CLINICAL STUDY PROTOCOL

Study Title:	GENETIC-AF – A **Gen**otype-Directed Comparative **E**ffectiveness **Tri**al of Bu**c**indolol and Toprol-XL for Prevention of Symptomatic **A**trial **F**ibrillation/Atrial Flutter in Patients with Heart Failure
Sponsor:	ARCA biopharma, Inc. 11080 CirclePoint Road, Suite 140 Westminster, Colorado 80020 Phone: 720.940.2100
Study Drug:	Bucindolol hydrochloride (bucindolol)
Comparator:	Metoprolol succinate (Toprol-XL, metoprolol)
IND No.:	118,935
Indication:	Atrial Fibrillation
Protocol ID:	BUC-CLIN-303
EudraCT Number	2016-000302-12
Protocol Version:	Version 4.0
Date:	29 January 2016
Ethics Statement:	The study will be completed according to the ICH guidelines of Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki.
Proprietary Notice:	The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of ARCA biopharma, Inc.

TABLE OF CONTENTS

TABLE OF FIGURES

LIST OF TABLES

1.0 SYNOPSIS

Name of Sponsor/Company ARCA biopharma, Inc.	**Name of Test Product** bucindolol	**Name of Active Ingredient** bucindolol hydrochloride
IND / Protocol Number 118,935 / BUC-CLIN-303	**Phase / Indication** Phase 2B-3 / Atrial Fibrillation	**Version / Date** Version 4.0 / 29 January 2016

Study Title: GENETIC-AF: A **Gen**otype-Directed Comparative **E**ffectiveness **Tri**al of Bu**c**indolol and Toprol-XL for Prevention of Symptomatic **A**trial **F**ibrillation/Atrial Flutter in Patients with Heart Failure.

Study Rationale: Most anti-arrhythmic agents currently approved for the treatment of atrial fibrillation (AF) and atrial flutter (AFL) are either contraindicated or have label warnings for use in heart failure (HF) patients due to an increased risk of mortality in this patient population.

Bucindolol hydrochloride (bucindolol) is a nonselective β-adrenergic receptor (AR) blocking agent with mild vasodilator properties, which was previously studied in the BEST Phase 3 HF trial. In a large pharmacogenomic substudy of the BEST trial, two unique pharmacologic properties of bucindolol, sympatholysis and inverse agonism, were shown to interact with AR polymorphisms in such a way that targeting specific genotypes of these variants could improve therapeutic index. Specifically, patients with the $\beta_1$389Arg/Arg AR variant had more efficacious treatment responses to bucindolol, as assessed by HF clinical outcomes and the reduction of new onset AF, compared to patients with the $\beta_1$389Gly polymorphism (i.e., Gly carriers).

Metoprolol succinate (Toprol-XL, henceforth referred to as metoprolol) is a β_1-AR selective β-blocker indicated for the treatment of stable, symptomatic (NYHA Class II or III) HF of ischemic or non-ischemic origin. Metoprolol has demonstrated mild efficacy for the prevention of new onset AF in a HF patient population and is often used off-label in this setting (Class IIa indication with a "C" level of evidence for AF prevention per ACC/AHA/ESC Joint Guidelines). In a previous study, metoprolol decreased the incidence of AF recurrence, compared to placebo, in patients with persistent AF who had recently undergone electrical cardioversion (ECV) to sinus rhythm (SR). In contrast to bucindolol, metoprolol does not appear to confer added clinical benefits in HF with reduced left ventricle ejection fraction (HFREF) patients that possess the $\beta_1$389Arg/Arg AR variant. In addition, limited data from the MERIT-HF DNA substudy did not indicate any evidence of a $\beta_1$389 Arg/Gly polymorphism differential effect for preventing AF.

The goal of the GENETIC-AF trial is to demonstrate the superiority of pharmacogenetically targeted bucindolol compared to metoprolol for the prevention of symptomatic AF/AFL in a genotype-defined $\beta_1$389Arg/Arg HFREF population at high risk of AF/AFL recurrence. The trial utilizes an interim analysis/adaptive design element that will examine preliminary data from the initial Phase 2B population. If the independent Data and Safety Monitoring Board (DSMB) determines that the preliminary Phase 2B data are consistent with pre-trial assumptions (i.e., absence of futility, event rate), the trial will proceed to Phase 3.

Objectives: The primary objective of this study is to compare the effects of bucindolol and metoprolol on the recurrence of symptomatic AF/AFL in patients with HFREF who have a $\beta_1$389 arginine homozygous ($\beta_1$389Arg/Arg) genotype.

The secondary objectives of this study are to compare the effects of bucindolol and metoprolol on clinical outcomes and other electrocardiographic parameters, and to assess the effects on rate control in patients who have developed recurrent AF/AFL. The safety and tolerability of bucindolol and metoprolol will also be evaluated.

Study Design: GENETIC-AF is a double-blind, two-arm, genotype-directed, active-controlled, adaptive-designed, superiority study that compares the effects of bucindolol and metoprolol on the time to first event of symptomatic AF/AFL in HFREF patients in SR who are at high risk of AF/AFL recurrence.

Two patient populations at high risk of AF/AFL recurrence will be included in this study: 1) patients with symptomatic paroxysmal or persistent AF who are indicated for ECV to attain SR, and; 2) patients in SR who have experienced a recent episode (i.e., ≤ 180 days) of paroxysmal or persistent AF who are indicated for ECV to attain SR if AF/AFL recurs. Patients must have HF, a left ventricle ejection fraction (LVEF) < 0.50 in the past 12 months, and no contraindication for β-blocker therapy. β-blocker therapy is permitted at screening but is not required to be eligible for the study. Patients must be receiving optimal anticoagulation therapy for stroke prevention prior to randomization. Patients will be genotyped for $\beta_1$389 AR at screening and those who are $\beta_1$389Arg/Arg (~50% of patients) will be randomized to study drug.

A subset of patients participating in the trial will have their cardiac rhythm continuously monitored to assess AF burden (AFB). AFB monitoring will be done via the Medtronic Reveal insertable cardiac monitor (ICM) or a Medtronic pacemaker (IPG), implantable cardioverter-defibrillator (ICD), or cardiac resynchronization therapy (CRT) device with a minimum of an atrial and a ventricular lead. Patients participating in the optional AFB substudy must either have a pre-existing Medtronic device that can measure AFB, or agree to have one inserted as clinically indicated. Patients who agree to have a Medtronic device inserted may do so at the Randomization Visit or at any time prior to the start of the 24-week Follow-up Period.

Eligible patients will be randomized (1:1) to blinded treatment with bucindolol or metoprolol (i.e., study drug) and up-titrated weekly to target doses of 50 mg BID (< 75 kg) or 100 mg BID (≥ 75 kg) for bucindolol or 200 mg QD for metoprolol. Randomization will be centralized and stratified by: 1) HF etiology (ischemic vs. non-ischemic); 2) LVEF (< 0.35 vs. ≥ 0.35); 3) type of Medtronic device (Reveal vs. Non-Reveal vs. No Device), and; 4) rhythm status at randomization (SR vs. AF/AFL).

Patients in AF at randomization who do not spontaneously convert to stable SR and are in AF/AFL after 3 weeks of treatment with study drug will undergo ECV to establish stable SR. Patients in SR at randomization who are in AF/AFL after 3 weeks of study drug treatment will also undergo ECV to establish stable SR. Patients in SR at randomization who are in stable SR after 3 weeks (± 3 days) of study drug treatment will start the 24-week Follow-up Period at the Week 0 Visit.

ECV may be performed as early as 1 week after randomization if all of the following conditions are met: 1) the patient is receiving the target dose of study drug; 2) the patient is receiving guideline indicated oral anticoagulation therapy for stroke prevention, and; 3) a delay of ECV could be detrimental to patient outcome. The first ECV attempt may also be performed as late as 8 weeks after randomization if, in the opinion of the Investigator, additional time is needed to attain target doses of study drug or to achieve appropriate anticoagulation status prior to ECV.

The primary endpoint, i.e., time to first event of symptomatic AF/AFL or all-cause mortality (ACM), will be assessed during the 24-week Follow-up Period after establishment of stable SR on study drug. For patients requiring ECV, establishment of stable SR will be confirmed by electrocardiogram (ECG) at least 1 hour post-ECV. Patients who do not demonstrate stable SR following ECV will undergo a subsequent ECV to establish a baseline SR unless, in the opinion of the Investigator, it would not be the best course of treatment for the patient. The 24-week Follow-up Period will begin on the day of: 1) the ECG that establishes stable SR; 2) the last ECV attempt for patients who fail to convert to stable SR, or; 3) the Week 0 Visit for patients in AF/AFL who do not undergo ECV for any reason.

During the 24-week Follow-up Period, heart rhythm will be assessed by 12-lead ECG at scheduled clinic visits. At the time of each ECG assessment, patients will be queried for symptoms potentially related to AF/AFL. Scheduled telephone contacts will occur at Week 6, Week 10, Week 14, Week 18 and Week 22. Patients will be also be instructed to contact the site immediately if they experience new or worsening

symptoms. Patients will be queried for symptoms potentially related to AF/AFL during the scheduled and patient-initiated telephone contacts. If the Investigator suspects that a new AF/AFL event has occurred between scheduled clinic visits (i.e., a change in rhythm from SR to AF/AFL), the patient will be instructed to return to the clinic within 3 business days for further assessments. Patients experiencing recurrence of AF/AFL will be encouraged to remain on blinded study drug and may undergo subsequent ECV procedures or medical interventions as clinically indicated.

After the Week 24 Visit, patients will enter the Treatment Extension Period and continue to receive blinded study drug. Phase 3 follow-up will continue until a total of at least 330 primary endpoint events have been observed. After this event, all patients will complete the 24-week Follow-up Period or return to the clinic for an end of study visit if already in the Treatment Extension Period. At the end of the study, patients will discontinue study drug and should transition to commercially-available β-blocker therapy per Investigator discretion. Investigators and patients will not be informed of the blinded study drug assignment at the time of study completion.

Number of Patients: Approximately 250 patients will be randomized in Phase 2B and an additional 370 patients will be randomized in Phase 3 (i.e., a total of 620 patients). The $\beta_1$389Arg/Arg genotype is expected in approximately 50% of screened patients; therefore, a 65% screen-fail rate is assumed for the study (15% for general criteria and a 50% screen-fail rate due to genotype).

The DSMB will examine preliminary data from the initial Phase 2B population to assess the presence or absence of futility for proceeding to Phase 3, as well as consistency with other pre-trial assumptions including event rate. If the DSMB determines there is absence of futility, acceptable safety, and pre-trial assumptions regarding event rate and other factors are correct, the trial will proceed to Phase 3.

A second interim analysis will be conducted by the DSMB during Phase 3 to assess the absence of futility and whether an expansion of the total sample size is warranted. The DSMB may also make suggestions to the Steering Committee for adjustment in sample size based on other factors (e.g., event rate, discontinuation rate, etc.) or other modifications to the protocol that would improve trial conduct.

Number of Study Centers: Approximately 150 centers will be included in this study. Enrollment is competitive with a maximum of 62 randomized patients per center permitted in the overall study (10% of total enrollment).

Treatment Duration: Patients will be eligible to receive study drug for a minimum of 27 weeks and will continue to receive study drug until at least 330 primary endpoint events have been observed (currently estimated to require approximately 6 years from the time of first patient randomization).

Inclusion Criteria:

Patients must meet *all* of the following inclusion criteria to be eligible for randomization in this study.

1. Age ≥ 18 years and ≤ 85 years at the Screening Visit.
2. Weight ≥ 40 kg at the Randomization Visit.
3. Possess the $\beta_1$389Arg/Arg genotype.
4. History of heart failure with reduced left ventricle ejection fraction (HFREF).
   a. LVEF < 0.50 assessed at any time during the previous 12 months of the Screening Visit.
5. At least one symptomatic paroxysmal or persistent AF episode ≤ 180 days of the Screening Visit.
   a. Qualifying AF episode may be documented by ECG, Holter, TTM, or implanted device. AF documented by implanted device must be a single episode ≥ 60 minutes in duration. Atrial flutter is not considered a qualifying AF episode.
   b. Must have experienced AF symptoms ≤ 180 days of the Screening Visit, but these symptoms may

overlap with HF symptoms, i.e. may be "arrhythmic" (e.g. palpitations, dizziness) or "heart failure" (e.g. breathlessness, fatigability) in nature.

6. Clinically appropriate for ECV if AF/AFL is present at the Week 0 Visit, including:
   a. Patients with AF/AFL at randomization determined by the Investigator to require ECV.
   b. Patients in SR at randomization determined by the Investigator to require ECV if AF/AFL recurs.
7. Receiving guideline indicated oral anticoagulation therapy at the Randomization Visit, which is considered optimal for stroke prevention in the opinion of the Investigator.
8. Systolic blood pressure > 90 mmHg and < 150 mmHg at the Randomization Visit.
9. Female of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Randomization Visit.
   a. Female who is surgically sterile or post-menopausal for at least 12 months is not considered to be of childbearing potential.
10. Female of childbearing potential must agree to use a highly effective contraception for the duration of the trial and for at least 30 days following the last dose of study drug.
    a. Female who is surgically sterile or post-menopausal for at least 12 months is not considered to be of childbearing potential.
11. Must agree not to participate in a clinical study involving another investigational drug or device throughout the duration of this study.
12. Must be competent to understand the information given in the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved informed consent form (ICF). Must sign the ICF prior to the initiation of any study procedure and not withdraw consent prior to the Randomization Visit.

Exclusion Criteria:

Patients who meet *any* of the following exclusion criteria are not eligible for randomization in this study.

1. NYHA Class IV symptoms at the Randomization Visit.
2. Significant fluid overload at the Randomization Visit, in the opinion of the Investigator. Evidence of significant fluid overload may include:
   a. Mean jugular venous pressure above the clavicle at 90°.
   b. Liver congestion.
   c. Moist pulmonary rales post-cough.
   d. Peripheral edema beyond 1+ pedal not explained by local factors.
3. Permanent AF at the Screening Visit.
   a. Permanent AF is defined as an ongoing AF event 1 year or longer in duration in which there is no intervening evidence of SR.
4. More than two ECV procedures within 6 months of the Randomization Visit or if the most recent ECV within 6 months of the Randomization Visit failed to produce SR.
5. Use of any of the following < 7 days of the Randomization Visit:
   a. Amiodarone, disopyramide, dofetilide, dronedarone, flecainide, propafenone, sotalol, non-dihydropyridine calcium channel blockers, daily NSAIDS (e.g., ibuprofen, celecoxib), thiazolidinediones, or frequent use of short acting nitroglycerin (e.g., > 6 sublingual tablets/week).
   b. Note: Amiodarone and dofetilide can be restarted after the start of follow-up if the patient experiences an AF/AFL event or after failure to convert to SR following ECV (see Section 5.8).
6. The presence of a left ventricular assist device (LVAD) or a condition that is likely to require LVAD placement within 6 months of the Randomization Visit.
7. History of a successful atrioventricular node ablation.
8. History of an AF ablation or AFL ablation within 30 days of the Randomization Visit.
9. History of untreated second degree Mobitz II or third degree heart block.
10. History of untreated symptomatic bradycardia or if symptomatic bradycardia is likely on full dose of study drug in the opinion of the Investigator.
11. Heart rate < 60 beats per minute at the Randomization Visit for patients who were not receiving β-blocker therapy during the screening period.

12. Heart rate > 180 beats per minute at the Randomization Visit.
13. Contraindication or previous history of intolerance to β-blocker therapy (e.g., untreated valvular disease) or Toprol-XL (e.g., inability to tolerate at least 25 mg QD).
14. Myocardial infarction, unstable angina, acute coronary syndrome, cardiac surgery (including PTCA or stent placement), or evidence of new ischemic changes as assessed by ECG ≤ 90 days of the Randomization Visit.
15. Moderate to severe asthma or other obstructive lung disease requiring chronic use (> 2 days/week) of an inhaled β_2-selective adrenergic agonist < 7 days of the Randomization Visit.
16. History of pulmonary hypertension, defined as a systolic pulmonary arterial pressure ≥ 70 mmHg at rest as assessed by echocardiography or right heart catheterization.
17. Known reversible causes of AF such as alcohol intoxication, pulmonary embolism, hyperthyroidism, acute pericarditis, or hypoxemia.
18. Evidence of an appropriate firing of an ICD device for ventricular tachycardia (VT) or ventricular fibrillation (VF) ≤ 90 days of the Randomization Visit.
    a. Exception: does not include anti-tachycardia pacing.
19. Untreated thyroid disease, in the opinion of the Investigator, at the Randomization Visit.
20. Serum potassium < 3.5 mmol/L at the Screening Visit.
    a. Lab value will be assessed by the central lab at the Screening Visit and any exclusionary results must be corrected prior to randomization as documented by either the central or local lab.
21. Renal failure requiring dialysis, serum creatinine > 2.5 mg/dL, or an estimated creatinine clearance < 30 mL/min (Cockcroft-Gault) at the Screening Visit.
    a. Lab values will be assessed by the central lab at the Screening Visit and any exclusionary results must be corrected prior to randomization as documented by either the central or local lab.
22. Significant intrinsic liver disease or a total bilirubin > 2.5 mg/dL at the Screening Visit.
    a. Lab value will be assessed by the central lab at the Screening Visit and any exclusionary results must be corrected prior to randomization as documented by either the central or local lab.
23. Use of strong inhibitors of cytochrome P450 2D6 (e.g., fluoxetine, paroxetine, propafenone, quinidine, or ritonavir) < 7 days prior to the Randomization Visit for patients who were <u>not</u> receiving β-blocker therapy during the screening period.
24. Participation in a clinical study or treatment with an investigational drug or device within 30 days of the Screening Visit (or 5 half-lives of the investigational agent, whichever is longer).
25. Comorbid condition or illness which, in the opinion of the Investigator, may limit life expectancy to less than 1 year.
26. Serious or active medical or psychiatric condition which, in the opinion of the Investigator, may interfere with treatment, assessment, or compliance with the protocol.
27. Treatment for a malignancy ≤ 2 years prior to screening, the presence of a treated malignancy that has evidence of disease progression, or the presence of a malignancy that is expected to require radiation therapy, chemotherapy, hormonal treatment, or surgical intervention during the study.
    a. Exceptions for localized, resectable skin carcinomas and in situ carcinoma of the cervix.
28. History of alcohol, drug, or chemical abuse that, in the opinion of the Investigator, could impair or limit the patient's full participation in the study.

