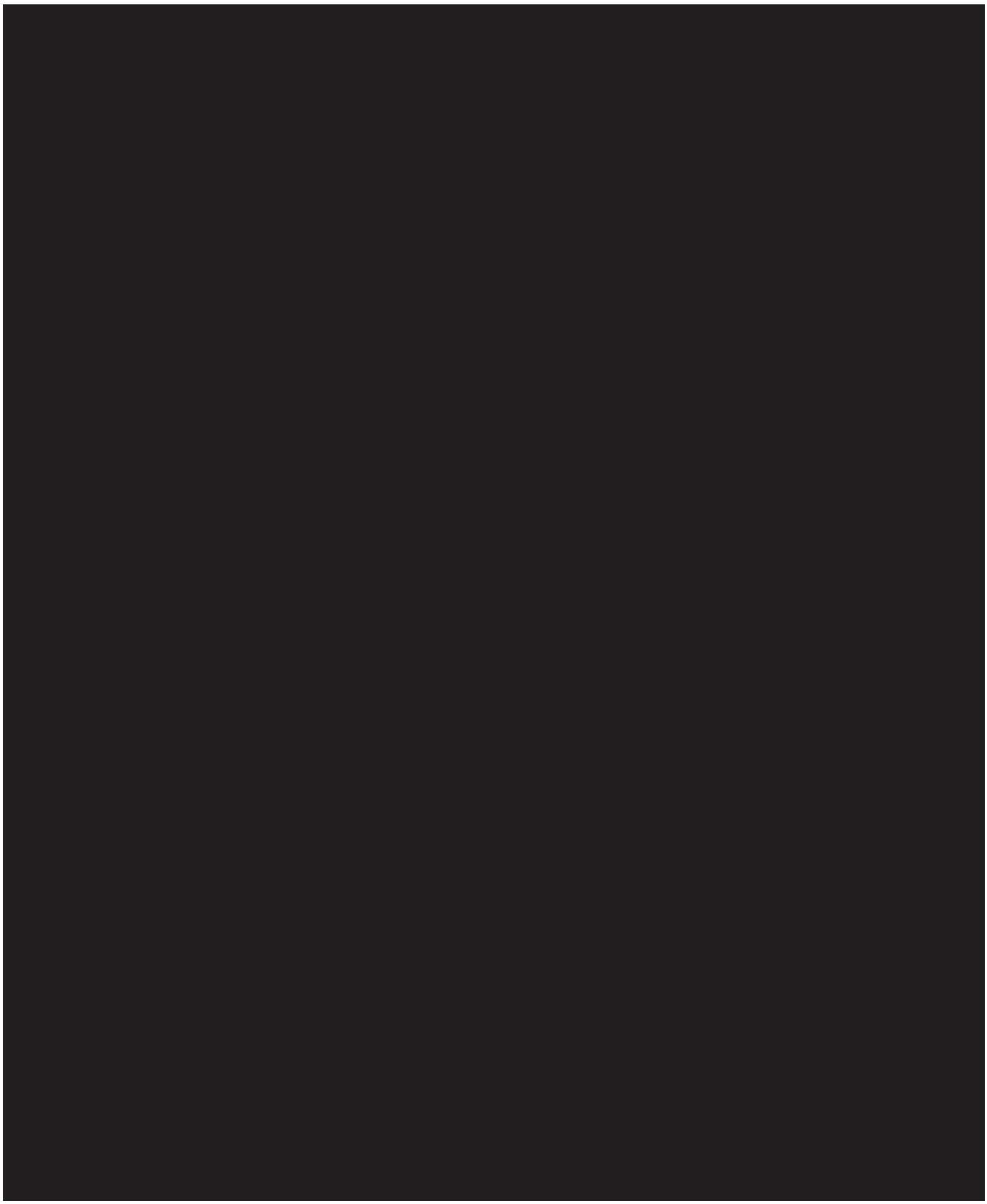
The table below provides the criteria for identifying adverse events within each category. Medical review of AEs prior to database lock will identify any additional adverse events.

