Statistical Analysis Plan

Protocol Title:	Open-label, Single-arm Study Assessing the Efficacy and Safety of Ivabradine (Corlanor) in African-American/Black Subjects With Heart Failure and Left Ventricular Systolic Dysfunction
Short Protocol Title:	A Phase 4 Study of Ivabradine in African-American/Black Subjects with Heart Failure and Left Ventricular Systolic Dysfunction
Protocol Number:	20160231
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	26 September 2018	

[Amendment 1 (v2.0)]	19 April 2019	• **Section: Title page**
		  • Update document date to 19 April 2019.
		  • Add new study statistician Da Geng in the author section.
		• **Section: Global**
		  • Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document.
		• **Section: 2.1 Objectives and Endpoints**
		  • Remove two genetic related exploratory endpoints to be consistent with protocol.
		• **Section: 5 Definitions**
		  • Make the following changes for the definitions to reflect the changes of the activity count analysis:
		  Remove:
		  Baseline activity counts
		  Total Number of Minutes Spent in Activity Category
		  Proportion of Time Spent in Activity Category
		  Add:
		  Total Number of Minutes Spent in Sedentary Activity Category
		  Total Number of Minutes Spent in Light Activity Category
		  Total Number of Minutes Spent in Moderate to Very Vigorous Activity Category
		  Proportion of Time Spent in Sedentary Activity Category
		  Proportion of Time Spent in

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
		Proportion of Time Spent in Light Activity Category **Proportion of Time Spent in Moderate to Very Vigorous Activity Category** • Add the definition of **HR for 6MWT** to define how to calculate HR for 6 minute walk test. • **Section: 8.3 Handling of Missing and Incomplete Data** • Add below text and **Table 8-1** to describe imputation rules for incomplete dates. **Add:** **"Adverse event and concomitant medication with completely or partially missing start dates will be queried. After the issue is queried, if the date is still incomplete with year only or year and month only, the start date will be imputed as described in Table 2 below."** • **Section: 9.5.2 Sensitivity Analysis of Primary Endpoint(s)** Adding detailed information for multiple imputation in sensitivity analysis: • Change **"A sensitivity analysis will be performed using multiple imputation to impute missing primary endpoint."** to **"A sensitivity analysis will be performed using multiple imputation."** • **Add:** "**A sensitivity analysis will be performed using multiple imputation to impute**

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
		missing primary endpoint. The primary analysis model will be repeated using FAS with missing values imputed. Missing values from patients who discontinued IP will be imputed using non-missing data from subjects who discontinued IP while missing values from patients who completed IP will be imputed using non-missing data from subjects who completed IP, provided that there is a sufficient number of subjects with non-missing endpoint data in both groups." • **Section: 9.5.4 Analyses of Exploratory Efficacy Endpoint(s)** Make the following changes to be consistent with protocol: [redacted]

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
		[redacted] • **Section: 9.5.4 Analyses of Exploratory Efficacy Endpoint(s)** Make the following changes to reflect the changes of the activity count analysis: [redacted] • **Section: 9.5.4 Analyses of Exploratory Efficacy Endpoint(s)** Add detail dose profile groups:

Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes

		[redacted]
		• **Section: 10 Changes from Protocol-specified Analyses**
		  • Replace "**There are no changes to the protocol specified analyses**" with "**For the endpoint of change in activity counts measured with an accelerometer from baseline to day 57, activity counts will not be summarized. Instead the weekly total number of minutes spent and weekly proportion of time spent in activity categories will be summarized, since time spent by activity categories represent clinical meaningful interpretation."**
		• **Section: Appendix A**
		Remove content related to the Accelerometer data as it is already defined in section 5.
		  • Change "**Analytical Study Week Assignments**" to "**Analytical Study Day Assignments**"
		  • Change "**Handling multiple records assigned to an**

