Title Page

Protocol Title:		Open-label, Single-arm Study Assessing the Efficacy and Safety of Ivabradine (Corlanor) in African-American/Black Subjects With Heart Failure and Left Ventricular Systolic Dysfunction
Short Protocol Title:		A Phase 4 Study of Ivabradine in African-American/Black Subjects with Heart Failure and Left Ventricular Systolic Dysfunction
Protocol Number:		20160231
Investigational Product:		Ivabradine
Trade Name:		Corlanor®
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I have read the attached protocol entitled Open-label, Single-arm Study Assessing the Efficacy and Safety of Ivabradine (Corlanor) in African-American/Black Subjects With Heart Failure and Left Ventricular Systolic Dysfunction, dated **14 February 2019**, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP), Declaration of Helsinki, and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by: me (including, if applicable, my spouse or legal partner and dependent children) and my subinvestigators (including, if applicable, their spouses or legal partners and dependent children) at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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1. Protocol Synopsis

Protocol Title: Open-label, Single-arm Study Assessing the Efficacy and Safety of Ivabradine (Corlanor) in African-American/Black Subjects With Heart Failure and Left Ventricular Systolic Dysfunction

Short Protocol Title: A Phase 4 Study of Ivabradine in African-American/Black Subjects with Heart Failure and Left Ventricular Systolic Dysfunction

Study Phase: 4

Indication: Heart Failure (HF)

Rationale

The goal of this study is to determine the impact of adding ivabradine therapy to the standard of care (SOC) in African-American/Black subjects with HF and reduced ejection fraction (HFrEF) on changes in heart rate (HR) from baseline (SOC alone). Changes in HR from baseline will be correlated with the changes from baseline in activity level of the subjects, as measured by both a standard 6-minute walk distance and an accelerometer device.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• Determine whether ivabradine effectively reduces HR from baseline to day 57 in African-American/Black subjects.	• Change in HR from baseline to day 57

Hypotheses

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

Overall Design

This study is a prospective, open-label, single-arm intervention study in African-American/Black subjects with HFrEF.

There will be a 7-day screening period, a 57-day open-label treatment period, and a safety follow-up at day 87 or 30 days after the last administration of the investigational product.

Number of Subjects

Approximately 30 to 100 subjects

Summary of Subject Eligibility Criteria

Subjects will be male or female ≥ 18 years of age, describing self as African-American/Black, with a diagnosis of HF confirmed by medical records, in stable condition, and treated with stable optimal pharmacological therapy. Subjects must also have left ventricular ejection fraction (LVEF) ≤ 35% confirmed prior to enrollment, New

York Heart Association class II to IV, and electrocardiogram documentation at the time of screening of sinus rhythm with resting HR ≥ 70 bpm.

For a full list of eligibility criteria, please refer to Section 6.1 to Section 6.2.

Treatments

The starting dose of ivabradine is 5 mg twice daily (BID). In subjects with a history of conduction defects, or in subjects in whom bradycardia could lead to hemodynamic compromise, therapy is to be initiated at 2.5 mg BID based on investigator discretion. At the day 15 visit, the dose will be titrated according to HR as defined in the table below. Ivabradine dose levels can be adapted to HR at any clinical visit if necessary.

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

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

Procedures

There will be a 7-day screening period that will allow accurate measurement of baseline activity as measured by the accelerometer. On day 1, eligible subjects with confirmed sinus rhythm and HR ≥ 70 bpm will be enrolled into a 57-day open-label treatment period. A safety follow-up will be conducted at day 87 or 30 days after the last administration of the investigational product.

For a full list of study procedures, including the timing of each procedure, refer to Section 9.2 and the Schedule of Activities in Section 2.2.

Statistical Considerations

The primary analysis for this study will be performed when all subjects have completed all planned study procedures. This primary analysis will evaluate the effect of ivabradine on HR reduction at day 57 in African-American/Black subjects overall (the primary endpoint). Descriptive statistics of the exploratory endpoints will be summarized. Safety data will be tabulated.

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

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

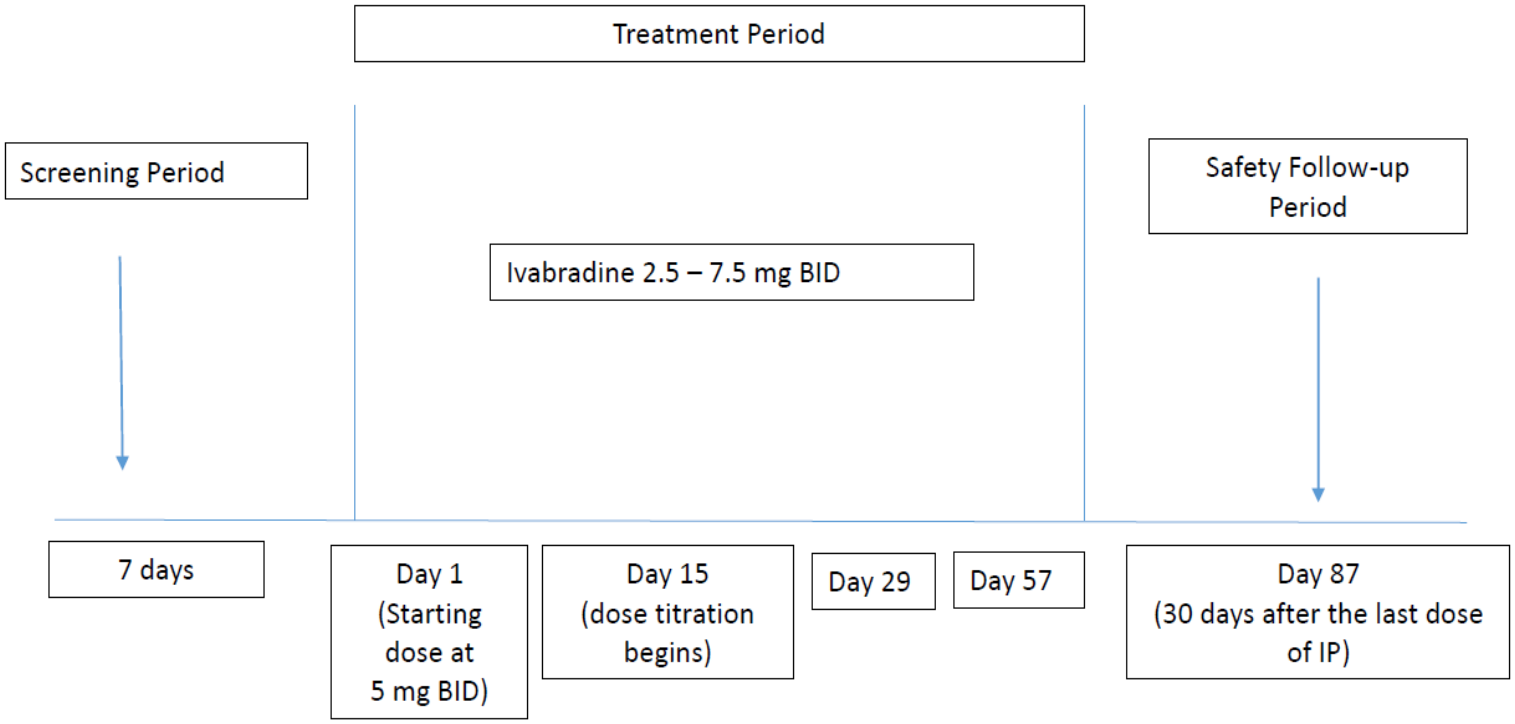
Efficacy analyses of the primary endpoint will test whether the mean reduction with ivabradine exceeds 5 bpm. Summary statistics and least-square means along with 95% confidence interval, analyzed by the repeated-measures linear model, will be provided for the primary endpoint.

For a full description of statistical analysis methods, please refer to Section 10.

Sponsor Name: Amgen Inc.

2. Study Schema and Schedule of Activities

2.1 Study Schema



Abbreviations: BID = twice daily; IP = investigational product

2.2 Schedule of Activities

Table 2-1. Schedule of Activities

Procedure	Screening Period	Treatment Period (Days)				Safety Follow-Up Period/ Early Termination Visit[a] (Phone Contact for Safety Follow-up only)
	Screening (7 days)	Day 1 ± 2 days	Day 15 ± 2 days (dose titration begins)	Day 29 ± 2 days	Day 57 ± 5 days	Day 87 or 30 days after the last dose of open-label IP
Informed consent	X					
Full physical examination	X				X	
Physical measurements[b] (height and weight)	X					
Medical history[c]	X					
Demographics[d]	X					
Vital signs[e]	X	X	X	X	X	
12-lead ECG	X	X	X		X	
Laboratory assessments	X					
Pregnancy test (urine) in women of childbearing potential only	X	X[i]				
Adverse event collection/ recording/reporting	X[f]	X	X	X	X	X
Serious adverse event collection/recording/reporting[f]	X	X	X	X	X	X

Footnotes defined on next page

Table 2-1. Schedule of Activities

Procedure	Screening Period	Treatment Period (Days)				Safety Follow-Up Period/ Early Termination Visit[a] (Phone Contact for Safety Follow-up only)
	Screening (7 days)	Day 1 ± 2 days	Day 15 ± 2 days (dose titration begins)	Day 29 ± 2 days	Day 57 ± 5 days	Day 87 or 30 days after the last dose of open-label IP
Disease-related event collection/ recording/reporting		X	X	X	X	X
Vital status						X
Concomitant medications	X	X	X	X	X	X
6-Minute walk test (6MWT)		X			X	
Accelerometer[g]	X	X	X	X	X	X[j]
Investigational product[h]		X	X	X	X	

Abbreviations: 6MWT = 6-Minute walk test; ECG = electrocardiogram; IP = investigational product

[a] If a subject discontinues the study, the subject must return to the study clinic in 30 days after discontinuation.

[b] Height in centimeters should be measured without shoes. Weight in kilograms should be measured without shoes.

[c] Medical history will include substance usage (eg, alcohol, tobacco, and caffeine).

[d] Demographics will include sex, age, race and ethnicity.

[e] Vital signs will include systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature. Subject must be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is unable to be in the supine position, the subject should be in most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign case report form (CRF).

[f] Adverse events related to any study procedures/study activity are collected, recorded, and reported from signing of the informed consent. All other adverse events including disease related events (DREs) are collected, recorded, and reported from day 1 (from first dose of investigational product). Serious adverse events are collected, recorded, and reported from signing of the informed consent through 30 days after the last dose of IP or end-of-study/safety follow-up visit, whichever is later.

[g] A 7-day screening with the accelerometer is required before day 1 dosing. The subjects will be instructed to wear the accelerometer every day except to be recharged. The accelerometer is to be worn daily from screening through the end of treatment period (day 57).

[h] On day 1, ivabradine will be dosed in the clinic and then will be dispensed at each study visit. At each clinic visit, the subject is to return investigational product for accountability. On day 15, dose titration will begin (7.5 mg twice daily [BID]) and subjects will begin to take ivabradine at home. The last dose of ivabradine will be taken on day 57.

[i] If screening pregnancy test is done ≥ 7 days from day 1, a repeat pregnancy test will be done on day 1 prior to dosing.

[j] If a subject discontinues from the study, the accelerometer and investigational product is to be returned to the study clinic.

3. Introduction

3.1 Study Rationale

The goal of this study is to determine the impact of adding ivabradine therapy to the standard of care (SOC) in African-American/Black subjects with heart failure (HF) and reduced ejection fraction (HFrEF) on changes in heart rate (HR) from baseline (SOC alone). Changes in HR from baseline will be correlated with the changes from baseline in activity level of the subjects, as measured by both a standard 6-minute walk distance and an accelerometer device.

3.2 Background

3.2.1 Disease

Chronic heart failure (HF) is a syndrome that results in inadequate systemic blood flow when normal neurohormonal mechanisms, namely, the sympathetic nervous system and the renin-angiotensin-aldosterone system, are exhausted or overwhelmed and are no longer able to deliver an adequate physiological response. While several interventions including angiotensin-converting-enzyme inhibitors (ACEi), beta (β)-blockers, aldosterone antagonists, coronary revascularization, and biventricular pacing (Jessup and Brozena, 2003) have been shown to improve symptoms, reduce the rate of HF hospitalizations, and improve mortality, both mortality and morbidity related to HF remain high. Chronic HF is associated with repeated hospitalizations, substantially reduced quality of life, a yearly mortality rate in the United States of 7.5% (Webster et al, 2006), and approximately 5.1 million persons in the US clinically manifest symptoms of chronic HF (Go et al, 2013). The etiology of chronic HF in adults is primarily myocardial dysfunction secondary to ischemic heart disease, usually as a consequence of coronary artery disease and myocardial infarction, although hypertensive cardiomyopathy is prevalent in African‑American/Black subjects (Yancy et al, 2013; McMurray et al, 2012).

