Predischa**R**ge Initiation of **I**vabradine in the **M**anagement of **H**eart **F**ailure **(PRIME-HF)**

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Duke Clinical Research Institute

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Protocol Version and Amendment Tracking

Version Number/Amendment	Approval Date
Version 1	May 2, 2016
Version 2	June 29, 2016
Version 3	July 19, 2017

Protocol Synopsis

Name of Study Sponsor	Dr. Robert Mentz, Duke Clinical Research Institute
Product	Ivabradine
Protocol Title	Predischarge Initiation of Ivabradine in the Management of Heart Failure
Main Criteria for Inclusion	Acute HF hospitalization
Study Objective	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 result in a greater proportion of participants using ivabradine at 180 days. To explore barriers to acquisition of new HF therapies in routine clinical practice.
Study Design	A multi-center, patient-level, randomized, open-label study of 180 days duration following index hospitalization in approximately 450 patients.
Treatment Regimen	Pre-discharge initiation of twice-daily oral ivabradine (starting at 5mg BID with encouraged dose titration to 7.5mg BID) versus usual care (i.e., post-discharge initiation of ivabradine at discretion of routine physician) for 180 days. Patients randomized to pre-discharge ivabradine who are not able to afford medication will enter a registry of ivabradine-eligible paitents with documentation of medication acquisition challenges.
Duration of Study Participation	180 days
Number of Subjects	Approximately 450
Number of Sites	Approximately 50 US
Primary Endpoint	Proportion of participants taking ivabradine at 180 days
Secondary Endpoints	Heart Rate Assessments: change in heart rate from baseline to 180 days; heart rate at 180 days; and proportion of patients with heart rate < 70 bpm at 180 days

Name of Study Sponsor	Dr. Robert Mentz, Duke Clinical Research Institute
Product	Ivabradine
	Changes in symptoms and quality of life from baseline to 180 days by KCCQ and PGA

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Abbreviations

bpm	Beats per minute
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
HF	Heart Failure
HFrEF	Heart failure with reduced ejection fraction
IRB	Institutional Review Board
IV	Intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left Ventricular ejection fraction
NYHA	New York Heart Association
PGA	Patient Global Assessment

Executive Summary

Title	**P**redischa**R**ge initiation of **I**vabradine in **M**anag**E**ment of **H**eart **F**ailure **(PRIME-HF)**
Patient Population	Post-Acute Heart Failure Syndrome with left ventricular ejection fraction (LVEF) ≤35%, New York Heart Association (NYHA) class II-IV symptoms despite guideline-directed medical therapy, documented clinical stability, and sinus rhythm with a resting heart rate of ≥70 beats per minute (bpm).
Location	Approximately 50 clinical centers in the United States
Brief Rationale	Heart failure (HF) affects over 5 million adults in the United States alone and the prevalence is expected to increase.[1] Despite promising advances in the treatment of chronic heart failure with reduced ejection fraction (HFrEF),[2] patient outcomes remain poor, especially after a hospitalization for HF, and there is an unmet need for novel treatment strategies. Previous data also suggest that the hospital setting may provide a unique opportunity for patients with HF to initiate guideline-directed medical therapy.[3] Ivabradine is an orally available, specific inhibitor of the I_f current in the sinoatrial node recently approved for use for patients with HFrEF by the Food and Drug Administration. A double-blind, randomized, placebo-controlled trial demonstrated that heart-rate reduction with ivabradine improves clinical outcomes for patients with chronic, symptomatic HF.[4] The initiation of ivabradine specifically in patients following stabilization for acute HF has not been evaluated. Since ivabradine was FDA approved relatively recently, this study also serves as a strategy trial to explore drug acquisition for a drug that has been proven efficacious to the heart failure population and has been added to 2016 ACC/AHA/HFSA

	guidelines, however, has not been adopted broadly into clinical practice. Ivabradine is not being provided for this study. Data are being captured to assess the number of subjects able to obtain ivabradine pre and post discharge as well as the barriers to obtaining ivabradine and reasons for non-initiation.
Study Design	A multi-center, patient-level, randomized, open-label study of 180 days duration following index hospitalization in approximately 450 patients. Given barriers to adoption of relatively novel therapeutics into clinical practice, those patients who are randomized to pre-discharge ivabradine but are not able to afford medication will enter a registry of ivabradine-eligible patients with documentation of the medication acquisition challenges experienced by the patient and provider.
Treatment	Pre-discharge initiation of twice-daily oral ivabradine (starting at 5mg BID with encouraged dose titration to 7.5mg BID) versus usual care (i.e., post-discharge initiation of ivabradine at discretion of routine physician) for 180 days.
Primary Objective	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.
Secondary Objectives	To assess the impact of predischarge 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)
Tertiary Objectives	To explore the impact of predischarge initiation of ivabradine on: 1) Evidence-Based Implementation a) Assessments of beta-blocker use at 180 days (e.g., proportion on beta-blocker, proportion on target dose, mean change in dose)

	b) Other assessments of ivabradine use at 180 days (e.g., mean dose, proportion with any initiation, proportion on maximum dose) i) 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 and events of interest a) Symptomatic bradycardia b) Symptomatic hypotension c) Other symptoms leading to ivabradine discontinuation To explore barriers to ivabradine acquisition in routine clinical practice.
Summary of Clinical Events	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) All-cause mortality
Primary Endpoint	Proportion of participants taking ivabradine at 180 days.
Secondary Endpoints	1) Heart Rate Assessments a) Change in heart rate from baseline to 180 days b) Heart rate at 180 days c) Proportion of patients with heart rate <70bpm at 180 days 2) Changes in symptoms and quality of life from baseline to 180 days as assessed by: a) KCCQ b) PGA
Tertiary Endpoints	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) the proportion

	discontinuing beta-blockers at 180 days and (d) the 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 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 twice daily), and (c) the 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.
Summary of Clinical Events	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) All-cause mortality
Abbreviated Study Flow	1) Patients with a reduced LVEF ($\leq$35%) will be identified during a hospitalization with acute HF. Patients will be screened throughout the hospital stay though heart rate will specifically be assessed ***following stabilization***. 2) Prior to discharge, clinical stability will be assessed including blood pressure and heart rate criteria. Patients with a pre-discharge blood pressure of $\geq$90/50 mm Hg and heart rate $\geq$ 70 bpm will be eligible and consent will be obtained. Subject should not have a planned/scheduled up-titration of beta-blocker in the following 4 weeks. However, adjustments of background therapy can be made at any point during the study period at the discretion of the treating physician. Patients can be consented and randomized prior to the day of discharge as long as they meet entry criteria.

