Predischa**R**ge Initiation of **I**vabradine in the **M**anagement

of **H**eart **F**ailure **(PRIME-HF)**

NCT02827500

Statistical Analysis Plan (SAP)

Version 2.0

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Abbreviations

BB	Beta-blocker
bpm	Beats per minute
ECG	Electrocardiogram
HF	Heart Failure
HR	Heart Rate
IV	Intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left Ventricular ejection fraction
NYHA	New York Heart Association
PGA	Patient Global Assessment

1 PURPOSE

This statistical analysis plan (SAP) reviews the study design and objectives, outlines the types of analyses and data presentations that address study objectives, and describes in detail the statistical methods for safety and efficacy analyses specified in the study protocol (PRIME-HF version 3, of July 19, 2017). Any additional analyses or deviations from the planned statistical analysis will be described in a supplement to this SAP for non-substantive changes, and in an SAP amendment, if the changes are substantive (CT Stats SOP ST-S-005, 5.0, 31Jan2017, V.L).

2 STUDY OVERVIEW

This section summarizes the study objectives and design.

2.1 Study Design

The PRIME-HF study is a multi-center, patient-level, randomized, open-label study with a target of enrolling approximately 450 participants (patients) with reduced LVEF of $\leq$35% and heart-rate $\geq$70 bpm who are being discharged from the hospital following stabilization from acute HF and will be randomized to a treatment strategy of pre-discharge initiation of ivabradine or usual care, involving post discharge initiation of ivabradine.

2.2 Study Objectives

The primary hypothesis of the PRIME-HF study is that, compared with usual care, a treatment strategy of initiation of ivabradine prior to discharge for a hospitalization for acute HF will be associated with a greater proportion of participants using ivabradine at 180 days.

2.2.1 Primary Objectives

To test the primary hypothesis that, compared with usual care, a treatment strategy of initiation of ivabradine prior to discharge for a hospitalization for acute HF will be associated with a greater proportion of participants using ivabradine at 180 days.

2.2.2 Secondary Objectives

To assess the impact of pre-discharge initiation of ivabradine on:

1) Heart rate

    a) Change in heart rate from baseline to 180 days

    b) Median heart rate at 180 days

2) Patient-centered outcomes

    a) Kansas City Cardiomyopathy Questionnaire (KCCQ)

    b) Patient Global Assessment (PGA)

2.2.3 Tertiary Objectives

Tertiary objectives will be to explore the impact of pre-discharge initiation of ivabradine on:

1) Other assessments of evidence-based implementation of ivabradine and beta-blockers at 180 days. Evaluations will incorporate data based on whether or not indication status was retained and whether or not an ivabradine prescription was provided.

2) Tolerability of ivabradine based on events of interest during study follow-up:

    a) Symptomatic bradycardia

    b) Symptomatic hypotension

    c) Other symptoms leading to ivabradine discontinuation

3) To explore barriers to the acquisition of ivabradine.

2.3   Sample Size Determination

For sample size determination, it was assumed that 35% of participants randomized to the usual care arm would be treated with ivabradine at 180 days, and the pre-discharge initiation of ivabradine would increase the use at 180 days to 50%. The usual care event rate is based on investigator estimates of clinical use in the first year following approval by the Food and Drug Administration. At a two-sided Type I error rate of 0.05, 450 participants would provide 85% power to detect a significant difference in the rate of ivabradine use between groups. The original plan was to randomize 450 participants in the study. However, due to enrollment challenges faced in the study, enrollment was stopped after enrolling a total of 104 participants.

2.4   Study Populations

Participants suitable for this protocol are individuals with chronic HF who are hospitalized with acute heart failure, have achieved clinical stability and have an LVEF$\leq$35% and heart-rate $\geq$70 bpm in normal sinus rhythm. Participants should not have a planned/scheduled up titration of

beta-blocker in the following 4 weeks. Adjustments of background therapy can be made at any point during the study period at the discretion of the attending physician.

All participants randomized to the study constitute the intent to treat (ITT) population. Participants that receive ivabradine at the week 6 visit constitute the treated population. The primary efficacy endpoint will be evaluated based on the ITT population. As a sensitivity analysis, the primary and key secondary endpoints will be evaluated on the treated population.

2.5   Study Endpoints

2.5.1 Primary Endpoint

The study protocol (in section 10.1) states that the primary endpoint of the study is the proportion of participants using ivabradine at 180 days. The endpoint for each participant will be determined from ivabradine use at 180 days evaluated as a binary outcome.