Observational and interventional studies in adults demonstrate that relatively high resting HR is not only a biomarker correlated with poor clinical outcomes, but is also a validated surrogate marker and a modifiable risk factor for chronic HF (Swedberg et al, 2010; McAlister et al, 2009; Flannery et al, 2008; Lechat et al, 2001). Recently reported data from registries and clinical studies suggest that more than half the patients with HF receiving β-blockers will nevertheless have a resting HR > 70 beats per minute (bpm) (Maggioni et al, 2012; Maggioni et al, 2010). The ability to achieve further HR reduction

beyond what is achieved with β-blockers would therefore constitute a significant therapeutic advance.

Racially diverse populations may exhibit differences in drug response that may be due, in part, to variations in gene sequences. Functional single-nucleotide polymorphisms (SNPs) are common in the genes encoding β-adrenergic receptors (adrenergic receptors alpha2A, as well as beta-1 and beta-2-adrenergic receptor), and in a gene that regulates the response of these receptors to catecholamines, the G-protein receptor kinase 5 (*GRK5*) (Liggett et al, 2006; Liggett et al, 2008). Importantly, both the β-1 adrenergic receptor (*ADRB1)* Arg389 > Gly and the *GRK5* Gln41>Leu SNPs are over-represented in African-American/Black subjects. The *ADRB1* Arg389>Gly SNP is found in about 42% of African-American/Black and 27% of Caucasians, and the distribution of the *GRK5* Gln41 > Leu SNP shows even more ethnic divergence, as it is found in about 33% of African-American/Black but only 1% of Caucasians (Moore et al, 1999; Liggett et al, 2008). Both SNPs result in a blunted response of the β-adrenergic receptor to catecholamines and may therefore affect individual clinical responses to β-blockers in patients with HF (Liggett et al, 2006; Liggett et al, 2008).

3.2.2 Amgen Investigational Product Background: Ivabradine

Ivabradine is a hyperpolarization-activated cyclic nucleotide-gated channel blocker that reduces the spontaneous pacemaker activity of the cardiac sinus node by selectively inhibiting the cardiac *f*-current (I_f), resulting in HR reduction with no effect on ventricular repolarization and no effects on myocardial contractility.

Refer to the specific sections of the US product label for additional information related to the physical, chemical, and pharmaceutical properties and formulation(s), as well as pivotal clinical studies in HFrEF.

A detailed description of the chemistry, pharmacology, efficacy, and safety of ivabradine is provided in the Corlanor® (ivabradine) US Prescribing Information.

4. Objectives, Endpoints and Hypotheses

4.1 Objectives and Endpoints

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

4.2 Hypotheses

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

5. Study Design

5.1 Overall Design

Currently, there are no data available on the efficacy of ivabradine to reduce HR in African-American/Black subjects with HFrEF, due to the fact that the pivotal outcome study, SHIFT, was conducted outside of the US (Swedberg, et al, 2010).

African-American/Black subjects have a significantly higher prevalence of HF and generally experience worse outcomes than Caucasians (Yancy et al, 2013).

Considering the absence of representation of African-American/Black subjects with HFrEF in SHIFT and the potential limitations of β–blockade in that population, as described above, the primary objective of this study is to assess the efficacy of ivabradine in reducing HR in that population on top of optimal SOC.

As exploratory endpoints, [redacted]

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

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

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

Table 5-1. Ivabradine Dose Titration at Day 15 Based on Heart Rate From Electrocardiogram

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

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

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

The overall study design is described by a study schema in Section 2.1. The endpoints are defined in Section 4.1.

5.2 Number of Subjects

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

Subjects in this clinical investigation shall be referred to as “subjects”. For the sample size justification, see Section 10.1.

5.2.1 Replacement of Subjects

Subjects who are withdrawn or removed from treatment or the study will not be replaced.

5.2.2 Number of Sites

One to 3 investigative sites in the US will be included in the study.

5.3 End of Study

5.3.1 End of Study Definition

Primary Completion: The primary completion date is defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.

The primary completion date is the date when the last subject has completed the assessments for day 57.

If the study concludes prior to the primary completion date originally planned in the protocol (ie, early termination of the study), then the primary completion will be the date when the last subject is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

End of Study: The end of study date is defined as the date when the last subject across all sites is assessed or receives an intervention for evaluation in the study (ie, last subject last visit), following any additional parts in the study (eg, safety follow-up), as applicable.

5.3.2 Study Duration for Subjects

For an individual subject, the length of participation includes a 7-day screening period, a 57-day open-label treatment period, and a 30-day safety follow-up period.

5.4 Justification for Investigational Product Dose

Ivabradine will be initiated at 5 mg BID daily dosing (with option to reduce initial dosing to 2.5 mg BID based on investigator discretion), and the dose titration will follow the Corlanor® (ivabradine) US Prescribing Information, as indicated in Table 5-1.

6. Study Population

Eligibility criteria will be evaluated during screening.

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening).

Before any study-specific activities/procedures, the appropriate written informed consent must be obtained (see Appendix 3).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions will not be provided.

6.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

101 Subject has provided informed consent/assent prior to initiation of any study-specific activities/procedures.

102 Male or female subject ≥ 18 years of age, describing self as African-American/Black

103 Subject must have a diagnosis of HF confirmed by medical records, be in stable condition, and treated with stable optimal pharmacological therapy as per their personal physician's care.

104 LVEF ≤ 35% confirmed by investigator

105 NYHA class II to IV assessed at the time of screening

106 Electrocardiogram (ECG) documentation at the time of screening of sinus rhythm with resting HR ≥ 70 bpm by local ECG reading

107 Subject must be able to complete a 6MWT and wear an accelerometer

6.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply.

Disease Related

201 Recent myocardial infarction (≤ 2 months) or stroke (≤ 1 month) prior to enrollment

202 If the subject received within 3 months before or is scheduled to receive within 42 days after enrollment any of the following: revascularization, ventricular assist device, continuous or intermittent inotropic therapy, hospice care, major organ transplant, or is receiving renal replacement therapy by dialysis

203 If the subject received implantation of a cardioverter defibrillator or cardiac resynchronization therapy within 42 days before or is scheduled to receive implantation of a cardioverter defibrillator or cardiac resynchronization therapy within 42 days after enrollment

204 Severe primary valve disease or scheduled for surgery for valvular heart disease

205 Pacemaker with atrial or ventricular pacing (except bi-ventricular pacing) > 40% of the time, or with a stimulation threshold at the atrial or ventricular level ≥ 60 bpm

206 Permanent atrial fibrillation or flutter

207 Sick sinus syndrome, sinoatrial block, or second and third degree atrio-ventricular block

208 History of symptomatic or sustained (≥ 30 sec) ventricular arrhythmia unless a cardioverter defibrillator was implanted

209 History of congenital QT syndrome

210 Any cardioverter defibrillator shock experienced within 1 month of enrollment

211 Hypertrophic obstructive cardiomyopathy, active myocarditis or constrictive pericarditis, or clinically significant congenital heart disease

212 Chronic antiarrhythmic therapy (except digitalis)

213 Scheduled outpatient intravenous (IV) infusions for HF (eg, inotropes, vasodilators [eg, nesiritide], diuretics) or routinely scheduled ultrafiltration

214 Evidence of digitalis intoxication within 7 days prior to screening

215 Systolic blood pressure > 180 mm Hg or < 90 mm Hg, or diastolic blood pressure > 110 mm Hg or < 50 mm Hg at any time during the screening phase

216 Known untreated hypothyroidism or hyperthyroidism, adrenal insufficiency, active vasculitis due to collagen vascular disease

217 Have known acute or serious co-morbid condition (eg, major infection or hematologic, renal, hepatic, metabolic, gastrointestinal or endocrine dysfunction) that may interfere with the study, or severe concomitant non-cardiovascular disease that is expected to reduce life expectancy to less than 1 year or malignancy within 5 years prior to enrollment with the following exceptions: localized basal or squamous cell carcinoma of the skin or cervical intraepithelial neoplasia

Prior/Concomitant Therapy

218 Subjects taking QT prolonging medicinal products for cardiovascular (eg, but not limited to, quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone) or non-cardiovascular disease (eg, but not limited to, pimozide, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, IV erythromycin)

219 Subjects exposed to a strong CYP3A4 inhibitor (examples of strong CYP3A4 inhibitors include; azole antifungals [eg, itraconazole], macrolide antibiotics [eg, clarithromycin, telithromycin], human immunodeficiency virus (HIV) protease inhibitors, [eg, nelfinavir], and nefazodone]) within 14 days prior to enrollment, or to a strong CYP3A4 inducer (examples of CYP3A4 inducers include; St. John's wort, rifampicin, barbiturates, and phenytoin) within 28 days prior to enrollment

220 Subjects who received diltiazem or verapamil within 48 hours prior to enrollment

Prior/Concurrent Clinical Study Experience

221 Previously received ivabradine prior to participation in this study

222 Currently receiving treatment in another investigational device or drug study, or less than 30 days since ending treatment on another investigational device or drug study(ies). Other investigational procedures while participating in this study are excluded.

Other Exclusions

223 Female subject is pregnant or breastfeeding or planning to become pregnant or breastfeed during treatment and for an additional 14 days after the last dose of investigational product. Females of childbearing potential should only be included in the study after a confirmed menstrual period and a negative highly sensitive urine pregnancy test.

224 Female subjects of childbearing potential unwilling to use 1 highly effective method of contraception during treatment and for an additional 14 days after the last dose of investigational product. Refer to Appendix 5 for additional contraceptive information.

225 Subject has known sensitivity to any of the products or components to be administered during dosing.

226 Subject likely not to be available to complete all protocol required study visits or procedures, and/or to comply with all required study procedures to the best of the subject and investigator's knowledge.

227 History or evidence of any other clinically significant disorder, condition or disease (with the exception of those outlined above) that, in the opinion of the investigator or Amgen physician, if consulted, would pose a risk to subject safety or interfere with the study evaluation, procedures or completion.

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

Ivabradine should be taken with meals.

6.3.2 Caffeine, Alcohol, and Tobacco

At screening and throughout the duration of the study, subjects are encouraged to limit intake of caffeine containing beverages, alcohol, and tobacco.

6.3.3 Activity

Subjects are to maintain regular activities.

6.4 Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written institutional review board (IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Appendix 3).

The subject or the subject's legally acceptable representative must personally sign and date the IRB and Amgen approved informed consent before commencement of study-specific procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and in/on the enrollment case report form (CRF).

Each subject who enters into the screening period for the study (screening period starts when the subject signs and dates the informed consent form) receives a unique subject identification number before any study-related activities/procedures are performed. The subject identification number will be assigned manually. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject.

The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

6.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information will be collected that includes demographics, screen failure details, eligibility criteria, medical history, concomitant medications, and any serious adverse events.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time.

7. Treatments

Study treatment is defined as any investigational product(s), non-investigational product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

Note that in several countries, investigational product and non-investigational product are referred to as investigational medicinal product and non-investigational medicinal product, respectively.

The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, destruction, and administration of each treatment shown in Table 7-1.

7.1 Treatment Procedures

7.1.1 Investigational Products

The amount dispensed, amount returned, date dispensed, date returned, and lot number of the investigational product are to be recorded on each subject's CRF.

Table 7-1. Study Treatment

Study Treatment Name	**Amgen Investigational Product:**[a] Ivabradine (Corlanor) tablets
Dosage Formulation	Salmon colored, oval-shaped, film-coated tablets, scored on both edges debossed with "5" on one face and bisect on the other face per product specification PRDS-002165. Ivabradine will be provided in bottles (60 tablets per bottle) labeled ivabradine 5 mg and ivabradine 7.5 mg. Subjects splitting the 5.0 mg tablets into equal halves will achieve the 2.5 mg dose of ivabradine. Tablets cannot be crushed or liquefied.
Unit Dose Strength(s)/ Dosage Level(s) and Dosage Frequency	5 mg BID daily. After 14 days, tolerability to be assessed as well as resting HR with dose adjustment, as recommended in the Corlanor® (ivabradine) US Prescribing Information. At the investigator's discretion.
Route of Administration	Oral
Accountability	The amount dispensed, amount returned, date dispensed, date returned, and lot number of investigational product are to be recorded on each subject's CRF(s).
Dosing Instructions	Subjects will take the investigational product with food.