	3) Consented patients will undergo baseline examination, KCCQ, and PGA. Baseline heart rate will be assessed on at least one 12-lead ECG (screening ECG may be used). 4) Participants will then be randomized to predischarge initiation of ivabradine or usual care. Randomization will be stratified by clinical site. 5) Participants randomized to predischarge initiation of ivabradine should receive at least the initial dose of 5mg BID *prior* to discharge from the hospital if possible. 6) If the patient is randomized to pre-discharge initiation, the study team and/or inpatient care team (e.g., providers and care coordinator) should initiate the process to acquire outpatient medication, explore patient costs and consider support options for the patient. If the patient is not able to pay for the medication, they will continue in the study and will enter a registry of ivabradine-eligible patients with documentation of the medication acquisition challenges experienced by the patient and provider. 7) Consistent with current HF guidelines,[2] all participants should have a follow-up visit within 7-14 days of hospital discharge. Heart rate and systolic blood pressure will be assessed at this clinical visit. For participants randomized to predischarge initiation of ivabradine and on ivabradine 5mg BID, the heart rate may be used to adjust the dose the dose to 2.5mg BID or 7.5mg BID. For participants randomized to usual care, ivabradine may be initiated at the provider's discretion. 8) All participants will have a second follow-up study visit 6 weeks (42 +/- 14 days) post-discharge. Heart rate, systolic blood pressure and quality of life (KCCQ and PGA) will be assessed. For participants already taking ivabradine in either treatment group, the heart rate may again be used to adjust the dose of ivabradine. For participants not yet receiving ivabradine, it may be initiated at the provider's discretion. 9) All participants will receive a 90 (+/-7) day post-discharge phone call by site to assess for event status and tolerability of ivabradine.

	10) All participants will have a final study visit at 180 (+/-14) days post-discharge. Heart rate (on exam and 1 ECG), systolic blood pressure and quality of life (KCCQ and PGA) will be assessed. The treating physician may initiate ivabradine per usual care clinical practice.

1 INTRODUCTION

1.1 Background

Heart failure is a major public health issue. More than 5 million Americans have HF and the prevalence is expected to increase as the population ages and survival from coronary, hypertensive, and valvular heart disease improves.[1,5] Data from randomized clinical trials have established the efficacy of a number of medical and device therapies for patients with chronic HFrEF,[2] but patient outcomes remain poor, especially after a hospitalization for heart failure. The 1-year mortality rate after a HF hospitalization is 20-30%, and this number has been relatively unchanged over the past decade.[6,7] ***These data suggest that there is an unmet need for novel treatment strategies and supports the assessment of new approaches in the post-acute HF setting.***

There is also wide variation in the implementation of clinical trial evidence into routine practice. Previous data highlight a multi-year gap between the generation of new evidence through clinical trials and the adoption of the data into routine clinical practice.[8,9] This gap in care translates into many unnecessary deaths and hospitalizations each year for patients with HFrEF.[10] While there are multiple reasons for this quality gap, clinical inertia has most often been noted as a major barrier. Ivabradine have been approved for use in Europe for several years[11] for patients with symptomatic chronic HFrEF (LVEF $\leq$35%) and a heart rate $\geq$75 bpm on guideline-directed medical therapy (or intolerance/contra-indication to beta-blocker use). Ivabradine was recently approved for use in the United States. However, ***no US data exist regarding the potential adoption of ivabradine into routine clinical care***.

Since ivabradine is a newly approved drug, this study also serves as a strategy trial to challenge study sites to explore drug acquisition for a drug that has been proven efficacious to the heart failure population and has been added to 2016 ACC/AHA/HFSA guidelines, however, has not been adopted rapidly into clinical practice. Ivabradine is not being provided for this study. Data are being captured to assess the number of subjects

who were able to obtain ivabradine pre and post discharge as well as the barriers to acquisition.

Previous data for patients with HFrEF suggest that ***the hospital setting may provide a unique opportunity for patients to initiate guideline-directed medical therapy***. In the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in HF (IMPACT-HF) study, patients with an LVEF<40% hospitalized for HF that were started on carvedilol prior to hospital discharge were more likely to be on a beta-blocker at 60 days post-randomization compared to those receiving usual care.[3] These improvements in care were achieved without increasing side effects or index hospitalization length of stay. Similar to beta-blockers and other medical therapies for HF, ivabradine was initially studied in patients with chronic HF.[4] ***The initiation of ivabradine specifically in patients following stabilization for acute HF has not been evaluated.***

1.2 Prior data

The Systolic Heart failure treatment with Ivabradine Trial (SHIFT) enrolled 6,558 patients with chronic, symptomatic heart failure with reduced ejection fraction.[4] In this double-blind, randomized, placebo-controlled trial, patients treated with ivabradine were less likely to experience the primary composite endpoint of cardiovascular death or hospitalization for HF (HR 0.82, 95% CI 0.75, 0.90). These results support that ivabradine represents a novel treatment strategy for patients with HFrEF already on optimal medical therapy including a beta-blocker.

A prior study of data from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry suggest that a substantial proportion of patients hospitalized with HFrEF have an elevated heart rate at discharge.[12] This study analyzed 10,696 hospitalizations of patients with acute HF from United States hospitals with a LVEF <40%. Patients with a history of atrial arrhythmia or with a pacemaker or cardiac resynchronization therapy were excluded. At the time of discharge, the median heart rate was 72 bpm (interquartile range, 65-80 bpm)

for patients on high-dose beta-blockers and increased to 80 bpm (interquartile range, 70-89 bpm) for patients on no beta-blockers. Most patients, 7647 (71%), had a discharge heart rate of ≥70 bpm, including 1460 of 2301 patients (63%) discharged on ≥50% of target dose of beta-blocker therapy.

1.3 Rationale

Outcomes for patients with HFrEF remain poor after a hospitalization for HF, and there is an unmet need for novel treatment strategies in HF. Previous data suggest that the hospital setting may provide a unique opportunity for patients with HF to initiate guideline-directed medical therapy.[3]

A double-blind, randomized, placebo-controlled trial demonstrated that heart-rate reduction with ivabradine improves clinical outcomes for patients with chronic, symptomatic HF[4], but the initiation of ivabradine in patients following stabilization for acute HF has not been evaluated.

2 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***.

2.1 Primary Objective

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 Secondary Objectives

To assess the impact of predischarge 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)

2.3 Tertiary Objectives

Tertiary objectives will be to explore the impact of predischarge 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.

3 SUBJECT SELECTION

3.1 Study Population

Patients suitable for this protocol are individuals with chronic HF who are hospitalized with acute heart failure, have achieved clinical stability and have an LVEF≤35% and heart-rate ≥70 bpm in normal sinus rhythm. Subjects should not have a planned/scheduled uptitration 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.