Randomized Treatment:

Previous Commercial β-blocker Dose[1]												Randomized β-blocker Dose	
Metoprolol XL/CR (mg QD)		Metoprolol IR (mg BID)		Carvedilol CR (mg QD)		Carvedilol IR (mg BID)		Bisoprolol (mg QD)		Nebivolol (mg QD)		Metoprolol XL (mg QD)	Bucindolol (mg BID)
>	≤	>	≤	>	≤	>	≤	>	≤	>	≤	=	=
-	50	-	25	-	20		6.25	-	2.5	-	1.25	25	6.25
50	100	25	50	20	40	6.25	12.5	2.5	5	1.25	2.5	50	12.5
100	200	50	100	40	80	12.5	25	5	10	2.5	5	100	25
200[3]	-	100[3]	-	80[3]	-	25[3]	-	10[3]	-	5	10[3]	200	50
-	-	-	-			-	-			-	-	200	100[2]
Transition to Starting Dose of Study Drug ➡➡➡												Up-titration ⬇	

[1]Transition from β-blockers other than those above requires approval from the Sponsor or its designee prior to randomization.

[2]Patients who weigh < 75 kg at randomization will receive a maximum bucindolol dose of 50 mg BID.

[3]Patients receiving commercial β-blocker doses higher than those currently approved will require pre-approval from the Sponsor or its designee prior to randomization.

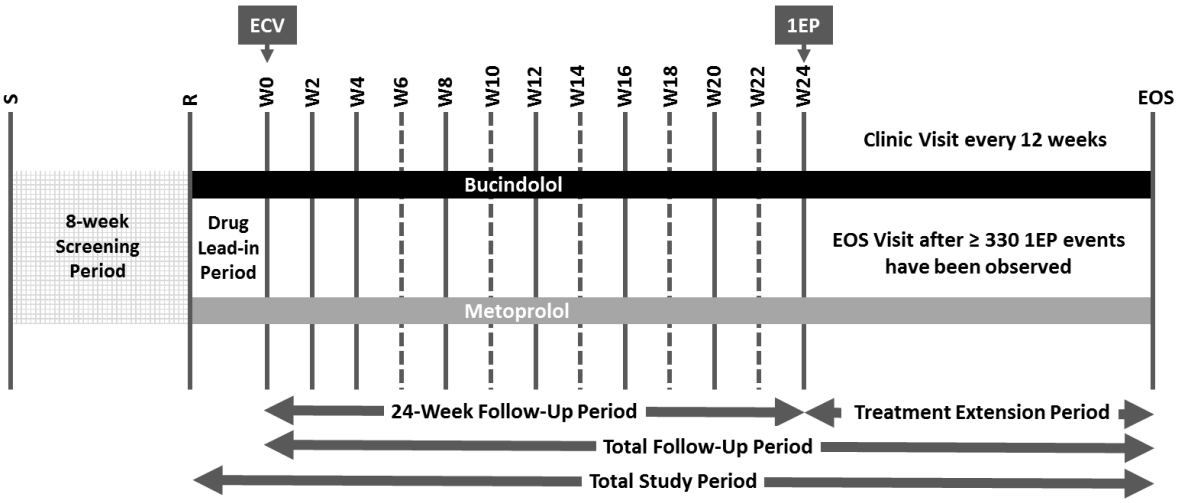
- Patients who are not receiving β-blocker therapy at randomization will initiate treatment with either 6.25 mg twice daily (BID) bucindolol or 25 mg once daily (QD) metoprolol and will be up-titrated in a blinded manner to the target doses.
- Patients receiving β-blocker therapy at baseline will discontinue this treatment at the time of randomization, initiate blinded β-blocker therapy as described below, and will be up-titrated in a blinded manner to the target doses.
- Study drug should be up-titrated to the target dose for all patients unless clinically contraindicated. Target doses for study drug are: 1) 200 mg QD metoprolol; 2) 50 mg BID bucindolol for patients who weigh < 75 kg, and; 3) 100 mg BID bucindolol for patients who weigh ≥ 75 kg.
- Investigators should make every reasonable attempt to up-titrate study drug on a weekly schedule, but can delay up-titration if required clinically (i.e., up-titration at a two week interval). Up-titration intervals shorter than one week are not permitted without prior approval from the Sponsor or its designee.
- Study drug may continue to be up-titrated to target β-blocker doses after ECV and/or the start of the 24-week Follow-up Period.
- Study drug dose may be reduced at any time in the event of documented intolerance.
- At the end of the study, patients will discontinue study drug and should transition to commercially-available β-blocker therapy per Investigator discretion. Transition to commercial β-blocker therapy is recommended to occur in a similar manner as described for initiation of blinded β-blocker therapy.

Visit Schedule:

- There is a maximum of 8 weeks between the Screening Visit and the Randomization Visit.
- Unscheduled visits are allowed during titration to achieve maximum tolerated dose of study drug or anytime during the study to assess heart rhythm, associated symptoms or adverse events.
- If needed, the first ECV should be performed 3 weeks after randomization, but it may be performed as early as 1 week or as late as 8 weeks after randomization, if clinically required (Section 6.1.3).
- During the 24-week Follow-up Period, patients will return to the clinic at scheduled intervals for routine assessments of safety and efficacy. In addition, telephone contacts will be required at Week 6,

Week 10, Week 14, Week 18, and Week 22 to administer the AF Symptom Questionnaire (AFSQ) and determine if the patient has experienced any new or worsening symptoms that could potentially be related to AF/AFL.

- During the Treatment Extension Period, patients will return to the clinic every 12 weeks for routine assessments of efficacy and safety.
- Phase 3 follow-up will continue until a total of at least 330 primary endpoint events have been observed. After this event, all patients will complete the 24-week Follow-up Period or return to the clinic for an end of study visit if already in the Treatment Extension Period.



Note: ECV should be performed 3 weeks after randomization, but may be performed as early as 1 week or as late as 8 weeks after randomization, if clinically required. Week 0 for patients in SR at randomization is 3 weeks (± 3 days) unless ECV is required (see Section 6.1.3). Patients who agree to have a Medtronic device inserted may do so at the Randomization Visit or at any time prior to the start of the 24-week Follow-up Period. S = Screening Visit; R = Randomization Visit; W = week; ECV = electrical cardioversion; 1EP = primary endpoint; EOS = end of study. Solid line = clinic visit, dashed line = telephone contact.

Primary Efficacy Endpoint:

- Time to first event of symptomatic AF/AFL or ACM during the 24-week Follow-up Period after establishment of stable SR on study drug.
  - Stable SR on study drug is defined as any of the following:
    – SR confirmed ≥ 1 hour after ECV.
    – SR confirmed ≥ 1 hour after spontaneous conversion from AF/AFL.
    – SR confirmed ≥ 1 hour at the Week 0 Visit for patients randomized in SR.
  - An AF/AFL event is defined as AF or AFL observed on two consecutive measures separated by at least 10 minutes as assessed by ECG.
  - A symptomatic AF/AFL event is defined as an AF/AFL event that is associated with a clinically relevant change in patient-reported symptoms, as determined by the Clinical Events Committee (CEC) examination of blinded data.

Secondary Efficacy Endpoints:

- Time to first event of AF/AFL (i.e., symptomatic or asymptomatic) or ACM during the 24-week Follow-up Period.
- Proportion of patients with VT, VF, or symptomatic supraventricular tachycardia (SVT) during the 24-week Follow-up Period.
  - Includes VF and symptomatic SVT events of any duration, VT events of ≥ 15 seconds, and VT events that result in appropriate firing of an ICD.
- Total number of hospitalization days per patient (all-cause) during the Total Study Period.

- Time to first event of AF/AFL (i.e., symptomatic or asymptomatic), HF hospitalization (as assessed by the Investigator), or ACM during the Total Study Period.
- Proportion of patients with adequate ventricular rate control in the setting of AF/AFL.
  - Defined by (a) a ventricular response rate (VRR) between 40 and 80 beats per minute at rest on the last tracing demonstrating AF/AFL during the 24-week Follow-up Period and (b) the absence of symptoms associated with bradycardia.

Safety Endpoints:

- Incidence of ACM during the Total Study Period.
- Incidence of ACM, cardiovascular-related hospitalization (as assessed by the Investigator), or withdrawal of study drug due to an adverse event (AE) during the Drug Titration Period.
- Incidence of heart block during the Total Study Period.
  - Defined as third degree heart block, second degree heart block requiring pacemaker implantation, or symptomatic second degree heart block as determined by the CEC.
- Incidence and severity of treatment-emergent AEs/SAEs over time during the Total Study Period.
- Incidence of neoplasm-related AEs/SAEs during the Total Study Period.
- Change from baseline in clinical laboratory tests over time during the Total Study Period.
- Change from baseline in vital signs and weight over time during the Total Study Period.
- Change from baseline in quantitative ECG parameters (i.e., QTc, QRS, PR and HR).
- Proportion of patients attaining target study drug dose during the Drug Titration Period.

Optional Substudies:

- DNA Bank for patients who agree to participate in the substudy.
- AFB for patients who agree to participate in the AFB substudy.
  - AFB is defined as the amount of time per day that a patient is in AF/AFL, as measured by a Medtronic implanted device.
  - VRR during periods of AF/AFL, as collected by implanted Medtronic devices, will also be evaluated.

2.0 BACKGROUND

2.1 Atrial Fibrillation in Patients with Heart Failure

Atrial fibrillation (AF) is increasing in incidence in the U.S. to epidemic proportions.[1,2] Currently 2.7 to 3.2 million people in the U.S. have AF, with 40,000-50,000 new cases per year.[2] AF and chronic heart failure (CHF) are the two cardiovascular (CV) diseases/disease syndromes that are exhibiting a steady increase in prevalence.[3] This is not coincidental, as both AF and CHF are related to dysfunction and remodeling of the myocardium, and as such share many pathophysiologic features including chamber dilatation, increased interstitial fibrosis and cardiac myocyte apoptosis.[4-6] Unfortunately, most anti-arrhythmic agents with AF indications are either contraindicated or have significant label warnings for use in HF patients due to an increased risk of mortality. Considering these safety concerns, as well as the negative clinical consequences of AF in heart failure (HF) patients described below, there is a clear unmet medical need for a drug that is effective in preventing AF in HF patients with reduced left ventricle ejection fraction (HFREF).

2.1.1 Relationship of AF to Clinical Outcomes

AF is an important CV endpoint and it has an even greater impact in patients with HFREF. A major important clinical consequence of AF in HFREF is an increase in the risk of embolic events including stroke,[3] and for this reason alone it is preferable for a HF patient to be in sinus rhythm (SR). In patients with established HF it is clear that new onset AF, including new AF events after conversion of persistent AF to SR, is associated with increased mortality and worsening HF risks. Framingham data indicate there is an interrelationship between the development of AF and CHF, with each condition developing as HF progresses and often (i.e., 21% of the time) both presenting contemporaneously.[6] In the Framingham study, when AF developed after CHF there was a 1.6-fold (95% CI: 1.2, 2.1) increase in mortality after adjusting for potential modifiers, and when CHF developed after AF the hazard ratio was 2.7 (95% CI: 1.9, 3.7).[6]

Even more impressive are recently published data from the Women's Health Study, which were based on 1011 AF cases developed over a 15.4 year span.[7] In this study, new onset AF was associated with a 2.1-fold (95% CI: 1.6, 2.8) increase in all-cause mortality (ACM) and a 4.2-fold (95% CI: 2.7, 6.5) increase in CV mortality (CVM). *Moreover, in women with new onset AF the risk of developing HF increased by 14.7-fold (95% CI: 11.2, 19.2)*.[7] New onset AF also worsens the prognosis[8-10] in patients with established HFREF, a finding that was clearly observed in the BEST trial as well (Table 1).

Table 1: New Onset AF in BEST and Relationship to Annualized Clinical Outcomes

Group	Mean f/u days	ACM event rate	CV event rate	CVH days/pt	HFH days/pt	ACH days/pt
No new onset AF, (n = 2202)	722	15.1%	12.8%	6.9 ± 0.5	6.2 ± 0.5	10.4 ± 0.6
New onset AF, (n = 190)¶	794‡	32.1%	28.4%	13.3 ± 2.1	11.4 ± 2.0	17.2 ± 2.1
Fold increase [p-value§]	–	2.13 [< 0.0001]	2.22 [< 0.0001]	1.93 [< 0.0001]	1.84 [< 0.0001]	1.65 [< 0.0001]
Hosp. pre AF event, (n = 190)	381	–	–	4.4 ± 0.7	3.5 ± 0.6	6.1 ± 0.8
Hosp. during/post AF event	413	–	–	13.8 ± 2.0	11.9 ± 1.9	19.0 ± 2.1
Fold increase [p-value†]	–	–	–	3.14 [< 0.0001]	3.40 [< 0.0001]	3.11 [< 0.0001]

AF as determined by AE and ECG assessments. Data are presented as annualized event rates. ACM = All-cause mortality; CV = cardiovascular mortality; HFH=total # days hospitalized for HF (Investigator/CRF determined); CVH = total # days hospitalized for cardiovascular causes (adjudicated by committee); ACH = total # days hospitalized for all causes. § log rank statistic for ACM and CV, Wilcoxon Rank sum Test for HFH, CVH and ACH; † Wilcoxon Signed-Ranks test; ‡mortality endpoint length of follow-up = 413 days; ¶ for ACM and CV, follow-up calculated from the date of new onset AF.

2.1.2 Treatment of Atrial Fibrillation in Heart Failure

Unfortunately, most anti-arrhythmic agents approved for the treatment of AF and atrial flutter (AFL) are either contraindicated or have label warnings for use in HF patients due to an increased risk of mortality in this patient population. Dronedarone (Multaq, potassium channel blocker), dofetilide (Tykosyn, potassium channel blocker), propafenone (Rythmol, sodium channel blocker), flecainide (Tambocor, sodium channel blocker) and sotalol (Betapace AF, multi-channel blocker with β-blocking activity) are FDA-approved for prevention of recurrent AF, but dronedarone is contraindicated in HF, and propafenone, flecainide, and sotalol have warnings in their labels. Although dofetilide is effective in treating and preventing AF in patients with HFREF, it is pro-arrhythmic and treatment must be initiated in the hospital in order to monitor rhythm and QTc. Amiodarone is widely used off-label for AF prevention and may be the outpatient drug of choice in patients with HFREF,[5] but this multichannel anti-arrhythmic is also pro-arrhythmic and is associated with a multitude of serious adverse effects that require careful surveillance. Considering these safety concerns, there is a clear unmet medical need for a drug that is effective in preventing AF, which does not have unfavorable effects on the natural history of HF.

β-blockers, which are currently indicated for the treatment of HF, have demonstrated mild efficacy for the prevention of new onset AF (Table 2) and are often used off-label in this setting (Class IIa indication with a "C" level of evidence for AF prevention per ACC/AHA/ESC Joint Guidelines). Therefore, β-blockers may be a more appropriate treatment for the prevention of AF in a setting of HFREF, particularly if a β-blocker could be developed with greater efficacy than those currently being used off-label.

Table 2: Meta-analysis of New Onset AF from β-blocker Heart Failure Trials

Data Source	Patients in SR at baseline (N)	Patients with new onset AF during trial		
		Placebo N (%)	β-blockers N (%)	Relative Risk (95% CI)
CIBIS I (bisoprolol)	556	13 (4.7)	9 (3.2)	0.68 (0.29, 1.57)
MERIT HF (metoprolol)	3,358	54 (3.2)	33 (2.0)	0.61 (0.39, 0.94)
BEST (bucindolol)	2,405	111 (9.3)	78 (6.5)	0.69 (0.52, 0.92)
COPERNICUS (carvedilol)	2,289	22 (1.9)	12 (1.0)	0.53 (0.26, 1.07)
Waagstein (metoprolol)	165	8 (10.1)	1 (1.2)	0.11 (0.01, 0.89)
SENIORS (nebivolol)	1,390	74 (10.8)	78 (11.0)	1.02 (0.75, 1.37)
CAPRICORN (carvedilol)	1,789	31 (3.5)	16 (1.8)	0.51 (0.28, 0.93)
Total	11,951	313 (5.3)	227 (3.8)	0.73 (0.61, 0.86)
Adapted from Nasr et al[11]				

2.1.3 β-Blocker Therapy for Prevention of Atrial Fibrillation

In the meta-analysis summarized in Table 2,[11] the annualized event rate for new onset AF was 5.3% for placebo and 3.8% for active β-blocker treatment. This low order event rate would dictate a very large sample size (i.e., > 4,000 patients) if new onset AF in HFREF patients were the primary endpoint in a clinical trial. However, there is a patient population in which the onset of AF is much higher in frequency – patients with persistent AF who have recently undergone electrical cardioversion (ECV) to SR.

In this setting, approximately 50% of patients will experience a recurrence of AF within 6 months of ECV to SR, even with the use of Class I and Class III anti-arrhythmic drugs.[12] In study populations that included both HFREF and non-HF/left ventricle (LV) dysfunction patients, β-blockers have demonstrated a reduction in risk (effect size) for the recurrence of AF on the order of 30%,[13,14] which is similar to the effects observed in major β-blocker HF trials for new onset AF (Table 2).

In a recent study, patients with symptomatic persistent AF were treated with metoprolol (n = 83) or placebo (n = 85) and underwent ECV to SR approximately one week after treatment initiation.[12] At the end of the 6 month follow-up period, the incidence of AF recurrence was significantly lower ($p < 0.01$) in the metoprolol group (52%) compared to the placebo group (74%), with significant differences observed between the groups as early as one week post-ECV ($p < 0.05$).

Earlier studies in similar patient populations (i.e., persistent AF recently converted to SR) have shown similar event rates for the recurrence of AF following ECV. For example, Katritsis et al compared the effects of carvedilol (n = 43) and bisoprolol (n = 47) in patients with persistent AF recently converted to SR and observed AF recurrence rates of 32% and 46%, respectively.[13] Similarly, Plewan et al compared the effects of sotalol (n=64) and bisoprolol (n=64) in patients with persistent AF recently converted to SR and observed AF recurrence rates of 41% and 42%, respectively.[14] In both of these studies, nearly all AF

events occurred during the first 6 months post-ECV. Importantly, it should be noted that all of these studies examined mixed populations that included both HFREF and non-HF/LV dysfunction patients. A significantly greater event rate would be expected for a pure HFREF population with persistent symptomatic AF converted to SR since HF progression and AF are related.[5] In contrast to the low order event rates observed for new onset AF, the event rates expected for recurrent symptomatic AF would allow for adequately-powered and well-controlled comparative studies to be conducted in a reasonable timeframe.