2.5.2 Secondary Endpoints

The secondary endpoints are:

1) Heart rate assessments

   a)   Change in heart rate from baseline to 180 days

   b)   Heart rate at 180 days

   c)   Proportion of participants with heart rate < 70 bpm at 180 days

2) Change in symptoms and quality of life from baseline to 180 days as assessed by:

   a) KCCQ

   b) PGA

2.5.3 Tertiary endpoints

Tertiary endpoints are

1) Beta-blocker use at 180 days as assessed by the:

    a) Proportion of participants on beta-blocker at 180 days

    b) Proportion on target dose[1]

    c) Proportion discontinuing beta-blockers at 180 days and

    d.) Mean change in beta-blocker dose from discharge to 180 days.

2). Ivabradine use at 180 days as assessed by the:

    a) Proportion of appropriate[2] participants with any initiation[3] of ivabradine at 180 days

    b) Proportion of appropriate participants at the maximum dose of ivabradine at 180 day.

    c) Mean dose of ivabradine achieved at 180 days.

3). Tolerability of ivabradine and events of interest:

    a) Symptomatic bradycardia

    b) Symptomatic hypotension

    c) Other symptoms leading to ivabradine discontinuation

4). Summary of barriers to acquisition of ivabradine

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[1] Beta-blocker target dose is defined as participants who receive Carvedilol equivalent total daily dose of 50 mg
[2] Appropriate participants are defined as participants who have a sinus rhythm (participants excluding those with AF) and heart rate of $\geq$70 bpm. For participants missing 180 day ECG, results from the baseline ECG are used to determine appropriateness.
[3] Receiving ivabradine at any time point during the study.

3 DATA SOURCES

Clinical data are collected within the IBM Clinical Development (IBM CD, formerly eCOS) database. Protocol deviation data are collected within the Clinical Trial Management System (CTMS) database.

4 PARTICIPANT DISPOSITION

The number of participants randomized, the number who dropped out early and the number that completed[4] the study will be summarized by randomization arm and overall.

5 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

5.1 Demographics and Baseline Characteristics

Participant demographics will be summarized by randomization arm using descriptive statistics (mean, SD, median, inter-quartile range, min and max) for continuous and counts (percentages) for categorical variables. Demographics will include age, sex, race and ethnicity. Baseline characteristics will include BMI, LVEF and number of prior HF hospitalization, medical history and baseline medications.

5.2 Vital Signs and NYHA Class

Participant vital signs will be summarized by randomization arm over time and analyzed with a mixed model approach, described in Appendix 2. Statistical test for the treatment and the

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[4] Completers are participants who had an in-person day 180 visit.

treatment * time interaction will be done. -The vital signs   summarized include heart rate[5], systolic blood pressure, diastolic blood pressure and weight. NYHA class will be summarized by randomization arm in shift tables from baseline to worst post-baseline and baseline to 180 days. Improvement (worsening) will be evaluated using the Chi-Square test. Improvement is defined as moving from a higher NYHA class to a lower class from baseline. Worsening is defined as moving from a lower class to a higher class from baseline.   A data listing of vital signs and NYHA class will be presented.

5.3   Medical History

Detailed information from the relevant medical history is reviewed during screening for each body system. Incidences of medical diagnostic conditions found during assessment will be tabulated by randomization arm.

5.4   Clinical Laboratory Results

 Descriptive summary of lab results of BNP and NT-proBNP[6] will be presented by randomization arm over time. Moreover, summary change from baseline to 180 days will be presented by randomization arm. The data will be analyzed using the mixed model approach described in Appendix 2 after log transformation to correct the highly skewed nature of the data. A data listing of the lab measures BNP and NT-proBNP will be presented.

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[5] The primary source of heart rate (at baseline and 180 days) is ECG assessment, if ECG assessment was not done at the 180 day visit, heart rate from vital signs assessment is used.
[6] BNP and NT-proBNP labs are deemed most relevant for this presentation.

6 MEDICATIONS

A summary of medication usage will be presented by randomization arm over time. The summary will show the frequencies and percentages of participants using the medications. Beta-blocker and Ivabradine doses taken will be summarized by randomization arm. Beta-blocker dose descriptive summary will be will be presented in Carvedilol equivalent unit. Reasons for not taking beta-blocker will be summarized as frequencies and percentages by randomization arm over time. Dose data will be analyzed using the mixed model approach described in Appendix 2. A data listing of the medications will be presented.

7 PROTOCOL DEVIATIONS

Protocol deviations will be summarized as frequencies and percentages by deviation type on a participant basis. A data listing of protocol deviations will also be presented.

8 SAFETY ASSESSMENTS

8.1 12-Lead ECG

Summary of ECG findings will be presented by randomization arm by assessment time point. Specifically, frequencies and percentages of rhythm, and descriptive summaries of QRS duration and QTc interval will be presented at baseline and 180 days post-discharge. ECG data will be analyzed using the Wilcoxon rank sum test. A data listing of ECG findings will be presented.