3.2 Inclusion Criteria

To be eligible for the study subject must meet the inclusion criteria listed below:

1) Hospitalized with acute HF (primary or secondary diagnosis) based on clinician assessment
2) A prior clinical diagnosis of HF (i.e., not a new diagnosis of heart failure during the current hospitalization)
3) Most recent LVEF ≤ 35% and within 6 months of randomization or LVEF ≤ 25% within 12 months of randomization
4) On optimal guideline-directed medical therapy for HFrEF (or previously deemed intolerant) as determined by the clinician including ACE-inhibitors or angiotensin receptor antagonists or neprilysin inhibition, aldosterone receptor antagonists, and maximally-tolerated doses of beta-blockers at the time of current evaluation (which may differ from long-term targets)
    - Maximally-tolerated doses of beta-blockers will be defined by the treating physician when considering aspects such as current dose relative to the target dose used in clinical trials, patient heart rate and blood pressure, and patient symptoms
    - Patients with intolerance or contraindication to beta-blocker use are eligible for enrollment (details will be documented in the case report form)

5) Age ≥18 years
6) Willingness to provide informed consent from the subject (or at the discretion of the local IRB, the subject's guardian or legally authorized representative [LAR])
7) On the day of planned randomization, all participants:
   - Must be in sinus rhythm with a resting heart rate ≥70 bpm as measured on ECG or a 10 second rhythm strip
   - Must have a blood pressure of ≥90/50 mm Hg

3.3 Exclusion Criteria

If a subject meets any of the following criteria, he or she cannot be enrolled in the study:

1) Documented plan for uptitration of beta-blocker in the following 4 weeks
2) Permanent atrial fibrillation or atrial flutter
3) Patients with recent atrial fibrillation or flutter defined by either precipitating the current HF hospitalization or occurring during the current HF hospitalization
4) History of untreated sick sinus syndrome, sinoatrial block, or second and third degree atrio-ventricular block
5) Pacemaker with atrial or ventricular pacing (except biventricular pacing) ≥40% of the time
6) Family history or congenital long QT syndrome
7) Recent myocardial infarction (<2 months prior to screening) [troponin elevation secondary to acute HF as determined by the clinician is not an exclusion]
8) Acute or chronic severe liver disease as evidenced by any of the following: encephalopathy, variceal bleeding, INR > 1.7 in the absence of anticoagulation treatment
9) Creatinine clearance <15 mL/min within 48 hours of screening that was not due to acute kidney injury that resolved
10) Planned mechanical circulatory support within 180 days

11) Pregnant or breastfeeding women. Women of child-bearing potential should use effective contraception
12) Medical conditions likely to lead to poor non-cardiac survival at 180 days (e.g., cancer)
13) Inability to comply with planned study procedures
14) If the following medications are needed at inclusion or during the study:
    a) Non-dihydropyridine calcium channel blockers (e.g., diltiazem and verapamil)
    b) Class I anti-arrhythmics (e.g., quinidine, procainamide, lidocaine, phenytoin)
    c) Strong inhibitors of cytochrome P450 3A4 (CYP3A4), including some macrolide antibiotics (e.g., clarithromycin, erythromycin), cyclosporine, antiretroviral drugs (e.g., ritonavir, nelfinavir), and systemic azole antifungal agents (e.g., ketoconazole, itraconazole), and nefazodone
    d) Inducers of cytochrome P450 3A4 (CYP3A4) including St. John's wort, rifampicin, barbiturates, and phenytoin.
    e) Treatments known to be associated with significant prolongation of the QT interval, including sotalol

4 STUDY DESIGN

4.1 Overview of Study

The PRIME-HF study is a multi-center, patient-level, randomized, open-label study of approximately 450 patients with reduced LVEF of ≤35% and heart-rate ≥70 bpm who are being discharged from the hospital following stabilization from acute HF and will be randomized to a treatment strategy of predischarge initiation of ivabradine or usual care.

4.2 Screening Phase

Patients admitted with acute HF will be screened for basic entry criteria. To be eligible, patients should be hospitalized with acute HF (primary or secondary diagnosis). Patients hospitalized with acute HF will be treated with standard therapy at the discretion of the treating physician including adjustment of guideline-directed medical therapies such as beta-blockers. Patients will be screened for potential eligibility during the index hospitalization but study inclusion criteria including clinical stability, heart rate, and blood pressure will be assessed once the patient is stable and approaching discharge. Patients can be consented and randomized prior to the day of discharge as long as they meet entry criteria.

4.3 Clinical Evaluation Prior to Randomization

When patients are approaching the time for discharge, final study eligibility will be determined. Prior to discharge, clinical stability will be assessed to ensure resolution of signs and symptoms of acute HF. Blood pressure and resting heart rate will be assessed. Patients with a pre-discharge blood pressure of ≥90/50 mm Hg and heart rate ≥ 70 bpm will be eligible and approached for consent. Subjects should not have a planned/scheduled uptitration of beta-blocker in the following 4 weeks. Willing participants meeting entry criteria will provide written informed consent. Baseline heart rate must be ≥70bpm on ECG or a 10-second rhythm strip.

4.4 Randomization

After signing the informed consent form, all subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be randomized. All patients will be randomized using an electronic system in a 1:1 allocation ratio to either predischarge initiation of ivabradine or usual care. Randomization will be stratified by clinical site.