These data also indicate that metoprolol, and potentially other drugs in the β-blocker class, have favorable effects on the prevention of AF recurrence in patients with persistent symptomatic AF who have recently undergone ECV to SR. As β-blockers are also indicated in HF populations to improve survival and other outcome measures, it stands to reason that this class of drugs may be a more appropriate treatment for AF in the setting of HFREF than the currently approved anti-arrhythmic drugs. However, as seen in the placebo-controlled metoprolol trial, more than half of the patient population still reverted to AF from SR within 6 months of ECV, so clearly there is still a significant unmet medical need for the treatment of AF in HFREF patients.

2.2 Rationale for Pharmacogenetic Targeting of Bucindolol Therapy

Bucindolol hydrochloride (bucindolol) is a nonselective β-adrenergic receptor (AR) blocking agent with mild vasodilator properties, which was previously studied in the Beta Blocker Evaluation of Survival Trial (BEST).[15] Bucindolol has two unique anti-adrenergic properties not possessed by other β-blockers currently approved for the treatment of HF: 1) it is moderately sympatholytic, i.e., it lowers adrenergic drive to a level that can be easily detected on measurements of central or systemic venous norepinephrine levels,[15,23] and, 2) through "inverse agonism" promotes inactivation of active-state human myocardial β_1-ARs in a genotype specific manner.[16] As described below, these properties were shown to interact with AR polymorphisms in such a way that targeting specific genotypes of these variants could improve therapeutic index. Thus, bucindolol is likely to be most effective in $\beta_1$389 arginine homozygous ($\beta_1$389Arg/Arg, also known as *ADRB1* Arg389Arg) HF patients, which comprise approximately 50% of the general United States (US) population.[17]

2.2.1 Genotype-Dependent Effects on Clinical Outcome in HFREF Patients

Recent data indicate that human β_1-ARs are genetically and functionally quite heterogeneous, comprised of a population of high efficiency signal transduction/high cardiomyopathic potential receptors and another population with lower functional activity and low cardiomyopathic potential.[16,18-20] These two genetic variants of the β_1-AR (which have very different functional properties) are the result of a single nucleotide (nt) polymorphism at nt position 1165, resulting in an arginine (Arg, higher function) or a

glycine (Gly, lower function) at amino acid 389.[19] Specifically, the $\beta_1$389Arg/Arg variant has increased affinity for norepinephrine[21] and increased coupling to G_s resulting in greater downstream stimulation of adenylyl cyclase.[16,19] The $\beta_1$389Arg/Arg variant also has a greater constitutive activity in the absence of catecholamine agonist.[16,20] Considering this functional heterogeneity, the therapeutic challenge for β-blocker therapy is to down-modulate adrenergic signaling towards normal without eliminating adrenergic support completely, as there is evidence that excessively lowering adrenergic drive may compromise the benefits of β-blockade or may even be harmful in CHF.[21,22] In particular, because of its increased potential to mediate adverse biologic signaling,[22] the 389 Arg version of the β_1-AR needs specific therapeutic intervention, by a treatment that lowers constitutive activity[16] as well as addresses its high affinity for norepinephrine.[21]

Optimal modulation of adrenergic signaling can be accomplished with bucindolol through pharmacogenetic targeting. This hypothesis was demonstrated in the prospectively designed analysis that was conducted on a large pharmacogenomic substudy of the BEST trial, which evaluated the effects of bucindolol vs. placebo in an advanced HFREF population.[21] In this analysis, two unique pharmacologic properties of bucindolol, sympatholysis and inverse agonism, were shown to interact with AR polymorphisms in such a way that targeting specific genotypes of these variants could improve therapeutic index. Specifically, the $\beta_1$389Arg/Arg higher functioning variant was associated with more efficacious HF endpoint treatment responses to bucindolol than the lower functioning Gly polymorphism (Table 3).[16,21]

Table 3: Major Clinical Endpoints in the BEST trial by Genotype Subgroup

Endpoint	$\beta_1$389 Arg/Arg (n = 493)		$\beta_1$389 Gly carrier (n = 547)	
ACM, TTE	0.62 (0.39, 0.99)	p = 0.042	0.92 (0.63, 1.35)	p = 0.661
CV, TTE	0.52 (0.31, 0.88)	p = 0.014	0.78 (0.51, 1.18)	p = 0.233
HF progression, TTE	0.66 (0.49, 0.88)	p = 0.005	0.85 (0.66, 1.11)	p = 0.233
HF Hosp days/pt[§]	48% reduction	p = 0.008	7% reduction	p = 0.232
CV Hosp, TTE	0.64 (0.48, 0.86)	p = 0.002	0.93 (0.72, 1.21)	p = 0.588

Notes: ACM = all-cause mortality; CV = cardiovascular mortality; HF progression = time to sudden death, death from pump failure, HF hospitalization or ER visit for HF w/o a hospital admission; TTE = time to event. For all endpoints except HF Hosp days/pt, a hazard ratio and 95% confidence interval from a COX model are presented, along with a p-value generated using the logrank statistic. For HF days/pt, the p-value is generated using the Wilcoxon Rank Sum statistic.

Based on data from BEST and from molecular pharmacology studies, the basis for this enhanced effect of bucindolol in patients with the $\beta_1$389Arg/Arg variant is not a disproportionally higher event rate in the Arg/Arg placebo-treated subgroup that is then abrogated by bucindolol, but rather a greater therapeutic effect of bucindolol on the Arg/Arg vs. Gly receptor. This effect is likely mediated by inactivation of active state Arg/Arg receptors plus greater absolute inhibition of signal transduction due in part to norepinephrine lowering. The enhanced clinical responses in patients with the $\beta_1$389Arg/Arg genotype is

the cornerstone for a genetically based treatment algorithm where approximately 50% of the general US population have this genotype, and would be expected to have therapeutic effects that are better than for non-genetically targeted β-blocker therapy.

2.2.2 Genotype-Dependent Effects on New Onset AF in HFREF Patients

AF was not an efficacy endpoint in the BEST trial, but it was captured via adverse events (AEs) and limited electrocardiogram (ECG) assessments (i.e., baseline, 3 months, and 12 months).[23] As shown in Table 4, the vast majority of AF events were symptomatic and associated with one or more AEs (n = 161); whereas relatively few AF events were captured on routine ECGs that were not also reported as an AE (n = 29).

Most of the 2708 BEST trial patients were not in AF at baseline (88.8%, 2176 in SR and 216 other rhythms), with similar incidence in the two treatment groups (Table 4). During the trial, 7.4% of these patients developed new onset AF, with a greater incidence observed in the placebo group (9.7%) compared to the bucindolol group (6.2%). This corresponded to a 36.1% reduction in the incidence of new onset AF (i.e., crude effect size) for patients receiving bucindolol (p = 0.002). Similar results were observed when the analysis excluded AF events captured on routine ECGs that were not reported as an AE (39.3% reduction, p = 0.0012). In a time to event analysis, the risk of new onset AF was reduced by 41% (p = 0.0004) with bucindolol treatment, and by 45% (p = 0.0002) when excluding AF events that were captured by routine ECGs only.

Genotype analyses from the 1040 patient DNA substudy demonstrate that the drug-related reduction in new onset AF was driven almost exclusively by the response of the $\beta_1$389 Arg/Arg subgroups (Table 4).[23] For example, there was a 65.9% reduction in new onset AF in the $\beta_1$389 Arg/Arg subgroup (p = 0.001) compared to no reduction (0.0%) in the $\beta_1$389 Gly carrier subgroup (p = 0.98). Importantly, a test for interaction between genotypes and treatment groups was significant for total new onset AF (p = 0.016). A similar genotype-dependent reduction in new onset AF was observed when excluding AF events that were captured by routine ECGs only (70.9% and 10.8%, respectively) and a significant interaction by treatment and genotype was also observed (p = 0.024).

In a time to event analysis, the risk of new onset AF was reduced by 74% (p = 0.0003) with bucindolol treatment in the $\beta_1$389Arg/Arg subgroup, and by 78% (p = 0.0002) when excluding AF events that were captured by routine ECGs only (Table 4 and Figure 1). In contrast, no reduction was observed for the $\beta_1$389Gly carrier subgroup. A test for interaction between genotypes and treatment groups was also significant for the time to event analysis of new onset AF (p = 0.008). A significant interaction by treatment and genotype was also observed when excluding AF events that were captured by routine ECGs only (p = 0.013).

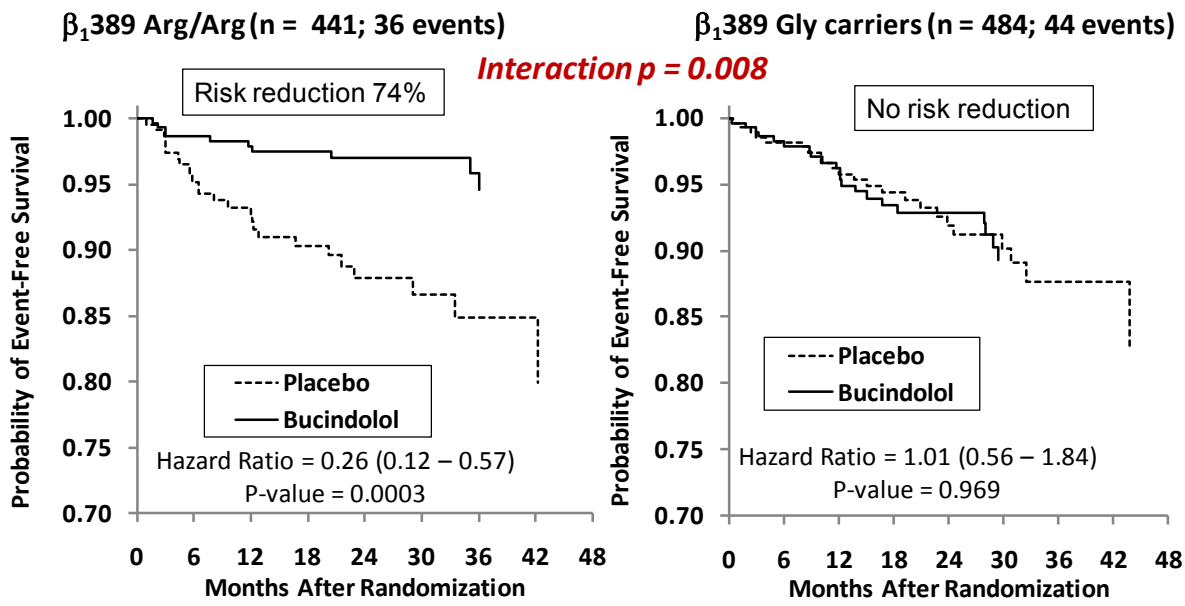
Table 4: New Onset AF in the BEST DNA Substudy by $\beta_1$389 Arg/Gly Genotype

Treatment Group	Patients not in AF at baseline assessed by ECG	Patients with new onset AF reported as AE during trial	Total patients with new onset AF during trial[#]
Entire study cohort			
All, n (%)	2392 (88.8%)	161 (6.7%)	190 (7.4%)
Placebo, n (%)	1190 (88.3%)	100 (8.4%)	115 (9.7%)
Bucindolol, n (%)	1202 (89.2%)	61 (5.1%)	75 (6.2%)
Reduction of new onset AF in bucindolol group (%)*		39.3 p = 0.0012	36.1 p = 0.002
Time to first event of new onset AF, hazard ratio (95% CI)[†]		0.55 (0.44, 0.76) p = 0.0002	0.59 (0.44, 0.79) p = 0.0004
$\beta_1$389 Arg/Arg subgroup			
Placebo, n (%)	206 (87.3%)	24 (11.7%)	26 (12.6%)
Bucindolol, n (%)	235 (91.4%)	8 (3.4%)	10 (4.3%)
Reduction of new onset AF in bucindolol group (%)*		70.9 p = 0.001	65.9 p = 0.001
Time to first event of new onset AF, hazard ratio (95% CI)[†]		0.22 (0.09, 0.52) p = 0.0002	0.26 (0.12, 0.57) p = 0.0003
$\beta_1$389 Gly carrier subgroup			
Placebo, n (%)	254 (88.5%)	21 (8.3%)	23 (9.1%)
Bucindolol, n (%)	230 (89.8%)	17 (7.4%)	21 (9.1%)
Reduction of new onset AF in bucindolol group (%)*		10.8 p = 0.72	0.0 p = 0.98
Time to first event of new onset AF, hazard ratio (95% CI)[†]		0.91 (0.47, 1.74) p = 0.77	1.01 (0.56, 1.84) p = 0.97
Interaction by genotype and treatment group			
Reduction of new onset AF		p = 0.024	p = 0.016
Time to first event of new onset AF		p = 0.013	p = 0.008

Total patients include AF as reported by AEs plus AF as assessed via ECG only; *based on crude effect size; p-value is Chi-square statistic for bucindolol vs. placebo; [†] Cox proportional hazards regression model. Data are based on the bucindolol NDA safety database, which features a customized version of COSTART resulting in minor changes in the AF events but no change in the bucindolol treatment effect.

Finally, the genotype-dependent reduction in AF event rate is consistent with the $\beta_1$389 Arg/Gly polymorphism-dependent effects of bucindolol on major HF clinical endpoints (Table 3). These data suggest that new onset AF has the same pharmacogenetic patterns of $\beta_1$389Arg/Gly differentiation of treatment effects as do major HF endpoints, which most likely is due to a common pathophysiological mechanism.[23]

Figure 1: New Onset AF in the BEST Trial for $\beta_1$389 Subgroups



Note: The p-value for the interaction test is based on a Cox proportional hazards logistic regression model with terms for genotype, treatment, treatment x genotype and the four strata (CAD, RACE, SEX, Baseline LVEF).

3.0 STUDY PLAN

3.1 Study Rationale

Most anti-arrhythmic agents currently approved for the treatment of AF and AFL are either contraindicated or have label warnings for use in HF patients due to an increased risk of mortality in this patient population.

Bucindolol hydrochloride (bucindolol) is a nonselective β-AR blocking agent with mild vasodilator properties, which was previously studied in the BEST Phase 3 HF trial. In a large pharmacogenomic substudy of the BEST trial, two unique pharmacologic properties of bucindolol, sympatholysis[21,24] and inverse agonism,[16] were shown to interact with AR polymorphisms in such a way that targeting specific genotypes of these variants could improve therapeutic index. Specifically, patients with the $\beta_1$389Arg/Arg AR variant had more efficacious treatment responses to bucindolol, as assessed by HF clinical outcomes and the reduction of new onset AF, compared to patients with the $\beta_1$389Gly polymorphism (i.e., Gly carriers).[16,21]

Metoprolol succinate (Toprol-XL, henceforth referred to as metoprolol) is a β_1-AR selective β-blocker indicated for the treatment of stable, symptomatic (NYHA Class II or III) HF of ischemic or non-ischemic origin. Metoprolol has demonstrated mild efficacy for the prevention of new onset AF in a HF patient population[11,25] (Table 2) and is often used off-label in this setting (Class IIa indication with a "C" level of evidence for AF prevention per ACC/AHA/ESC Joint Guidelines). In a previous study, metoprolol

decreased the incidence of AF recurrence, compared to placebo, in patients with persistent AF who had recently undergone ECV to SR.[12] In contrast to bucindolol, metoprolol does not appear to confer added clinical benefits in HFREF patients that possess the $\beta_1$389Arg/Arg AR variant.[26,27] In addition, limited data from the MERIT-HF DNA substudy[27] do not indicate any evidence of a $\beta_1$389Arg/Gly polymorphism differential effect for preventing AF (van Velduisen DJ, personal communication).

The goal of the GENETIC-AF trial is to demonstrate the superiority of pharmacogenetically targeted bucindolol compared to metoprolol for the prevention of symptomatic AF/AFL in a genotype-defined $\beta_1$389Arg/Arg HFREF population at high risk of AF/AFL recurrence. The trial utilizes an interim analysis/adaptive design element that will examine preliminary data from the initial Phase 2B population. If the independent Data and Safety Monitoring Board (DSMB) determines that the preliminary Phase 2B data are consistent with pre-trial assumptions (i.e., absence of futility, event rate), the trial will proceed to Phase 3.

3.2 Study Objectives

The primary objective of this study is to compare the effects of bucindolol and metoprolol on the recurrence of symptomatic AF/AFL in patients with HFREF who have a $\beta_1$389 arginine homozygous ($\beta_1$389Arg/Arg) genotype.

The secondary objectives of this study are to compare the effects of bucindolol and metoprolol on clinical outcomes and other electrocardiographic parameters, and to assess the effects on rate control in patients who have developed recurrent AF/AFL. The safety and tolerability of bucindolol and metoprolol will also be evaluated.

The study endpoints are described in Section 8.0.

3.3 Study Design

GENETIC-AF is a double-blind, two-arm, genotype-directed, active-controlled, adaptive-designed, superiority study that compares the effects of bucindolol and metoprolol on the time to first event of symptomatic AF/AFL in HFREF patients in SR who are at high risk of AF/AFL recurrence.

Two patient populations at high risk of AF/AFL recurrence will be included in this study: 1) patients with symptomatic paroxysmal or persistent AF who are indicated for ECV to attain SR, and; 2) patients in SR who have experienced a recent episode (i.e., $\leq$ 180 days) of paroxysmal or persistent AF who are indicated for ECV to attain SR if AF/AFL recurs. Patients must have HF, a left ventricle ejection fraction (LVEF) < 0.50 in the past 12 months, and no contraindication for β-blocker therapy. β-blocker therapy is permitted at screening but is not required to be eligible for the study. Patients must be receiving optimal anticoagulation therapy for stroke prevention prior to randomization. Patients will be genotyped for

$\beta_1$389 AR at screening and those who are $\beta_1$389Arg/Arg (~50% of patients) will be randomized to study drug.

A subset of patients participating in the trial will have their cardiac rhythm continuously monitored to assess AF burden (AFB). AFB monitoring will be done via the Medtronic Reveal insertable cardiac monitor (ICM) or a Medtronic pacemaker (IPG), implantable cardioverter-defibrillator (ICD), or cardiac resynchronization therapy (CRT) device with a minimum of an atrial and a ventricular lead. Patients participating in the optional AFB substudy must either have a pre-existing Medtronic device that can measure AFB, or agree to have one inserted as clinically indicated. Patients who agree to have a Medtronic device inserted may do so at the Randomization Visit or at any time prior to the start of the 24-week Follow-up Period.