8.2 Adverse Events

Adverse events (AEs) will be summarized for each randomization arm by body system and preferred term using MedDRA. The adverse events include events of interest, serious and unexpected events, and events which are related to ivabradine use in the opinion of site investigators. The summaries will show participant level and event level counts. Events will be sorted alphabetically by body systems and preferred terms. A data listing of adverse events will be presented.

9 ENDPOINT ANALYSES

9.1 Primary Analysis

The primary analysis will be performed on an intention-to-treat (ITT) basis including all randomized participants. Participant who are not assessed at the 180 day visit due to death or other reasons of early termination, and otherwise medication data not being collected will be coded as failures (ivabradine use=0). The primary analysis will be based on the imputed data. For sensitivity analysis, observed ivabradine use will be used. Given that death is a competing risk of ivabradine use, a competing risk analysis will be performed (see section 11).

The primary analysis will be performed with a logistic regression model, with ivabradine use[7] at 180 days as the binary outcome variable and indicator variables for treatment group main effects

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[7] Ivabradine use will be determined from the Ivabradine use pane and will be coded as a "0/1" (no/yes) variable.

and category (0/1) of baseline beta-blocker (BB) use[8]. The treatment effect for the ivabradine at

discharge group will be summarized by the odds ratio and associated 95% confidence interval.

Ivabradine use in the ivabradine arm at 180 days is expected to be higher than in the usual care

arm.

Model (logistic):

Ivabradine use at 180 days= Intercept+ β_1* treatment + β_2* baseline beta-blocker use

> **Hypothesis:**

> **H$_0$: β_1=0**

> **H$_1$: $\beta_1 \neq$0.**

> **The null hypothesis will be rejected if the p-value of the treatment effect is <0.05.**

9.2 Secondary Analyses

1. Heart Rate Assessments
    a. Change in heart rate from baseline to 180 days will be compared across
       randomization groups. Change will be calculated as follows: (Baseline heart rate
       – 180 day heart rate)[9]. Comparisons across randomization groups will be
       performed using a linear model with adjustment for baseline heart rate and beta-
       blocker use. Randomization groups will be included in the regression model as
       main effect.

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[8] Baseline beta-blocker use will be coded as a "0/1" variable with participants who received beta-blocker coded as "1" and those who did not receive beta-blocker as "0".
[9] All change from baseline results presented are calculated similarly.

Heart rate is expected to be lower in the ivabradine arm than the usual care arm.

Thus, change from baseline is expected to be higher in the ivabradine arm.

Model (linear):

Change in Heart Rate (HR) at 180 days = Intercept + β_1* treatment + β_2* baseline HR + β_3* baseline BB use

> **Hypothesis:**
>
> **H_0: $\beta_1 = 0$**
>
> **H_1: $\beta_1 \neq 0$.**

The null hypothesis will be rejected if the p-value of the treatment effect is <0.05

> b. Heart rate in bpm at 180 days in the pre-discharge ivabradine group will be compared to the usual care group. Comparisons across randomization groups will be performed using a linear model with adjustment for the baseline heart rate and beta-blocker use. Treatment groups will be included in the regression model as main effects.

> **Model (linear):**
>
> **HR at 180 days = Intercept + β_1*treatment + β_2* baseline HR + β_3* baseline BB use**
>
> **Hypothesis:**
>
> > **H_0: $\beta_1 = 0$**
> >
> > **H_1: $\beta_1 \neq 0$.**

The null hypothesis will be rejected if the p-value of the treatment effect is <0.05

c. The proportion of participants with heart rate < 70 bpm at 180 days will be evaluated. Differences between the randomization arms will be evaluated using the Chi-square test[10].

2. Changes in symptoms and quality-of-life from baseline to 180 days as assessed by KCCQ and PGA will be evaluated across randomization groups using a linear model with adjustment for the baseline quality-of-life and beta-blocker use. The differences between the randomization arms will be estimated using point estimates and the associated two-sided 95% confidence intervals

Model (linear):

Change in KCCQ at 180 days= Intercept + β_1*treatment + β_2* baseline KCCQ + β_3* baseline BB use

Hypothesis:

H_0: β_1=0

H_1: $\beta_1 \neq 0$.

The null hypothesis will be rejected if the p-value of the treatment effect is <0.05

Change in PGA at 180 days = Intercept + β_1*treatment + β_2* baseline PGA + β_3* baseline BB use

Hypothesis:

H_0: β_1=0

H_1: $\beta_1 \neq 0$.