Figure 1. Study Flow Diagram

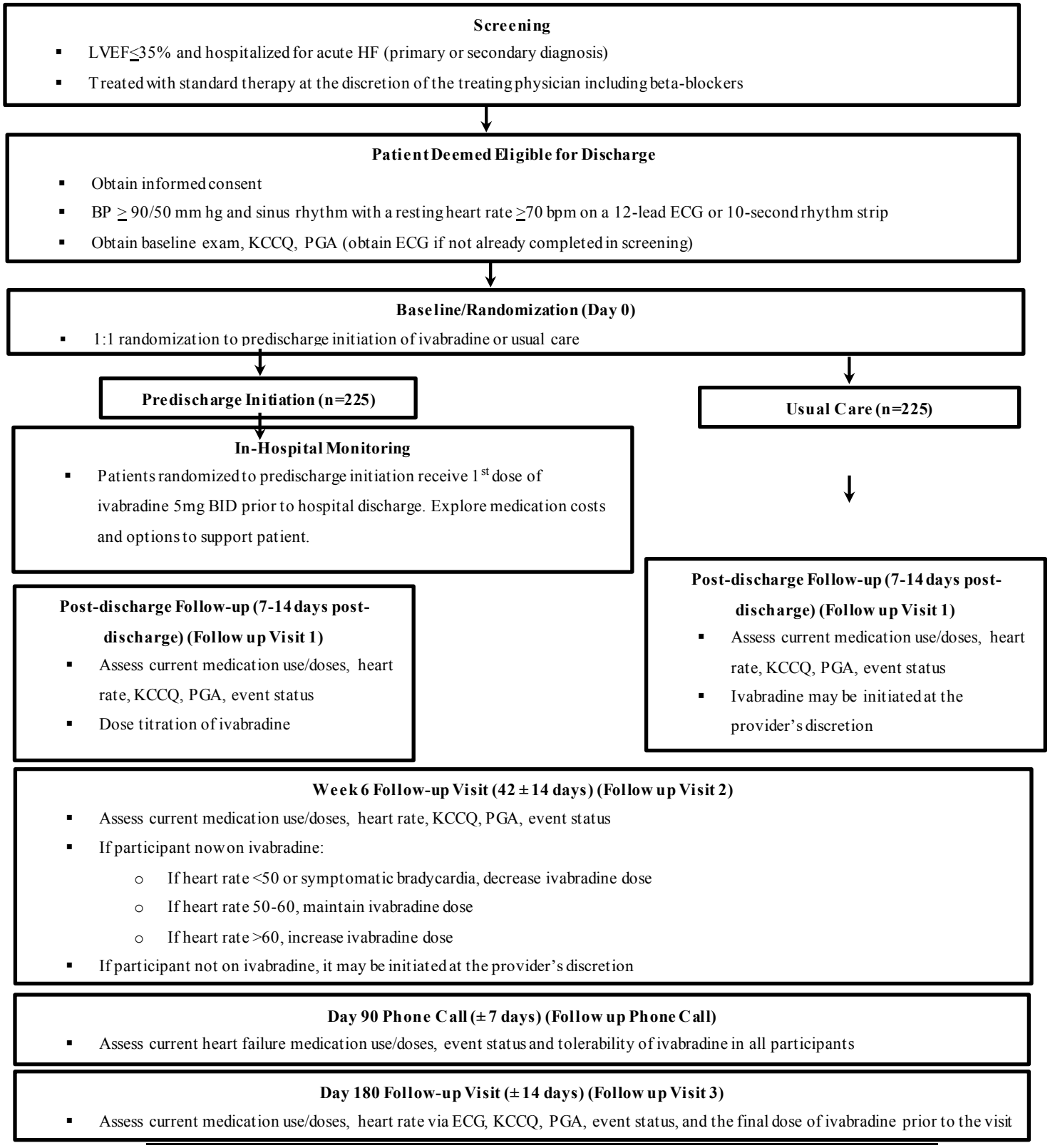
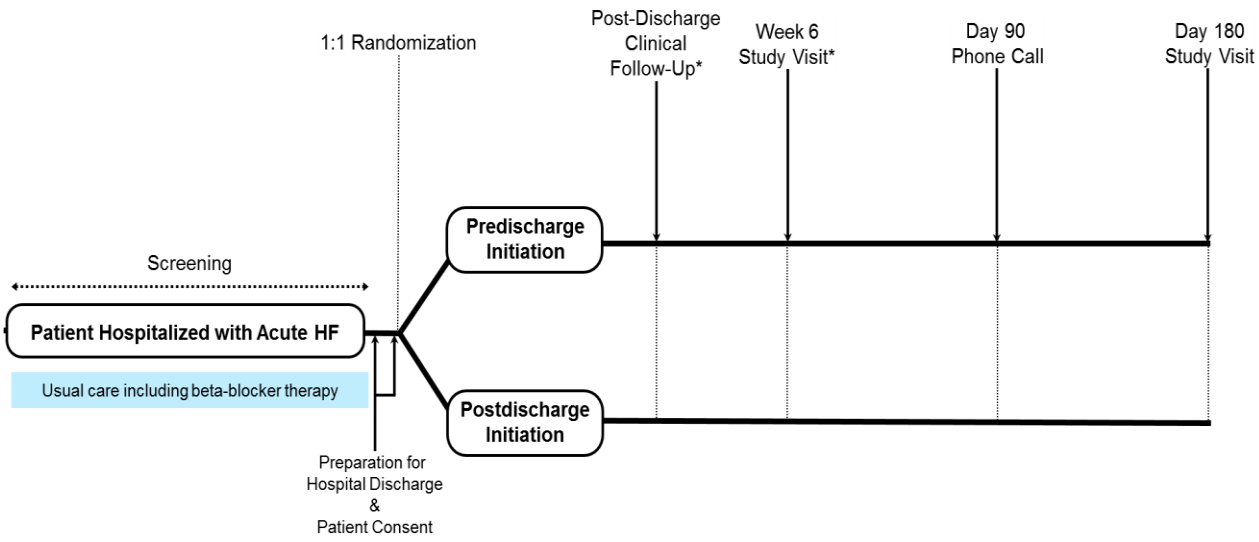


Figure 2. Schematic of Study Design

Figure 2. Schematic of Study Design



4.5 Treatment Arms

The treatment arms for this study are pre-discharge initiation of twice-daily oral ivabradine (starting at 5mg BID with encouraged dose titration to 7.5mg BID) versus usual care (i.e., post-discharge initiation of ivabradine at discretion of routine physician) for 180 days.

4.6 Patient Safety and Concomitant Medical Therapy

Patients will receive standard medical therapy throughout the study. Adjustments of background therapy can be made at any point during the study period at the discretion of the attending physician. Therapy may include diuretics, ACE-inhibitors or ARBs, neprilysin inhibition, beta-blockers, and mineralocorticoid receptor antagonists. Patients ***may have adjustments of beta-blocker therapies up until 24 hours prior to randomization and still be eligible for the study***. Subject should not have a planned/scheduled uptitration of beta-blocker in the following 4 weeks.

Sites will report events of interest to include SAEs related to Ivabradine, Pregnancy, or lactation exposure. Additional details are found in Section 8.

5 STUDY PROCEDURES

5.1 Screening and Prerandomization Procedures

Potentially eligible subjects will be identified from inpatient admissions and screened by interview. Interested subjects will be asked to give written informed consent and undergo a screening evaluation to include a complete history, physical examination, and laboratory tests. Study personnel will assess each subject against each inclusion and each exclusion criterion, and the investigator will determine the subject's eligibility for study participation. The informed consent process and all assessments will be documented in the subject's medical record.

5.2 Baseline Evaluations

At the baseline visit and the time of randomization (prior to administration of ivabradine), all study participants will undergo the following:

- History and physical examination
- Baseline heart rate assessment via ECG (if ECG not already obtained in screening)
- KCCQ and PGA

5.3 Treatment Intervention

Participants randomized to predischarge initiation of ivabradine should receive the first dose of medication prior to discharge if possible. If ivabradine is administered and then discharge is delayed, participants should continue on open-label ivabradine until hospital discharge. Participants should then receive a prescription for outpatient ivabradine. Study drug will not be provided as part of the study. If the patient is randomized to pre-discharge initiation, the study team and/or inpatient care team (e.g., providers and care coordinator) should initiate the process to acquire outpatient medication, explore patient costs and consider support options for the patient. If the patient is not able to pay for the medication, they will continue in the study and will enter a registry of ivabradine-eligible

patients with documentation of the medication acquisition challenges experienced by the patient and provider. All participants will be counseled on the signs and symptoms of bradycardia including lightheadedness, dizziness, and syncope. Participants will also be followed carefully for the remainder of the hospitalization and monitored for adverse events including bradycardia or recurrence of heart failure signs or symptoms.

5.4 Follow-up Evaluations

5.4.1 Clinical Follow-up Visit (Study Visit 1)

Consistent with current HF guidelines,[2] all participants should have a follow-up study visit within 7-14 days of hospital discharge. The timing of this visit will be determined by treating physicians. Current medication use and doses, physical examination, heart rate, systolic blood pressure and quality of life (KCCQ and PGA) will be assessed at this clinical visit. For participants randomized to predischarge initiation of ivabradine and on 5mg BID, the heart rate may be used to adjust the dose of ivabradine to 2.5mg BID or 7.5mg BID (Table 1). For participants randomized to usual care, ivabradine may be initiated at the provider's discretion. Participants not eligible for ivabradine at this visit will be documented and continue study follow-up.