Eligible patients will be randomized (1:1) to blinded treatment with bucindolol or metoprolol (i.e., study drug) and up-titrated weekly to target doses of 50 mg BID (< 75 kg) or 100 mg BID (≥ 75 kg) for bucindolol or 200 mg QD for metoprolol. Randomization will be centralized and stratified by: 1) HF etiology (ischemic vs. non-ischemic); 2) LVEF (< 0.35 vs. ≥ 0.35); 3) type of Medtronic device (Reveal vs. Non-Reveal vs. No Device), and; 4) rhythm status at randomization (SR vs. AF/AFL).

Patients in AF at randomization who do not spontaneously convert to stable SR and are in AF/AFL after 3 weeks of treatment with study drug will undergo ECV to establish stable SR. Patients in SR at randomization who are in AF/AFL after 3 weeks of study drug treatment will also undergo ECV to establish stable SR. Patients in SR at randomization who are in stable SR after 3 weeks (± 3 days) of study drug treatment will start the 24-week Follow-up Period at the Week 0 Visit.

ECV may be performed as early as 1 week after randomization if all of the following conditions are met: 1) the patient is receiving the target dose of study drug; 2) the patient is receiving guideline indicated oral anticoagulation therapy for stroke prevention, and; 3) a delay of ECV could be detrimental to patient outcome. The first ECV attempt may also be performed as late as 8 weeks after randomization if, in the opinion of the Investigator, additional time is needed to attain target doses of study drug or to achieve appropriate anticoagulation status prior to ECV.

The primary endpoint, i.e., time to first event of symptomatic AF/AFL or ACM, will be assessed during the 24-week Follow-up Period after establishment of stable SR on study drug. For patients requiring ECV, establishment of stable SR will be confirmed by ECG at least 1 hour post-ECV. Patients who do not demonstrate stable SR following ECV will undergo a subsequent ECV to establish a baseline SR unless, in the opinion of the Investigator, it would not be the best course of treatment for the patient. The 24-week Follow-up Period will begin on the day of: 1) the ECG that establishes stable SR; 2) the last

ECV attempt for patients who fail to convert to stable SR, or; 3) the Week 0 Visit for patients in AF/AFL who do not undergo ECV for any reason.

During the 24-week Follow-up Period, heart rhythm will be assessed by 12-lead ECG at scheduled clinic visits. At the time of each ECG assessment, patients will be queried for symptoms potentially related to AF/AFL. Scheduled telephone contacts will occur at Week 6, Week 10, Week 14, Week 18 and Week 22. Patients will be also be instructed to contact the site immediately if they experience new or worsening symptoms. Patients will be queried for symptoms potentially related to AF/AFL during the scheduled and patient-initiated telephone contacts (Section 6.2.6). If the Investigator suspects that a new AF/AFL event has occurred between scheduled clinic visits (i.e., a change in rhythm from SR to AF/AFL), the patient will be instructed to return to the clinic within 3 business days for further assessments (Section 6.1.4.2). Patients experiencing recurrence of AF/AFL will be encouraged to remain on blinded study drug and may undergo subsequent ECV procedures or medical interventions as clinically indicated.

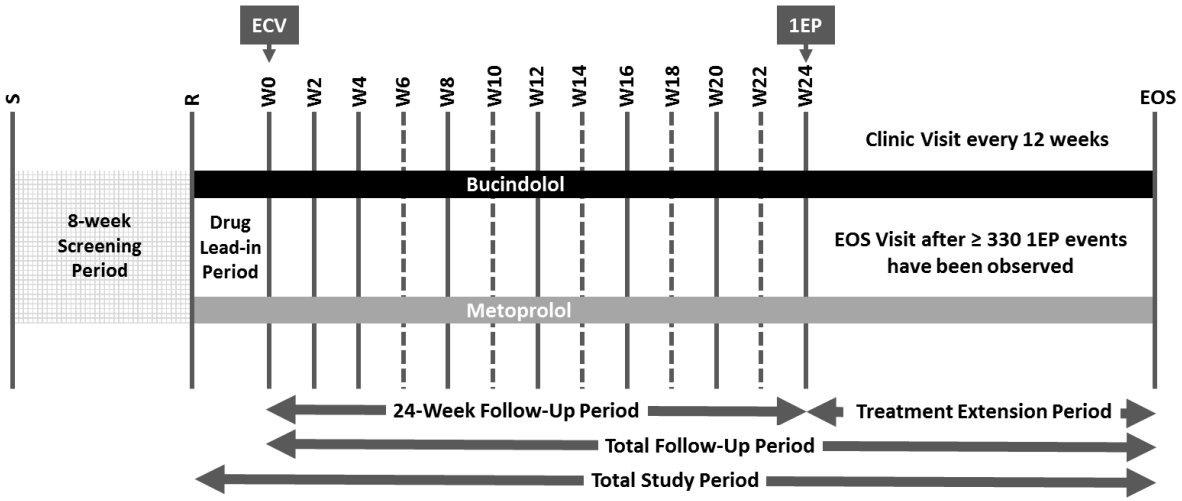
After the Week 24 Visit, patients will enter the Treatment Extension Period and continue to receive blinded study drug. Phase 3 follow-up will continue until a total of at least 330 primary endpoint events have been observed. After this event, all patients will complete the 24-week Follow-up Period or return to the clinic for an end of study visit if already in the Treatment Extension Period. At the end of the study, patients will discontinue study drug and should transition to commercially-available β-blocker therapy per Investigator discretion. Investigators and patients will not be informed of the blinded study drug assignment at the time of study completion.

3.4 Study Visits

- There is a maximum of 8 weeks between the Screening Visit and the Randomization Visit.
- Unscheduled visits are allowed during titration to achieve maximum tolerated dose of study drug or anytime during the study to assess heart rhythm, associated symptoms or adverse events.
- If needed, the first ECV should be performed 3 weeks after randomization, but it may be performed as early as 1 week or as late as 8 weeks after randomization, if clinically required (Section 6.1.3).
- During the 24-week Follow-up Period, patients will return to the clinic at scheduled intervals for routine assessments of safety and efficacy. In addition, telephone contacts will be required at Week 6, Week 10, Week 14, Week 18, and Week 22 to administer the AF Symptom Questionnaire (AFSQ) and determine if the patient has experienced any new or worsening symptoms that could potentially be related to AF/AFL.

- During the Treatment Extension Period, patients will return to the clinic every 12 weeks for routine assessments of efficacy and safety.
- Phase 3 follow-up will continue until a total of at least 330 primary endpoint events have been observed. After this event, all patients will complete the 24-week Follow-up Period or return to the clinic for an end of study visit if already in the Treatment Extension Period.

Figure 2: GENETIC-AF Study Visit Schedule



Note: ECV should be performed 3 weeks after randomization, but may be performed as early as 1 week or as late as 8 weeks after randomization, if clinically required. Week 0 for patients in SR at randomization is 3 weeks (± 3 days) unless ECV is required (see Section 6.1.3). Patients who agree to have a Medtronic device inserted may do so at the Randomization Visit or at any time prior to the start of the 24-week Follow-up Period. S = Screening Visit; R = Randomization Visit; W = week; ECV = electrical cardioversion; 1EP = primary endpoint; EOS = end of study. Solid line = clinic visit, dashed line = telephone contact.

4.0 PATIENT POPULATION

4.1 Number of Patients and Study Centers

Approximately 250 patients will be randomized in Phase 2B and an additional 370 patients will be randomized in Phase 3 (i.e., a total of 620 patients). The $\beta_1$389Arg/Arg genotype is expected in approximately 50% of screened patients; therefore, a 65% screen-fail rate is assumed for the study (15% for general criteria and a 50% screen-fail rate due to genotype).

The DSMB will examine preliminary data from the initial Phase 2B population to assess the presence or absence of futility for proceeding to Phase 3, as well as consistency with other pre-trial assumptions including event rate. If the DSMB determines there is absence of futility, acceptable safety, and pre-trial assumptions regarding event rate and other factors are correct, the trial will proceed to Phase 3.

A second interim analysis will be conducted by the DSMB during Phase 3 to assess the absence of futility and whether an expansion of the total sample size is warranted. The DSMB may also make suggestions to

the Steering Committee for adjustment in sample size based on other factors (e.g., event rate, discontinuation rate, etc.) or other modifications to the protocol that would improve trial conduct.

Approximately 150 centers will be included in this study. Enrollment is competitive with a maximum of 62 randomized patients per center permitted in the overall study (10% of total enrollment).

4.2 Patient Characteristics and Screening Procedures

Patients must meet *all* of the following inclusion criteria and none of the exclusion criteria to be eligible for randomization in this study. Any patient who fails screening for any reason (other than genotype) may be re-screened two additional times. Patients who are re-screened will be assigned a new screening number and will sign a new informed consent form (ICF). Each screening must be adequately documented in the source documents. Previous screening tests that still meet the study entry criteria do not need to be repeated for patients who are being re-screened.

4.2.1 Inclusion Criteria

Patients must meet *all* of the following inclusion criteria to be eligible for randomization in this study.

1. Age ≥ 18 years and ≤ 85 years at the Screening Visit.
2. Weight ≥ 40 kg at the Randomization Visit.
3. Possess the $\beta_1$389Arg/Arg genotype.
4. History of heart failure with reduced left ventricle ejection fraction (HFREF).
   a. LVEF < 0.50 assessed at any time during the previous 12 months of the Screening Visit.
5. At least one symptomatic paroxysmal or persistent AF episode ≤ 180 days of the Screening Visit.
   a. Qualifying AF episode may be documented by ECG, Holter, TTM, or implanted device. AF documented by implanted device must be a single episode ≥ 60 minutes in duration. Atrial flutter is not considered a qualifying AF episode.
   b. Must have experienced AF symptoms ≤ 180 days of the Screening Visit, but these symptoms may overlap with HF symptoms, i.e. may be "arrhythmic" (e.g. palpitations, dizziness) or "heart failure" (e.g. breathlessness, fatigability) in nature.
6. Clinically appropriate for ECV if AF/AFL is present at the Week 0 Visit, including:
   a. Patients with AF/AFL at randomization determined by the Investigator to require ECV.
   b. Patients in SR at randomization determined by the Investigator to require ECV if AF/AFL recurs.
7. Receiving guideline indicated oral anticoagulation therapy at the Randomization Visit, which is considered optimal for stroke prevention in the opinion of the Investigator.
8. Systolic blood pressure > 90 mmHg and < 150 mmHg at the Randomization Visit.

9. Female of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Randomization Visit.
    a. Female who is surgically sterile or post-menopausal for at least 12 months is not considered to be of childbearing potential.
10. Female of childbearing potential must agree to use a highly effective contraception for the duration of the trial and for at least 30 days following the last dose of study drug.
    a. Female who is surgically sterile or post-menopausal for at least 12 months is not considered to be of childbearing potential.
11. Must agree not to participate in a clinical study involving another investigational drug or device throughout the duration of this study.
12. Must be competent to understand the information given in the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) approved ICF. Must sign the ICF prior to the initiation of any study procedure and not withdraw consent prior to the Randomization Visit.

4.2.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria are not eligible for randomization in this study.

1. NYHA Class IV symptoms at the Randomization Visit.
2. Significant fluid overload at the Randomization Visit, in the opinion of the Investigator.
   Evidence of significant fluid overload may include:
    a. Mean jugular venous pressure above the clavicle at 90°.
    b. Liver congestion.
    c. Moist pulmonary rales post-cough.
    d. Peripheral edema beyond 1+ pedal not explained by local factors.
3. Permanent AF at the Screening Visit.
    a. Permanent AF is defined as an ongoing AF event 1 year or longer in duration in which there is no intervening evidence of SR.
4. More than two ECV procedures within 6 months of the Randomization Visit or if the most recent ECV within 6 months of the Randomization Visit failed to produce SR.
5. Use of any of the following < 7 days of the Randomization Visit:
    a. Amiodarone, disopyramide, dofetilide, dronedarone, flecainide, propafenone, sotalol, non-dihydropyridine calcium channel blockers, daily NSAIDS (e.g., ibuprofen, celecoxib), thiazolidinediones, or frequent use of short acting nitroglycerin (e.g., > 6 sublingual tablets/week).

b. Note: Amiodarone and dofetilide can be restarted after the start of follow-up if the patient experiences an AF/AFL event or after failure to convert to SR following ECV (see Section 5.8).

6. The presence of a left ventricular assist device (LVAD) or a condition that is likely to require LVAD placement within 6 months of the Randomization Visit.
7. History of a successful atrioventricular node ablation.
8. History of an AF ablation or AFL ablation within 30 days of the Randomization Visit.
9. History of untreated second degree Mobitz II or third degree heart block.
10. History of untreated symptomatic bradycardia or if symptomatic bradycardia is likely on full dose of study drug in the opinion of the Investigator.
11. Heart rate < 60 beats per minute at the Randomization Visit for patients who were not receiving β-blocker therapy during the screening period.
12. Heart rate > 180 beats per minute at the Randomization Visit.
13. Contraindication or previous history of intolerance to β-blocker therapy (e.g., untreated valvular disease) or Toprol-XL (e.g., inability to tolerate at least 25mg QD).
14. Myocardial infarction, unstable angina, acute coronary syndrome, cardiac surgery (including PTCA or stent placement), or evidence of new ischemic changes as assessed by ECG ≤ 90 days of the Randomization Visit.
15. Moderate to severe asthma or other obstructive lung disease requiring chronic use (> 2 days/week) of an inhaled β_2-selective adrenergic agonist < 7 days of the Randomization Visit.
16. History of pulmonary hypertension, defined as a systolic pulmonary arterial pressure ≥ 70 mmHg at rest as assessed by echocardiography or right heart catheterization.
17. Known reversible causes of AF such as alcohol intoxication, pulmonary embolism, hyperthyroidism, acute pericarditis, or hypoxemia.
18. Evidence of an appropriate firing of an ICD device for ventricular tachycardia (VT) or ventricular fibrillation (VF) ≤ 90 days of the Randomization Visit.
    a. Exception: does not include anti-tachycardia pacing.
19. Untreated thyroid disease, in the opinion of the Investigator, at the Randomization Visit.
20. Serum potassium < 3.5 mmol/L at the Screening Visit.
    a. Lab value will be assessed by the central lab at the Screening Visit and any exclusionary results must be corrected prior to randomization as documented by either the central or local lab.

21. Renal failure requiring dialysis, serum creatinine > 2.5 mg/dL or an estimated creatinine clearance < 30 mL/min (Cockcroft-Gault) at the Screening Visit.
    a. Lab values will be assessed by the central lab at the Screening Visit and any exclusionary results must be corrected prior to randomization as documented by either the central or local lab.
22. Significant intrinsic liver disease or a total bilirubin > 2.5 mg/dL at the Screening Visit.
    a. Lab value will be assessed by the central lab at the Screening Visit and any exclusionary results must be corrected prior to randomization as documented by either the central or local lab.
23. Use of strong inhibitors of cytochrome P450 2D6 (e.g., fluoxetine, paroxetine, propafenone, quinidine, or ritonavir) < 7 days prior to the Randomization Visit for patients who are not receiving β-blocker therapy at screening.
24. Participation in a clinical study or treatment with an investigational drug or device within 30 days of the Screening Visit (or 5 half-lives of the investigational agent, whichever is longer).
25. Comorbid condition or illness which, in the opinion of the Investigator, may limit life expectancy to less than 1 year.
26. Serious or active medical or psychiatric condition which, in the opinion of the Investigator, may interfere with treatment, assessment, or compliance with the protocol.
27. Treatment for a malignancy ≤ 2 years prior to randomization, the presence of a treated malignancy that has evidence of disease progression, or the presence of a malignancy that is expected to require radiation therapy, chemotherapy, hormonal treatment, or surgical intervention during the study.
    a. Exceptions for localized, resectable skin carcinomas and in situ carcinoma of the cervix.
28. History of alcohol, drug, or chemical abuse that, in the opinion of the Investigator, could impair or limit the patient's full participation in the study.

5.0 STUDY DRUGS AND DEVICES

5.1 Investigational Agent

Bucindolol hydrochloride (bucindolol) is a nonselective β-AR blocking agent with mild vasodilator properties, which was previously studied in the BEST trial.[15] Bucindolol has two unique anti-adrenergic properties not possessed by other β-blockers currently approved for the treatment of HF: 1) it is moderately sympatholytic, i.e., it lowers adrenergic drive to a level that can be easily detected on measurements of central or systemic venous norepinephrine levels,[24,28] and, 2) through "inverse agonism" promotes inactivation of active-state human myocardial β_1-ARs in a genotype specific manner.[16] As

described in Section 2.2, these properties were shown to interact with AR polymorphisms in such a way that targeting specific genotypes of these variants could improve therapeutic index. Thus, bucindolol is most effective in $\beta_1$389Arg/Arg homozygous HF patients, which comprise approximately 50% of the general US population.

Unlike metoprolol (i.e., active comparator; Section 5.2), bucindolol induces a mild degree of vasodilation, through slight α_1 AR blockade[29] and nitric oxide generation.[30] In contrast to metoprolol and carvedilol, the only two currently FDA-approved HF β-blockers, bucindolol also possesses β_3 agonist activity which promotes the release of nitric oxide.[30] The hemodynamic benefit of vasodilation is a slight reduction in both pulmonary capillary wedge pressure and systemic vascular resistance, which results in a slight increase in cardiac index. The favorable effect on hemodynamic parameters creates an optimal pharmacologic profile for use in patients with HF. The vasodilation confers an "unloading effect" which helps support the failing heart as it adjusts to the initial negative chronotropic and inotropic effects of β-blockade.

Consistent with this mechanism, the BEST trial showed that 75% of patients were able to reach the target dose of bucindolol.[15] This is in contrast to a lower percentage of HF patients that achieved the target dose in COPERNICUS[31] (66%) with carvedilol, or in MERIT-HF[32] (64%) with metoprolol. This is particularly impressive when considering that patients in BEST were more hemodynamically compromised than patients in either COPERNICUS or MERIT-HF, based on the sensitive indicator of average systolic blood pressure at entry. Importantly, this high target dose attainment was achieved without causing symptoms typically associated with excess vasodilation such as dizziness, orthostatic hypotension, and syncope.