The null hypothesis will be rejected if the p-value of the treatment effect is <0.05

Missing values of 180 day heart rate, KCCQ and PGA will be imputed if missing values

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[10] If events are rare, p-value from the Fisher's exact test will be reported.

exceed 10% of the observations (see section 12.5).

9.3   Tertiary Analyses

1. Beta-blocker use at 180 days as assessed by the (a) proportion of participants on a beta-blocker at 180-days, (b) proportion on target dose, (c) proportion of participants who are at $\geq 50\%$ target dose (d) the proportion discontinuing beta-blockers at 180 days and (e) the mean change[11] in beta-blocker dose from discharge to 180 days will be compared between the randomization arms. - The mean change of beta-blocker dose will be calculated for participants who provide data at baseline and at 180 days post-discharge visits.

The proportions of participants on beta-blocker, the proportions on target dose, the proportion on at least 50% of the target dose, and the proportions discontinuing beta-blocker at 180 days will be summarized by randomization arms and tested using the Chi-square test. The change in beta-blocker dose from discharge to 180 days will be summarized and compared using the Wilcoxon rank sum test.

2. Ivabradine use at 180 days as assessed by the (a) proportion of appropriate participants with any initiation of ivabradine at 180 days, (b) the proportion of appropriate participants at the maximum dose of ivabradine at 180 day (i.e., 7.5 mg

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[11] Comparing the mean change in beta-blocker dose is interpreted as comparing the distribution of dose changes between the randomization arms.

twice daily), and (c) the mean dose of ivabradine achieved at 180 days will be compared between the randomization arms.

Participants who do not provide the 180 day visit data will be coded as failures (ivabradine=0 and dosage=0.0). The mean dose of ivabradine achieved will be calculated for participants who provide data at 180 days post-discharge visit and using imputed values for the participants who do not provide 180 day visit data. As a sensitivity analysis, data will also be analyzed on observed data without imputing missing values. In addition, ivabradine dosage will be summarized for participants on ivabradine at the 180 day visit.

The proportions of appropriate participants with any initiation of ivabradine and the proportion of appropriate participants at the maximum dose of ivabradine at 180 days will be summarized as incidences by the randomization arms and tested using the Chi-Square test. The dose of ivabradine achieved at 180 days will be summarized and compared using the Wilcoxon rank sum test.

3. The event incidences for the following adverse events will be summarized by the randomization arms.

    a. Symptomatic bradycardia

    b. Symptomatic hypotension

    c. Other symptoms leading to ivabradine discontinuation

Other symptoms leading to ivabradine discontinuation will be determined using data collected in the AE CRF panel. .

Differences between the randomization arms of the events will be tested using the Chi-square test.

4. Barriers to acquisition of ivabradine.

Reasons for not obtaining ivabradine will be summarized by randomization arm over time as classified in the case report form. Frequencies and percentages of the classified reasons will be presented for each visit and overall. Results will be presented as descriptive summaries.

10   CLINICAL EVENTS

The following clinical events occurring within 180 + 14 days will be summarized by randomization arm. The summaries will be presented as incidences and rates.

The clinical events include:

1) Worsening HF defined as hospital admission for worsening signs and/or symptoms of HF or receiving unplanned intravenous (IV) diuretics for HF as an outpatient.

2) HF hospitalization

3) All-cause hospitalization

4) All-cause mortality

5) Composite of all-cause mortality and HF hospitalization

Incidences of the events will be tabulated by randomization arm and differences between the randomization arms will be tested using the Chi-square test.

11 COMPETING RISK ANALYSIS OF DEATH

Participants are at risk of dying before the final visit, and thus death is a competing risk to ivabradine use. In order to account for participants who die prior to the 180 day visit, a competing risk analysis of time to ivabradine discontinuation will be conducted. Participants who die during the study will be coded separately from those who discontinue ivabradine use. The analysis will be performed using the cumulative incidence function (CIF) method with death as an additional censoring variable[12]. The Gray's test (Gray, 1988) will be used to evaluate hypothesis of equality of the cumulative incidence functions.

12 SUB-GROUP ANALYSES

To evaluate differences in ivabradine use among participant sub-groups, pre-specified sub-group analysis will be performed. For each subgroup, the analysis specified for the primary endpoint in section 9.1 will be performed. Accordingly, ivabradine use rates will be summarized by randomization arm, odds ratio with their 95% CI and p-value of the treatment effect will be presented. Also, a forest plot of ivabradine use will be presented.

The sub-groups are:

Variable	Criteria
Age (years)	<75 vs. >=75
Sex:	Male vs. female
Baseline beta-blocker use	Yes vs. No
Race	White vs. Non-white

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[12] Participants who did not receive any ivabradine dose will be censored at time 0.