Abbreviations: BID = twice daily; CRF = case report form; HR = heart rate
[a] Ivabradine will be manufactured and packaged by Amgen and distributed using Amgen clinical study drug distribution procedures.

7.1.2 Non-investigational Products

Not applicable.

7.1.3 Medical Devices

Other non-investigational medical devices may be used in the conduct of this study as part of standard care.

Non-investigational medical devices (eg, syringes, sterile needles), that are commercially available are not usually provided or reimbursed by Amgen (except, for example, if required by local regulation). The investigator will be responsible for obtaining supplies of these devices.

Heart rate during the 6MWT will be measured by an HR monitor at specified time points (see Table 2-1 for 6MWT schedules). An accelerometer will also be used throughout the study. Any adverse events associated with the accelerometer (eg, allergic reaction to components of the instrument) will be captured in the Events CRF as a procedure-related event. Data collected from the accelerometer will not be available nor reviewed until after the end of the study (ie, last subject, last visit).

7.1.4 Other Protocol-required Therapies

Not applicable.

7.1.5 Other Treatment Procedures

There are no other treatment procedures in this study.

7.1.6 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug(s) or device(s) after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material.

This includes any drug(s), device, or combination product(s) provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

Any product complaint(s) associated with an investigational product(s), non-investigational product(s), device(s), or combination product(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

For devices not provided by Amgen, refer to the device manual for product complaint procedures.

7.1.7 Excluded Treatments, Medical Devices, and/or Procedures During Study Period

Other investigational procedures and products while participating in this study are prohibited.

Strong CYP3A4 inhibitors are contraindicated. Concomitant use of diltiazem and verapamil and CYP3A4 inducers is discouraged per label. QT-prolonging medications are prohibited. Consumption of grapefruit juice is not recommended.

7.2 Method of Treatment Assignment

All subjects will receive open-label ivabradine.

The treatment assignment date is to be documented in the subject's medical record and on the enrollment CRF.

7.3 Blinding

This is an open-label study; blinding procedures are not applicable.

7.4 Dose Modification

Refer to Table 5-1 for dose titration according to HR and/or signs/symptoms of bradycardia.

7.4.1 Hepatotoxicity Stopping Rules

Refer to Appendix 7 for details regarding drug-induced liver injury (DILI) guidelines, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

7.4.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

7.4.2.1 Amgen Investigational Product: Ivabradine

Ivabradine will be initiated at a 5 mg BID dosing (with option to reduce initial dosing to 2.5 mg BID based on investigator discretion as per Corlanor® (ivabradine) US Prescribing Information). On day 15, subjects will be reassessed as to tolerability and clinical status as well as resting HR. Dose of study drug will be up-titrated to 7.5 mg BID (maximum dose), remain at 5 mg BID or down-titrated to 2.5 mg BID based on guidance in Table 5-1 and the investigator's clinical judgment. If the subject does not tolerate the lowest dose of ivabradine 2.5 mg BID, or continues to experience symptomatic bradycardia (eg, dizziness, fatigue, or hypotension), or has a resting HR of < 50 bpm on that dose, the study drug will be discontinued.

Discontinuation of study drug at any time during the study will be left up to the discretion of the investigator.

The reason for dose change of ivabradine is to be recorded on each subject's CRF.

7.5 Preparation/Handling/Storage/Accountability

Guidance and information on preparation, handling, storage, accountability, destruction, or return of the investigational product during the study are provided in the IPIM.

7.6 Treatment Compliance

Subjects should be informed to return to the study site all bottles with all remaining tablets at each study visit. To monitor dosage compliance, a manual tablet count will be performed by the site at the time of drug return to calculate the number of expected tablets that should have been taken versus the amount of remaining tablets. Subjects should be re-educated on the importance of adhering to the study drug administration schedule (BID, every 12 hours ± 4 hours) if inventory of remaining tablets indicates medication non-compliance.

7.7 Treatment of Overdose

Overdose of ivabradine may lead to severe and prolonged bradycardia. In the event of bradycardia with poor hemodynamic tolerance, temporary cardiac pacing may be required. Supportive treatment, including IV fluids, atropine, and IV beta-stimulating agents such as isoproterenol, may be considered.

7.8 Prior and Concomitant Treatment

7.8.1 Prior Treatment

Prior therapies that were being taken/used from 30 days prior to the screening period through the end of the screening period will be collected. For prior therapies, therapy name, indication, dose, unit, frequency, route, start date, and stop date will be collected.

7.8.2 Concomitant Treatment

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 7.1.7.

Concomitant therapies (including but not limited to β-blocker, ACEi, and angiotensin II receptor blocker) are to be collected from day 1 through the end of the safety follow-up period at day 87 or 30 days after the last administration of investigational product, whichever is later. Subjects should avoid concomitant use of moderate CYP3A4

inhibitors when using ivabradine. Examples of moderate CYP3A4 inhibitors include diltiazem, verapamil, and grapefruit juice.

8. Discontinuation Criteria

Subjects have the right to withdraw from investigational product and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

The investigator and/or sponsor can decide to withdraw a subject(s) from investigational product, device, and/or other protocol-required therapies, protocol procedures, or the study as a whole at any time prior to study completion for the reasons listed in Sections 8.1, 8.2.1, and 8.2.2.

8.1 Discontinuation of Study Treatment

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study.

Reasons for removal from protocol-required investigational product(s) or procedural assessments include any of the following:

- Decision by Sponsor
- Lost to follow-up
- Death
- Ineligibility determined
- Protocol deviation
- Non-compliance
- Adverse event
- Subject request
- Pregnancy

If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product or other protocol-required therapies and must discuss with the subject the possibilities for continuation of the Schedule of Activities (see Table 2-1) including different options of follow-up (eg, in person, by phone/mail, through family/friends, in correspondence/communication with other treating physicians, from the review of medical records) and collection of data, including endpoints, adverse events, disease-related events, and must document this decision in

the subject's medical records. Subjects who have discontinued investigational product and/or other protocol-required therapies or procedures should not be automatically removed from the study. Whenever safe and feasible, it is imperative that subjects remain on-study to ensure safety surveillance and/or collection of outcome data.

Subjects may be eligible for continued treatment with Amgen investigational product(s) and/or other protocol-required therapies by a separate protocol or as provided for by the local country's regulatory mechanism, based on parameters consistent with Appendix 3.

8.2 Discontinuation From the Study

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study, and must document the subject's decision to withdraw in the subject's medical records.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must notify Amgen accordingly (see Appendix 6 for further details). Refer to the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.2.1 Reasons for Removal From Washout, Run-in or Invasive Procedures

Not applicable.

8.2.2 Reasons for Removal From Study

Reasons for removal of a subject from the study are:

- Decision by sponsor
- Withdrawal of consent from study
- Death
- Lost to follow-up

8.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or is able to continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts are to be documented in the subject's medical record.
- If the subject continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.
- For subjects who are lost to follow-up, the investigator can search publically available records (where permitted) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

9. Study Assessments and Procedures

Study procedures and their time points are summarized in the Schedule of Activities (see Table 2-1).

As protocol waivers or exemptions are not allowed if an enrolled subject is subsequently determined to be ineligible for the study, this must be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject is to continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities (Table 2-1), is essential and required for study conduct.

9.1 General Study Periods

9.1.1 Screening, Enrollment and/or Randomization

Informed consent must be obtained before completing any screening procedure or discontinuation of standard therapy for any disallowed therapy. After the subject has signed the informed consent form, the site will register the subject manually and screen the subject in order to assess eligibility for participation. The screening window is 7 days.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

If a subject has not met all eligibility criteria at the end of the screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening 1 time.

Rescreened subjects must first be registered as screen failures and subsequently registered as rescreens. Once the subject is registered as rescreened, a new 7-day screening window will begin. Subjects will retain the same subject identification number assigned at the original screening. If the rescreening period begins more than 30 days after the original signing of the informed consent form, all screening procedures, including informed consent, must be repeated.

9.1.2 Treatment Period

Visits will occur per the Schedule of Activities (Table 2-1). On-study visits may be completed within ± 2 days for days 1, 15, and 29 and to be completed within ± 5 days for day 57. The date of the first dose of ivabradine is defined as day 1. All subsequent doses and study visits will be scheduled based on the day 1 date. Administration of ivabradine is to be administered during each visit according to the Schedule of Activities (Table 2-1).

9.1.3 Safety Follow-up

A safety follow-up period (phone contact) will be conducted at the study clinic at day 87 or 30 days after the last dose of ivabradine.

9.1.4 Early Termination

If a subject discontinues study drug administration before the day 57 visit, the subject will return to the study clinic in 30 days after study discontinuation and return the accelerometer and investigational product. Subjects ending investigational product early will be asked to complete the early termination visit procedures outlined per the Schedule of Activities (Table 2-1).

9.2 Description of General Study Assessments and Procedures

The sections below provide a description of the individual study procedures for required time points.

9.2.1 General Assessments

9.2.1.1 Informed Consent

All subjects or their legally authorized representative must sign and personally date the IRB approved informed consent before any study-specific procedures are performed.

9.2.1.2 Demographics

Demographics data collection including sex, age, race, and ethnicity will be collected in order to study their possible association with subject safety and treatment effectiveness.

9.2.1.3 Medical History

The Investigator or designee will collect targeted medical cardiovascular disease history along with the functional NYHA class history that started within 5 years prior to enrollment through screening. Medical history will include information on the subject's concurrent medical conditions. Record all findings on the medical history CRF.

9.2.1.4 Physical Examination

Physical examination will be performed as per standard of care. Physical examination findings should be recorded (eg, medical history, event).

9.2.1.5 Physical Measurements

Height in centimeters should be measured without shoes. Weight in kilograms should be measured without shoes.

9.2.1.6 Substance Abuse History

Obtain a detailed history of prior and/or concurrent use of alcohol, tobacco, caffeine.

9.2.2 Efficacy Assessments

9.2.2.1 Electrocardiogram

Change in HR will be assessed by ECG. Refer to Section 9.2.3.3 for further details.

9.2.2.2 6-Minute Walk Test

The 6MWT will be conducted at baseline (day 1) and at the end of treatment period (day 57). The 6MWT will be recorded by standard methods (see Appendix 8 for 6MWT instructions and Appendix 9 for 6MWT for recording form). Heart rate (HR) during the 6MWT will be recorded by an HR monitor.

9.2.2.3 Accelerometer

An accelerometer will be provided to each subject at screening. A 7-day screening visit with the accelerometer is required before day 1 dosing. The subjects will be instructed to wear the accelerometer every day continuously, except to be recharged. The accelerometer is to be worn daily from screening through the end of treatment period (day 57). The accelerometer will record the subject’s physical activity. Refer to the accelerometer manual for further details.

Data collected from wearable devices will not be available nor reviewed until after the end of the study (ie, last subject, last visit).

9.2.3 Safety Assessments

Planned time points for all safety assessments are listed in the Table 2-1.

9.2.3.1 Adverse Events

9.2.3.1.1 Time Period and Frequency for Collecting and Reporting Safety Event Information

9.2.3.1.1.1 Disease-related Events

Disease-related events are defined in Appendix 4.

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after the first dose of investigational product(s)/study treatment/protocol-required therapies through the end of study/safety follow-up visit or 30 days after the last administration of investigational product, whichever is later, are collected/recorded/reported using the Event CRF.

Disease-related events assessed by the investigator to be more severe than expected and/or related to the investigational product(s)/study treatment/protocol-required therapies, and determined to be serious, must be reported on the Event CRF as serious adverse events.

In this study, subjects will have HF and left ventricular systolic dysfunction. Therefore, disease-related events potentially include manifestation and complications of HF and left ventricular systolic dysfunction such as: left ventricular dilatation, cardiopulmonary failure, cardiomyopathy, decreased cardiac output, low cardiac output syndrome, ejection fraction decreased, pulmonary edema, orthopnea, nocturnal dyspnea, peripheral edema, and testing suggesting progression of HF.

- Disease-related events that would qualify as an adverse event or serious adverse event:
    - In case of an event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.

- Disease-related events that do not qualify as adverse events or serious adverse events:
    - An event which is part of the normal course of disease under study (eg, disease progression in HF or hospitalization due to disease progression) is to be reported as a disease-related event.

9.2.3.1.1.2 Adverse Events

The adverse event grading scale to be used for this study will be the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 and is described in Appendix 4.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur after the first dose of investigational product through the end of study/safety follow-up visit or 30 days after the last administration of investigational product, whichever is latest, are reported using the Event CRF.