Table 1. Recommended Dose Adjustments for Patients Taking Ivabradine

Heart Rate	Dose Adjustment
>60 bpm	Increase dose by 2.5 mg (given twice daily) up to a maximum dose of 7.5mg twice daily
50-60 bpm	Maintain current dose
<50 bpm or signs and symptoms of bradycardia	Decrease dose by 2.5mg (given twice daily); if current dose is 2.5 mg twice daily, then discontinue therapy

5.4.2 Clinical Follow-up Visit (Study Visit 2)

At 6 weeks (42 +/- 14 days) post-discharge, all participants will have follow-up study visit. The study visit will include an assessment of current medication use and doses,

physical examination, heart rate, and systolic blood pressure. For participants on ivabradine, the heart rate may be used to adjust the dose (Table 1). For participants with a resting heart rate >60 bpm, the dose may be increased to either 5mg or 7.5mg BID. If the resting heart rate is <50 bpm or the participant is experiencing signs or symptoms related to bradycardia, then the dose may be reduced to 2.5mg BID or the study drug should be discontinued. If the heart rate is 50 to 60 bpm, then the dose may be maintained. For participants not yet taking ivabradine, then it may be initiated at the provider's discretion. Participants not eligible for ivabradine at this visit will be documented and continue study follow-up. Study investigators or designee will assess quality of life (KCCQ and PGA).

5.4.3 Phone Call

At 90 (+/-7) days post-discharge, participants should be contacted by the site (phone call) to assess for event status, current medication use and doses, and tolerability of ivabradine, specifically

- Symptomatic bradycardia
- Symptomatic hypotension
- Other symptoms leading to ivabradine discontinuation

5.4.4 Final Study Visit (Study Visit 3)

At 180 (+/- 14) days post discharge, all participants will have a routine clinic visit. The visit will include an assessment of current medication use and doses, physical examination including heart rate assessment (by exam and 1 ECG), and systolic blood pressure. The final dose of ivabradine prior to the visit will be recorded. Participants never initiated on or eligible for ivabradine will also be recorded. The study investigators or designee will assess quality of life (KCCQ and PGA).

Using the study schedule of assessments, provider-determined heart rate will be assessed at the following time points: baseline, post-discharge clinical follow-up visit (within 7-14

days of hospital discharge), week 6, and day 180. Patient quality of life assessment will be assessed at the following time points: baseline, post-discharge clinical follow-up visit (within 7-14 days of hospital discharge), week 6, and day 180.

5.5 Schedule of Assessments

	Baseline				
Time (Day)	Pre-discharge	Day 7-14 post discharge	6 Weeks post-discharge (42 +/- 14 days)	90 Days post-discharge (+/-7 days)	180 Days post-discharge (+/- 14 days)
Visit	Baseline/Randomization	FU Visit 1	FU Visit 2	FU Phone Call	FU Visit 3
Subject consent	X				
Medical History	X				
Physical examination	X	X	X		X
Vital signs (HR,BP)	X	X	X		X
ECG	X				X
KCCQ	X	X	X		X
PGA	X	X	X		X
Medication assessment	X	X	X	X	X
Events of interest assessment		X	X	X	X

6 ENROLLMENT AND RANDOMIZATION

6.1 Enrollment

Eligible subjects who have given written informed consent and meet all inclusion and no exclusion criteria will be randomized.

6.2 Randomization

After signing the informed consent form, all subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be randomized. All patients will be randomized using an electronic system in a 1:1 allocation ratio to either predischarge initiation of ivabradine or usual care. Randomization will be stratified by clinical site.

7 PARTICIPANT SAFETY

7.1 Patient Safety and Concomitant Therapies

This study will evaluate and compare pre-discharge initiation of ivabradine versus usual care in patients stabilized after an acute HF exacerbation requiring hospitalization. Although investigators are encouraged to follow the assigned treatment strategy, in all cases the patient's safety based on the clinical judgment of the treating physician will take priority over the specific treatment assignment. Concomitant therapies will be at the discretion of the treating physician. All subjects will receive standard of care which can be adjusted by their usual care provider(s) during the study according to clinical need. Usual care providers will be encouraged to follow the most up to date guidelines for cardiovascular care based upon local and institutional practice patterns and relevant published practice guidelines.

7.2 Institutional Review Boards

All sites will submit the study protocol, informed consent form, and other relevant study documents to their Institutional Review Board (IRB) for approval.

7.3 Informed Consent

All patients will have the purpose of the study, the study interventions and evaluations, and the potential risks and benefits of participation explained to them and their questions answered. If they consent to participation in this study, they will review and sign the informed consent form.

7.4 Study Discontinuation

Subjects may withdraw at any time during the study without prejudice or be discontinued from study treatment at the discretion of the investigator if medically necessary. In addition, a subject may be withdrawn by the investigator or the sponsor if the subject violates the study plan or for administrative and/or other safety reason.

The investigator or designee will document in the eCRF when a subject has been discontinued or withdrawn from study treatment because of an adverse experience. When a subject discontinues or is withdrawn from treatment before study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences that are present at the time of discontinuation/withdrawal should be followed by the site PI until resolution.

8 ADVERSE EVENT REPORTING AND FOLLOW-UP

8.1 Safety

In this study, all medications and procedures commonly used or performed as a part of standard of care for the management of HF have well-defined safety profiles. For this trial, defined clinical endpoints and events of interest will be recorded in the eCRF. In addition, events that are Serious and Unexpected will be reported by a site investigator to the local IRB per the IRB's instructions and will be the subject of a MedWatch report, based on local requirements.

The investigator is responsible for monitoring the safety of subjects enrolled into the study at the study site. The investigator or qualified designee will enter the required initial and follow-up information regarding events into the appropriate module of the eCRF. Investigators are to report serious adverse events in accordance with their local IRB requirements. Investigators should follow usual clinical practices at their institution for reporting to regulatory authorities serious, unexpected events related to standard of care medications and devices.

8.2 Definitions

8.2.1 Events of Interest

Sites will record in the eCRF Events of Interest which include

1) Symptomatic bradycardia
2) Symptomatic hypotension
3) Other symptoms leading to ivabradine discontinuation
4) Any Adverse Event that, in the opinion of the site investigator, is related to ivabradine and is:
    a) Serious, and
    b) Unexpected

8.3 Protocol Specific Exceptions to SAE Reporting

The following events will be collected in the CRF but are not the subject of a MedWatch report. These events will be captured on anticipated/disease related events pages, not on the SAE eCRF page. Anticipated, disease related-event in patients with acute decompensated heart failure include:

- Ventricular tachycardia
- Atrial fibrillation
- Myocardial infarction
- Acute coronary syndrome
- Acute renal failure
- Worsening heart failure
- Death

With the exception of the events listed above, all serious adverse events the site PI determines to be related to ivabradine must be recorded in the Serious Adverse Event eCRF and should be monitored until stabilization or resolution.

Site investigators are responsible for knowing the local requirements for prompt reporting of an adverse event to the reviewing IRB/EC and for reporting an SAE to FDA via a MedWatch.

An Independent Data and Safety Monitoring Board (DSMB) will review safety composite data at regular intervals throughout the study. The DSMB will be empowered to stop the study for evidence of harm but not for evidence of efficacy.