EF	<25 vs. ≥25
NYHA class	I and II vs. III and IV
Systolic blood pressure	<120 vs. ≥120
GFR	< 60 vs. ≥ 60
Diabetes	Yes vs. No
Etiology of HF	Ischemic vs. Non-ischemic

13 STATISTICAL CONSIDERATIONS

13.1 Data Collection Windows and Conventions

Data will be presented according to the schedule of assessments in the study protocol. The possible visits and windows are baseline, Day 7-14 post discharge, 6 weeks post-discharge (42±14 days), 90 days post-discharge (±7 days), and 180 days post-discharge (±14 days). If participants missed their scheduled window, data collected from clinic visits and entered in the EDC system will be used if clinic visits occurred within 60 days of the assessment window.

Heart rate obtained from ECG assessment is the primary data source. If, however, ECG assessment was not performed, heart rate results from vital signs collected during the scheduled visit or clinical visit close to the visit window will be used.

For participants who are lost to follow-up, the latest date available is used as date of last contact for the purpose of determining their vital status. Lost to follow-up participants whose survival status are ascertained beyond the study period will be censored at 194 days (180 +14). Those whose last contact date falls within the study period will be censored at their date of last contact for any time to event analysis.

13.2 General Analysis Conventions/Rules

All analyzed continuous variables will be summarized using descriptive statistics including number of observations, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum. All analyzed categorical variables will be summarized using frequency counts and percentages. Percentages are calculated out of non-missing values unless stated otherwise. Comparisons of continuous (or discrete ordered) variables between randomization groups will generally be tested using the Wilcoxon rank sum test. For the secondary endpoint (change from baseline of the measures), analyses will be conducted using the general linear model approach. For comparisons over more than 2 time points, when appropriate, mixed effects models[13] will be used to account for correlation within participant observations and assess time-by-treatment interactions (see Appendix 2 for details).Tests of binomial outcomes between randomization groups will generally be done with a Chi-square statistic. Tests of treatment effects will generally be 2-sided, with type I error = 0.05. Interaction tests will generally be done at the 0.10. Statistical significance is determined at a $\leq$ 0.05 alpha level.

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13.3 Documentation Conventions

Statistical analyses will be performed using SAS$^{\circledR}$, version 9.4 or higher (SAS Institute, Cary, NC). Additional statistical software may be used as needed. Where applicable, all the tables and listings will be presented by study randomization arm and overall.

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[13] See Appendix 2 for details

13.4 Verification of SAS® Codes

All tables, listings, and graphs will be verified and reviewed before being considered final. The verification process will ensure that the numbers are produced by a statistically valid method and that the execution of the computations is correct. Suitably qualified personnel who have not been previously involved in the production of the original SAS® code will perform the verification procedures. Methods of verification will include independent programming of all analysis datasets and comparison to data listings as specified in the verification plan. Tables will be reviewed for accuracy, consistency with this analysis plan, consistency within tables, and consistency with corresponding output. Once verification is complete, all documentation of the verification process will be filed in a statistical programming documentation as required by the Statistical Standard Operations Procedure (CT Stats SOP ST-S-010, 11.0, 31Jan2017, V.E) of the Duke Clinical Research Institute (DCRI).

13.5 Handling of Missing Data

All efforts will be made to make sure all data needed for the analyses outlined in the SAP are complete. However, it is possible that some data will be missing. Missing data is a common problem in clinical research. It reduces statistical power (the probability that the test will reject the null hypothesis when it is false) and results in biased parameter estimates (Kang, 2013). Outcomes for participants who do not provide data during the 180 day visit will be imputed as failures. Missing heart rate, PGA and KCCQ values will be imputed for the final (180 day) visit using multiple imputation technique if more than 10% of the measures are missing.

It is expected that missing 180 day visit values constitute > 10% of the secondary endpoints (Heart rate, KCCQ and PGA). Thus, multiple imputation (MI) will be performed and presented for the ITT and Treated populations, respectively.

Imputation will be conducted using PROC MI and imputed data analyzed with PROC MIANALYZE in SAS 9.4.

The following variables shall be used in the imputation:

AGE, SEX, RACE, ETHNICITY, WEIGHT, NYHA class, LVEF, and baseline value of the imputed variable) – For NYHA class, WEIGHT and LVEF, baseline values will be used.

RACE shall be recoded to: White, Black and Others (combining American Indian, other, and mixed - as they are of very low frequency)

Results of the imputation shall be presented as the primary result of the secondary endpoints. A total of 25 imputations will conducted for each imputed value.

Sensitivity analyses will be conducted by analyzing these endpoints with and without imputation.