All adverse events observed by the investigator or reported by the subject that are related to study procedures/study activities will be reported from signing the informed consent form through end of study/safety follow-up visit or 30 days after last dose of investigational product administration, whichever is later, are to be collected/recorded/reported using the Event CRF.

9.2.3.1.1.3 Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the end of study/safety follow-up visit or 30 days after the last administration of investigational product, whichever is later, are reported using the Event CRF.

All serious adverse events will be collected, recorded, and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

The criteria for grade 4 in the (CTCAE), version 4.0 grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator's judgment to report these grade 4 abnormalities as serious adverse events.

9.2.3.1.1.4 Serious Adverse Events After the Protocol-required Reporting Period

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to Amgen. Per local requirements in some countries, investigators are required to report serious adverse events that they become aware of after end of study. If serious adverse events are reported, the investigator is to report them to Amgen within 24 hours following the investigator's knowledge of the event.

Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases and handled accordingly based on relationship to investigational product.

The method of recording, evaluating, and assessing causality of adverse events, disease-related events, and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 4.

9.2.3.1.1.5 Serious Adverse Events That are not to be Reported by the Sponsor to Regulatory Agencies in an Expedited Manner

Serious adverse events (eg, population-related events) that are not planned to be reported individually in an expedited manner as they are anticipated to occur in the study population at some frequency independent of the protocol-required therapies are as follows:

Hospitalizations and deaths due to chronic heart failure complications are anticipated to occur in the enrolled population. The Amgen safety and medical team will review accumulating events on a regular basis.

9.2.3.1.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

9.2.3.1.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial adverse event/serious adverse event report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All adverse events and serious adverse events will be followed until resolution, stabilization, until the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

All new information for previously reported serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. Information provided about the serious adverse event must be consistent with that recorded on the Event CRF.

9.2.3.1.4 Regulatory Reporting Requirements for Serious Adverse Events

If subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Prompt notification by the investigator to the sponsor of serious adverse events is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and investigators.

Individual safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an individual safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

9.2.3.1.5 Pregnancy and Lactation

Details of all pregnancies and/or lactation in female subjects and in female partners of male subjects will be collected after the start of study treatment and until 14 days after the last dose of study drug.

If a pregnancy is reported, the investigator is to inform Amgen within 24 hours of learning of the pregnancy and/or lactation and is to follow the procedures outlined in Appendix 5. Amgen Global Patient Safety will follow-up with the investigator regarding additional information that may be requested.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered serious adverse events.

Further details regarding pregnancy and lactation are provided in Appendix 5.

9.2.3.2 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, HR, respiratory rate, and temperature. Subject should preferably be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. If the subject is not in the supine position, the subject should be in the most recumbent position as possible. The position selected for a subject should be the same that is used throughout the study and documented on the vital sign CRF. The temperature location selected for a subject should be the same that is used throughout the study and documented on the vital signs CRF. Record all measurements on the vital signs CRF.

9.2.3.3 Electrocardiograms (ECGs)

Subject must be in supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the subject is unable to be in the supine position, the subject should be in the most recumbent position as possible. The ECG must include the following measurements: HR, QRS, QT, QTc, and PR intervals. The primary investigator will review all ECGs. Once signed, the original ECG tracing will be retained with the subject's source documents. At the request of the sponsor, a copy of the original ECG will be made available to Amgen.

9.2.3.4 Vital Status

Vital status must be obtained for all subjects within the limits of local law. This includes subjects who may have discontinued study visits with or without withdrawing consent and should include interrogation of public databases, if necessary. If deceased, the date and reported cause of death should be obtained.

9.2.3.5 Suicidal Risk Monitoring

Not applicable.

9.2.4 Clinical Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities Table 2-1, for the timing and frequency.

The investigator is responsible for reviewing laboratory test results and recording any clinically relevant changes occurring during the study in the Event CRF. The investigator

must determine whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (Table 2-1).

9.2.4.1 Pregnancy Testing

A high sensitive urine pregnancy test should be completed at screening and within 7 days of initiation of investigational product for females of childbearing potential.

Note: Females who have undergone a bilateral tubal ligation/occlusion should have pregnancy testing per protocol requirements. (If a female subject, or the partner of a male subject, becomes pregnant it must be reported on the Pregnancy Notification Worksheet, see Figure 12-2). Refer to Appendix 5 for contraceptive requirements.

Additional on-treatment pregnancy testing may be performed at the investigator's discretion or as required per local laws and regulations.

9.2.4.2 Prespecified Biomarker Assessments

Not applicable.

9.2.5 Pharmacokinetic Assessments

Not applicable.

9.2.6 Pharmacodynamic Assessments

Not applicable.

9.2.7 Pharmacogenetic Assessments

Not applicable.

10. Statistical Considerations

10.1 Sample Size Determination

The primary endpoint is HR reduction from baseline at day 57 greater than 5 bpm. Based on HR reduction results observed in the overall placebo-treated subjects of the SHIFT study as well as in the placebo-treated subjects of the subgroup analysis of

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

10.2 Analysis Sets, Subgroups, and Covariates

10.2.1 Analysis Sets

10.2.1.1 Full Analysis Set

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

10.2.1.2 Safety Analysis Set

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

10.2.2 Covariates

Baseline covariates include, but are not limited to:

- Age: < 65 years, ≥ 65 years
- Sex

10.2.3 Subgroups

Subgroups might include, but are not limited to:

- Age: < 65 years, ≥ 65 years
- Sex

10.2.4 Handling of Missing and Incomplete Data

No missing data will be imputed for efficacy and safety endpoints.

10.3 Adaptive Design

Not applicable.

10.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock. Below is a summary of the timing and methods for the planned statistical analyses. To preserve study integrity, the primary analysis will be conducted and reported following the end of study, as defined in Section 5.3.1.

10.4.1 Planned Analyses

10.4.1.1 Interim Analysis and Early Stopping Guidelines

No interim analysis will be conducted in this study.

10.4.1.2 Primary Analysis

The primary analysis for this study will be performed when all subjects have completed all planned study procedures. This primary analysis will evaluate whether the effect of ivabradine on HR reduction at day 57 in African-American/Black subjects overall (the primary endpoint) exceeds 5 bpm. Descriptive statistics of the exploratory endpoints will be summarized. Safety data will be tabulated.

10.4.1.3 Final Analysis

Not applicable.

10.4.2 Methods of Analyses

10.4.2.1 General Considerations

At the time of primary analysis, the database will be cleaned, processed and a snapshot will be taken. Based on the snapshot, efficacy and safety analyses will be performed on the FAS and safety analysis set respectively.

Efficacy analyses of the primary endpoint will test whether the mean reduction with ivabradine exceeds 5 bpm. Summary statistics and least-square means along with 95% confidence interval, analyzed by the repeated-measures linear model, will be provided for the primary endpoint.

Subject disposition, demographics, baseline characteristics, medical history, baseline concomitant medications, and exposure to investigational product will be summarized. Continuous variables will be summarized using descriptive statistics, including the number of observations (n), mean, standard deviation or standard error, median, the first quartile and third quartile, minimum, and maximum. Categorical variables will be summarized using the number and percent of subjects.

10.4.2.2 Efficacy Analyses

10.4.2.2.1 Primary Endpoint

- HR reduction from baseline to day 57 for the overall African-American/Black subjects.

The repeated measures linear model will be used to evaluate ivabradine efficacy on HR reduction from baseline to day 57 for the overall African-American/Black subjects. The model will include terms of scheduled visits and baseline HR measurement as

covariates and will test whether the mean reduction with ivabradine exceeds 5 bpm, which is the reduction assumed with placebo. Missing values will not be imputed when the repeated measures linear model is used. Based on the model, the least-square means along with 95% confidence interval will be provided. In addition, descriptive statistics of HR reduction by scheduled visit will be summarized.

10.4.2.2.2 Secondary Endpoints

Not applicable.

10.4.2.2.3 Exploratory Endpoints

[redacted]

10.4.2.3 Safety Analyses

10.4.2.3.1 Analyses of Primary Safety Endpoint

Endpoint	Statistical Analysis Methods
Primary	Descriptive statistics

10.4.2.3.2 Adverse Events and Disease-related Events

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

10.4.2.3.3 Laboratory Test Results

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

10.4.2.3.4 Vital Signs

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

10.4.2.3.5 Physical Measurements

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

10.4.2.3.6 Electrocardiogram

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

The ECG measurements from this clinical study will be performed as per standard of care for routine safety monitoring, rather than for purposes of assessment of potential QTc effect. Since these evaluations may not necessarily be performed under the rigorous conditions expected to lead to meaningful evaluation of QTc data, summaries and statistical analyses of ECG measurements are not planned, and these data would not be expected to be useful for meta-analysis with data from other studies.

10.4.2.3.7 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by visit.

10.4.2.3.8 Exposure to Concomitant Medication

Information regarding concomitant medications of interest, including but not limited to β-blockers, ACEi, and angiotensin II receptor blockers, will be summarized.

11. References

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12. Appendices

12.1 Appendix 1. List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition/Explanation
6MWT	6-minute walk test
ACEi	angiotensin-converting-enzyme inhibitors
ANC	absolute neutrophil count
BID	twice daily
bpm	beats per minute
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug induced liver injury
DLRT	dose level review team
DMC	data monitoring committee
DRE	device-related event
DRT	data review team
ECG	electrocardiogram
EDC	electronic data collection
Electronic Source Data (eSource)	source data captured initially into a permanent electronic record used for the reconstruction and evaluation of a trial.
End of Study	The end of study date is defined as the date when the last subject at the site is assessed or receives an intervention for evaluation in the study (ie, last subject last visit)
End of Study for Individual Subject	defined as the last day that protocol-specified procedures are conducted for an individual subject
End of Treatment	defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
Enrolled	A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria.
FAS	Full analysis set
GRK5	G-protein receptor kinase 5

Abbreviation or Term	Definition/Explanation
HF	heart failure
HFrEF	heart failure and reduced ejection fraction
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormonal replacement therapy
IP	investigational product
IPIM	Investigational Product Instruction Manual
IRB	institutional review board
IUD	Intrauterine device
IUS	Intrauterine hormonal-releasing system
IV	Intravenous
LVEF	left ventricular ejection fraction
NASH	Nonalcoholic fatty liver disease including steatohepatitis
NYHA	New York Heart Association
SAS	Safety analysis set
SNP	single-nucleotide polymorphisms
SOC	standard of care
Source Data	information from an original record or certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH Guideline [E6]). Examples of source data include Subject identification, Enrollment Randomization identification, and Stratification Value.
Study Day 1	defined as the first day that protocol-specified investigational product(s)/protocol-required therapies is/are administered to the subject
SUSAR	suspected unexpected serious adverse reactions
ULN	upper limit of normal

12.2 Appendix 2. Clinical Laboratory Tests

The tests detailed in Table 12-1 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 6.1 to Section 6.2.

Additional tests may be performed at any time during the study as deemed necessary by the investigator or required by local regulations.

Table 12-1. Analyte Listing

Local Laboratory Chemistry	Local Laboratory Hematology	Local Laboratory Other Labs
Carbon dioxide (Bicarbonate)	RBC	Urine pregnancy test
Chloride	Hemoglobin	BNP
Potassium	Hematocrit	
Sodium	Platelets WBC	
BUN		
Creatinine eGFR		
total protein		
albumin		
total bilirubin		
ALT AST		
HbA1c		
Glucose		

Abbreviations; ALT = alanine aminotransferase; AST = aspartate aminotransferase;
BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c;
BNP = b-type natriuretic peptide; RBC = red blood count; WBC = white blood count

12.3 Appendix 3. Study Governance Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form, Investigator's Brochure, and other relevant documents (eg, subject recruitment advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

Amgen may amend the protocol at any time. The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator must send a copy of the approval letter from the IRB and amended protocol Investigator's Signature page to Amgen prior to implementation of the protocol amendment at their site.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Obtaining annual IRB approval/renewal throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be sent to Amgen
- Notifying the IRB of serious adverse events occurring at the site, deviations from the protocol or other adverse event reports received from Amgen, in accordance with local procedures
- Overall conduct of the study at the site and adherence to requirements of Title 21 of the US Code of Federal Regulations (CFR), ICH guidelines, the IRB, and all other applicable local regulations

Informed Consent Process

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Trial Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

The investigator or his/her delegated representative will explain to the subject, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study before any protocol-specific screening procedures or any investigational product(s) is/are administered, and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative defined as an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study will then be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study site.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the informed consent form.