8.3.1 Suspected Adverse Reaction

In PRIME-HF a suspected adverse reaction (SAR) is any AE for which there is a reasonable possibility that ivabradine caused the event. “Reasonable possibility” suggests there is a causal relationship between the drug and the AE. “Suspected adverse reaction”

implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

8.4 Assessment of Adverse Event Severity

The determination of AE severity rests on medical judgment of a medically qualified investigator. The severity of AEs will be graded using the following definitions:

- **Mild**: Awareness of sign, symptom, or event, but easily tolerated.
- **Moderate**: Discomfort enough to cause interference with usual activity and may warrant intervention.
- **Severe**: Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention.

8.5 Assessment of Causal Relationship

A medically qualified investigator must assess the relationship of any AE to the use of study drug, based on available information, using the following guidelines:

- **Not related**: There is not a reasonable causal relationship between the investigational product and the AE.
- **Unlikely related**: No temporal association or cause of the event has been identified, or the drug or biologic cannot be implicated.
- **Possibly related**: There is reasonable evidence to suggest a causal relationship between the drug and AE.
- **Probably related**: There is evidence to suggest a causal relationship between the drug and AE, and the influence of other factors is unlikely.

8.6 Expectedness

The Investigative site PI or designee will determine expectedness of an SAE according to the package insert for U.S. marketed ivabradine. Any SAE that is not identified in nature, severity, or specificity in the current study drug reference documents is considered unexpected. Events that are listed in the package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but not specifically listed as occurring with the particular drug under investigation, are considered unexpected. As per the ivabradine package insert, the most common adverse reactions occurring in ≥ 1% of patients are bradycardia, hypertension, atrial fibrillation and luminous phenomena (phosphenes).

8.7 Adverse Event Reporting

All SAEs obtained via direct subject reporting and/or clinical staff observation that the site PI determined to be related to ivabradine will be captured within the electronic case report form (eCRF).

8.8 Serious Adverse Events

The investigator must record, via the EDC system, all SAEs that the site PI determined to be related to ivabradine occurring at visit 1 through visit 3 within 24 hours of knowledge of the event. If the eCRF system is temporarily unavailable, notify the sponsor or designee of the event, including investigator-determined causality assessment, via a paper back-up SAE form. Upon return of the availability of the EDC system, the SAE information must be entered into the eCRF.

The investigator must record in the EDC system when important follow-up information (final diagnosis, outcome, results of specific investigations, etc.) becomes available after submission of the initial SAE information. Follow-up information should be submitted according to the same process used for reporting the initial event as described above (i.e.,

within 24 hours of knowledge, via the EDC system). All SAEs will be followed until resolution, stabilization, until otherwise explained.

Research sites are expected to follow local IRB policies and procedures for reporting AEs/SAEs.

8.9 Pregnancy

During the course of the trial, if any female subject who is receiving ivabradine becomes pregnant, or if any person is exposed to ivabradine by a lactating female subject, this information will be recorded in the eCRF and reported via the pregnancy form. While a subject's pregnancy is not considered an SAE, it must be reported within the same timelines as an SAE (within 24 hours). Any AEs or SAEs associated with ivabradine that occur to the female subject or fetus/child will be recorded in the eCRF on the AE or SAE form, as appropriate.

8.10 Withdrawal of Subjects from Study

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to future medical care. In the case of subject withdrawal, the investigator will discuss with the subject the most appropriate way to terminate study participation to ensure the subject's health. All efforts will be made to complete and report the observations as thoroughly as possible up to the date of study termination. All applicable activities scheduled for the final study visit should be preformed at the time of discontinuation. Randomized subjects who withdraw from the study will not be replaced.

9 SUMMARY OF CLINICAL EVENTS

Additional data on clinical events of interest will be collected.

a. Worsening HF defined as either hospital admission for worsening signs and/or symptoms of HF or receiving unplanned intravenous (IV) diuretics for HF as an outpatient.
b. All-cause mortality

10 STATISTICAL ANALYSIS PLAN AND DETERMINATION OF SAMPLE SIZE

10.1 Overview

All planned analyses will be prospectively defined for this study and approved by the Steering Committee. In addition, exploratory analyses will be performed to help explain and understand findings observed from the planned analyses. Statistical tests with a 2-sided p-value <0.05 will be considered statistically significant, unless otherwise stated. Analyses will be performed using SAS software (SAS Institute, Inc, Cary, NC).
The primary endpoint of the study is proportion of participants using ivabradine at 180 days.

10.2 Sample Size Justification

We assumed that 35% of participants randomized to the usual care arm will be treated with ivabradine at 180 days, and the predischarge 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. This sample size estimate is based on a two-group continuity corrected chi-square test and assumes a 1:1 allocation ratio between the predischarge initiation of ivabradine and usual care groups. This sample size estimate allows for 8% missing primary endpoint data.

For the KCCQ overall summary endpoint we have made a conservative assumption of 16 points for the standard deviation. For this measure, the medium and large clinically meaningful differences are 5 and 10 points for the KCCQ overall summary measure, respectively. Allowing for approximately 8% missing data, the proposed sample size of 450 participants provides approximately 90% power to detect a difference of 5 points

(medium clinically meaningful difference). The power calculations are based on the two sample t-test with a two-sided Type I error rate of 0.05.

10.3 Analysis of the Primary Endpoint

The primary analysis will be conducted on an intention-to-treat (ITT) basis including all randomized participants. A logistic regression model with ivabradine use at 180 days as the binary outcome variable and indicator variables for treatment group main effects and category of baseline beta-blocker use. The treatment effect for the ivabradine at discharge group will be summarized by the odds ratio and the associated 95% confidence interval.

10.4 Analysis of Secondary and Tertiary Endpoints

- Heart Rate Assessments
    - Change in heart rate from baseline to 180 days across treatment groups. Change will be calculated as follows: (Baseline heart rate – 180-day heart rate). Comparisons across treatment 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. Multiple imputation will be used to impute 180-day missing HR observations if missing is > 10%.
    - Heart rate in bpm at 180 days will be compared in the predischarge ivabradine group compared across treatment groups. Comparisons across treatment 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. Multiple imputation will be used to impute 180-day missing HR observations if missing is > 10%.
- Changes in symptoms and quality-of-life from baseline to 180 days as assessed by KCCQ and PGA will be evaluated across treatment groups using a linear model with adjustment for the baseline quality-of-life and beta-blocker use. A multiple imputation approach will be used to account for possible missing data. The

differences between treatment groups will be estimated using point estimates and the associated two-sided 95% confidence intervals.

- 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) the proportion discontinuing beta-blockers at 180 days and (d) the mean change in beta-blocker dose from discharge to 180 days will be compared between treatment groups.
- 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 twice daily), and (c) the mean dose of ivabradine achieved at 180 days will be compared between treatment groups.
- The event counts and subject incidences for the following adverse events will be presented for the treatment groups:
    - Symptomatic bradycardia
    - Symptomatic hypotension
- Barriers to the acquisition of ivabradine. Barriers will be documented in the case report form and reported in tabular format.

10.5 Interim Analyses

Interim data analysis for efficacy will not be conducted due to modest size and short duration of this study. Safety data will be periodically assessed by the DSMB.