5.2 Active Comparator

Metoprolol succinate (metoprolol; Brand name: Toprol-XL), the active comparator, is a β_1-selective β-blocker indicated for the prevention of mortality plus hospitalization in patients with NYHA Class II or III HF of ischemic, hypertensive or cardiomyopathic origin, and showed a 34% reduction in mortality in its pivotal trial, MERIT-HF.[32,33]

Metoprolol has demonstrated mild efficacy for the prevention of new onset AF in a HF patient population (Table 2) and is often used off-label in this setting (Class IIa indication with a "C" level of evidence for AF prevention per ACC/AHA/ESC Joint Guidelines). In a recent study, metoprolol decreased the incidence of AF recurrence compared to placebo in patients with persistent AF who had recently undergone ECV to SR (Section 2.1.3).[12]

Importantly, metoprolol does not appear to confer added clinical benefits in patients that possess the $\beta_1$389Arg/Arg ARs.[26,27] The molecular basis for this may be that, unlike bucindolol, metoprolol does not

possess inverse agonist activity for the $\beta_1$389Arg/Arg ARs.[34] Metoprolol was therefore the most logical choice as a comparator β-blocker in this study, as it is critical that the selected comparator have no pharmacogenetic treatment effect.

The other possible comparator is carvedilol.[22] Neither carvedilol nor metoprolol have been shown to possess differential treatment effects on clinical endpoints by genotype;[26] however, the negative clinical evidence against modulation of effectiveness by $\beta_1$389Arg/Gly polymorphisms is less robust for carvedilol. In addition, compared to metoprolol,[25] the efficacy of carvedilol is not established in HFREF, and in patients with permanent AF who are $\beta_1$389Arg homozygotes carvedilol does not provide rate control.[35] In the Treatment Extension Period of the protocol, the majority of patients in the study will likely be in permanent AF, and rate control may be important in HFREF-AF patients.[36] Thus, in order to select a comparator that has unequivocal evidence of no differential effect on the $\beta_1$389Arg/Gly polymorphisms, as well as to provide the most effective active control for the study population, metoprolol is the appropriate choice.

5.3 Dose Rationale

The starting dose of bucindolol will be 6.25 mg BID with weekly dose titrations as tolerated until the target dose, or the maximum tolerated dose, is achieved. This is similar to the dosing protocol employed in the BEST trial, where on average patients had clinical HF that was more advanced (NYHA Class III or IV) than is anticipated to be the case for the current protocol (i.e., NYHA Class II-III).[15] The bucindolol target dose varies based on the patient's weight on the day of randomization: patients < 75 kg receiving a target dose of 50 mg BID (100 mg daily) and patients $\geq$ 75 kg receiving a target dose of 100 mg BID (200 mg daily).

The dosing of metoprolol is consistent with the prescribing information for HFREF, which is based on the methods used in the MERIT-HF trial.[32] Specifically, the starting dose is 25 mg daily with dose titrations until 200 mg once daily or the maximum tolerated dose is achieved.

Blinding of study drug will be achieved by over-encapsulation of bucindolol and metoprolol tablets using the same capsule size and color. See Section 5.7.1 for more details.

5.4 Risk/Benefits

In patients with established HF it is clear that new onset AF, including new AF events after conversion of persistent AF to SR, is associated with increased mortality and worsening HF risks (Section 2.1.1). However, all anti-arrhythmic agents currently approved for the treatment of AF are either contraindicated or have label warnings for use in HF patients due to an increased pro-arrhythmia or worsening HF risk in this patient population (Section 2.1.2).

β-blocker therapy is considered a standard of care in patients with HF.[22] β-blocker therapy has also demonstrated mild efficacy for the prevention of new onset AF in a HF patient population[11,25] (Table 2) and is often used off-label in this setting (Class IIa indication with a "C" level of evidence for AF prevention per ACC/AHA/ESC Joint Guidelines). In a recent study, metoprolol (the active comparator in this trial) decreased the incidence of AF recurrence, compared to placebo, in patients with persistent AF who had recently undergone ECV to SR (Section 2.1.3).

In a large pharmacogenomic substudy of the BEST HF trial, patients with the $\beta_1$389Arg/Arg AR variant had a greater treatment responses to bucindolol, as assessed by HF clinical outcomes (Table 3) and the reduction of new onset AF (Table 4) compared to patients with the Gly polymorphism (i.e., Gly carriers). Metoprolol does not appear to confer added clinical benefits in HFREF patients that possess the $\beta_1$389Arg/Arg AR variant.[26,27] In addition, limited data from the MERIT-HF DNA substudy[27] do not indicate any evidence of a $\beta_1$389Arg/Gly polymorphism differential effect for preventing AF (DJ van Velduisen, personal communication).

Considering the lack of available treatment for AF in the setting of HF, as well as the established use of β-blocker therapy for the treatment of both HF and AF, this active-controlled, comparative β-blocker study provides sufficient potential for benefit and an acceptable potential for risk for the planned study population.

5.5 Dosage and Administration of Study Drug

Patients who are not receiving β-blocker therapy at randomization will initiate treatment with either 6.25 mg BID bucindolol or 25 mg QD metoprolol and will be up-titrated in a blinded manner to the target doses (Table 5). Patients receiving β-blocker therapy at baseline will discontinue this treatment at the time of randomization, initiate blinded β-blocker therapy as described in Table 5, and will be up-titrated in a blinded manner to the target doses.

One capsule of study drug (i.e., bucindolol or metoprolol) should be taken twice daily (BID), in the morning and then approximately 12 hours later in the evening, unless instructed otherwise. Study drug can be taken with or without food.

The first dose of study drug should be administered in the clinic on the day of randomization after all protocol-specified assessments are completed. Therefore, patients receiving commercial β-blocker therapy during the screening period should be instructed to withhold this medication on the day of the Randomization Visit. Patients who do not qualify for randomization may immediately reinitiate their commercial β-blocker therapy per the Investigator's discretion.

For all randomized patients, the first evening dose of study drug should be taken approximately 12 hours after the first dose, but no earlier than 6 hours after the first dose of study drug. If this is not possible,

then the patient should skip the Day 1 evening dose and take the first Day 2 dose the following morning. Similarly, if a patient does not withhold their morning dose of commercial β-blocker therapy on the day of the Randomization Visit, they should be instructed to skip the first morning dose and take the first evening dose approximately 12 hours, but no earlier than 6 hours, after their last dose of commercial β-blocker therapy.

Table 5: Study Drug Titration Schedule

Previous Commercial β-blocker Dose[1]												Randomized β-blocker Dose	
Metoprolol XL/CR (mg QD)		Metoprolol IR (mg BID)		Carvedilol CR (mg QD)		Carvedilol IR (mg BID)		Bisoprolol (mg QD)		Nebivolol (mg QD)		Metoprolol XL (mg QD)	Bucindolol (mg BID)
>	≤	>	≤	>	≤	>	≤	>	≤	>	≤	=	=
-	50	-	25	-	20		6.25	-	2.5	-	1.25	25	6.25
50	100	25	50	20	40	6.25	12.5	2.5	5	1.25	2.5	50	12.5
100	200	50	100	40	80	12.5	25	5	10	2.5	5	100	25
200[3]	-	100[3]	-	80[3]	-	25[3]	-	10[3]	-	5	10[3]	200	50
-	-	-	-			-	-			-	-	200	100[2]
Transition to Starting Dose of Study Drug ➡➡➡												Up-titration ⬇	

[1]Transition from β-blockers other than those above requires approval from the Sponsor or its designee prior to randomization.
[2]Patients who weigh < 75 kg at randomization will receive a maximum bucindolol dose of 50 mg BID.
[3]Patients receiving commercial β-blocker doses higher than those currently approved will require pre-approval from the Sponsor or its designee prior to randomization.

Study drug should be up-titrated to the target dose for all patients unless clinically contraindicated. Target doses for study drug are: 1) 200 mg QD metoprolol; 2) 50 mg BID bucindolol for patients who weigh < 75 kg, and; 3) 100 mg BID bucindolol for patients who weigh ≥ 75 kg. Investigators should make every reasonable attempt to up-titrate study drug on a weekly schedule, but can delay up-titration if required clinically (i.e., up-titration at a two week interval). Up-titration intervals shorter than one week are not permitted without prior approval from the Sponsor or its designee. Study drug dose may be reduced at any time in the event of documented intolerance. The goal of up-titration should be to reach the target dose of study drug within 3 weeks of randomization. For patients who are in AF/AFL requiring ECV, the pre-ECV Drug Lead-in Period may be prolonged if they have not attained target dose within 3 weeks of randomization (see Section 6.1.3). In the event that ECV cannot be delayed and/or a patient cannot tolerate the target dose, it is recommended to reach at least study drug level M100/B25 (Table 5) prior to ECV. Patients who cannot reach target dose by the time of ECV should have up-titration continued to target levels after SR is achieved, as achievement of SR may improve study drug tolerability.

Patients who forget to take a dose of study drug by more than 6 hours should be instructed to skip that dose and take the subsequent dose of study drug at the next designated interval. Patients who experience

dose interruptions of more than 2 days (i.e., 4 doses) should contact the site to determine if dose adjustment is necessary prior to re-initiation of study drug.

At the end of the study, patients will discontinue study drug and should transition to commercially-available β-blocker therapy per Investigator discretion. Transition to commercial β-blocker therapy is recommended to occur in a similar manner as the dosing algorithm described for initiation of blinded β-blocker therapy. If commercial β-blocker therapy is not being considered at the end of the study, then transition off study drug will require down-titration over several weeks. This will be accomplished via unscheduled visits prior to the end of study (EOS) Visit.

5.6 Randomization and Blinding

The Sponsor or a specified designee will prepare the randomization code. Only persons not involved in the day-to-day conduct of the study will know the randomization code before unblinding. The randomization will be performed with the use of an Interactive Voice/Web Response System (IVRS/IWRS) via the telephone or internet. Randomization will be centralized and stratified by: 1) HF etiology (ischemic/non-ischemic); 2) LVEF ($< 0.35 / \geq 0.35$); 3) type of Medtronic device (Reveal/Non-Reveal/No Device) and; 4) rhythm status at randomization (SR vs. AF/AFL). The 'Non-Reveal' stratum will include patients with a Medtronic pacemaker (IPG), ICD, or CRT devices with a minimum of an atrial and a ventricular lead. The 'No Device' stratum will include: a) patients who have a Medtronic device that cannot assess AFB; b) patients who have a Medtronic device who do not consent to participate in the AFB substudy; c) patients who have a device from any other manufacturer, and; d) patients who have no device.

Blinding will be accomplished by providing study drug (i.e., bucindolol or metoprolol tablets) in capsules that are visually indistinguishable and provided in numbered kits. Only the numbers of the kits to be administered to a given patient, and not the identity of the study drug, will be provided to sites. Investigators, site personnel, and patients will not be informed of the blinded study drug assignment at the time of study completion.

In the case of a medical emergency, the Investigator may request unblinding of the study drug assignment for a patient via IVRS/IWRS. Unblinding should only be done if diagnosis or treatment of the medical emergency is dependent on knowledge of study drug received. The Sponsor or its designee must be contacted immediately and informed of any unblinding events. Once unblinded, the patient may be required to discontinue from study drug but he/she should continue to participate in all other study-related activities including assessments of efficacy. The Sponsor or its designee will document any patient who is unblinded, including the rationale for and date of unblinding.

5.7 Description and Handling of Study Drug

5.7.1 Formulation

Clinical supplies of study drug, which include the investigational medicinal product (bucindolol hydrochloride) and the active comparator (metoprolol succinate), are supplied by the Sponsor. The metoprolol succinate used in this study is Toprol-XL (AstraZeneca). Blinding is achieved by over-encapsulation of bucindolol and metoprolol tablets using the same capsule size and color. Since bucindolol is administered twice daily, and metoprolol is given once per day, a placebo capsule has been manufactured for the active comparator arm.

Over-encapsulated bucindolol is provided in the following dosage strengths: 6.25, 12.5, 25, 50 and 100 mg. Over-encapsulated metoprolol is provided in the following dosage strengths: 25, 50, 100, and 200 mg.

Small quantities of microcrystalline cellulose have been added to the study drug capsules as part of the over-encapsulation process to backfill the remaining void space. Placebo capsules for the metoprolol arm of the study have been prepared by filling the over-capsules with microcrystalline cellulose.

5.7.2 Packaging and Labeling

Over-encapsulated bucindolol and metoprolol tablets have identical packaging for blinding purposes. Capsules are packaged in a PVC/aluminum blister card format in a 2 x 9 format. This provides enough study drug for a 7 day (weekly) dosing regimen, plus two extra days. In the case of bucindolol, both capsules for a daily treatment contain active drug product. In the case of metoprolol, one of the capsules for a daily treatment is active, and one is placebo. Blister strips are coded with a unique batch number assigned to each dose strength. The batch number on each blister strip is obscured within the sealed portion of the study drug kit, and is not visible to patients or Investigators. Study drug kits are child resistant to meet FDA and other regulatory agency requirements and are pre-printed as approved by the Sponsor. The study drug kits contain a clinical trial label containing a unique kit number, as well as pertinent dosing and storage information.

Study drug kits are packaged and supplied to clinical pharmacies either as individual weekly titration cards, or in cartons of four cards, which are adequate for four weeks of dosing. Cartons are labeled with a single panel clinical trial label similar to the individual cards.

5.7.3 Storage and Handling

The study drug must be kept in a secure cabinet or room with access restricted to only necessary study personnel. Temperature must be maintained at controlled room temperature, 15°C to 30°C (59°F to 86°F). Excursions outside of this range must be reported to the Sponsor or designee.

5.8 Concomitant and Prohibited Medications

Previous β-blocker therapy must be discontinued at the time of randomization to study drug and concomitant use is not permitted at any time during the study.

Usage of the following anti-arrhythmic medications is prohibited < 7 days prior to randomization and at any time during the study, unless otherwise stated. Concomitant usage of these anti-arrhythmic medications is allowed after the start of follow-up if the patient experiences an AF/AFL event or after failure to convert to SR following ECV. Similarly, non-investigational procedures to treat arrhythmia (e.g., ablation, ECV) are also allowed after the start of follow-up if the patient experiences an AF/AFL event or after failure to convert to SR following ECV. If this occurs, the patient should remain in the study and complete all follow-up visits and assessments.

- Amiodarone (e.g., Pacerone®, Nexterone®, Cordarone®)
- Dofetilide (e.g., Tikosyn®)

Usage of any of the following medications is prohibited < 7 days prior to randomization and at any time during the study while receiving study drug.

- Disopyramide (e.g., Norpace®, Norpace CR®, Rythmodan®, Rythmodan-LA®)
- Dronedarone (e.g., Multaq®)
- Flecainide (e.g. Tambocor®)
- Propafanone (e.g. Rythmol®, Rythmol SR®, Rytmonorm®)
- Non-dihydropyridine calcium channel blockers (e.g., verapamil, diltiazem)
- Sotalol (e.g., Betapace®, Betapace AF®, Sotalex®, Sotacor®)
- Daily NSAIDs (e.g., ibuprofen, celecoxib, diclofenac)
- Thiazolidinediones (e.g., rosiglitazone, pioglitazone, troglitazone)
- Frequent use of short acting nitroglycerin (e.g., > 6 sublingual tablets/week)

5.9 Medtronic Devices for AF Burden Substudy

Patients who choose to participate in the optional AFB substudy will have their cardiac rhythm monitored continuously via a Medtronic implanted device. Eligible Medtronic devices must be able to measure AFB, which include the Medtronic Reveal ICM (Section 5.9.2), and Medtronic pacemaker (IPG), ICD, or CRT devices with a minimum of an atrial and a ventricular lead. Eligible devices can be previously placed or de novo inserted as clinically indicated. Patients who agree to have a Medtronic device inserted may do so at the Randomization Visit or at any time prior to the start of the 24-week Follow-up Period.

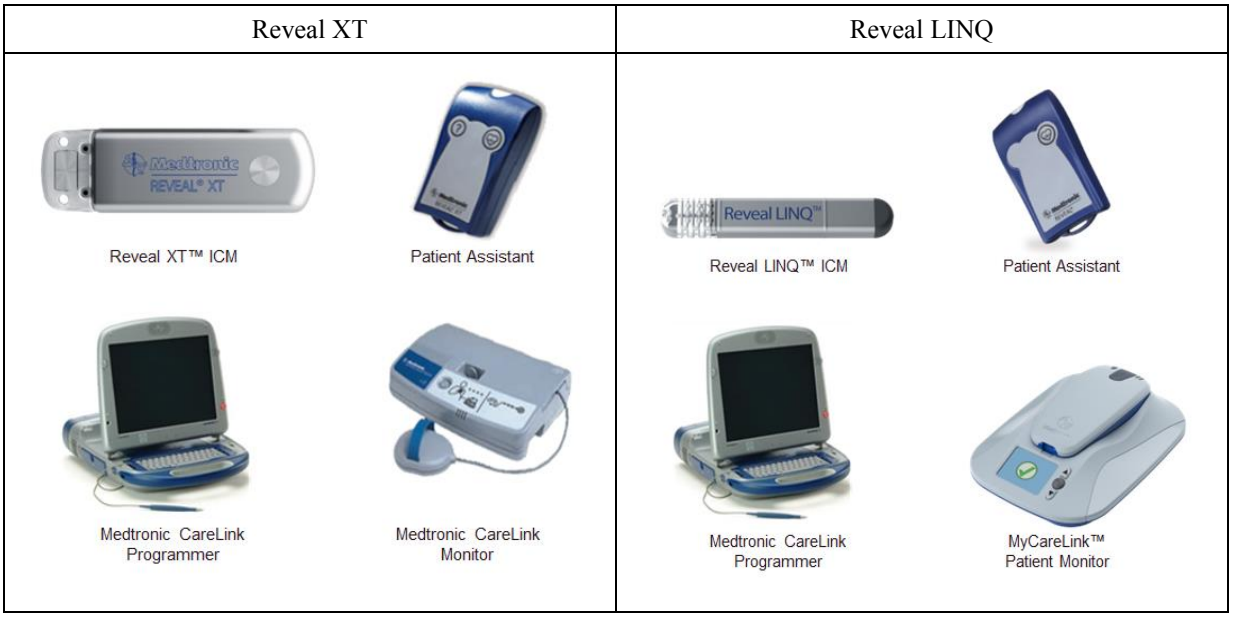
5.9.1 System Description and Intended Use of Reveal ICM

Depicted in Figure 3 and outlined in Table 6 are the components for the Reveal insertable cardiac monitor (ICM). The Medtronic Reveal ICM system is being used within the study in accordance with the FDA-approved indications for the device.