The investigator is also responsible for asking the subject if the subject has a primary care physician and if the subject agrees to have his/her primary care physician informed of the subject's participation in the clinical study unless it is a local requirement. The investigator shall then inform the primary care physician. If the subject agrees to such notification, the investigator is to inform the subject's primary care physician of the subject's participation in the clinical study. If the subject does not have a primary care physician and the investigator will be acting in that capacity, the investigator is to document such in the subject's medical record.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. Subject withdrawal of consent or discontinuation from study treatment and/or procedures must also be documented in the subject's medical records; refer to Section 8.

Subjects must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the subject or the subject's legally authorized representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood. (Refer to ICH GCP guideline, Section 4.8.9.)

A subject who is rescreened is not required to sign another informed consent form if the rescreening occurs within 30 days from the previous informed consent form signature date.

The informed consent will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate will not provide this separate signature.

Data Protection/Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

Subject will be assigned a unique identifier by the sponsor. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

On the CRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.

For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and age (in accordance with local laws and regulations).

Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with governmental regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

Publication Policy

To coordinate dissemination of data from this study, the investigator will obtain input and assistance from Amgen staff as appropriate.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct of Reporting, Editing, and Publications of Scholarly Work in Medical Journals, which states:

Authorship credit is to be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors need to meet conditions 1, 2, 3, and 4.

When a large, multicenter group has conducted the work, the group is to identify the individuals who accept direct responsibility for the manuscript. These individuals must fully meet the criteria for authorship defined above.

Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.

All persons designated as authors must qualify for authorship, and all those who qualify are to be listed.

Each author must have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- A recognized expert in the therapeutic area
- An Investigator who provided significant contributions to either the design or interpretation of the study
- An Investigator contributing a high number of eligible subjects

Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data, centrally or adjudicated data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Clinical monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements per the sponsor's monitoring plan.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Research & Development Compliance and Audit function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Retention of study documents will be governed by the Clinical Trial Agreement.

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

Source Documents

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

Data reported on the CRF or entered in the electronic CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the (IRB) and Amgen
- Investigational product-related correspondence including Proof of Receipts (POR), Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable
- Non-investigational product(s), and/or medical device(s) or combination product(s) documentation, as applicable

Retention of study documents will be governed by the Clinical Trial Agreement.

Study and Site Closure

Amgen or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the Clinical Trial Agreement. The investigator is to notify the IRB in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

12.4 Appendix 4. Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

Definition of Disease-related Event

Disease-related Event Definition

• Disease-related events are events (serious or non-serious) anticipated to occur in the study population due to the underlying disease. See Section 9.2.3.1.1.1 for the list of disease-related events.
• Disease-related events that would qualify as an adverse event or serious adverse event:
  o An event based on the underlying disease that is worse than expected as assessed by the investigator for the subject's condition or if the investigator believes there is a causal relationship between the investigational product(s)/study treatment/protocol-required therapies and disease worsening, this must be reported as an adverse event or serious adverse event.
• Disease-related events that do not qualify as adverse events or serious adverse events:
  o An event which is part of the normal course of disease under study (eg, disease progression in oncology or hospitalization due to disease progression) is to be reported as a disease-related event.

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a clinical study subject irrespective of a causal relationship with the study treatment. • Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a treatment, medical device or procedure.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [ECG], radiological scans, vital signs measurements), including those that worsen from baseline, that are considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an adverse event/serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses are to be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

A Serious Adverse Event is defined as any untoward medical occurrence that, meets at least 1 of the following serious criteria:
• Results in death (fatal)
• Immediately life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
• Requires in-patient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are an adverse event. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event is to be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.
• Results in persistent or significant disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
• Is a congenital anomaly/birth defect
• Other medically important serious event Medical or scientific judgment is to be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events are typically to be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording Adverse Events, Disease-related Events (if applicable), and Serious Adverse Events

Adverse Event, Disease-related Event (if applicable) and Serious Adverse Event Recording

• When an adverse event, disease-related event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
• The investigator will then record all relevant adverse event/disease-related event/serious adverse event information in the Event CRF.
  o Additionally, the investigator is required to report a fatal disease-related event on the Event CRF.
• The investigator must assign the following adverse event attributes:
  o Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms);
  o Dates of onset and resolution (if resolved);
  o Severity (or toxicity defined below);
  o Assessment of relatedness to investigational product: ivabradine, and/or other protocol‑required therapies and/or study‑mandated procedure/study mandated activity.
  o Action taken.
  o If the severity of an adverse event changes from the date of onset to the date of resolution, record a single event for each level of severity on the Event CRF.
• It is not acceptable for the investigator to send photocopies of the subject's medical records to the sponsor in lieu of completion of the Event CRF page.
• If specifically requested, the investigator may need to provide additional follow-up information, such as discharge summaries, medical records, or extracts from the medical records. In this case, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to the sponsor.
• The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event/serious adverse event.

Evaluating Adverse Events and Serious Adverse Events

Assessment of Severity
The investigator will make an assessment of severity for each adverse event and serious adverse event reported during the study. The assessment of severity will be based on: The Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 which is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Assessment of Causality
• The investigator is obligated to assess the relationship between investigational product, protocol-required therapies, and/or study-mandated procedures and each occurrence of each adverse event/serious adverse event. • Relatedness means that there are facts or reasons to support a relationship between investigational product and the event. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment. • For each adverse event/serious adverse event, the investigator must document in the medical notes that he/she has reviewed the adverse event/serious adverse event and has provided an assessment of causality. • There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data. • The investigator may change his/her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
Follow-up of Adverse Event and Serious Adverse Event
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen. • If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed Event CRF. • The investigator will submit any updated serious adverse event data to Amgen within 24 hours of receipt of the information.

Reporting of Serious Adverse Event

Serious Adverse Event Reporting via Electronic Data Collection Tool
• The primary mechanism for reporting serious adverse event will be the electronic data collection (EDC) system via the Safety Report Form. • If the EDC system is unavailable for more than 24 hours, then the site will report the information to Amgen using an electronic Serious Adverse Event (eSAE) Contingency Report Form (paper based form see Figure 12-1) within 24 hours of the investigator's knowledge of the event. • The site will enter the serious adverse event data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new serious adverse event from a study subject or receives updated data on a previously reported serious adverse event after the EDC has been taken off-line, then the site can report this information on a paper Serious Adverse Event Report Form (eg, Serious Adverse Event Contingency Report Form, see Figure 12-1).

Figure 12-1. Sample Electronic Serious Adverse Event Contingency Report Form

Completion Instructions - Electronic Adverse Event Contingency Report Form
(For use for clinical trial studies using Electronic Data Capture [EDC])

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used ONLY to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

Types of Events to be reported on this form

- **Serious Adverse Events (regardless of causal relationship to IP)**

1. **Site Information**

   Site Number* – Enter your assigned site number for this study

   Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. **Subject Information**

   Subject ID Number* – Enter the entire number assigned to the subject

   Age at event onset, Sex, and Race – Enter the subject's demographic information

   End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the serious adverse event term for the previous report as well as the start date for the initial event.

3. **Serious Adverse Event**

   Provide the date the Investigator became aware of this Information

   Serious Adverse Event Diagnosis or Syndrome* –
   - If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
   - If a diagnosis is not known, the relevant signs/symptoms should be entered.
   - If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

   Date Started* – Enter date the adverse event first started (not the date on which the event met serious criteria)rather than the date of diagnosis or hospitalizion. . **This is a mandatory field.**

   Date Ended – Enter date the adverse event ended and not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

   If event occurred before the first dose of Investigational Product (IP)/drug under study, add a check mark in the corresponding box.

   Is event serious?* – Indicate Yes or No. This is a mandatory field.

   Serious Criteria Code* – This is a mandatory field for serious events. Enter all reasons why the reported event has met serious criteria:
   - Immediately life-threatening – Use only if the subject was at immediate risk of death from the event as it occurred. Emergency treatment is often required to sustain life in this situation.
   - If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

   Relationship to IP – The Investigator must determine and enter the relationship of the event to the IP at the time the event is initially reported. **This is a mandatory field.**

   Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

   Outcome of Event* – Enter the code for the outcome of the event at the time the form is completed. **This is a mandatory field.**
   - Resolved – End date is known
   - Not resolved / Unknown – End date is unknown
   - Fatal – Event led to death

   If event is related to a study procedure, such as a biopsy, radiotherapy or withdrawal of a current drug treatment during a wash-out period, add a check mark to the corresponding box. This does not include relationship to IP or concomitant medication – only diagnostic tests or activities mandated by the protocol.

4. **Hospitalization**

   If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

FORM-056006 *Instructions Page 1 of 2* *Version 7.0 Effective Date: 1 February 2016*

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

5. **IP/Drug Under Study Administration including Lot # and Serial # when known / available.**
   Blinded or open-label – If applicable, indicate whether the investigational product is blinded or open-label
   Initial Start Date – Enter date the product was first administered, regardless of dose.
   Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.
   Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.
   Action Taken with Product – Enter the status of the product administration.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

6. **Concomitant Medications**
   Indicate if there are any medications.
   Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.
   Co-suspect – Indicate if the medication is co-suspect in the event
   Continuing – Indicate if the subject is still taking the medication
   Event Treatment – Indicate if the medication was used to treat the event
7. **Relevant Medical History**
   Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.
8. **Relevant Laboratory Tests**
   Indicate if there are any relevant laboratory values.
   For each test type, enter the test name, units, date the test was run and the results.
9. **Other Relevant Tests**
   Indicate if there are any tests, including any diagnostics or procedures.
   For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

10. **Case Description**
    Describe Event – Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

AMGEN Study # 20160231 Ivabradine	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

☐ Is not available due to internet outage at my site

☐ Is not yet available for this study

☐ Has been closed for this study

AMGEN SAFETY US FAX#: 888 814 8653

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Age at event onset	Sex	Race	If applicable, provide End of Study date
		☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____ and start date: Day _____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day____ Month____ Year_____

Serious Adverse Event diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Is event serious?	If serious enter Serious Criteria code *(see codes below)*	Relationship Is there a reasonable possibility that the Event may have been caused by IP (Ivabradine) or an Amgen device used to administer the IP? Ivabradine No✓ Yes✓	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐ Yes ☐ No				
				☐ Yes ☐ No				
				☐ Yes ☐ No				

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required/prolonged hospitalization; **04** Persistent or significant disability /incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP/drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

IP/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
Ivabradine	☒ *open label*							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

AMGEN Study # 20160231 Ivabradine	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

	Site Number	Subject ID Number	

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date (Day Month Year)	Stop Date (Day Month Year)	Co-suspect No✓	Co-suspect Yes✓	Continuing No✓	Continuing Yes✓	Dose	Route	Freq.	Treatment Med No✓	Treatment Med Yes✓

7. RELEVANT MEDICAL HISTORY *(include dates, allergies and any relevant prior therapy)*

8. RELEVANT LABORATORY VALUES *(include baseline values)* Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Test											
	Unit											

9. OTHER RELEVANT TESTS *(diagnostics and procedures)* Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

AMGEN Study # 20160231 Ivabradine	**Electronic Serious Adverse Event Contingency Report Form** **For Restricted Use**

Site Number	Subject ID Number

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee –	Title	Date
_____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*		

12.5 Appendix 5. Contraceptive Guidance and Collection of Pregnancy and Lactation Information

Study-specific contraception requirements for female of childbearing potential are outlined in Section 6.2.

Female subjects of childbearing potential must receive pregnancy prevention counseling and be advised of the risk to the fetus if they become pregnant during treatment and for 14 days after the last dose of protocol-required therapies.

Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female subjects to use highly effective methods of contraception for an increased length of time. In addition, male subjects may also be required to use contraception. The investigator must discuss these contraceptive changes with the subject.

Definition of Females of Childbearing Potential

A female is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Females in the following categories are not considered female of childbearing potential:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy;
  - Documented bilateral salpingectomy; or
  - Documented bilateral oophorectomy.

Note: Site personnel documentation from the following sources is acceptable: 1) review of subject's medical records; 2) subject's medical examination; or 3) subject's medical history interview.

- Premenarchal female
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Methods for Female Subjects

Highly Effective Contraceptive Methods

Note: Failure rate of < 1% per year when used consistently and correctly.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Bilateral tubal ligation/occlusion
- Vasectomized partner (provided that partner is the sole sexual partner of the female subject of childbearing potential and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments; the reliability of sexual abstinence must be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the subject)

Unacceptable Methods of Birth Control for Female Subjects

Birth control methods that are considered unacceptable in clinical studies include:

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method
- Barrier methods (condoms, diaphragm, cervical cap, or sponge)
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

Collection of Pregnancy Information

Female Subjects who Become Pregnant

- Investigator will collect pregnancy information on any female subject who becomes pregnant while taking protocol-required therapies through 14 days.
- Information will be recorded on the Pregnancy Notification Worksheet (see Figure 12-2). The worksheet must be submitted to Amgen Global Patient Safety within 24 hours of learning of a subject's pregnancy.