<table>
<tr><th>Version Number</th><th>Date (DDMMMYYYY)</th><th>Summary of Changes, including rationale for changes</th></tr>
<tr><td></td><td></td><td>
analytical study week” to “Handling multiple records assigned to an analytical study day”
• Remove:
<table>
<tr><td><s>Accelerometer</s></td><td><s>(8, 15]</s></td><td><s>(22, 29]</s></td><td><s>(50,57]</s></td></tr>
</table>
• Remove: “For accelerometer, the analytical record for the scheduled visit is defined as the average 7 days prior/on the target study day.”
• Section: Appendix C
• Remove Appendix C.
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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
6MWT	6-minute walk test
ACEi	angiotensin-converting-enzyme inhibitors
BID	twice daily
bpm	beats per minute
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
End of Study	The end of study date is defined as the date when the last subject at the site is assessed or receives an intervention for evaluation in the study (ie, last subject last visit)
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
Enrolled	A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria
FAS	Full analysis set
HF	heart failure
HFrEF	heart failure and reduced ejection fraction
HR	heart rate
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
SAS	Safety analysis set
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject

1. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for study 20160231, Ivabradine dated **14 February 2019**. The scope of this plan includes the primary analysis that is planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• Determine whether ivabradine effectively reduces **heart rate (HR)** from baseline to day 57 in African-American/Black subjects	• Change in HR from baseline to day 57
Exploratory	
[redacted]	
Safety	
• Evaluate the safety and tolerability of ivabradine in African-American/Black subjects with HFrEF	• Subjects incidence of treatment emergent adverse events • Vital signs at each scheduled assessment

2.2 Hypotheses and/or Estimations

The primary hypothesis is that ivabradine effectively reduces HR between baseline and day 57 in African-American/Black subjects. Because mean reductions of approximately 5 beat per minute (bpm) have been observed in the overall placebo-treated subjects in the SHIFT study as well as in the placebo-treated subjects of the subgroup analysis of non-African-American/Black subjects enrolled in the SHIFT study, we will test whether the mean reduction with ivabradine exceeds 5 bpm, and estimate the degree to which the mean reduction with ivabradine exceeds 5 bpm.

3. Study Overview

3.1 Study Design

This study is a prospective, open-label, single-arm intervention study in African-American/Black subjects with HfrEF. Approximately 30 to 100 subjects will be enrolled to receive ivabradine in an open-label design.

Eligible subjects will include African-American/Black subjects with chronic HFrEF, New York Heart Association (NYHA) classes II to IV, with baseline HR ≥ 70 bpm in sinus rhythm and an left ventricular ejection fraction (LVEF) ≤ 35% who are on stable (≥ 4 weeks) optimal HF therapy, including maximally tolerated dose of β-blockers.

After signing the informed consent form, subjects will enter a 7-day screening period that will allow accurate measurement of baseline activity as measured by the accelerometer (which is a non-Amgen, medical device). On day 1, eligible subjects with confirmed sinus rhythm and HR ≥ 70 bpm will be enrolled into a 57-day open-label treatment period. The starting dose of ivabradine is 5 mg twice daily (BID). In subjects with a history of conduction defects, or in subjects in whom bradycardia could lead to hemodynamic compromise, therapy is to be initiated at 2.5 mg BID, based on investigator discretion. On day 15, the dose will be titrated according to HR as defined in Table 3-1. Ivabradine dose levels can be adapted to HR at any clinical visit if necessary.

Table 3-1. Ivabradine Dose Titration at Day 15 Based on Heart Rate From Electrocardiogram

	Initial Dose: 5 mg BID	Initial Dose: 2.5 mg BID
HR ≥ 60 bpm	7.5 mg BID	5.0 mg BID
HR ≥ 50 bpm, < 60 bpm	5.0 mg BID	2.5 mg BID
HR < 50 bpm and/or signs or symptoms of bradycardia	2.5 mg BID	Discontinue therapy

Abbreviations: BID = twice daily; bpm = beats per minute; HR = heart rate

The primary efficacy measurement for this study is HR and will be measured at Screening, Day 1, Day 15 and Day 57. This study include**s** the collection of the continuous daytime physical activity counts measured by a wearable device (accelerometer) from baseline (7-day screening period prior to initiation of ivabradine) until the end of the course of the interventional treatment. This device will record continuous parameters of physical activity, which will be used for analysis. These data will be compared to those obtained by a standard 6MWT (performed at baseline and end

of treatment). Heart rate response to the standard 6MWT between baseline and end of treatment will also be compared with an HR monitor.