The Reveal ICM is indicated for:

- Individuals with clinical syndromes or situations at increased risk of cardiac arrhythmias.
- Individuals who experience transient symptoms such as dizziness, palpitation, syncope, and chest pain that may suggest a cardiac arrhythmia.

Figure 3: Components of the Medtronic Reveal ICM System



Instructions for use of the devices are provided in their respective manuals. Study system components are being used without modification.

Table 6: System Component Information

Model Number	Component	Market-released
Model 9529 with FullViewTM Software (or later Medtronic releases)	Reveal Insertable Cardiac Monitor	Yes
Model 2090 with FullViewTM Software (or later Medtronic releases)	Medtronic CareLink Programmer	Yes
9538/9539 (or later Medtronic releases)	Reveal Patient Assistant	Yes
2490G (or later Medtronic releases)	Medtronic CareLink Monitor	Yes
Note: The labels for the Reveal ICM components are available in English and where available in the local language.		

5.9.2 Reveal Insertable Cardiac Monitor

The Reveal ICM (model 9529 with FullView™ software Model SW007 or later Medtronic releases) is a leadless device that is typically implanted under the skin in the region of the thorax. Two electrodes on the body of the device continuously monitor the patient's subcutaneous ECG. The device can store up to 22.5 minutes of ECG recordings from the patient-activated episodes and up to 27 minutes of ECG recordings from automatically detected arrhythmias. When the ECG storage log within the monitor is full, the ECG record from the most recent episode will overwrite the ECG data from the oldest stored episode for that same arrhythmia category. Documentation of episode occurrence will be retained.

5.9.3 Medtronic CareLink Programmer

The Medtronic CareLink Programmer (Model 2090 with FullView™ software Model SW007 or later Medtronic releases) is used to program the Reveal ICM to detect arrhythmias with various pre-specified characteristics. In addition, the programmer allows the physician to view, save, and print the ECG records currently held within the Reveal ICM.

5.9.4 Reveal Patient Assistant

The Reveal Patient Assistant (Model 9538 or later Medtronic releases) is a battery-operated, hand-held telemetry device that enables the patient, on experiencing symptoms potentially indicative of a cardiac event, to manually trigger the Reveal ICM to collect and store an ECG record. When the recording is manually triggered in this way (i.e., the Symptoms button is pressed), the Patient Assistant device also shows the patient whether it successfully received the telemetry transfer from the Reveal ICM, as well as whether the battery of the Patient Assistant device is low.

The patient can also use a query button on certain models of the Patient Assistant device for direct feedback about whether the Reveal has registered an arrhythmia and/or whether criteria have been met for the patient to take action to contact the physician or clinic. The notification criteria are selected and pre-programmed by the care provider.

5.9.5 Medtronic CareLink Monitor

The CareLink Monitor (Model 2490G or later Medtronic releases) is a device that enables the device diagnostic data (which includes ECG data) to be transmitted directly from the Reveal ICM to the Medtronic CareLink Network for review by the physician.

5.9.6 Medtronic CareLink Network

The Medtronic CareLink Network is an internet-based remote service for monitoring patients with implanted Medtronic cardiac devices. The physician can access the CareLink Network, a secured

network with restricted access, to review the device data that has been uploaded from the implanted Reveal monitor.

6.0 STUDY PROCEDURES

6.1 Timing of Study Procedures

6.1.1 Screening and Randomization

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for all screened patients, including patients who are not subsequently randomized (i.e. screen failures), will be maintained at the study site. Screening tests and evaluations will be performed within 8 weeks prior to the Randomization Visit, unless otherwise specified. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Any patient who fails screening for any reason (other than genotype) may be re-screened two additional times. Patients who are re-screened will be assigned a new screening number and will sign a new ICF. Each screening must be adequately documented in the source documents. Previous screening tests that still meet the study entry criteria do not need to be repeated for patients who are being re-screened.

During screening, potential patients must be assessed to ensure that they meet inclusion/exclusion criteria prior to collection of samples for central laboratory tests and β_1AR genotyping. At the Randomization Visit, potential patients must meet all inclusion/exclusion criteria prior to collection of samples for additional required genotyping, optional DNA banking, norepinephrine, and N-terminal pro B-type natriuretic peptide (NT-proBNP). All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. There is a maximum of 8 weeks between the Screening Visit and the Randomization Visit.

Patients who agree to have a Medtronic device inserted may do so at the Randomization Visit or at any time prior to the start of the 24-week Follow-up Period.

6.1.1.1 Screening Visit

At the Screening Visit, the following procedures will be done as per Appendix 4:

- Obtain written informed consent.
- Procedures to be performed prior to collection of laboratory samples:
  - Review inclusion/exclusion criteria (Section 4.2).
  - Assess medical history including arrhythmia, cardiovascular and neoplasm history (Section 6.2.1).

- Review historical diagnostic tests including ECGs and echocardiograms (Section 6.2.1).
- Collect vital signs, including height and weight (Section 6.2.2).
- Record concomitant medications including all medications taken within 4 weeks of the Screening Visit (Sections 5.8 and 6.2.14).

- Collect laboratory samples for $B_1$389 AR genotype (Section 6.2.9).
- Collect laboratory samples for chemistry and hematology, as well as serum pregnancy if applicable (Section 6.2.8).
- Complete the Screening Module in IVRS/IWRS.
- Complete applicable electronic case report forms (eCRFs).

A 12-lead ECG is not required at the Screening Visit; however, if one is collected during this visit the results should be entered into the Screening ECG eCRF (Section 6.2.4).

Patients who meet all entry criteria will return to the clinic within 8 weeks of screening for the Randomization Visit.

6.1.1.2 Randomization Visit

At the Randomization Visit the following procedures will be done as per Appendix 4:

- Procedures to be performed prior to collection of laboratory samples:
  - Review inclusion/exclusion criteria (Section 4.2).
  - Assess vital signs and weight (Section 6.2.2).
  - Perform physical exam (Section 6.2.1).
  - Assess NYHA class (Section 6.2.7).
  - Administer EQ-5D questionnaire (Section 6.2.13).
  - Administer the AFSQ prior to determination of the patient's current rhythm (Section 6.2.6).
  - Perform 12-lead ECG (Section 6.2.4).
  - Assess for clinical events (Section 6.2.12).
  - Record all reported AEs (Section 7.0).
  - Record all concomitant medications (Sections 5.8 and 6.2.14).
- Collect central laboratory samples for NT-proBNP and plasma norepinephrine (Section 6.2.8).
- Collect central laboratory samples for α_2c AR and CYP2D6 genotype (Section 6.2.8).
- Collect central laboratory samples for DNA Bank, if patient has consented (Section 6.2.10).
- Perform urine pregnancy test, if applicable (Section 6.2.8).
- Record coagulation status if patient is receiving warfarin (Section 6.2.8).
- Complete Randomization Worksheet:

- If patient meets all entry criteria, access IVRS/IWRS to randomize and receive initial study drug assignment.
- Dispense study drug and administer the first dose to the patient (Section 5.5).
- If patient fails to meet all entry criteria, access IVRS/IWRS to register screen failure.

- Complete applicable eCRFs and update Master Drug Log and Patient Drug Accountability Log.
- Schedule the Week 0 Visit and ECV if applicable.

Patients participating in the optional AFB substudy who require implant of a Medtronic REVEAL device may do so at the Randomization Visit or at any time prior to the start of the 24-week Follow-up Period (Section 6.2.5).

6.1.2 Drug Lead-In Period

During the Drug Lead-in Period (i.e., after randomization at the Randomization Visit and prior to the start of the 24-week Follow-up Period at the Week 0 Visit), patients will have their study drug dose up-titrated. Investigators should make every reasonable attempt to up-titrate study drug on a weekly schedule, but can delay up-titration if required clinically (i.e., up-titration at a two week interval).

As starting doses and titration schedules will vary for individual patients, the up-titration of study drug will be managed via unscheduled visits during the Drug Lead-in Period to provide flexibility for optimal patient management. After the Week 0 Visit, Investigators may continue to up-titrate study drug via scheduled and unscheduled clinic visits to achieve maximum tolerated dose of study drug.

6.1.2.1 Drug Titration Visits

During any unscheduled visit for drug titration, the following procedures will be performed:

- Collect used/unused drug dispensed at prior visit and assess accountability.
- Access IVRS/IWRS Unscheduled Visit Module to obtain next study drug assignment.
- Complete Master Drug Log, Patient Accountability Drug Log, and eCRF Drug Log.

No additional assessments are required at these titration visits; however, if any procedures and/or safety evaluations are performed, they will be entered on an unscheduled visit eCRF.

6.1.3 Start of 24-Week Follow-up Period (Week 0 Visit)

The primary endpoint and multiple secondary and tertiary endpoints will be assessed from the start of the 24-week Follow-up Period (i.e., Week 0 Visit) and all subsequent study visits will be relative to this time point (Appendix 4). The 24-week Follow-up Period will begin on the day of: 1) the ECG that establishes stable SR; 2) the last ECV attempt for patients who fail to convert to stable SR, or; 3) the Week 0 Visit, for patients in AF/AFL who do not undergo ECV for any reason.

If a patient is in AF/AFL after 3 weeks of study drug treatment, they will undergo ECV to establish stable SR (Section 6.1.3.2). ECV may also be performed as early as 1 week after randomization if all of the following conditions are met: 1) the patient is receiving the target dose of study drug; 2) the patient is receiving guideline indicated oral anticoagulation therapy for stroke prevention and; 3) a delay of ECV could be detrimental to patient outcome. The first ECV attempt may also be performed as late as 8 weeks after randomization if, in the opinion of the Investigator, additional time is needed to attain target doses of study drug or to achieve appropriate anticoagulation status prior to ECV. Conversion to stable SR will be confirmed at least 1 hour after ECV by ECG. Patients who do not establish stable SR post-ECV will undergo a second ECV procedure to establish stable SR unless, in the opinion of the Investigator, it would not be the best course of treatment for the patient. No more than two ECV attempts are permitted per protocol prior to the start of the 24-week Follow-up Period. If a patient does not establish stable SR after the second ECV attempt, the patient is considered an 'ECV failure' and will enter the 24-week Follow-up Period.

If a patient who was in AF/AFL at randomization undergoes spontaneous conversion to stable SR prior to the protocol-specified ECV procedure, then all procedures and assessments required for the Week 0 Visit (except ECV) must be performed at that time (Section 6.1.3.1).

If a patient who was in SR at randomization is in AF/AFL following 3 weeks (± 3 days) of study drug treatment, then the patient will undergo ECV to establish stable SR on study drug (Section 6.1.3.2). For patients in SR at randomization, it is recommended that ECV be scheduled at the time of study drug initiation to allow the patient to undergo ECV 3 weeks (± 3 days) after randomization (without reschedule) if they have reverted from SR to AF/AFL.

If a patient who was in SR at randomization is in stable SR following 3 weeks (± 3 days) of study drug treatment, then all procedures and assessments required for the Week 0 Visit (except ECV) must be performed at that time (Section 6.1.3.1).

6.1.3.1 Patients in Stable SR Who Do Not Require ECV

Unless noted otherwise, all of the following procedures will be performed as per the Week 0 Visit in Appendix 4 for: 1) patients in AF/AFL at randomization who spontaneously (medically) convert to stable SR prior to ECV, and; 2) patients in SR at randomization who are in stable SR after 3 weeks (± 3 days) of study drug treatment.

- Administer the AFSQ prior to determination of the patient's current rhythm (Section 6.2.6).
- Perform a 12-lead ECG to determine rhythm (Section 6.2.4).
- Do NOT perform the ECV procedure (patient is in SR).
- Perform a 12-lead ECG at least 1 hour after the first ECG to confirm rhythm (Section 6.2.4).

- Assess vital signs and weight (Section 6.2.2).
- Assess for clinical events (Section 6.2.12).
- Record all reported AEs (Section 7.0).
- Record concomitant medications, including all changes and additions (Sections 5.8 and 6.2.14).
- Record coagulation status if patient is receiving warfarin (Section 6.2.8).
- Collect used/unused drug dispensed at prior visit and assess accountability (Section 6.2.15).
- Access IVRS/IWRS to register the Week 0 Visit (i.e., start of follow-up, use the date of the first ECG) and obtain next study drug assignment, if needed.
- Update Master Drug Log and Patient Drug Accountability Log.
- Enter data from this visit into the eCRF as the Week 0 Visit.
- Schedule the Week 2 Visit.
- ***For patients who spontaneously convert from AF to SR prior to ECV.***
    - Instruct the patient to return to the clinic within 48 hours of spontaneous conversion to SR to obtain a trough blood sample for Population PK analysis. On the day of this visit, the patient should be instructed to withhold their morning dose of study drug. After the sample has been obtained the patient should be administered the next dose of study drug (Section 6.2.11).

6.1.3.2 Patients in AF/AFL Who Require ECV

Unless noted otherwise, all of the following procedures will be performed as per the Week 0 Visit in Appendix 4 for: 1) patients in AF/AFL at randomization who do not spontaneously convert to SR and require ECV to establish stable SR, and; 2) patients in SR at randomization who are in AF/AFL after 3 weeks (± 3 days) of study drug treatment and require ECV to establish stable SR.

- Administer the AFSQ prior to determination of the patient's current rhythm (Section 6.2.6).
- Perform a 12-lead ECG to determine rhythm (Section 6.2.4).
- Assess vital signs and weight (Section 6.2.2).
- Assess for clinical events (Section 6.2.12).
- Record all reported AEs (Section 7.0).
- Record concomitant medications, including all changes and additions (Sections 5.8 and 6.2.14).
- Record coagulation status if patient is receiving warfarin (Section 6.2.8).
- Collect used/unused drug dispensed at prior visit and assess accountability (Section 6.2.15).
- Perform the ECV procedure per standard of care (Section 6.2.3).
- Perform a 12-lead ECG at least 1 hour after ECV to confirm rhythm (Section 6.2.4).
    - ***If the patient is in SR at least 1 hour after ECV:***
        - Schedule a time to call the patient the following day to collect the AFSQ.

- Access IVRS/IWRS to register the Week 0 Visit (i.e., start of follow-up) and obtain next study drug assignment, if needed.
- Update Master Drug Log and Patient Drug Accountability Log.
- Schedule the Week 2 Visit.
- The next day, contact the patient and administer the AFSQ (Section 6.2.6).
- Enter data from this visit into the eCRF as the Week 0 Visit.

- ***If the patient is in AF/AFL following ECV and an additional ECV attempt is clinically appropriate and permitted per protocol:***
  - If needed, access IVRS/IWRS Unscheduled Visit Module to obtain next study drug assignment.
  - Update Master Drug Log and Patient Drug Accountability Log.
  - Enter all data from this visit into the eCRF as an Unscheduled Visit.
  - Schedule the next ECV procedure, which should be performed within 2 weeks of the initial ECV attempt. Note: only two ECV attempts are permitted per protocol prior to the start of follow-up.
- ***If the patient is in AF/AFL following ECV and an additional ECV attempt is <u>NOT</u> clinically appropriate or permitted per protocol (i.e., ECV failure):***
  - Access IVRS/IWRS to register the Week 0 Visit (i.e., start of follow-up) and obtain next study drug assignment, if needed.
  - Update Master Drug Log and Patient Drug Accountability Log.
  - Enter data from this visit into the eCRF as the Week 0 Visit.
  - Schedule the Week 2 Visit.

6.1.4 24-week Follow-Up Period

During the 24-week Follow-up Period, patients will return to the clinic at scheduled intervals for routine assessments of safety and efficacy. During these visits, heart rhythm will be assessed by 12-lead ECG and the patient will be queried for symptoms potentially related to AF/AFL. Scheduled telephone contacts will occur at Week 6, Week 10, Week 14, Week 18 and Week 22. Patients will be also be instructed to contact the site immediately if they experience new or worsening symptoms. Patients will be queried for symptoms potentially related to AF/AFL during the scheduled and patient-initiated telephone contacts (Section 6.2.6). If the Investigator suspects that a new AF/AFL event has occurred between scheduled clinic visits (i.e., a change in rhythm from SR to AF/AFL), the patient will be instructed to return to the clinic within 3 business days for further assessments (Section 6.1.4.2).

6.1.4.1 Clinic Visits during the 24-week Follow-up Period

The following procedures will be performed at all clinic visits, unless otherwise noted, as per Appendix 4:

- Assess vital signs and weight (Section 6.2.2).
- Administer the AFSQ prior to determination of the patient's current rhythm (Section 6.2.6).
- Perform 12-lead ECG (Section 6.2.4).
- *Week 12 and Week 24 only:* Perform Medtronic device interrogation if patient is participating in AFB substudy (Section 6.2.5.3).
- *Week 12 and Week 24 only:* Assess NYHA class (Section 6.2.7).
- Assess for clinical events (Section 6.2.12).
- *Week 12 and Week 24 only:* Administer EQ-5D questionnaire (Section 6.2.13).
- *Week 4, Week 12, and Week 24 only:* Collect central laboratory samples for chemistry, hematology, NT-proBNP and plasma norepinephrine (Section 6.2.8).
- *Week 4 and Week 12 only:* Collect central laboratory samples for Population PK analysis (Section 6.2.11). Patients must be reminded via a documented telephone contact 24 - 72 hours in advance of these visits to withhold their morning dose of study drug until a pre-dose (trough) sample for Population PK analysis has been collected at the clinic.
- Record coagulation status if patient is receiving warfarin (Section 6.2.8).
- Record all reported AEs (Section 7.0).
- Record concomitant medications, including all changes and additions (Sections 5.8 and 6.2.14).
- *Not required at Week 2:* Collect used/unused drug dispensed at prior visit and assess accountability (Section 6.2.15).
- *Not required at Week 2:* Access IVRS/IWRS to register visit and obtain next study drug assignment.
- *Weeks 4, 8, 12, 16, and 20:* Schedule the next telephone contact (Section 6.1.4.2).
- Schedule the next Clinic Visit (i.e., Week 4, Week 8, etc.).
- Complete applicable eCRFs and update Master Drug Log and Patient Drug Accountability Log.

6.1.4.2 Telephone Contact during the 24-week Follow-up Period

Scheduled telephone contacts will occur at Week 6, Week 10, Week 14, Week 18 and Week 22. Patients will be also be instructed to contact the site immediately if they experience new or worsening symptoms. Patients will be queried for symptoms potentially related to AF/AFL during the scheduled and patient-initiated telephone contacts. Telephone contacts will continue through the 24-week Follow-up Period regardless of heart rhythm status, (i.e., even if the patient has subsequently reverted to AF/AFL). No telephone contact is required for patients who did not established stable SR at the start of follow-up (i.e.,

ECV failures) and no telephone contact is required for any patients during the Treatment Extension Period.