13.6 Exploratory Analyses

All analyses that are not specified as the primary or the secondary or tertiary endpoints are to be considered exploratory. All exploratory analyses are considered descriptive and are used as further hypothesis generating endeavors and no p-values will be calculated.

13.7 Multiple Comparisons

No multiple comparison adjustment will be used implemented in this study.

14 REFERENCES

Gray, R. (1988), "A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk," The Annals of Statistics, 16, 1141–1154.

Kang, H. (2013, May). Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3668100/

PRIME-HF. (July 19, 2017). PredischaRge Initiation of Ivabradine in the Management of Heart

Failure (PRIME-HF), Protocol Version 3.

15   APPENDICES

Appendix 1

Data Sources for Endpoints

1. Ivabradine use

     a) Ivabradine use (1/0) at 180 days comes from either the current medications data (CM) or the ivabradine usage data (DRG).
     If CM.CMIVA=1 and VISITID=50 or DRG.DRIVA=1 and VISITID=50. If missing then it is imputed to 0. (Note: analysis will also be done without imputation).

     b) Ivabradine dose change from baseline to 180 days
     Ivabradine use and dose at baseline comes from the ivabradine initiation in hospital (EXH) data EXH.EXRECH (use) and EXH.EXLDH (dose) EXH.EXRECH (use) and EXH.EXLDH (dose) (VISITID=10) and ivabradine obtaining the first time (outpatient) (EX) EX.EXREC and EX.EXPDOS (VISITID=60 study wide to be merged in)

     For other time points use the ivabradine usage data DRG.DRIVA (use) DRG.DRDSG (dose). Missing doses will be imputed to 0. (Note: analysis will also be done without imputation).

     Dose change from baseline to 180 days = EXH.EXLDH, EX.EXDOS (VISITID=10)- DRG.DRDSG (where VISITID=50)

     c) Proportion with any initiation
     If participant received ivabradine at any time during the visits
     If EXH.EXRECH=1 or EX.EXREC=1 or CM.CMIVA=1 or DRG.DRIVA=1 at any visit then ANYIVA=1 else ANYIVA=0; (Note: No imputation of missing ivabradine use occurs for this derivation)

     d) Proportion on maximum dose at 180 days
     Use ivabradine usage data
     If DRG.DRSG =15 (mg) and VISITID=50 then on ivabradine maximum dose=1; else if DRG.DRSG not missing on ivabradine maximum dose=0.

2. Heart rate (HR)

Heart rate is obtained from the ECG (EG) data where available. If 180 day ECG data is not available, heart rate from the vitals data for the visit or from the medical record close to the visit is used. For participants who have two baseline ECG measurements average is taken prior to calculating change from baseline.

     a) HR change from baseline to 180 days = EG.ECGHR (where VCISITID=10) – EG.EGHR (where VISITID=50) if 180 day ECG is not missing.
or

= EG.ECGHR (where VISITID=10)-VS.PULSE (where VISITID=50) if 180 day ECG is missing.

b) HR at 180 days= EG.ECGHR (where VISITID=50) if 180 day ECG is not missing
or
=VS.PULSE (where=VISITID=50) if 180 day ECG is missing
Note: missing HR at 180 days will be imputed using MI technique per (Section 12.5)

c) Proportion of participants with heart rate < 70 bpm at 180 days
If HR at 180 days (see b) above) is < 70bpm (but not missing) then HR less than 70 bpm=1; else HR less than 70 bpm=0.

3. Kansas City Cardiomyopathy Questionnaire (KCCQ)

KCCQ change from baseline to 180 days is obtained from the KCCQ analysis (KCCQD) data created from the KCCQ survey using the KCCQ scoring algorithm.
KCCQ change= KCCQD.KCQOSBL –KCCQD.KCCQOSS (where VISITN=50)

Note: missing KCCQ values at 180 days will be imputed using MI technique per (Section 12.5)

4. Patient Global Assessment (PGA)

PGA change from baseline to 180 days is obtained from the PGA (PGA) data.
PGA change from baseline to 180 days= PGA. PGAMM (where VISITID=10) – PGA.PGAMM (Where VISITID=50)

Note: missing PGA values at 180 days will be imputed using MI technique per (Section 12.5)

5. Beta-blocker (BB) use

Beta-blocker use measures were obtained from the current medication (CM) data
Baseline BB use at baseline = CM.CMBB =1 where VISITID=10).