A safety follow-up will be conducted at day 87 or 30 days after the last administration of the investigational product.

3.2 Sample Size

A minimum of 30 subjects with up to approximately 100 subjects with HFrEF will be enrolled in the study.

The primary endpoint is HR reduction from baseline at day 57 greater than 5 bpm. Based on HR reduction results observed in the overall placebo-treated subjects of the SHIFT study as well as in the placebo-treated subjects of the subgroup analysis of non-African-American/Black subjects enrolled in the SHIFT study, the mean change HR in the ivabradine group was 13 bpm with a standard deviation of 10.4 bpm at end of 28 days and maintained until end of study. In addition, the mean change in the placebo group was 5 bpm observed at end of 28 days, so the hypothesis is to evaluate the HR reduction from baseline at day 57 greater than 5 bpm. Based on a 2-sided, 1-sample t-test with significance level of 0.05, the planned sample size of 30 to 100 subjects will provide approximately 97% to >99% power. The sample size considerations incorporate an assumption of a study drop out of 10%.

4. Covariates and Subgroups

4.1 Planned Covariates

- Age
- Sex
- Baseline HR

4.2 Subgroups

- Age: < 65 years, ≥ 65 years
- Sex
- Baseline HR (< 77 bpm, >= 77 bpm)

A subgroup variable will be eliminated if one of the two subgroups levels is <10% of overall group.

5. Definitions

Treatment Emergent Disease-Related Event

Events categorized as Disease-related Events (DREs) starting on or after first dose of investigational product as determined by the flag indicating if the event started prior to the first dose on the Events eCRF and up to the EOS/Safety Follow-up visit or 30 days after the last administration of investigational product (IP), whichever is earlier.

Treatment Emergent Adverse Event

Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by the flag indicating if the event started prior to the first dose on the Events eCRF and up to the EOS/Safety Follow-up visit or 30 days after the last administration of IP, whichever is earlier.

Treatment Emergent Serious Adverse Event

Treatment emergent adverse events (as defined above) that are indicated as serious on the Events eCRF.

End of Investigational Product (EOIP) Date

For each subject, the end of investigational product date is defined as the date recorded in the EOIP administration form,

Last Dose Date

For each subject, the last dose date is defined as the stop date on the last record of administration of IP page.

End of Study (EOS) Date

For each subject, the End of Study Date is the date recorded on the End of Study eCRF.

Baseline

For all variables, the baseline value is defined as the last non-missing value collected prior to or on Study Day 1.

Change from Baseline

The arithmetic difference between a post-baseline value and the baseline value:
Change (absolute) from Baseline = (Post-baseline Value – Baseline Value)

Percent change from Baseline

Percent Change from Baseline = [(Post-baseline Value – Baseline Value) / Baseline Value] x 100

Enrollment Date

Enrollment Date is defined as the date collected on the Subject Enrollment eCRF.

Investigational Product (IP)

The term investigational product is used in reference to Ivabradine.

Study Day 1

Day 1 is defined as the day that IP is first administered to the subject. If a subject enrolled but never received IP, Study Day 1 is defined as the enrollment day.

Study Day

For each subject, and for a given date of interest, Study Day is defined as the number of days since Study Day 1:

Study Day = (date of interest - date of Study Day 1) +1

If the date of interest is prior to the Study Day 1:

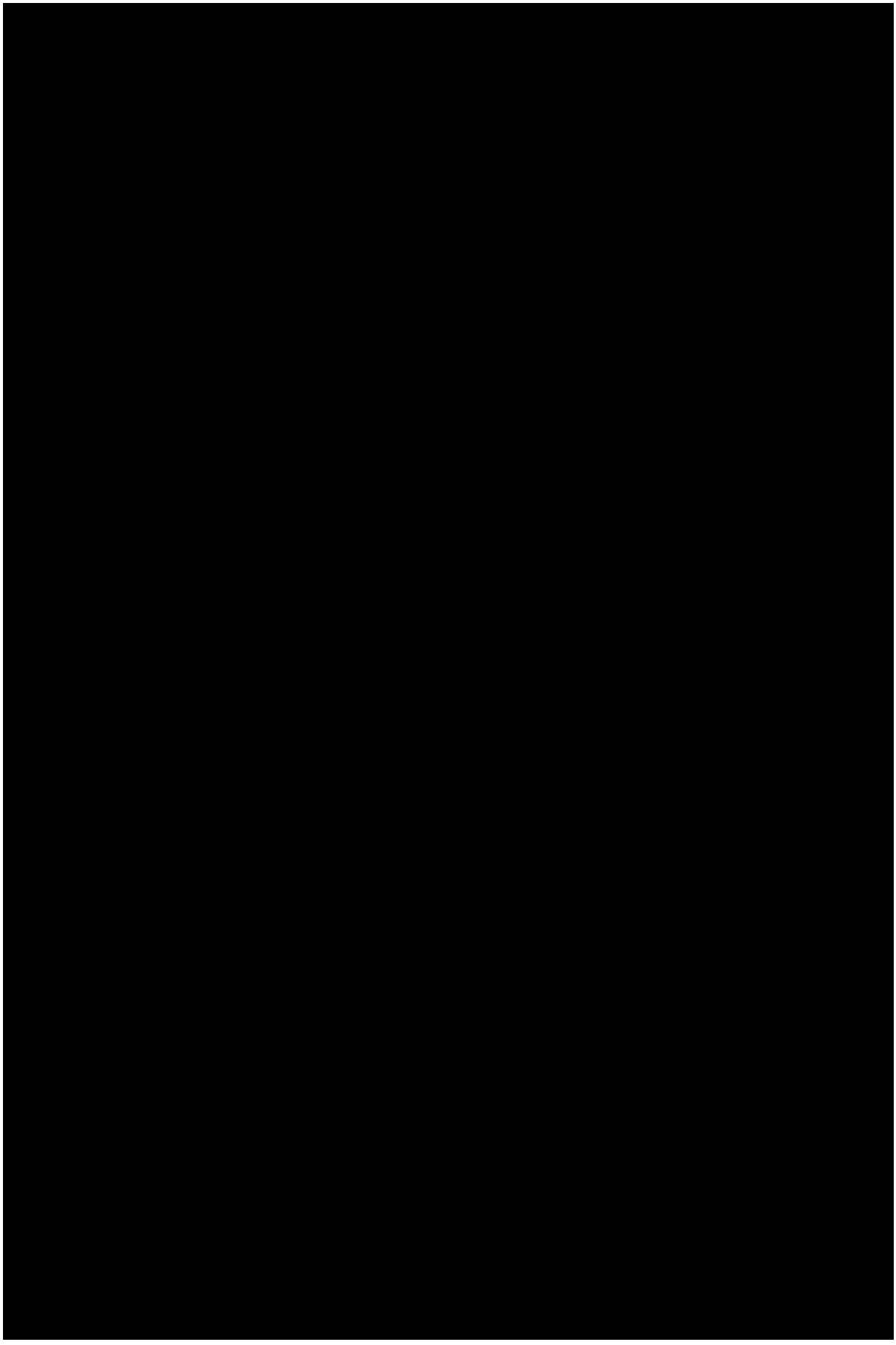
Study Day = (date of interest – date of Study Day 1), so the day of the first IP dose is Study Day 1 and the day prior to the Study Day 1 is Study Day -1.

IP Exposure in Months

IP Exposure in Months = [min (last IP dose date + 2 days, EOS Date) – study day 1 + 1]/ 365.25 ×12

Study Exposure in Months

Study Exposure in Months = (EOS date – Enrollment Date + 1)/ 365.25 ×12



6. Analysis Sets

6.1 Full Analysis Set

Efficacy analyses will be performed on the full analysis set (FAS), which includes all enrolled subjects.

6.2 Safety Analysis Set

Safety analyses will be performed on the safety analysis set (SAS), which includes all enrolled subjects who receive at least 1 dose of investigational product on study.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

No interim analysis will be conducted in this study.

7.2 Primary Analysis

The primary analysis for this study will be performed when all subjects have either early terminated from the study or completed all planned study procedures. At that time, the database will be cleaned, processed, locked, and a snapshot will be taken. Based on the snapshot **of the locked database**, efficacy and safety analyses will be performed.