The following procedures will be performed at telephone contacts required during the 24-week Follow-up Period.

- Contact the patient and administer the AFSQ (Section 6.2.6).
- If the Investigator suspects that a new AF/AFL event has occurred between scheduled clinic visits (i.e., a change in rhythm from SR to AF/AFL), the patient will be instructed to return to the clinic within 3 business days for an unscheduled visit to administer the AFSQ and perform a 12-lead ECG. Additional assessments performed during this visit should also be documented in the eCRF.

6.1.5 Treatment Extension Period and End of Study

After the Week 24 Visit, patients will enter the Treatment Extension Period and continue to receive blinded study drug. During the Treatment Extension Period, patients will return to the clinic every 12 weeks for routine assessments of efficacy and safety (Appendix 4).

Phase 3 follow-up, which is inclusive of patients enrolled during Phase 2B, will continue until a total of at least 330 primary endpoint events have been observed. After this event, all patients will complete the 24-week Follow-up Period or return to the clinic for an EOS Visit if already in the Treatment Extension Period. At the EOS Visit, patients will return all remaining study drug and should transition to commercially-available β-blocker therapy per Investigator discretion. Transition to commercial β-blocker therapy is recommended to occur in a similar manner as described for initiation of blinded β-blocker therapy. If commercial β-blocker therapy is not being considered at the end of the study, then transition off study drug will require down-titration over several weeks. This will be accomplished via unscheduled visits prior to the EOS Visit.

Investigators and patients will not be informed of the blinded study drug assignment at the time of study completion.

6.1.5.1 Treatment Extension Visits

At the Treatment Extension Visits, the following procedures will be performed as per Appendix 4:

- Assess vital signs and weight (Section 6.2.2).
- Assess NYHA class (Section 6.2.7).
- Assess for clinical events (Section 6.2.12).
- Record all reported AEs (Section 7.0).
- Administer the AFSQ prior to determination of the patient's current rhythm (Section 6.2.6).
- Perform 12-lead ECG (Section 6.2.4).

- Perform Medtronic device interrogation if patient is participating in the AFB substudy (Section 6.2.5.3).
- Collect central laboratory samples for chemistry and hematology (Section 6.2.8).
- Record coagulation status if patient is receiving warfarin (Section 6.2.8).
- Record concomitant medications, including all changes and additions (Sections 5.8 and 6.2.14).
- Collect used/unused drug dispensed at prior visit and assess accountability (Section 6.2.15).
- Access IVRS/IWRS to register visit and obtain next study drug assignment.
- Complete applicable eCRFs and update Master Drug Log and Patient Drug Accountability Log.
- Schedule the next clinic visit.

6.1.5.2 End of Study Visit

At the EOS Visit, the following procedures will be performed as per Appendix 4:

- Assess vital signs and weight (Section 6.2.2).
- Assess NYHA class (Section 6.2.7).
- Assess for clinical events (Section 6.2.12).
- Record all reported AEs (Section 7.0).
- Administer the AFSQ prior to determination of the patient's current rhythm (Section 6.2.6).
- Perform 12-lead ECG (Section 6.2.4).
- Perform Medtronic device interrogation if patient is participating in the AFB substudy (Section 6.2.5.3).
- Collect central laboratory samples for chemistry and hematology (Section 6.2.8).
- Record coagulation status if patient is receiving warfarin (Section 6.2.8).
- Record concomitant medications, including all changes and additions (Sections 5.8 and 6.2.14).
- Collect used/unused drug dispensed at prior visit and assess accountability (Section 6.2.15).
- Prescribe commercial β-blocker therapy as clinically indicated.
- Access IVRS/IWRS to register End of Study.
- Contact patient by telephone 72 hours (± 24 hours) following study discontinuation to check health status, record AEs and concomitant medications.
- Complete applicable eCRFs and update Master Drug Log and Patient Drug Accountability Log.

6.1.6 Premature Discontinuation of Study Drug

The Investigator has the right to discontinue a patient from study drug at any time. In addition, patients have the right to voluntarily discontinue study drug at any time for any reason. Reasons for discontinuation of study drug may include, but are not limited to, the following:

- Patient withdrawal of consent at any time.
- Any medical condition that the Investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study.
- Investigator or Sponsor determines it is in the best interest of the patient.
- Patient noncompliance, such as missing scheduled visits, non-adherence with concomitant medications, etc.
- Discontinuation of the study at the request of the Sponsor, a regulatory agency, or an IRB/IEC.
- Lost to follow-up.

If possible, the patient should return to the clinic for an end of treatment (EOT) Visit prior to discontinuation of study drug and complete all assessments (Appendix 4). After study drug is discontinued, the patient should remain in the study whenever possible and complete all study visits according to the planned schedule of assessments (except for patients who have withdrawn consent). The primary reason for premature discontinuation of study drug should be documented on the appropriate eCRF.

If a patient chooses to discontinue study drug and withdraw from the study, then the patient should return to the clinic for an EOS Visit (Section 6.1.5.2).

Patients who prematurely discontinue study drug will not be replaced.

6.1.6.1 End of Treatment Visit

At the EOT Visit, the following procedures will be performed as per Appendix 4:

- Assess vital signs and weight (Section 6.2.2).
- Assess NYHA class (Section 6.2.7).
- Assess for clinical events (Section 6.2.12).
- Record all reported AEs (Section 7.0).
- Administer the AFSQ prior to determination of the patient's current rhythm (Section 6.2.6).
- Perform 12-lead ECG (Section 6.2.4).
- Perform Medtronic device interrogation if patient is participating in the AFB substudy (Section 6.2.5.3).
- Collect central laboratory samples for chemistry and hematology (Section 6.2.8).
- If possible, a trough blood sample for Population PK analysis (Section 6.2.11) should also be obtained prior to discontinuation of study drug for any patient who experiences a SAE leading to permanent discontinuation of study drug.
- Record coagulation status if patient is receiving warfarin (Section 6.2.8).

- Record concomitant medications, including all changes and additions (Sections 5.8 and 6.2.14).
- Collect used/unused drug dispensed at prior visit and assess accountability (Section 6.2.15).
- Initiate commercial β-blocker therapy as clinically indicated.
- Access IVRS/IWRS to register End of Treatment.
- Contract patient by telephone 72 hours (± 24 hours) following study discontinuation to check health status, record AEs and concomitant medications.
- Complete applicable eCRFs and update Master Drug Log and Patient Drug Accountability Log.

6.1.7 Premature Study Withdrawal

All patients have the right to withdraw from study participation without prejudice at any time during the study. If a patient terminates participation in the study, the Investigator should make a reasonable effort to determine the cause for study withdrawal. If, for whatever reason, a patient withdraws from the study or the study is terminated while the patient is receiving study drug, an EOS Visit should be performed (Section 6.1.5.2).

Patients who withdraw from the study must be contacted by telephone 72 hours (± 24 hours) following study drug discontinuation to check on their health status, and this telephone contact must be documented in the eCRFs. If the patient has experienced any AEs or changes to medications, all pertinent information must be collected and recorded on the appropriate eCRF(s).

Patients who withdraw from the study will be asked to sign a separate consent form to allow telephone contacts by the site for the periodic assessment of vital status.

Patients who prematurely withdraw from study participation will not be replaced.

6.1.8 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.

The Sponsor will notify the Investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment.
- Poor protocol adherence.
- Inaccurate or incomplete data recording.
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice.

6.2 Description of Study Procedures

6.2.1 Medical History, Diagnostic Test History, and Physical Exam

All ongoing conditions and relevant/significant medical history from the past five years (including all major hospitalizations and surgeries) will be recorded. Any neoplastic conditions, irrespective of the time of diagnosis, should be noted. Symptoms related to AF, HF, and/or the underlying etiology of either condition should be listed on the arrhythmia and heart failure history form.

Historical diagnostic tests, such as ECGs and echocardiograms, will be reviewed to ensure that all of the inclusion and none of the exclusion criteria are met. The historical determination of LVEF for study inclusion can be based on echocardiogram, cardiac catheterization, radionuclide, angiography, or MRI studies and must have been performed within 12 months prior to the Screening Visit. If the historical determination of LVEF has not been assessed within 12 months of screening, it can be re-assessed during the Screening Period per standard of care.

A physical exam of the major body systems will be conducted at the Randomization Visit. Patient vital signs and weight will also be assessed during the physical exam.

6.2.2 Vital Signs, Height and Weight

Vital signs (including sitting blood pressure, heart rate, and respiratory rate) and weight will be collected throughout the study. Height will be collected once at the Screening Visit. One measurement of blood pressure and heart rate after the patient has been sitting quietly for at least 5 minutes should be taken. This same procedure should be followed throughout the study.

Vital Signs must be assessed prior to, or at least one hour after, a blood draw. All measures of blood pressure will be performed using standard sphygmomanometry. If possible, the same sphygmomanometer and arm should be used.

6.2.3 Electrical Cardioversion

Patients in AF/AFL at randomization who are in AF/AFL after 3 weeks of treatment with study drug will undergo direct current ECV to establish stable SR per standard of care according to standard clinical practice.[4] Cardioversion via ICD or a comparable implanted device cannot substitute for direct current

ECV. Patients in SR at randomization who are in AF/AFL after 3 weeks of study drug treatment will also undergo ECV to establish stable SR. Patients in AF/AFL at randomization who spontaneously convert to stable SR and patients in SR at randomization who are in SR after 3 weeks (± 3 days) of study drug treatment will not undergo ECV (Section 6.1.3.1).

ECV may be performed as early as 1 week after randomization if all of the following conditions are met: 1) the patient is receiving the target dose of study drug; 2) the patient is receiving guideline indicated oral anticoagulation therapy for stroke prevention, and; 3) a delay of ECV could be detrimental to patient outcome. The first ECV attempt may also be performed as late as 8 weeks after randomization if, in the opinion of the Investigator, additional time is needed to attain target doses of study drug or to achieve appropriate anticoagulation status prior to ECV.

A 12-lead ECG will be performed prior to ECV and at least 1 hour post-ECV to determine if SR has been achieved. If the Investigator assessment of the post-ECV ECG indicates that the patient has achieved SR, the patient will complete the Week 0 Visit and will be contacted the following day to be assessed for potential AF/AFL symptoms via the AFSQ (Section 6.2.6).

Patients who do not demonstrate SR at the post-ECV time point will undergo a subsequent ECV to establish a baseline SR unless, in the opinion of the Investigator, it would not be the best course of treatment for the patient. Secondary ECV procedures should be performed within 2 weeks of the initial ECV attempt. Patients who fail to convert to SR following a second ECV attempt will be considered ECV failures and will be included in the endpoint calculation as experiencing the event on Day 1 of follow-up (Section 8.3).

Patients who revert to AF/AFL after the start the 24-week Follow-up Period may undergo additional ECV procedures or medical interventions as clinically indicated; however, the schedule for the 24-week Follow-up Period will not be restarted.

6.2.4 Electrocardiogram

At clinic visits, patients will be queried *prior* to ECG assessment to determine if they have experienced any symptoms since their last clinic visit that could potentially be related to AF/AFL (Section 6.2.6).

AF will be assessed at scheduled clinic visits via a 12-lead ECG (Appendix 4). To minimize variability, it is important that patients be in a resting position for several minutes prior to ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. ECGs should be performed prior to meals and any scheduled vital sign measurements or blood draws.

ECGs will be labeled with the following: patient number, patient initials, protocol number, and date recorded. In addition, the Investigator is required to sign and date the ECG after they have reviewed and assessed the data.

During the follow-up period, if a 12-lead ECG indicates a change in rhythm from SR to AF/AFL, the patient should remain in the resting position and a second rhythm assessment must be collected at least 10 minutes after the initial read. If AF/AFL is confirmed with the second read, this will be considered an AF/AFL event.

A 12-lead ECG is not required at the Screening Visit; however, if one is collected during this visit the results should be entered into the Screening ECG eCRF. Two ECGs are required at the Week 0 Visit. For patients in SR who do not require ECV, these two ECGs must be performed at least 1 hour apart to establish stable SR and the start of the 24-week Follow-up Period. For patients in AF/AFL who require ECV, one ECG will be performed before ECV and one ECG will be performed at least 1 hour after ECV to establish stable SR and the start of the 24-week Follow-up Period.

In addition to all scheduled ECGs, if the Investigator becomes aware of any non-protocol specified ECGs or other rhythm assessments that indicate a change in rhythm during the 24-week Follow-up Period, these must also be documented in the eCRF and may be requested for potential adjudication by the CEC.

Any clinically relevant findings, as assessed by the Investigator, will be captured in the eCRFs. Potential AF/AFL events will be adjudicated by a blinded Clinical Events Committee (CEC) until the primary endpoint has been met.

Patients experiencing recurrence of AF/AFL will be encouraged to remain on blinded study drug and continue their participation in the study. These patients may undergo subsequent ECV procedures or other medical interventions, as clinically indicated. If this occurs, the patient should still complete all remaining assessments as described in Appendix 4.

6.2.5 Medtronic Device Procedures

6.2.5.1 Implantation of Medtronic Device

Patients who agree to have a Medtronic device inserted may do so at the Randomization Visit or at any time prior to the start of the 24-week Follow-up Period. Implantation of the Medtronic ICM must be performed in accordance with the hospital's standard implant practice and in accordance with the Medtronic Reveal ICM implant instructions. After the Reveal ICM device is implanted, the surgical team should perform diagnostic testing specific to R-wave sensing to ensure that the Reveal ICM device is accurately identifying R-waves and calculating heart rate from R-R intervals per standard implant recommendations. The programmer ECG trace with marker annotations is used to evaluate R-wave

sensing and adjust gain as necessary to prevent under- or over-sensing. Ideally, this should be done at the time of implantation, and then repeated post-operatively prior to discharge from the hospital.

The following information will be collected at the time of implant:

- Reveal ICM device serial number.
- Device interrogation and data transfer (e.g. save-to-disk, USB data transfer).

6.2.5.2 Programming Requirements

The Reveal ICM device is to be programmed according to Table 7. Reprogramming of the parameters that are "OFF" may be done only if needed for clinical reasons. However, they should be reprogrammed again back to the initial settings as soon as clinically feasible and a protocol deviation should be reported.

Table 7: ICM Device Programming Requirements

Parameter	Required Setting	
	REVEAL-XT	REVEAL-LINQ
Type of AT/AF detection	AF only	AF only
AF Detection	Balanced sensitivity	Balanced sensitivity
AT/AF Record ECG of/Recording Threshold	≥ 60 minutes	≥ 60 minutes
Ectopy Rejection	ON	Nominal
FVT Detection	OFF	Tachy Detection OFF
FVT ECG recording	OFF	
VT Detection	OFF	
VT ECG recording	OFF	
Brady Detection	OFF	Brady Detection OFF
Brady ECG recording	OFF	
Asystole Detection	OFF	Pause Detection OFF
Asystole ECG recording	OFF	
AT/AF Detection	AF Only	AF Only

For patients who have a pre-existing or newly implanted Medtronic pacemaker (IPG), ICD, or CRT device, Table 8 outlines the recommended programming for these devices. The other parameters for these devices are to be programmed based on the Investigator's opinion.

Table 8: Programming Parameters for Medtronic IPG, ICD or CRT devices

Parameter	Recommended Setting
Atrial preference pacing (APP)	OFF
Atrial rate stabilization (ARS)	OFF
Post-mode switch overdrive pacing (PMOP)	OFF
Atrial Anti-tachycardia pacing (ATP)	OFF
AT/AF detection and EGM collection	Nominal

6.2.5.3 Device Data Interrogations

Some Medtronic devices can be interrogated by the patient and uploaded directly to the CareLink Network. However, to ensure consistent data collection, all patients participating in the AF burden substudy will have their devices interrogated at specific clinic visits (Appendix 4) via the Medtronic Carelink Programmer and the data will be electronically sent to Medtronic.

AFB data cannot substitute for ECG assessments required to define an AF/AFL event; however, these data may be considered by the CEC as supplemental information to adjudicate individual events.

6.2.5.4 Device System Modification

A system modification will be reported in the event that the Reveal ICM device requires invasive modification, i.e., the implanted monitor is repositioned, replaced or explanted. If the Reveal ICM is explanted and a Medtronic pacemaker (IPG), ICD, or CRT device is implanted the patient can continue participation in this study. For a system modification the following activities are required:

- Pre-modification: device interrogation with download.
- Post-modification: device interrogation with download (if the modification involved only repositioning or explant with replacement).

6.2.6 AF Symptoms Questionnaire

The AFSQ is attached as Appendix 6 and will be administered by the site to the patient prior to each ECG assessment (Appendix 4). At the time of ECV (if needed), the AFSQ will be administered prior to the pre-ECV ECG assessment and a second AFSQ will be administered the following day for those patients achieving stable SR post-ECV. For patients in SR who do not require ECV at this visit, the AFSQ collected prior to the Week 0 ECG must be recorded but a second AFSQ the following day is not required.

Scheduled telephone contacts will occur at Week 6, Week 10, Week 14, Week 18 and Week 22. Patients will be also be instructed to contact the site immediately if they experience new or worsening symptoms.

Patients will be queried via the AFSQ for symptoms potentially related to AF/AFL during the scheduled and patient-initiated telephone contacts (Section 6.1.4.2). If the Investigator suspects that a new AF/AFL event has occurred between scheduled clinic visits (i.e., a change in rhythm from SR to AF/AFL), the patient will be instructed to return to the clinic within 3 business days for further assessments (Section 6.1.4.2).

6.2.7 NYHA Functional Class

The Investigator or designee will complete the NYHA functional class assessment at specific clinic visits (Appendix 4). Every effort should be made to have the same Investigator assess the patient at each study visit.

Table 9: New York Heart Association Functional Class

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
III	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

6.2.8 Clinical Laboratory Tests

A central laboratory will analyze the following protocol-specified laboratory tests collected at specific clinic visits (Appendix 4); collection, processing, labeling, and shipping of the samples will be completed following central laboratory guidelines.

Chemistry: The following chemistry tests are required: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, creatinine, blood urea nitrogen, bicarbonate, calcium, chloride, magnesium, sodium, phosphorous, potassium, total cholesterol, uric acid, glucose, total protein, and albumin.