- After obtaining the female subject's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant while taking protocol-required therapies through 2 weeks of the study drug. This information will be forwarded to Amgen Global Patient Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of pregnancy will be reported to Amgen Global Patient Safety, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, fetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a fetal congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case.
- If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.
- Any serious adverse event occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to Amgen Global Patient Safety as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female subject who becomes pregnant while participating will discontinue study treatment (see Section 8.1 for details).

Male Subjects with Partners Who Become Pregnant or Were Pregnant at the Time of Enrollment

- In the event a male subject fathers a child during treatment, and for an additional 14 days after discontinuing protocol-required therapies, the information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Figure 12-2) must be submitted to Amgen Global Patient Safety within 24 hours of the site's awareness of the pregnancy.
- The investigator will attempt to obtain a signed authorization for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information.
- After obtaining the female partner's signed authorization for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Global Patient Safety.

- Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).
- Any termination of the pregnancy will be reported to Amgen Global Patient Safety regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

- Investigator will collect lactation information on any female subject who breastfeeds while taking protocol-required therapies through 14 days.
- Information will be recorded on the Lactation Notification Worksheet (see below) and submitted to Amgen Global Patient Safety within 24 hours of the investigator's knowledge of event.
- Study treatment will be discontinued if female subject breastfeeds during the study as described in exclusion criterion 223.
- With the female subjects signed authorization for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds while taking protocol-required therapies through 14 days after discontinuing protocol-required therapies.

Figure 12-2. Sample Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20160231

Study Design: ■ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm____ / dd____ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
Ivabradine				mm /dd /yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm / dd / yyyy_____ ☐ Unknown

Estimated date of delivery mm_____ / dd_____ / yyyy ___ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm / dd / yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm _____ / dd_____ / yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: March 27, 2011 Page 1 of 1

AMGEN® Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20160231

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
Ivabradine				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

****

Effective Date: 03 April 2012, version 2.

Page **1** of **1**

12.6 Appendix 6. Sample Storage and Destruction

Any blood sample collected according to the Schedule of Activities (Table 2-1) can be analyzed for any of the tests outlined in the protocol and for any tests necessary to minimize risks to study subjects. This includes testing to ensure analytical methods produce reliable and valid data throughout the course of the study. This can also include, but is not limited to, investigation of unexpected results, incurred sample reanalysis, and analyses for method transfer and comparability.

All samples and associated results will be coded prior to being shipped from the site for analysis or storage. Samples will be tracked using a unique identifier that is assigned to the samples for the study. Results are stored in a secure database to ensure confidentiality.

If informed consent is provided by the subject, Amgen can do additional testing on remaining samples (ie, residual and back-up) to investigate and better understand the heart failure and left ventricular systolic dysfunction in African-American/Black Subjects, the dose response and/or prediction of response to ivabradine, and characterize aspects of the molecule (eg, mechanism of action/target, metabolites). Results from this analysis are to be documented and maintained, but are not necessarily reported as part of this study. Samples can be retained for up to 20 years.

Since the evaluations are not expected to benefit the subject directly or to alter the treatment course, the results of pharmacogenetics, or other exploratory studies are not placed in the subject's medical record and are not to be made available to the subject, members of the family, the personal physician, or other third parties, except as specified in the informed consent.

The subject retains the right to request that the sample material be destroyed by contacting the investigator. Following the request from the subject, the investigator is to provide the sponsor with the required study and subject number so that any remaining sample types (eg, blood, tumor) samples and any other components from the cells can be located and destroyed. Samples will be destroyed once all protocol-defined procedures are completed. However, information collected from samples prior to the request for destruction, will be retained by Amgen.

The sponsor is the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the subject through the investigator, at the end of the storage period, or as

appropriate (eg, the scientific rationale for experimentation with a certain sample type no longer justifies keeping the sample). If a commercial product is developed from this research project, the sponsor owns the commercial product. The subject has no commercial rights to such product and has no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample (See Appendix 3 for subject confidentiality).

12.7 Appendix 7. Hepatotoxicity Stopping Rules: Suggested Actions and Follow-up Assessments

Subjects with abnormal hepatic laboratory values (ie, alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis (as described below) may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies, as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

Criteria for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies Due to Potential Hepatotoxicity

The following stopping and/or withholding rules apply to subjects for whom another cause of their changes in liver biomarkers (TBL, INR, and transaminases) has not been identified.

Important alternative causes for elevated AST/ALT and/or TBL values include, but are not limited to:

- Hepatobiliary tract disease
- Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, herpes simplex virus, varicella, toxoplasmosis, and parvovirus)
- Right sided heart failure, hypotension or any cause of hypoxia to the liver causing ischemia
- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants and mushrooms
- Heritable disorders causing impaired glucuronidation (eg, Gilbert's syndrome, Crigler-Najjar syndrome) and drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir)
- Alpha-one antitrypsin deficiency
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson's disease and hemochromatosis
- Nonalcoholic fatty liver disease including steatohepatitis (NASH)
- Non-hepatic causes (eg, rhabdomylosis, hemolysis)

If investigational product(s) is/are withheld, the subject is to be followed for possible DILI according to recommendations in the last section of this appendix.

Rechallenge may be considered if an alternative cause for impaired liver tests (ALT, AST, ALP) and/or elevated TBL, is discovered and the laboratory abnormalities resolve to normal or baseline (see next section in this appendix).

Table 12-2. Conditions for Withholding and/or Permanent Discontinuation of Amgen Investigational Product and Other Protocol-required Therapies due to Potential Hepatotoxicity

Analyte	Temporary Withholding	Permanent Discontinuation
TBL	> 3x ULN at any time	> 2x ULN
		OR
INR	--	> 1.5x ULN (for subjects not on anticoagulation therapy)
	OR	AND
AST/ALT	> 8x ULN at any time > 5x ULN but < 8x ULN for ≥ 2 weeks > 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule > 3x ULN with clinical signs or symptoms that are consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, and jaundice)	In the presence of no important alternative causes for elevated AST/ALT and/or TBL values > 3x ULN (when baseline was < ULN)
	OR	
ALP	> 8x ULN at any time	--

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR = international normalized ratio; TBL = total bilirubin; ULN = upper limit of normal

Criteria for Rechallenge of Amgen Investigational Product and Other Protocol-required Therapies After Potential Hepatotoxicity

The decision to rechallenge the subject is to be discussed and agreed upon unanimously by the subject, investigator, and Amgen.

If signs or symptoms recur with rechallenge, then Amgen investigational product is to be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Table 12-2) are never to be rechallenged.

Drug-induced Liver Injury Reporting and Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST or ALT and TBL and/or INR elevation, according to the criteria specified in the above, require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate CRF (eg, Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities is to be completed and sent to Amgen

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Appendix 4.

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI as specified in Table 12-2 or who experience AST or ALT elevations > 3 x upper limit of normal (ULN) or 2-fold increases above baseline values for subjects with elevated values before drug are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels.

Assessments that are to be performed during this period include:

- Repeat AST, ALT, ALP, bilirubin (total and direct), and INR within 24 hours
- In cases of TBL > 2x ULN or INR > 1.5, retesting of liver tests, BIL (total and direct), and INR is to be performed every 24 hours until laboratory abnormalities improve

Testing frequency of the above laboratory tests may decrease if the abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued AND the subject is asymptomatic.

Initiate investigation of alternative causes for elevated AST or ALT and/or elevated TBL. The following are to be considered depending on the clinical situation:

- Complete blood count (CBC) with differential to assess for eosinophilia
- Serum total immunoglobulin IgG, anti-nuclear antibody (ANA), anti smooth muscle antibody, and liver kidney microsomal antibody -1 (LKM1) to assess for autoimmune hepatitis
- Serum acetaminophen (paracetamol) levels

- A more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity-type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant use of medications (including non-prescription medicines and herbal and dietary supplements), plants, and mushrooms
- Viral serologies
- Creatine phosphokinase (CPK), haptoglobin, lactate dehydrogenase (LDH), and peripheral blood smear
- Appropriate liver imaging if clinically indicated
- Appropriate blood sampling for pharmacokinetic analysis if this has not already been collected
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist)

Follow the subject and the laboratory tests (ALT, AST, TBL, INR) until all laboratory abnormalities return to baseline or normal or considered stable by the investigator. The "close observation period" is to continue for a minimum of 4 weeks after discontinuation of all investigational product(s) and protocol-required therapies.

The potential DILI event and additional information such as medical history, concomitant medications and laboratory results must be captured in the corresponding CRFs.

12.8 Appendix 8. Six Minute Walk Test Instructions

HEART online
Heart Education Assessment Rehabilitation Toolkit

Six Minute Walk Test (6MWT) instructions

Set up

Ideally the test should be conducted on a straight 30 metre track[1]. If the track needs to be adapted or shortened due to lack of space, ensure that the patient walks the same course on each re-test.

Suggested Equipment:

- 6MWT recording form
- Rate of perceived exertion - Borg scale
- Pulse oximeter with appropriate sensor
- Stop watch or timer
- Chairs (number will depend on patient's condition and risk)
- Sphygmomanometer and stethoscope, or similar method of accurately assessing BP
- Trundle wheel for measuring the 6MWT track and the distance walked
- Clip board and recording sheet
- Portable oxygen if required

Repeat measures

Two 6MWTs are often recommended for initial assessments due to a learning effect when performing the test. Recent studies have demonstrated however that a single measure is often acceptable[2,3].

Should you choose to do repeat measures in succession, this should be done each time so that measures are consistent and a duration of at least 15 minutes provided between tests to allow adequate recovery.

Administering test

1. Prior to walking say to patient:

The object of this test is to walk as FAR AS POSSIBLE for 6 minutes. You will walk back and forth along this course (demonstrate one lap) for six minutes.

You may slow down if necessary. If you stop, I want you to continue to walk again as soon as possible.

You will be informed of the time and encouraged each minute.

Please do not talk during the test unless you have a problem or I ask you a question. You must let know if you have any chest pain or dizziness.

When six minutes is up I will ask you to STOP where you are. Do you have any questions?

2. To begin say to patient:

Start now, or whenever you are ready (start stopwatch when walking starts).

3. During the test:

Provide the following standard encouragements in even tones. Do not use other words of encouragement or body language to speed up.

- At 1 minute: *You are doing well. You have 5 minutes to go.*
- At 2nd minute: *Keep up the good work. You have 4 minutes to go.*
- At 3rd minute: *You are doing well. You are halfway done.*
- At 4th minute: *Keep up the good work. You have only 2 minutes left.*
- At 5th minute: *You are doing well. You have only 1 minute to go.*
- At 6th minute: *Please stop where you are.*

If the patient stops during the test:

Allow the patient to rest or sit in a chair if they wish, and check SpO2 and heart rate. Ask the patient why they stopped.

Keep the stopwatch running and advise: *Please resume walking whenever you feel able.*

Heart Foundation

Source: www.heartonline.org.au/resources Reviewed 11/2014 1

HEART online
Heart Education Assessment Rehabilitation Toolkit

Six Minute Walk Test (6MWT) instructions

Set up

Ideally the test should be conducted on a straight 30 metre track[1]. If the track needs to be adapted or shortened due to lack of space, ensure that the patient walks the same course on each re-test.

Suggested Equipment:

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- Pulse oximeter with appropriate sensor
- Stop watch or timer
- Chairs (number will depend on patient's condition and risk)
- Sphygmomanometer and stethoscope, or similar method of accurately assessing BP
- Trundle wheel for measuring the 6MWT track and the distance walked
- Clip board and recording sheet
- Portable oxygen if required

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Two 6MWTs are often recommended for initial assessments due to a learning effect when performing the test. Recent studies have demonstrated however that a single measure is often acceptable[2,3].

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1. Prior to walking say to patient:

The object of this test is to walk as FAR AS POSSIBLE for 6 minutes. You will walk back and forth along this course (demonstrate one lap) for six minutes.

You may slow down if necessary. If you stop, I want you to continue to walk again as soon as possible.

You will be informed of the time and encouraged each minute.

Please do not talk during the test unless you have a problem or I ask you a question. You must let know if you have any chest pain or dizziness.

When six minutes is up I will ask you to STOP where you are. Do you have any questions?

2. To begin say to patient:

Start now, or whenever you are ready (start stopwatch when walking starts).

3. During the test:

Provide the following standard encouragements in even tones. Do not use other words of encouragement or body language to speed up.