11 DATA MONITORING AND QUALITY CONTROL

11.1 Required Data

The full study dataset will be collected for subjects who enter the randomization phase of the study. Limited data as available (i.e., demographics, serious adverse events related to ivabradine, selection criteria, and reason for discontinuation) will be collected for subjects who discontinue before the end of the protocol specified follow-up period.

All required data for this study will be entered into the electronic case report form (eCRF).

11.2 Data Collection and Tracking

Qualified study staff at each site will perform primary data collection from source-document reviews. The sponsor or designee will perform clinical monitoring, including review of eCRFs with verification to the source documentation.

This study will use Web-based e-CRFs developed through a validated, electronic reporting-electronic-signatures–compliant platform (21 Code of Federal Regulations Part 11). The investigator's site staff who will be entering data will receive training on the system, after which each person can set up their database account and request study access

For security reasons, and in compliance with regulatory guidelines, it is imperative that only the persons who own the user IDs and passwords access the system using their own unique access codes. Access codes are nontransferable. Site personnel who have not undergone training may not use the system and will not be granted access to the clinical database until appropriate training is completed.

During monitoring visits, the site will make their computer and/or high-speed Internet access available to the clinical research associate, so that he or she may verify the data entries with the source documentation. At the conclusion of the study, each enrolling site will be provided with a thumb drive containing PDF files of both the individual subject's

data and the audit trail (changes made to the database). This will be maintained at the site according to the requirements for records retention.

12 Study Responsibilities

12.1 Investigator Responsibility/Performance

The site principal investigator (PI) agrees to be responsible for implementing and maintaining quality control and quality assurance systems to ensure that all work incidental to this protocol is conducted and data are generated, documented, and reported in compliance with: the protocol; accepted standards of Good Clinical Practice (GCP); and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The PI will provide current copies of the study protocol to all subinvestigators or other site personnel responsible for study conduct.

The PI will provide the sponsor or designee with copies of all institutional review board (IRB) actions regarding the study.

12.2 Study Data Reporting and Processing

Each page of the electronic case report form (eCRF) will be reviewed by PI at the site. The PI is required to sign the eCRF on the appropriate pages to verify that he or she has reviewed the recorded data. This review and sign-off may be delegated to a qualified physician appointed as a subinvestigator by the PI. The transfer of duties to a subinvestigator will be recorded on the delegation list, which is kept on file at the site. The investigator must ensure that all site staff involved in the conduct of the trial are familiar with the protocol and all study-specific procedures, and that they have appropriate knowledge of the study agents.

12.3 Training

The initial training of appropriate clinical site personnel will be the responsibility of the sponsor or designee. The PI is responsible for ensuring that staff conduct the study according to the protocol. To ensure proper administration of study agents, uniform data

collection, and protocol compliance, the sponsor or designee will present a formal training session to study site personnel, to include instructions for study procedures, the investigational plan, instructions on in-hospital data collection, methods for soliciting data from alternative sources, schedules for follow-up with the study site coordinators, and regulatory requirements. Detailed feedback regarding completion of forms will be provided by the sponsor ot designee in the course of monitoring.

12.4 Monitoring the Investigational Sites

As part of a concerted effort to follow the study in a detailed and orderly manner in accordance with established principles of GCP and applicable regulations, a study monitor from the sponsor or designee will visit the study sites as appropriate and will maintain frequent telephone and written communication.

Periodic monitoring visits may be made at all active investigational sites throughout the clinical study as needed to assure that the investigator obligations are being fulfilled and all applicable regulations and guidelines are being followed. The goal of these visits are to assure the facilities are still acceptable, the protocol and investigational plan are being followed, the IRB/EC has been notified of approved protocol changes as required, complete records are being maintained, appropriate reports have been made to the sponsor or designee and the IRB/EC, and the investigator is carrying out all agreed-upon activities.

During monitoring visits, the monitor will perform a review of inclusion/exclusion criteria, informed consent, HIPAA authorization, events of interest , as well as safety and efficacy endpoints. Additional review will be performed on a site-by-site basis, as warranted by the findings of previous monitoring visits. Key variables will be confirmed through review of source documents for a sampling of patients.

Sites may be required to provide at a minimum the informed consent and discharge summary for subjects to the the sponsor or designee via a secure system.

Trends will be monitored and, if warranted, the frequency of onsite monitoring visits may be adjusted at sites. Details will be described in the clinical monitoring plan.

12.5 Study Documentation

Study documentation includes all electronic case report forms, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and regulatory documents (e.g., protocol and amendments, IRB or EC correspondence and approval, approved and signed subject consent forms, clinical supplies receipts and distribution records).

The site PI will prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules and regulations. For each subject participating in the study at the site, the investigator will promptly complete all eCRFs and such other reports as required by this protocol following completion or termination of the clinical study or as otherwise required pursuant to any agreement with the sponsor.

The site PI acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed to the sponsor or designee by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the sponsor or responsible government agencies as required by law.

The PI agrees to promptly take any reasonable steps that are requested by the sponsor or designee as a result of an audit to cure deficiencies in the study documentation and eCRFs.

12.6 Source Documentation

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical

study. Accordingly, source documents include, but are not limited to, laboratory reports, electrocardiogram (ECG) tracings, x-rays, radiologist reports, subject diaries, biopsy reports, ultrasound photographs, subject progress notes, hospital charts, pharmacy records, and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

The following information will be maintained and made available as required by the sponsor or designee and/or regulatory inspectors:

1. Medical history/physical condition of the study subject before involvement in the study sufficient to verify protocol entry criteria.

2. Documentation that informed consent was obtained for the subject's participation in the study.

3. Dated and signed notes for each subject visit, including results of examinations.

4. Notations on abnormal laboratory results and their resolution.

5. Dated printouts or reports of special assessments (e.g., ECG reports).

6. Description of adverse events (AEs) and follow-up of the AEs (minimally, event description, severity, onset date, duration, relation to study drug, outcome, and treatment for AE).

7. Notes regarding concomitant medications taken during the study (including start and stop dates).

8. Subject's condition upon completion of or withdrawal from the study.

12.7 Protocol Deviations

A protocol deviation is defined as an event where the investigator or site personnel did not conduct the study according to the investigational plan. Site investigators must also follow the policy of the reviewing IRB for reporting such deviations. to their reviewing IRB per local policy.

The IRB/EC will be informed of all protocol changes by the sponsor or the investigator in accordance with applicable regulations and the IRB/EC's established procedures. No deviations from the protocol of any type will be made without complying with the IRB/EC's established procedures.

Investigators will maintain documentation of the dates and reasons for each deviation from the protocol.

12.8 Data Transmittal and Record Retention

Required data will be entered in the eCRF at the time of or as soon as possible after the subject visit or the availability of test results

The PI will maintain final eCRFs, worksheets, and all other study-specific documentation (e.g., study file notebooks or source documentation) until notified by the sponsor that records may be destroyed. To avoid error, the investigator will contact the sponsor or designee before the destruction of any records pertaining to the study to ensure they no longer need to be retained. In addition, the sponsor or designee will be contacted if the PI plans to leave the institution so that arrangements can be made for the transfer of records.