a) BB use at 180 days = CM.CMBB=1 (where VISITID=50)
b) Proportion on target dose at 180 days (doses were calculated based on Carvedilol equivalent basis).
If VISITN =50 and Carvedilol equivalent dose = 50 mg then on target dose=1 (yes); else if Carvedilol equivalent dose is not missing on target dose=0(no).
c) Proportion on 50 % of target dose (Carvedilol equivalent) at 180 days.
If Carvedilol equivalent dose is at least 25 mg then on 50% target dose=1; else if Carvedilol equivalent dose is not missing on 50% target dose =0.
d) Proportion of participants discontinuing (No beta-blocker use at 180 days in those who used it during an early visit)
e) Mean change in dose (Carvedilol equivalent)
Change in dose from baseline to 180 days (converted to Carvedilol equivalent dose) = CM.CMBBDS (where VISITID=10) – CM. CMBBDS (where VISITID=50)

6. **Tolerability of ivabradine and events of interest**

   a) Symptomatic bradycardia

   Use the EVENT data to get unique participant level status.
   If EVENT.EVBRDC=1 and (non-missing EVENT.EVDT-PATIENT.DISDT <=194)
   then symptomatic bradycardia=1; else if participant is assessed at any time point,
   symptomatic bradycardia=0.

   b) Symptomatic hypotension

   Use the EVENT data to get unique participant level status.
   If EVENT.EVHYPO=1 and (non-missing EVENT.EVDT-PATIENT.DISDT<=194) then
   symptomatic hypotension=1; else if participant is assessed at any time point,
   symptomatic hypotension=0.
   c) Other symptoms leading to ivabradine discontinuation unique participant level status
   Other symptoms leading to ivabradine discontinuation is obtained from the AE data.
   If AE.AETYP=3and (non-missing AE.AESTDT-PATIENT.DISDT <=194) then other
   symptoms leading to ivabradine discontinuation=1;
   Else if participant is assessed at any time point, other symptoms leading to ivabradine
   discontinuation=0;

7. **Summary of clinical events**

a) All-cause mortality
   Death is obtained from the DEATH data
   If DEATH.DTHDT is not missing then DEATH=1; else if participant is assessed at any
   time point, DEATH=0.

   Restrict deaths to within 194 days of discharge. (non-missing DEATH.DTHDT –
   PATIENT.DISDT <= 194).

b) Worsening heart failure unique per participant
   Worsening heart failure is defined as hospital admission for worsening signs and/or
   symptoms of HF or receiving unplanned intravenous (IV) diuretics for HF as an
   outpatient is obtained from hospitalization data (REHOSP) and ER/Clinic Visits
   (ERCLIN) data sets.
   If REHOSP.RELHF=1 or ERCLIN.ERIVTMT=1 then Worsening heart failure =1;
   else if participant is assessed at any time point, worsening heart failure =0.
   Restrict HF hospitalizations or ER visits for unplanned IV diuretics to within 194
   days of discharge. (non-missing REHOSP.HOSPDT – PATIENT.DISDT <= 194)
   and (ERCLIN.ERVISDT- PATIENT.DISDT <=194).

c) HF hospitalization unique per participant

HF hospitalization is obtained from the hospitalization data (REHOSP),
If REHOSP.RELHF=1 then heart failure hospitalization=1; else if participant is assessed at any time point, heart failure hospitalization=0.
Restrict HF hospitalizations to within 194 days of discharge
(non-missing REHOSP.HOSPDT – PATIENT.DISDT   <= 194).

d) All-cause hospitalization unique per participant
> All-cause hospitalization is obtained from the hospitalization data (REHOSP).
> If REHOSP. HOSPDT is not missing then all-cause hospitalization =1; else if participant is assessed at any time point, all-cause hospitalization=0.
> Restrict all-cause hospitalizations to within 194 days of discharge
> (non-missing REHOSP.HOSPDT – PATIENT.DISDT   <= 194).

e) Composite endpoint of mortality or HF hospitalization
> If DEATH (see (a) above) =1 or HF hospitalization (see (c) above)=1 then Composite endpoint =1;
> Else if both are =0 then Composite endpoint=0.
> Event is restricted to within 194 days of discharge per component parts.

8) Barriers to acquisition of ivabradine

Barriers to the acquisition of ivabradine comes from two sources. Barriers to the first time acquisition of ivabradine comes from the ivabradine obtaining first time data (EX). Get variables EX.EXPRC, EX.EXPHRM, EX.EXAE, EX.EXLBL, EX.EXPDC, EX.EXDDC, EX.EXPAN, EX.EXPAS, EX.EXINS, EX.EXAPN, EX.EXAPA, EX.EXAPD, and EX.EXOTH (Note: VISITID=60)

For subsequent visits, the data sources is the ivabradine usage (DRG) data (Note: VISITID=20, 30, 40, 50). Get variables
DRG.DRPRC, DRG.DRPHRM, DRG.DRAE, DRG.DRLBL, DRG.DRPDC, DRG.DRDDC, DRG.DRPAN, DRG.DRPAS, DRG.DRINS, DRG.DRAPN, DRG.DRAPA, DRG.DRAPD, and DR.DROTH

Note: Since all reasons that apply are checked in both data sets, create separate (1/0) variables for each of them.