- At 1 minute: *You are doing well. You have 5 minutes to go.*
- At 2nd minute: *Keep up the good work. You have 4 minutes to go.*
- At 3rd minute: *You are doing well. You are halfway done.*
- At 4th minute: *Keep up the good work. You have only 2 minutes left.*
- At 5th minute: *You are doing well. You have only 1 minute to go.*
- At 6th minute: *Please stop where you are.*

If the patient stops during the test:

Allow the patient to rest or sit in a chair if they wish, and check SpO2 and heart rate. Ask the patient why they stopped.

Keep the stopwatch running and advise: *Please resume walking whenever you feel able.*

Heart Foundation

12.9 Appendix 9. Six Minute Walk Test Recording Form

(Affix patient label here)
Patient ID:
Family name:
Given name(s):
Date of birth: Sex: ☐ M ☐ F ☐ I

HEART online
Heart Education Assessment Rehabilitation Toolkit

Six Minute Walk Test (6MWT) recording form

☐ Medical history checked
☐ Medical clearance provided for the patient to participate in exercise testing

Contraindications to 6MWT:

☐ Resting heart rate > 120 beats / min after 10 minutes rest (relative contraindication)
☐ Systolic blood pressure > 180 mm Hg +/- diastolic blood pressure > 100 mm Hg (relative contraindication)
☐ Resting SpO2 < 85% on room air or on prescribed level of supplemental oxygen
☐ Physical disability preventing safe performance
☐ No contraindications identified

6MWT 1						Date:	Time:
Supplemental Oxygen						Mobility Aid	
Time mins	**BP**	**SpO2**	**HR**	**RPE**	**Distance walked**	**Rests / comments**	
Rest							
1							
2							
3							
4							
5							
6							
Recovery 1							
2							

Total distance: _____ **Symptom recovery:** _____ **HR recovery:** _____
Limiting factor: _____
Was test terminated? ☐ No ☐ Yes If yes: when?

6MWT Termination Criteria:	
☐ Chest pain or angina-like symptoms	☐ Intolerable dyspnoea, unrelieved by rest
☐ Heart rate > Predicted HR max.	☐ Persistent SpO2 <85% (Note: pending clinical presentation)
☐ Evolving mental confusion, light-headedness or incoordination	☐ Abnormal gait pattern (leg cramps, staggering, ataxia)
☐ Physical or verbal severe fatigue	☐ Other clinically warranted reason

Heart Foundation

Source: www.heartonline.org.au/resources Reviewed 11/2014 1

(Affix patient label here)
Patient ID:
Family name:
Given name(s):
Date of birth: Sex: ☐ M ☐ F ☐ I

HEART online
Heart Education Assessment Rehabilitation Toolkit

Six Minute Walk Test (6MWT) recording form

☐ Medical history checked
☐ Medical clearance provided for the patient to participate in exercise testing

Contraindications to 6MWT:

☐ Resting heart rate > 120 beats / min after 10 minutes rest (relative contraindication)
☐ Systolic blood pressure > 180 mm Hg +/- diastolic blood pressure > 100 mm Hg (relative contraindication)
☐ Resting SpO2 < 85% on room air or on prescribed level of supplemental oxygen
☐ Physical disability preventing safe performance
☐ No contraindications identified

6MWT 2						Date:	Time:
Supplemental Oxygen						Mobility Aid	
Time mins	**BP**	**SpO2**	**HR**	**RPE**	**Distance walked**	**Rests / comments**	
Rest							
1							
2							
3							
4							
5							
6							
Recovery 1							
2							

Total distance: _____ **Symptom recovery:** _____ **HR recovery:** _____
Limiting factor: _____
Was test terminated? ☐ No ☐ Yes If yes: when?

6MWT Termination Criteria:

☐ Chest pain or angina-like symptoms
☐ Heart rate > Predicted HR max.
☐ Evolving mental confusion, light-headedness or incoordination
☐ Physical or verbal severe fatigue
☐ Intolerable dyspnoea, unrelieved by rest
☐ Persistent SpO2 <85% (Note: pending clinical presentation)
☐ Abnormal gait pattern (leg cramps, staggering, ataxia)
☐ Other clinically warranted reason

Heart Foundation

Source: www.heartonline.org.au/resources Reviewed 11/2014 2

Amendment 2

Protocol Title: Open-label, Single-arm Study Assessing the Efficacy and Safety of Ivabradine (Corlanor) in African-American/Black Subjects With Heart Failure and Left Ventricular Systolic Dysfunction

Amgen Protocol Number Ivabradine 20160231

Amendment Date: 14 February 2019

Rationale:

This protocol is being amended to:

- [redacted]

Description of Changes

Section: Global

Change: Updated document date to **14 February 2019**.

Section: Global

Change: Editorial changes (including typographical, grammatical, and formatting) have been made throughout the document.

Section: Title Page, Key Sponsor Contact

Replace:

Name:	[redacted]
Address:	One Amgen Center Drive, Thousand Oaks, CA, 91320, USA
Telephone Number:	[redacted]
Email Address:	

With:

Name:	[redacted]
Address:	One Amgen Center Drive, Thousand Oaks, CA, 91320, USA
Telephone Number:	[redacted]
Email Address:	

Section: Title Page

Add:

Amendment 2 14 February 2019

Section: 1 Protocol Synopsis, Rationale

Delete:

The goal of this study is to determine the impact of adding ivabradine therapy to the standard of care (SOC) in African-American/Black subjects with HF and reduced ejection fraction (HFrEF) on changes in heart rate (HR) from baseline (SOC alone). Changes in HR from baseline will be correlated with [redacted] ~~, as well as with~~ the changes from

baseline in activity level of the subjects, as measured by both a standard 6-minute walk distance and an accelerometer device.

Section: 3.1 Study Rationale

Delete:

Changes in HR from baseline will be correlated with [redacted] ~~, as well as with~~ the changes from baseline in activity level of the subjects, as measured by both a standard 6-minute walk distance and an accelerometer device.

Section: 4.1 Objectives and Endpoints, Exploratory Endpoints

Delete:

Exploratory
[redacted]

Section: 5.1 Overall Design, Paragraph 4

Delete:

[redacted]

Section: 9.2.1.3 Medical History

Delete:

The Investigator or designee will collect targeted medical cardiovascular disease history~~, genetic history (if available),~~ along with the functional NYHA class history that started within 5 years prior to enrollment through screening.

Section: 10.4.2.2.3 Exploratory Endpoints, Paragraph 1, Bullets 4-5

Delete:

[redacted]

Section: 10.4.2.2.3 Exploratory Endpoints, Paragraph 3

Delete:

[redacted]

Section: 10.4.2.4 Other Analyses

Delete:

~~10.4.2.4 Other Analyses~~

~~The exploratory endpoints will be summarized descriptively.~~

Section: Appendix 1, List of Abbreviations and Definitions of Terms

Add:

Abbreviation or Term	Definition/Explanation
EDC	**electronic data collection**

Section: Appendix 3, Data Quality Assurance, Paragraph 10

Delete:

~~Amgen (or designee) will perform Self-Evident Corrections (SEC) to obvious data errors in the clinical trial database. SECs will be documented in the CRF Standard Instructions and the CRF Specific Instructions, both of these will be available through the electronic data capture (EDC) system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date with different visit) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).~~

Amendment 1

Protocol Title: Open-label, Single-arm Study Assessing the Efficacy and Safety of Ivabradine (Corlanor) in African-American/Black Subjects With Heart Failure and Left Ventricular Systolic Dysfunction

Amgen Protocol Number 20160231

Amendment Date: 02 April 2018

Rationale:

This protocol is being amended to:

- Change the secondary objective to an exploratory objective
- Clarify that the study will be conducted at 1 to 3 sites
- Clarify that between 30 to 100 subjects will be enrolled in the study
- Update informed consent inclusion criteria
- Clarify genetic background will be collected for a subset of subjects in the studied population
- Update the Schedule of Activities table to clarify that 12-lead electrocardiogram will be collected during screening
- Clarify that only urine pregnancy test will be utilized
- Clarify that heart rate will be measured during the 6-minute walk test
- Update the clinical laboratory tests that will be performed during the study
- Align end of study definitions with the protocol template language
- Clarify that a subject's treatment assignment date should be entered on enrollment case report form
- Recategorize the accelerometer as a medical device (instead of "other treatment procedure") per protocol template instructions
- Correct typographical and formatting errors throughout the document

Description of Changes:

Section: Global

Change: Replace the date 18 May 2017 to **02 April 2018**

Section: Global

Change: Make administrative updates and editorial corrections (including typographical, grammatical, and formatting errors) throughout the document.

Section: Global (Title)

Delete:

Open-label, Single-arm~~, Single Center~~ Study Assessing the Efficacy and Safety of Ivabradine (Corlanor) in African-American/Black Subjects With Heart Failure and Left Ventricular Systolic Dysfunction

Section: Title Page

Add:

Protocol Date:	Document Version	Date
	Original	18 May 2017
	Amendment 1	**02 April 2018**

Section: Protocol Synopsis, Rationale

Add:

Changes in HR from baseline will be correlated with the genetic background of **a subset of subjects with available genetic data in** the studied population, as well as with the changes from baseline in activity level of the subjects, as measured by both a standard 6-minute walk distance and an accelerometer device.

Section: Protocol Synopsis, Objective(s)/Endpoint(s), Secondary

Delete:

~~Secondary~~	
• ~~Assess association of proportion of genetic heritage background in African-American/Black subjects with HR lowering~~	• ~~Change in HR from baseline to day 57 among African-American/Black subjects associated with proportion of genetic heritage background~~ • ~~Change in HR from baseline to day 57 among African-American/Black subjects with 85% proportion of genetic background and African-American/Black subjects with < 85% proportion of genetic background~~

Section: Protocol Synopsis, Overall Design

Delete:

This study is a prospective, ~~single-site,~~ open-label, single-arm intervention study in African-American/Black subjects with HFrEF~~ nested in the Henry Ford Heart Failure Pharmacogenomics Registry, and will be conducted at the Henry Ford Health System in Detroit, MI~~.

Section: Protocol Synopsis, Number of Subjects

Add:

Approximately **30 to** 100 **subjects**

Section: Protocol Synopsis, Treatments

Add:

The starting dose of ivabradine is 5 mg twice daily (BID). In subjects with a history of conduction defects, or in subjects in whom bradycardia could lead to hemodynamic compromise, therapy is to be initiated at 2.5 mg BID **based on investigator discretion**.

Section: Protocol Synopsis, Statistical Considerations, Paragraph 1

Delete:

This primary analysis will evaluate the effect of ivabradine on HR reduction at day 57 in African-American/Black subjects overall (the primary endpoint)~~ as well as within each genetic background (secondary endpoints)~~.

Section: Protocol Synopsis, Statistical Considerations, Paragraph 4

Delete:

Efficacy analyses of the primary endpoint will test whether the mean reduction with ivabradine exceeds 5 bpm~~, which is the reduction that would be assumed with placebo~~. Summary statistics and least-square means along with 95% confidence interval, analyzed by the repeated-measures linear model, will be provided for the primary endpoint.~~ Correlation analyses will be provided between HR reduction and genetic background as determined by the proportion of African-American heritage (1 of the secondary endpoints). Summary statistics and least-square means along with 95% confidence interval, based on the repeated-measures linear model, will be summarized for the subgroups based on the proportion of African-American heritage with 85% as the cut-off (the other secondary endpoint).~~

Section: 2.2 Schedule of Activities, Table 2-1 and footnotes

Add:

Procedure	Screening Period	Treatment Period (Days)				Safety Follow-Up Period/ Early Termination Visit[a] (Phone Contact for Safety Follow-up only)
	Screening (7 days)	Day 1 ± 2 days	Day 15 ± 2 days (dose titration begins)	Day 29 ± 2 days	Day 57 ± 5 days	Day 87 or 30 days after the last dose of open-label IP
12-lead ECG	**X**	X	X		X	
6-Minute walk test **(6MWT)**		X			X	

Abbreviations: **6MWT = 6-Minute walk test;** ECG = electrocardiogram; IP = investigational product

Section: 2.2 Schedule of Activities, Table 2-1

Delete:

Procedure	Screening Period	Treatment Period (Days)				Safety Follow-Up Period/ Early Termination Visit[a] (Phone Contact for Safety Follow-up only)
	Screening (7 days)	Day 1 ± 2 days	Day 15 ± 2 days (dose titration begins)	Day 29 ± 2 days	Day 57 ± 5 days	Day 87 or 30 days after the last dose of open-label IP
Investigational product[h]		X	X	X	X	~~X~~[i]

Section: 3.1 Study Rationale

Add:

Changes in HR from baseline will be correlated with the genetic background of **a subset of subjects with available genetic data in** the studied population, as well as with the changes from baseline in activity level of the subjects, as measured by both a standard 6-minute walk distance and an accelerometer device.