7.3 Final Analysis

Not applicable.

8. Data Screening and Acceptance

8.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

8.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

8.3 Handling of Missing and Incomplete Data

For efficacy endpoints, where the analysis method is repeated measures linear model then missing heart rate measurements will not be imputed. For the sensitivity analysis of efficacy HR endpoints, the multiple imputation will be used to impute Day 15 and Day 57 missing heart rate measurements.

Adverse event and concomitant medication with completely or partially missing start dates will be queried. After the issue is queried, if the date is still incomplete

with year only or year and month only, the start date will be imputed as described in Table 8-1 below.

Table 8-1. Imputation Rules for Incomplete Dates

Start date (AE and concomitant medication)	Missing	Imputation	Exception
	Day	1	Default to Study Day 1 if an event starts the same year and month as Study Day 1
	Day / Month	1-Jan	Default to Study Day 1 if an event started the same year as Study Day 1

Missing data will not be imputed for safety endpoints.

8.4 Detection of Bias

Factors that may bias the results of the study are major protocol deviations likely to impact the analysis and interpretation of the endpoints. Important protocol deviations likely to impact the analysis and interpretation of the endpoints will be tabulated in the Clinical Study Report (CSR).

If any sensitivity analyses are required to evaluate potential biases in the study's conclusions, the sources of the potential biases and results of the sensitivity analyses will be documented in the CSR.

8.5 Outliers

Various methods, including univariate summaries, histograms, scatter plots, box plots, and line graphs, may be used to identify outliers in key variables. The primary analysis will include outliers in the data. Sensitivity analyses may be undertaken if extreme outliers for a variable are observed.

8.6 Distributional Characteristics

If the distributional assumptions are not met, then alternative methods will be utilized. The use of alternative methods will be fully justified in the CSR.

8.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures. Tables, figures, and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software; for example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

For efficacy endpoints, where the analysis method is repeated measures linear effects model then missing heart rate measurements will not be imputed. For the sensitivity analysis of efficacy HR endpoints, multiple imputation will be used to impute Day 15 and Day 57 missing heart rate measurements.

Missing data will not be imputed for safety endpoints.

Subject disposition, demographics, baseline characteristics, medical history, baseline concomitant medications, and exposure to investigational product will be summarized.

Continuous variables will be summarized with descriptive statistics, including the number of subjects (n), mean, standard deviation or standard error, median, the first quartile and third quartile, minimum, and maximum. Frequency and percentage will be given for categorical variables.

9.2 Subject Accountability

The number and percent of subjects enrolled who received, completed and discontinued from IP (including reasons for discontinuing), completed and discontinued the study (including reasons for discontinuing) will be summarized.

The number of subjects included in and excluded from each analysis set will be summarized.

Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented.

9.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's initial visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, subcategory codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

9.4 Demographic and Baseline Characteristics

Demographics data including sex, age, race, and ethnicity, baseline characteristics, medical history, and baseline concomitant medications will be summarized.

9.5 Efficacy Analyses

HR reduction from baseline to day 57 will be estimated from a repeated measures linear model. Summary statistics will be provided for exploratory endpoints.

9.5.1 Analyses of Primary Efficacy Endpoint(s)

The repeated measures linear model will be used to evaluate ivabradine efficacy on HR reduction from baseline to day 57 for subjects in FAS regardless of treatment adherence. The model will include terms of scheduled visits and baseline HR measurement as covariates and test whether the mean reduction with ivabradine exceeds 5 bpm, a reduction assumed with placebo. Missing values will not be imputed when the repeated measures linear model is used. Based on the model, the least-square means along with 95% confidence interval will be provided. Descriptive statistics of HR reduction by scheduled visit will also be summarized.

In addition, the primary endpoint will be analyzed within each of the subgroups (indicated in Section 4.2) using the same methodology as the primary endpoint based on the FAS of the treatment period.