Summarize reasons from the (1/0) variables.

9) Treatment

Treatment data come from the EDC system in the DAT_RAND data. The data shows both the treatment codes and their descriptions.

Appendix 2

Mixed effects model analysis of repeated measures

Data were collected over time on continuous variables such as vital signs, labs and medication doses. Since within participant observations are likely to be correlated, using an analytic method that accounts for the correlation is appropriate. The mixed effects modeling approach provides a mechanism for accounting such correlations. Further, the procedure can include data from participants with partially complete data, and unequally spaced measurements which are evident in the data collected. Thus, for measurements that are collected over more than two time points, the mixed effects modeling approach is used. The model chosen includes treatment, time, and time by treatment interactions. Time will be modeled as a continuous variable which is the time to actual measurement expressed as days from randomization (DAYS). The model will assume a linear relationship between response measure and time, and allow for the intercept and slope of the linear model to differ by treatment group

The model posited is:

Response (MEASURE) = intercept + Treatment (TRT) + Time (DAYS) + Treatment (TRT)*Time (DAYS)

However, the test for treatment effect in the above model tests effects at baseline which is of little value.

It is more valuable to test treatment effects after the intervention had time to affect outcomes. Accordingly, the 180 day time point is recoded to time zero as follows.

RDAYS=DAYS-180

And fit the model:

Response (MEASURE) = intercept + Treatment (TRT) + Time (RDAYS) + Treatment (TRT)*Time (RDAYS)

The within-patient residual covariance matrix will be modeled using a compound symmetry structure, which assumes equal correlation between measurement times within a patient. The residual covariance matrix will be assumed to be the same in the two treatment groups.

Tests of fixed effects in the model will be calculated using the Kenward-Roger method for estimating denominator degrees of freedom.

To fit the model the mixed effects model below is used;

```
proc mixed data=data;
Class TRT SUBNUM RDAYSC;  *RDAYSC is defined to be equal to RDAYS;
Model MEASURE= TRT RDAYS TRT*RDAYS / ddfm=KR;
Repeated RDAYSC /sub=SUBNUM TYPE=CS; /Compound symmetry covariance structure/
Run;
```

The test for treatment effect (TRT) in this model evaluates treatment effects at 180 days while the interaction term (TRT*RDAYS) tests whether treatment effects differ over time, i.e., whether the slope (average change in measure per unit time) differs by treatment. The p-values for the treatment effect and treatment * time interaction (when appropriate) will be reported.

If the equality of variance assumption does not hold (the variance differs a lot over time or across groups), the following code will be used. The model allows for unstructured covariance matrix.

```
proc mixed data=data method=reml;
  class TRT VISIT SUBNUM;
  Model Measure = TRT RDAYS TRT*RDAYS/ solution ddfm=KR;
  Repeated VISIT / subject=SUBNUM type=UN group=TRT;
  run;
```

Addendum to SAP version 2.0 (Dated 11January 2019)

Participant 107-002 was on Ivabradine until the day before (15 August 2018) the date of 180 day visit (16 August 2018).

On the 180 day visit:

To the question "Is subject currently taking Ivabradine" the site answered "No" due to "Physician decision".

So according to the CRF data, the participant was coded as "Ivabradine at 180 days=No"

However, the participant was on Ivabradine for a total of 210 days only missing a dose for one day.

According to the study PI, coding Ivabradine status of this participant as "Yes Ivabradine at 180 days=Yes" is most appropriate.

Consequently, coding of Ivabradine status at 180 days has been modified to "Ivabradine at day 180 = Yes" if a participant had last dose of Ivabradine administered on day 166 (180 $\pm$ 14 days) or later.

This action was take prior to unblinding treatment to avoid bias.

Addendum 2 to SAP version 2.0 (Dated 11 January 2019)

Modification to change calculation

The PRIME-HF protocol (Version 3, Dated July 19, 2017 section 10.4 on page 60), specifies that change in heart rate (HR) from baseline to 180 days be calculated as (baseline heart rate – 180-day heart rate). Accordingly, the statistical analysis plan (SAP) version 2.0 specified that changes (for HR and all other measures) to be calculated as baseline line- 180 days results for all change calculations. Post database lock and treatment unblinding, a decision was made to calculate change as 180 day – baseline results so that change signs align with the direction of change (increase or decrease