Section: 3.2.2 Amgen Investigational Product Background: Ivabradine, Paragraph 3

Replace:

A detailed description of the chemistry, pharmacology, efficacy, and safety of ivabradine is provided in the package insert.

With:

A detailed description of the chemistry, pharmacology, efficacy, and safety of ivabradine is provided in the **Corlanor® (ivabradine) US Prescribing Information**.

Section: 4.1 Objectives and Endpoints, Secondary

Delete:

~~Secondary~~	
• ~~Assess association of proportion of genetic heritage background in African-American/Black subjects with HR lowering~~	• ~~Change in HR from baseline to day 57 among African-American/Black subjects associated with proportion of genetic heritage background~~ • ~~Change in HR from baseline to day 57 among African-American/Black subjects with 85% proportion of genetic background and African-American/Black subjects with < 85% proportion of genetic background~~

Section: 4.1 Objectives and Endpoints, Exploratory, Bullet 2

Replace:

[redacted]

With:

[redacted]

Section: 4.1 Objectives and Endpoints, Exploratory, Bullet 4

Add:

[redacted]

Section: 4.1 Objectives and Endpoints, Safety

Add:

• Evaluate the safety and tolerability of ivabradine in African-American/Black subjects with **HFrEF**	• Subject incidence of treatment-emergent adverse events • Vital signs at each scheduled assessment

Section: 5.1 Overall Design, Paragraph 4

Replace:

A secondary objective will be to correlate the HR response to ivabradine in this population with the proportion of the specific genetic background characteristic of African-American/Black subjects.

With:

A**n exploratory** objective **in a** [redacted]

Section: 5.1 Overall Design, Paragraph 5

Delete:

This study is a prospective, ~~single-site,~~ open-label, single-arm intervention study in African-American/Black subjects with HFrEF ~~nested in the Henry Ford Heart Failure Pharmacogenomics Registry, and will be conducted at the Henry Ford Health System in Detroit, MI~~.

Section: 5.1 Overall Design, Paragraph 5

Add:

Approximately **30 to** 100 subjects will be enrolled to receive ivabradine in an open-label design.

Section: 5.1 Overall Design, Paragraph 7

Add:

In subjects with a history of conduction defects, or in subjects in whom bradycardia could lead to hemodynamic compromise, therapy is to be initiated at 2.5 mg BID, **based on investigator discretion**.

Section: 5.2.2 Number of Sites

Replace:

One investigative site in the US will be included in the study.

With:

One **to 3** investigative site**s** in the US will be included in the study.

Section: 5.3.1 End of Study Definition, Paragraphs 1 and 2

Replace:

Primary Completion: The primary completion date is the same as the end of study date and is the date when the last subject has completed the study (ie, last subject last visit).

With:

Primary Completion: The primary completion date is **defined as the date when the last subject is assessed or receives an intervention for the final collection of data for the primary endpoint(s), for the purposes of conducting the primary analysis, whether the study concluded as planned in the protocol or was terminated early.**

The primary completion date is the date when the last subject has completed the **assessments for day 57.**

Section: 5.3.1 End of Study Definition, Paragraph 4

Replace:

End of Study: The end of study date is defined as the date when the last subject at the site is assessed or receives an intervention for evaluation in the study (ie, last subject last visit).

With:

End of Study: The end of study date is defined as the date when the last subject **across all sites** is assessed or receives an intervention for evaluation in the study (ie, last subject last visit)**, following any additional parts in the study (eg, safety follow-up), as applicable**.

Section: 5.4 Justification for Investigational Product Dose

Replace:

Ivabradine will be initiated at 5 mg BID daily dosing (with option to reduce initial dosing to 2.5 mg BID based on investigator discretion), and the dose titration will follow the US package insert, as indicated in Table 5-1.

With:

Ivabradine will be initiated at 5 mg BID daily dosing (with option to reduce initial dosing to 2.5 mg BID based on investigator discretion), and the dose titration will follow the **Corlanor® (ivabradine) US Prescribing Information**, as indicated in Table 5-1.

Section: 6.1 Inclusion Criteria, Criterion 101

Replace:

101 Subject's legally acceptable representative has provided informed consent prior to any study-specific activities/procedures being initiated when the subject has any kind of condition that, in the opinion of the Investigator, may compromise the ability of the subject to give written informed consent.

With:

101 Subject has provided informed consent**/assent** prior to **initiation of** any study**-**specific activities/procedures.

Section: 7.1.1 Investigational Products, Table 7-1

Replace:

After 14 days, tolerability to be assessed as well as resting HR with dose adjustment, as recommended in the US package insert.

With:

After 14 days, tolerability to be assessed as well as resting HR with dose adjustment, as recommended in the **Corlanor® (ivabradine) US Prescribing Information**.

Section: 7.1.3 Medical Device, Paragraph 3 (moved original language from Section 7.1.5)

Add:

Heart rate (HR) **during the 6MWT** will be measured by an HR monitor at specified time points (see Table 2-1 **for 6MWT schedules**). An accelerometer will also be used throughout the study. Any **adverse** events associated with the accelerometer (eg, allergic reaction to components of the instrument) will be captured **in the Events CRF** as **a** procedure-related event. **Data collected from the accelerometer will not be available nor reviewed until after the end of the study (ie, last subject, last visit).**

Section: 7.1.5 Other Treatment Procedures

Replace:

Heart rate (HR) will be measured by an HR monitor at specified time points (see Table 2-1). An accelerometer will also be used throughout the study. Note that the accelerometer is not considered a medical device and is not manufactured by Amgen. Any events associated with the accelerometer (eg, allergic reaction to components of the instrument) will be captured as procedure-related events (see Section 9.2.3.1.1.2).

With:

There are no other treatment procedures in this study.

Section: 7.2 Method of Treatment Assignment, Paragraph 2

Add:

The treatment assignment date is to be documented in the subject's medical record and on the enrollment CRF.

Section: 7.4.2.1 Amgen Investigational Product: Ivabradine

Replace:

Ivabradine will be initiated at a 5 mg BID dosing (with option to reduce initial dosing to 2.5 mg BID based on investigator discretion as per US package insert.

With:

Ivabradine will be initiated at a 5 mg BID dosing (with option to reduce initial dosing to 2.5 mg BID based on investigator discretion as per **Corlanor® (ivabradine) US Prescribing Information**.

Section: 9.2.1.3 Medical History

Add:

The Investigator or designee will collect targeted medical cardiovascular disease history, genetic history **(if available)**, along with the functional NYHA class history that started within 5 years prior to enrollment through screening.

Section: 9.2.2.3 Accelerometer, Paragraph 2

Add:

Data collected from wearable devices will not be available nor reviewed until after the end of the study (ie, last subject, last visit).

Section: 9.2.3.1 Adverse Events

Delete:

~~All adverse events observed by the investigator or reported by the subject that occur after first dose of investigational product(s) through the end of study/safety follow-up visit or 30 days after the last administration of investigational product are to be collected/reported.~~

~~All adverse events related to any study procedures/activities will be collected/ recorded/reported after signing the informed consent form through the end of study/safety follow-up visit or 30 days after last dose of investigational product administration.~~

Section: 9.2.3.1.1.1 Disease-related Events, Paragraph 2

Replace:

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after the first dose of investigational product(s)/study treatment/protocol-required therapies through the end of study/safety follow-up visit of 30 days after the last administration of investigational product, are reported using the Event CRF.

With:

The investigator is responsible for ensuring that all disease-related events observed by the investigator or reported by the subject that occur after the first dose of investigational product(s)/study treatment/protocol-required therapies through the end of study/safety follow-up visit or 30 days after the last administration of investigational product, **whichever is later,** are **collected/recorded/**reported using the Event CRF.

Section: 9.2.3.1.1.2 Adverse Events, Paragraph 3

Add:

All adverse events **observed by the investigator or reported by the subject that are** related to study procedures/**study** activities will be reported from signing the informed consent form through end of study/safety follow-up visit or 30 days after last dose of investigational product administration**, whichever is later, are to be collected/recorded/reported using the Event CRF**.

Section: 9.2.3.1.1.3 Serious Adverse Events, Paragraph 1

Add:

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through the end of study/safety follow-up visit or 30 days after the last administration of investigational product, **whichever is later,** are reported using the Event CRF.

Section: 9.2.3.1.1.3 Serious Adverse Events, Paragraph 5

Delete:

~~Hospitalizations and deaths due to chronic heart failure complications are anticipated to occur in the enrolled subject population. The Amgen safety and medical team will review accumulating events on a regular basis.~~

Section: 9.2.3.1.1.5 Serious Adverse Events, Paragraph 1 (moved from existing Section 9.2.3.1.1.3)

Add:

Serious adverse events (eg, population-related events) that are not planned to be reported individually in an expedited manner as they are anticipated to occur in the study population at some frequency independent of the protocol-required therapies are as follows:

Section: 9.2.4.1 Pregnancy Testing, Paragraph 1

Delete:

A high sensitive ~~(~~urine ~~or serum)~~ pregnancy test should be completed at screening and within 7 days of initiation of investigational product for females of childbearing potential.

Section: 10.4.1.2 Primary Analysis

Delete:

This primary analysis will evaluate whether the effect of ivabradine on HR reduction at day 57 in African-American/Black subjects overall (the primary endpoint) exceeds 5 bpm~~, as well as HR reduction at day 57 within each of the genetic background groups (secondary endpoints)~~.

Section: 10.4.2.1 General Considerations, Paragraph 2

Delete:

Efficacy analyses of the primary endpoint will test whether the mean reduction with ivabradine exceeds 5 bpm~~, which is the reduction that would be assumed with placebo~~. Summary statistics and least-square means along with 95% confidence interval, analyzed by the repeated-measures linear model, will be provided for the primary endpoint. ~~Correlation analyses will be provided between HR reduction and genetic background as determined by the proportion of African-American heritage (1 of the secondary endpoints). Summary statistics and least-square means along with 95%~~

~~confidence interval, based on the repeated-measures linear model will be summarized for the subgroups based on the proportion of African-American heritage with 85% as the cut-off (the other secondary endpoint).~~

Section: 10.4.2.2.2 Secondary Endpoints

Replace:

- Change in HR from baseline to day 57 among African-American/Black subjects associated with proportion of genetic heritage background

Correlation analyses will be provided between change in HR from baseline to day 57 and proportion of genetic heritage background among African-American/Black subjects.

- Change in HR from baseline to day 57 among African-American/Black subjects with ≥ 85% proportion of genetic background and African-American/Black subjects with < 85% proportion of genetic background

The repeated measures linear model will be used to evaluate ivabradine efficacy on HR reduction from baseline to day 57 for subgroups based on the proportion of African/American heritage with 85% as the cut-off. The model will include terms of scheduled visits, subgroups based on the proportion of African/American heritage with 85% as the cut-off, baseline HR measurement, and the interaction of subgroups with scheduled visits. Missing values will not be imputed when the repeated measures linear model is used. Based on the model, the least-square means along with 95% confidence interval for each subgroup based on the proportion of African/American heritage with 85% as the cut-off will be provided. In addition, descriptive statistics of HR reduction by scheduled visit by each subgroup based on the proportion of African/American heritage with 85% as the cut-off will be summarized.

With:

Not applicable.

Section: 10.4.2.2.3 Exploratory Endpoints, Bullet 3

Replace:

[redacted]

With:

[redacted]

Section: 10.4.2.2.3 Exploratory Endpoints, Bullet 5

Add:

[redacted]

Section: 10.4.2.2.3 Exploratory Endpoints, Paragraph 3

Add:

[redacted]

Section: Appendix 2 Clinical Laboratory Tests, Table 12-1

Add:

Local Laboratory Chemistry

total bilirubin

Section: Appendix 2 Clinical Laboratory Tests, Table 12-1 and Footnotes

Delete:

Local Laboratory Other Labs

Urine pregnancy test

~~NT-pro~~BNP

~~NT-pro~~BNP = ~~N-terminal pro-~~b-type natriuretic peptide

Section: Appendix 4 Safety Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting, Recording Adverse Events, Disease-related Events (if applicable), and Serious Adverse Events, Bullet point 3, Sub-bullet 4

Add:

- Assessment of relatedness to **investigational product:** ivabradine, and/or other protocol-required therapies and/or study-mandated procedure/study mandated activity.