Table 8. Criteria for AECI

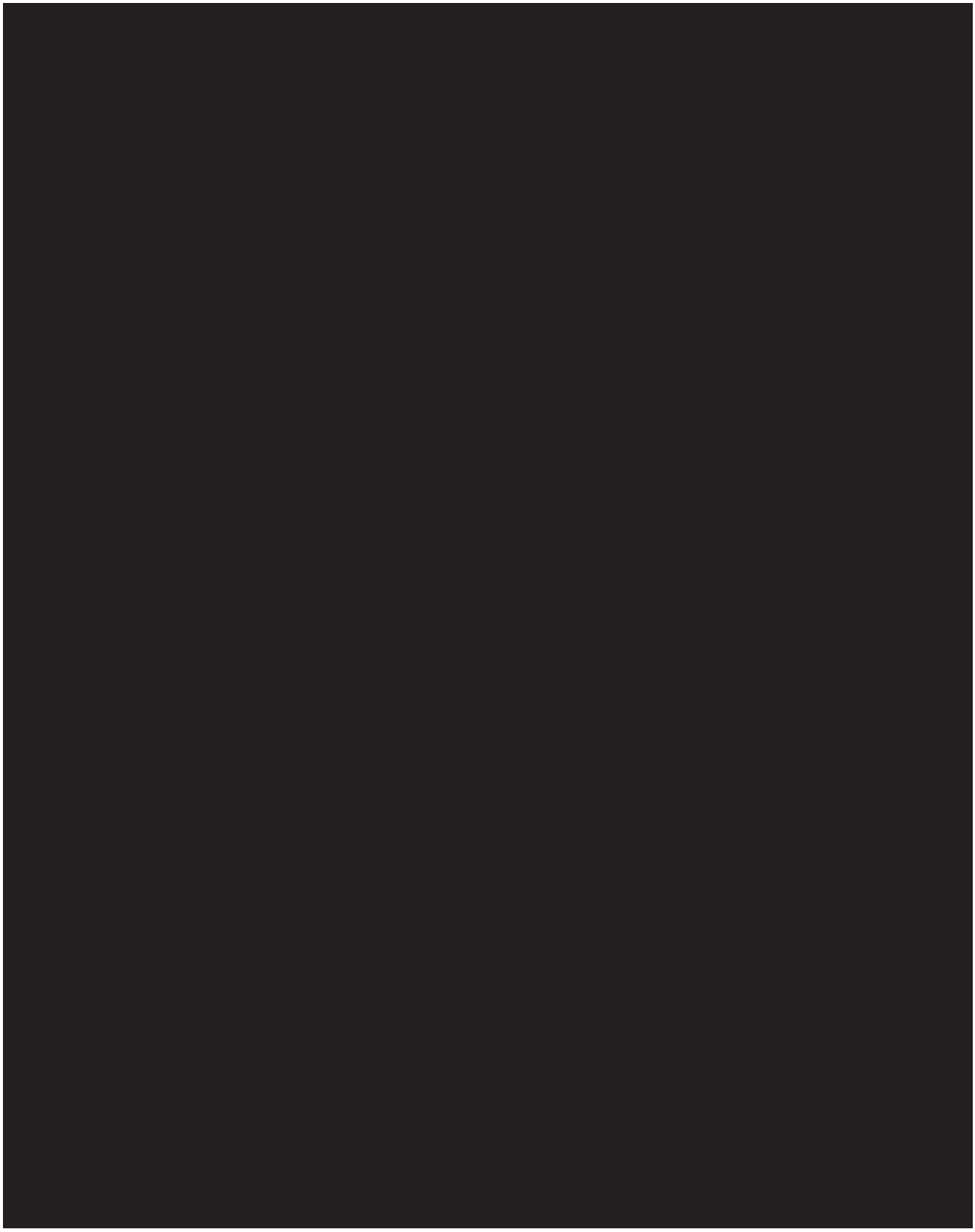
Event Category	AE Criteria	Labs/Vital Sign
Bleeding Events	Identify using MedDRA SMQ of 'haemorrhage terms (excluding laboratory terms)'	
Hypotensive Events	Identify using the following MedDRA preferred terms: Blood pressure ambulatory decreased Blood pressure decreased Blood pressure diastolic decreased Blood pressure systolic decreased Blood pressure orthostatic decreased Orthostatic hypotension Presyncope Syncope Dizziness Dizziness postural	decrease in SBP >20 mmHg from seated to standing Decrease in DBP>15 mmHg from seated to standing
Elevated Heart Rate	Identify using the following MedDRA preferred terms: Heart rate increased Orthostatic heart rate increased Tachycardia Palpitations	Increase in pulse>30 bpm from seated to standing
Headaches	Identify using MedDRA HLGT Headache	

SMQ=standardised MedDRA query.

11. APPENDIX 2 –



12. APPENDIX 3 –



13. APPENDIX 4 – POOLING OF TRIAL CENTERS

Because of the potential of many trial centers to have a small number of patients, the centers will be pooled by the following 6 geographic regions (as listed in Table 10): Northeast, Southeast, Midwest, Southwest, and West. Analyses using geographic region will use this 6-category geographic region variable.

Table 10. Definition of Geographic Regions

Northeast	*Southeast*	*Midwest*	*Southwest*	*West*	*Ex-US*
CT	AL	IA	AZ	CA	Canada
DC	AR	IL	NM	CO	
DE	FL	IN	OK	ID	
MA	GA	KS	TX	MT	
MD	KY	MI		NV	
ME	LA	MN		OR	
NH	MS	MO		UT	
NJ	NC	ND		WA	
NY	SC	NE		WY	
PA	TN	OH			
RI	VA	SD			
VT	WV	WI			

14. APPENDIX 5 [redacted]