9.5.2 Sensitivity Analysis of Primary Endpoint(s)

To evaluate the robustness of the analysis results, sensitivity analyses will be performed as follows:

- A sensitivity analysis will be performed using multiple imputation. **The primary analysis model will be repeated using FAS with missing values imputed. Missing values from patients who discontinued IP will be imputed using non-missing data from subjects who discontinued IP while missing values from patients who completed IP will be imputed using non-missing data from subjects who completed IP, provided that there is a sufficient number of subjects with non-missing endpoint data in both groups.**
- Analysis of covariance (ANCOVA) will be performed for day 57 data using covariates (described in Section 4.1) in the same model

9.5.3 Analyses of Secondary Efficacy Endpoint(s)

Not applicable.

9.5.4 Analyses of Exploratory Efficacy Endpoint(s)

[redacted]

9.6 Safety Analyses

9.6.1 Analyses of Safety Endpoint(s)

Treatment emergent adverse events and disease-related events will be summarized.

9.6.2 Adverse Events and Disease-related Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or later will be used to code all events categorized as adverse events and disease-related events to a system organ class and a preferred term.

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 or later.

Subject incidence of all treatment emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from investigational product will be provided.

Significant treatment emergent adverse events (if applicable) will also be provided.

Subject incidence of treatment emergent disease-related events and fatal disease-related events will also be tabulated by system organ class and preferred term.

9.6.3 Laboratory Test Results

The analyses of safety laboratory endpoints will include summary statistics at baseline.

9.6.4 Vital Signs

The analyses of vital signs including systolic blood pressure and diastolic blood pressure, and HR will be summarized using descriptive statistics at each scheduled visit.

9.6.5 Physical Measurements

The analyses of height and weight measurements will include summary statistics at baseline.

9.6.6 Electrocardiogram

All ECG measurements will be summarized using descriptive statistics at each scheduled visit. In addition, the change in HR from baseline will be summarized at each scheduled post-baseline visit (day 15 and 57).

The electrocardiogram (ECG) measurements from this clinical study were performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QT interval corrected (QTc) effect. Because these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data; neither summaries nor statistical analyses will be provided, and these data would not be expected to be useful for meta-analysis with data from other trials.

9.6.7 Exposure to Investigational Product

Descriptive statistics will be provided to describe the exposure to investigational product by visit. Dosage adjustments will also be summarized.

9.6.8 Exposure to Other Protocol-specified Treatment

Not applicable.

9.6.9 Exposure to Concomitant Medication

The number and proportion of subjects receiving medication of interest, including but not limited to β-blockers, ACEi, and angiotensin II receptor blockers, will be summarized by preferred term or category as coded by the World Health Organization Drug (WHO DRUG) dictionary (version March 1, 2017 or later).

9.7 Other Analyses

Not applicable.

10. Changes from Protocol-specified Analyses

For the endpoint of change in activity counts measured with an accelerometer from baseline to day 57, activity counts will not be summarized. Instead the weekly total number of minutes spent and weekly proportion of time spent in activity categories will be summarized, since time spent by activity categories represent clinical meaningful interpretation.

11. Literature Citations / References

Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376:875-885.

Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013;128:e240-327.

12. Appendices

Appendix A. Analytical Study Day Assignments

Selected endpoints will be summarized by scheduled study visits in descriptive analyses. Since the actual visits may not exactly coincide with their scheduled visit day, the actual visit day is mapped to the study visit generally by non-overlapping consecutive intervals covering the entire time continuum. The mapping intervals for all distinct schedules are summarized in the following table.

Handling multiple records assigned to an analytical study day:

Scheduled Visit Day	Day 15	Day 29	Day 57
Target Study Day	15	29	57
Vital signs	(1, 22]	(22, 43]	>43
12-lead ECG	(1, 36]		>36
6-Minute walk test			>1

If there is more than one record in a given analytical window, the analytical record for that scheduled visit will be defined as the record closest to target study day for that scheduled visit. If two records are equidistant from the scheduled visit day, then the earlier record will be chosen. If there are multiple records on the same day, the last record will be used.

Appendix B. Common Terminology Criteria for AEs (CTCAE)

Refer to the NCI Common Terminology Criteria for AEs (CTCAE) Version 5.0, published: November 27, 2017 for AE and lab shift grading and information. The CTCAE is available at the following link: http://evs.nci.nih.gov/ftp1/CTCAE/About.html