The site PI takes responsibility for maintaining adequate and accurate source documents of all observations and data generated during this study. Such documentation is subject to inspection by the sponsor or designee as well as by federal, state, and local regulatory agencies.

12.9 Study Closeout

Upon completion of the study (defined as all subjects have completed all follow-up visits, all eCRFs are complete, and all queries have been resolved), the sponsor or designee will notify the site of closeout, and a study closeout visit will be performed. All unused study materials can be destroyed by the site when the study is completed. The sponsor or designee will ensure that the PI's regulatory files are up-to-date and complete and that any outstanding issues from previous visits have been resolved. Other issues to be reviewed at the closeout visit include discussing retention of study files, possibility of site audits, publication policy, and notifying the IRB of study closure.

12.10 Audit/Inspections

As needed, quality assurance personnel from the sponsor or designee may conduct audits at the study sites at a reasonable time and in a reasonable manner. Audits will include, but not be limited to, audit trail of data handling and processes, standard operating procedures, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The site PI agrees to accommodate and participate in audits that are conducted.

Regulatory authorities from the U.S. or abroad may inspect the site during or after the study at a reasonable time and in a reasonable manner. The PI should contact the sponsor immediately if contacted regarding an inspection. Site personnel are expected to cooperate with personnel from regulatory agencies (e.g., FDA) audits conducted

12.11 Publication Policies

Members of the Steering Committee will be primarily responsible for creation, review, and submission of publications and presentations relating to the major aspects of the study and approved ancillary analyses within a timely fashion after completion of the study. Details will be contained in the Publication Plan.

13 Ethical Considerations

13.1 Informed Consent

The PI has both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the study. Written informed consent will be obtained from all subjects (or, at the discretion of the local IRB, the subject's guardian or legally authorized representative [LAR]) before any study-related procedures are performed or given.

Written informed consent will be documented on an informed consent form (ICF) approved by the local IRB/EC responsible for approval of this protocol. The ICF will conform to the applicable requirements of 45 CFR 46, ICH E6 and institutional requirements for informed consent. The site investigator agrees to obtain approval from the sponsor of any ICF intended for use in the study before submission of the ICF for IRB approval.

The ICF will be reviewed with the prospective study subject (or LAR), and the investigator or qualified designee will be available to answer questions regarding procedures, risks, and alternatives.

13.2 Confidentiality of Subjects

Subject confidentiality will be maintained throughout the clinical study in a way that ensures that study data can always be tracked back to the source data.

Subject information collected in this study will comply with the standards for protection of privacy of individually identifiable health information as promulgated by the U.S. Health Insurance Portability and Accountability Act (HIPAA). All records will be kept confidential, and the subject's name will not be released to persons outside the study site. Subject records will not be released to anyone other than the sponsor or its designees and responsible regulatory authorities when requested. In all cases, caution will be exercised to assure the data are treated confidentially and that the subject's privacy is guaranteed.

13.3 Authorization for Use and Disclosure of Protected Health Information (HIPAA)

An authorization for use and disclosure of protected health information (PHI) under the HIPAA Privacy Rule will be obtained from every trial subject before enrollment. The investigator is responsible for obtaining subjects' (or their LARs') authorizations and signatures and for explaining the elements of the HIPAA authorization form, if necessary.

The site PI will promptly inform the sponsor of any restrictions on the use or disclosure of any subject's PHI. The site investigator will also promptly inform the sponsor of written revocation of any subject's HIPAA authorization.

13.4 Human Subject Protections

13.4.1 Research Subject Selection and Justification of Exclusions

There will be no exclusion from participation in the study on the basis of ethnicity or race. Subjects younger than 18 years of age will be excluded from the study, as the target population is adults. Women of childbearing potential will have serum-hCG testing before randomization to avoid potential fetal exposure to ivabradine.

13.4.2 Risks/Discomforts of Study Participation

This study will evaluate the safety and efficacy of ivabradine following stabilization for acute HF. Oral ivabradine was found to be safe and efficacious in chronic HF patients in the SHIFT trial over a median follow-up of 22.9 mos. In SHIFT, the overall rate of SAEs was similar between the ivabradine and placebo arms; ivabradine was not associated with any evidence of harm over this follow-up period.

13.5 Institutional Review Board/Ethics Committee Review

The appropriate IRB/EC must approve the protocol and informed consent documents, agree to monitor the conduct of the study, and agree to review study progress periodically,

at intervals not to exceed 1 year. The investigator will provide the sponsor or designee with documentation that the IRB/EC has approved the study ***before*** the study may begin.

In addition, the investigator must provide the following documentation to DCRI:

1. IRB/EC annual reapproval of the protocol,.
2. IRB/EC approval of revisions to the informed consent documents or any amendments to the protocol. The investigator will provide the sponsor or designee with documentation of all approvals.

13.6 Steering Committee

The Steering Committee will be the primary decision making body of the study and is responsible for its successful completion. The Steering Committee will be comprised of the study principal investigators, the project leader, and selected other investigators with expertise in heart failure and clinical trials.

13.7 Data and Safety Monitoring Board

A data and safety monitoring board (DSMB) will be appointed for the PRIME-HF trial, which will include individuals with pertinent expertise in heart failure and clinical trials. The DSMB will advise the Steering Committee regarding safety concerns for current participants and those yet to be recruited.

14 Appendices

Appendix A. Safety Considerations

Similar to the SHIFT study, the following treatments are not allowed at inclusion or during the study:

- Non-dihydropyridine calcium channel blockers (e.g., diltiazem and verapamil)
- Class I anti-arrhythmics (e.g., quinidine, procainamide, lidocaine, phenytoin)
- Strong inhibitors of cytochrome P450 3A4 (CYP3A4), including some macrolide antibiotics (e.g., clarithromycin, erythromycin), cyclosporine, antiretroviral drugs (e.g., ritonavir, nelfinavir), and systemic azole antifungal agents (e.g., ketoconazole, itraconazole)
- Inducers of cytochrome P450 3A4 (CYP3A4) including St. John's Wort, rifampicin, barbiturates, and phenytoin
- Treatments known to be associated with significant prolongation of the QT interval, including sotalol

Appendix B. Cardiomyopathy Questionnaire and Patient Global Assessment

Kansas City Cardiomyopathy Questionnaire

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a self-administered, 23-item questionnaire developed to provide a better description of health-related quality of life (QOL) in patients with heart failure. It quantifies physical limitation, symptoms, QOL, social interference and self-efficacy. The survey requires 4-6 minutes to complete, and is scored by assigning each response an ordinal value, beginning with 1 for the response that implies the lowest level of functioning and summing items within each domain. Scale scores are transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100. A clinical summary score will be calculated by combining the functional status with the quality of life and social limitation domains.

Patient Global Assessment

A seven category global assessment of clinical status that is completed by the participant will be utilized in the assessment of the composite score. This Patient Global Assessment (PGA) tool consists of the categories of: markedly improved, moderately improved, mildly improved, no change, slightly worse, moderately worse and markedly worse. Participants will be asked to define their status using this tool at specified times during the protocol by marking their current status, relative to the baseline condition. The Patient Global Assessment tool will be prepared in a manner which is simple to read (large print) and will be retained as a source document.

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