Hematology: The following hematology tests are required: hemoglobin, hematocrit, complete blood count, red cell count, red cell indices, white blood cell count (total and differential) and platelet count.

Pregnancy: A serum pregnancy test will be required at the Screening Visit for all female patients of child-bearing potential. Bulk urine pregnancy tests will be included within the central laboratory supplies and will be performed at the site for all female patients of child-bearing potential at the Randomization Visit.

Biomarkers: The following biomarker tests are required: NT-proBNP, norepinephrine. Results of individual patient data for the NT-proBNP and norepinephrine will not be provided to sites to protect the treatment blind.

For patients receiving warfarin, coagulation status (i.e., INR) will be monitored per standard of care via local laboratories to ensure optimal anticoagulation therapy for stroke prevention (e.g., INR 2-3). Laboratory values and normal ranges from local laboratories will not be collected. However, coagulation status will be recorded categorically via INR ranges (e.g., < 1, ≥ 1 and < 2, ≥ 2 and < 3, ≥ 3 and < 4, ≥ 4) at specific clinic visits (Appendix 4).

6.2.9 Required Genetic Analyses ($\beta_1$389, α_{2C}, CYP2D6)

A blood sample to assess $\beta_1$389 AR genotype will be collected at the Screening Visit for all patients after written consent has been obtained. A central reference laboratory will analyze DNA from the $\beta_1$389 AR samples. Collection, processing, labeling, and shipping of the samples will be completed following central laboratory guidelines. $\beta_1$389 AR genotype results are expected 5-10 business days from the time of collection, and review of $\beta_1$389 AR genotype results is required prior to randomization. Only patients who have the $\beta_1$389Arg/Arg genotype will be eligible to be randomized and receive study drug.

A blood sample to assess other bucindolol-related genes will be collected at the Randomization Visit for all randomized patients. A central reference laboratory will analyze DNA from this sample for the following genes: α_{2C} AR and CYP2D6. Collection, processing, labeling, and shipping of the samples will be completed following central laboratory guidelines. Genotyping for α_{2C} AR and CYP2D6 is required for all randomized patients to explore the potential for polymorphisms in these genes to alter the effectiveness of bucindolol. However, as these data are not required to confirm study eligibility or patient management, they will not be provided to the Investigator.

Patients must consent to the required genetic analyses to participate in the trial. A duplicate sample may need to be collected at a later time if the original sample cannot be analyzed. Samples for the required genetic analyses will be coded in a manner which allows them to be matched to a study site and/or a patient number, but will *not* carry personal identifiers which could be traced to a specific individual. If DNA is extracted from the sample, the DNA may be subjected to sample quality control analysis. This analysis may involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are identified in the analysis, those samples may be destroyed.

Samples for the required genetic analyses may be kept by the Sponsor for up to 15 years after the last patient has completed study participation. However, if it is determined that a sample is not needed, the samples may be destroyed earlier.

If a patient withdraws from the study for any reason other than “lost to follow-up”, the patient will be given the following options regarding the required genetic analyses samples, if the sample has already been collected:

- The sample will be maintained per the patient's original consent.
- The patient's consent will be withdrawn and any remaining sample will be destroyed.

If a patient withdraws consent and requests sample destruction, the Investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by the Sponsor or its designee, and maintain documentation in the site study records. The Sponsor will only keep data that are collected or generated up to the point at which consent to use the sample is withdrawn by the patient.

6.2.10 Optional Genetic Analyses (DNA Bank)

Blood samples for future genetic analyses will be collected on a subset of patients who choose to participate in an optional DNA bank substudy. Patients may consent to participate in the clinical study and still decline participation in the optional DNA bank substudy. Patients will be asked to accept or decline participation in the DNA bank substudy at the time the ICF is reviewed and signed. Consent for participation in the DNA bank substudy must be obtained *in addition* to the patient's consent to participate in the clinical study and the patient may still withdraw consent for participation in the DNA bank substudy at any time without withdrawing consent for participation in the clinical study.

For patients who agree to participate in the DNA bank substudy, a sample for potential genetic analyses will be collected at the Randomization Visit for all randomized patients. Complete instructions regarding the processing, packaging, and shipping of samples will be provided in separate laboratory guidelines. A duplicate sample may need to be collected at a later time if the original sample cannot be analyzed. Samples for the DNA bank substudy will be coded in a manner which allows them to be matched to a study site and/or a patient number, but will *not* carry personal identifiers which could be traced to a specific individual. If DNA is extracted from the sample, the DNA may be subjected to sample quality control analysis. This analysis may involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are identified in the analysis, those samples may be destroyed.

Samples for the DNA bank substudy may be kept by the Sponsor for up to 15 years after the last patient has completed study participation. However, if it is determined that a sample is not needed, the samples may be destroyed earlier. In some cases, the samples may never be utilized, for example, if there are not an adequate number of samples to perform the analysis.

If a patient who has consented to participate in the genetic analysis withdraws from the study for any reason other than "lost to follow-up", the patient will be given the following options regarding the DNA bank substudy sample, if the sample has already been collected:

- The sample will be maintained per the patient's original consent.
- The patient's consent will be withdrawn and any remaining sample will be destroyed.

If a patient withdraws consent from the DNA bank substudy and/or requests sample destruction, the Investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by the Sponsor or its designee, and maintain documentation in the site study records. The Sponsor will only keep data that are collected or generated up to the point at which consent to use the sample is withdrawn by the patient. Withdrawal of consent from the DNA bank substudy does not affect consent to participate in the clinical study.

6.2.11 Population Pharmacokinetic Analysis

Pharmacokinetic (PK) samples will be collected at specific clinic visits to determine plasma concentrations of bucindolol hydrochloride and metoprolol succinate (Appendix 4). For patients who spontaneously convert to stable SR, an additional trough blood sample will be collected within 48 hours of spontaneous conversion to SR. If possible, a trough blood sample should also be obtained prior to discontinuation of study drug for any patient who experiences a SAE leading to permanent discontinuation of study drug.

Patients will be reminded via a documented telephone contact 24 - 72 hours in advance of these visits to withhold their morning dose of study drug until a pre-dose (trough) sample for Population PK analysis has been collected at the clinic. Patients will be queried to determine the approximate times of study drug dosing for the previous two doses and to determine if the patient missed any study drug doses during the previous two days. The trough blood sample will be collected and the time will be recorded. The patients will then receive the morning dose of study drug and will continue with the remainder of their clinical assessments.

A designated reference laboratory will analyze all PK samples. Collection, processing, labeling, and shipping of the samples will be completed following central laboratory guidelines.

6.2.12 Clinical Events Assessment

Patients will be queried at specific clinic visits (Appendix 4) to determine if any significant clinical events have occurred since their last clinic visit and these events will be recorded in the eCRF. Details of the event(s) will be recorded, including any AE/SAE that led to the event(s) and Investigator assessment of cause (e.g., CV/other, HF/ischemia/arrhythmia/stroke/other CV). Clinical events include cardiovascular events (e.g. CAD intervention, stroke, TIA, etc.) and intervention for rhythm events (e.g. catheter ablation, initiation of anti-arrhythmic therapy, implantation of a therapeutic device, etc.).

Vital status will also be determined at regular intervals (e.g., annually) for all patients, including those who have withdrawn from the study and have consented to routine telephone contact.

6.2.13 EQ-5D Questionnaire

The EQ-5D Questionnaire is provided in Appendix 5. A paper copy of the questionnaire will be completed by the patient at specific clinic visits (Appendix 4) and the responses will be recorded in the eCRF.

6.2.14 Concomitant Medications

At the Screening Visit, review all medications currently ongoing or that have been administered within 4 weeks of the Screening Visit. If a patient is receiving any prohibited concomitant medications (Section 5.8), determine if the patient can discontinue treatment prior to randomization to maintain study eligibility.

At each study visit, all medications will be reviewed and any changes will be documented in the source documents and captured on the appropriate eCRF. Document any changes in concomitant medication via a telephone call 72 hours following discontinuation of study and any changes in concomitant medication associated with SAEs identified within 30 days of last study drug dose or within 30 days of last study evaluation, whichever is longer.

6.2.15 Study Drug Compliance

Patients should be instructed to bring their used and unused study drug containers with them to every visit to assess compliance and drug accountability. At each clinic visit the patient will be reminded of the importance of taking the study medication exactly as prescribed. The study drug will be supplied in packaging containing adequate study medication to last until the next clinic visit. Capsule counts will be made, with or without the patient's knowledge (at discretion of study personnel), as a means of assessing patient compliance. Site staff should calculate and review compliance, and counsel the patient if compliance issues are observed.

6.3 Protocol Deviations

This study will be conducted as described in this protocol except for emergency situations in which the protection, safety, and well-being of the patient requires immediate intervention based upon the judgment of the Investigator (or a responsible, appropriately trained and credentialed professional(s) designated by the Investigator). In the event of any deviation from the protocol, the Investigator or a specified designee must notify the Sponsor and/or specified designee. This will allow an early joint decision to be made as to whether or not the patient should continue in the study. Both the Investigator and Sponsor or specified designee will document this decision.

7.0 ASSESSMENTS OF SAFETY

7.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product (or medical device), and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE. All AEs will be recorded after the patient signs informed consent and throughout the study, regardless of study drug administration.

AEs may also include, but are not limited to, the following:

- Pre- or post-treatment complications that occur as a result of a protocol-associated procedure (e.g., invasive procedures such as venipuncture or biopsy) during or after screening (before the administration of study drug).
- Sequelae of overdose or drug abuse/misuse.
- Any pre-existing condition that increases in severity or changes in nature during or as a consequence of the study drug phase of this clinical study.

An AE does not include the following:

- Arrhythmia and heart failure diagnoses, events, and interventions with an onset date before screening; these should be documented on the Arrhythmia and Heart Failure History eCRF.
- AF/AFL events (other than those resulting in death), as these are being assessed as study endpoints. This includes symptoms related to AF/AFL events, which will be collected via the AFSQ for the primary endpoint.
- Any medical condition or clinically significant laboratory abnormality with an onset date before screening that is not related to arrhythmia or heart failure; it is considered to be pre-existing and should be documented on the Medical History eCRF.
- Any medical condition or clinically significant laboratory abnormality present or detected before screening that does not worsen.
- Anticipated day-to-day fluctuations of pre-existing conditions that do not represent a clinically significant exacerbation or worsening.

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae (Section 7.7).

7.2 Assessment of Adverse Events

All AEs will be assessed by the Investigator and recorded on the AE eCRF. For each patient, the safety reporting period begins immediately following the signing of informed consent and continues until the end of study participation, regardless of study drug administration. See Section 7.3.2.3 for additional post-study reporting requirements.

An AE entry should indicate whether or not the AE was serious, the start date (AE onset), the stop date (date of AE resolution), whether or not the AE was related to study drug, or to a study procedure, the action taken with study drug due to the AE, the severity of the AE, and the outcome of the AE.

AEs already documented in the eCRF (i.e., at a previous assessment) and designated as "ongoing" should be reviewed at subsequent visits as necessary. Upon resolution, the date and time (if applicable) of resolution should be recorded in the eCRF. If an AE increases in frequency or severity during a study period, a new record of the event should be started.

AEs should be documented in terms of a medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the Investigator or reported by the patient at each study visit.

For AEs associated with laboratory abnormalities, the AE should be graded on the basis of the clinical severity in the context of the underlying conditions. Collection of changes in laboratory values as AEs should be restricted to those considered clinically significant by the Investigator that result in a change, interruption, or discontinuation of study drug; that are considered a SAE; or that require medical intervention or treatment. Laboratory values associated with clinical signs and symptoms should be reported as an AE based on the clinical signs and symptoms, not as the laboratory value.

7.2.1 Assessment of Causality

Every effort should be made by the Investigator to explain each AE and assess its relationship, if any, to study drug treatment. Causality should be assessed using the following categories:

- *Unrelated:* Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- *Possibly Related:* A direct cause and effect relationship between the study drug and adverse experience has not been demonstrated, but there is a reasonable possibility that the experience was caused by the study drug.
- *Probably Related:* A temporal relationship exists between the event onset and the administration of the study drug, and appears with some degree of certainty to be related based on the known therapeutic and pharmacological actions of the study drug. It cannot be readily explained by the patient's clinical state or concomitant therapies. In the case of cessation or reduction of the dose, the event abates or resolves.

The degree of certainty with which an AE is attributed to study drug treatment (or alternative causes, e.g., natural history of the underlying disease, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

- Temporal relationship of event onset to the initiation of study drug.
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable).
- Known association of the event with the study drug or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

7.2.2 Assessment of Intensity

Adverse events will be graded and reported as indicated on the eCRF. Maximum intensity should be assigned to one of the following categories:

- *Mild:* Discomfort noticed, but no disruption of normal daily activity.
- *Moderate:* Discomfort sufficient to reduce or affect normal daily activity.
- *Severe:* Incapacitating with inability to work or to perform normal daily activity.

7.3 Serious Adverse Events

7.3.1 Definition of Serious Adverse Events

A serious adverse event (SAE) is any AE that meets any of the following criteria:

- Fatal (i.e., the AE actually causes or leads to death).

- Life-threatening (i.e., the AE, in the view of the Investigator, places the patient at immediate risk of death). This does not include any AE that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization.
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.
- Significant medical event in the Investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE, rated as mild, moderate, or severe (Section 7.2.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

SAEs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

7.3.2 Serious Adverse Event Reporting Requirements

7.3.2.1 Standard Reporting Requirements

The Sponsor, or the Contract Research Organization (CRO) on the behalf of the Sponsor, must be notified immediately regarding the occurrence of any SAE that occurs after the patient signs informed consent and throughout the study, regardless of study drug administration, including SAEs resulting from protocol-associated procedures, as defined in relevant legislation. The procedures for reporting all SAEs, regardless of causal relationship, are as follows:

- Record the SAE on the AE eCRF and complete the "Serious Adverse Event Report" form within the electronic database.
- In the event the electronic database is not functional, a paper SAE form will be available for the reporting of SAEs.

The Sponsor may request additional information from the Investigator to ensure the timely completion of accurate safety reports.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications and/or procedures or interventions necessary for treatment of the SAE must be recorded in

the event description section of the online SAE event form as well as in the CONMED section of the patient's eCRF.

Follow-up of AEs/SAEs will continue through the last day on study and/or until the Investigator and/or the Sponsor determine that the patient's condition is stable. The Sponsor may request that certain AEs/SAEs be followed until resolution.

7.3.2.2 Expedited Reporting Requirements

The Sponsor will promptly evaluate all SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Bucindolol Investigator's Brochure
- Toprol-XL US Package Insert

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Certain events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting. These anticipated events include, but are not limited to, the following:

- Recurrence of AF/AFL (symptomatic or asymptomatic), hospitalizations or procedures related to AF/AFL recurrence, or subsequent AEs/SAEs related to AF/AFL recurrence.
- Worsening HF, hospitalizations or procedures related to worsening HF, or subsequent AEs/SAEs related to worsening HF.

The DSMB will monitor these anticipated events at regular intervals during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

7.3.2.3 Post-Study Reporting Requirements

Any SAEs, regardless of cause or relationship, occurring within 30 days of last study drug dose or within 30 days of last study evaluation, whichever is longer, must also be reported.

Investigators are not obligated to actively seek out SAEs beyond the follow-up period for patients. However, if the Investigator learns of an SAE occurring after the completion/termination visit he/she should promptly report the event to the Sponsor.

7.4 Device Related Safety Reporting Requirements

All Medtronic devices used in this study are market released. It is the responsibility of the Investigator to report all product complaints and malfunctions immediately via the regular channels for market approved products. Per FDA regulations, Device User Facilities are required to report Medical Device Reports (MDR) on market approved products (21 CFR 803, subpart C). A Device User Facility is defined as a hospital, an ambulatory surgical facility, a nursing home, an outpatient treatment facility, or an outpatient diagnostic facility which is not a physician's office.

The reporting of product complaints and malfunctions for market released devices is not part of the clinical study and should be done independent of any AE reporting requirements. However, any untoward medical occurrence (i.e., AEs) associated with a device-related procedure (e.g., hematoma following device insertion) should be reported as an AE for this study as described in Section 7.2.

7.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology) independent of the underlying medical condition that require medical or surgical intervention or lead to study drug interruption or discontinuation must be entered as an AE, as well as an SAE, if applicable.

In addition, laboratory or other abnormal assessments (e.g., ECG, X-rays, vital signs) that are associated with signs and/or symptoms must be entered as an AE or SAE if they meet the definition of an AE or SAE. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis should be recorded.

If the changes are mild and in the opinion of the Investigator not clinically significant, the Investigator should continue to carefully monitor the values. Local laboratory tests may be repeated, as clinically indicated, without prior approval by the Sponsor or specified designee.

7.6 Neoplasms

In the BEST study, a numerical imbalance in the incidence of neoplasms was observed at baseline in patients randomized to bucindolol compared to placebo. This imbalance was maintained during the trial with the addition of new treatment-emergent neoplasms. Although there is no known class effect or mechanism of action associated with this observation, the Sponsor will collect a detailed history of all historical and treatment-emergent neoplastic events as AEs of special interest.

The following events will be considered AEs of special interest for this study:

- Development of treatment-emergent neoplastic conditions.
- Progression or worsening of pre-study neoplastic conditions.
- Progression or worsening of treatment-emergent neoplastic conditions.

During the Screening Period, all pre-existing neoplastic conditions should be recorded as part of the medical history assessment. After randomization, record any changes in historical neoplastic conditions and describe any new neoplastic events that have occurred during the study as AEs. Neoplasm AEs of special interest should be entered into the AE eCRF within 7 days of identification. Supplemental information will also be recorded on a neoplasm specific eCRF for all neoplasm AEs. The eCRF will include, but is not limited to:

- History of pre-study neoplastic conditions (e.g., description, type, severity date of onset).
- Description of treatment-emergent neoplastic condition suitable for MedDRA coding.
- Type of treatment-emergent neoplastic condition (e.g., benign, pre-cancerous, malignant).
- Severity of treatment-emergent neoplastic condition (e.g., early [Stage 1 or 2], locally-advanced [Stage 3], metastatic [Stage 4]).
- Estimated date of onset of neoplastic condition and details of the diagnosis.
- Current status of disease (e.g., resolved, in remission, active/ongoing).

The DSMB will closely monitor neoplasm AEs during the study and an aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

7.7 Overdose

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the eCRF. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the AE eCRF.

An overdose will be considered a SAE only if any of the seriousness criteria are met. If the associated AE fulfills serious criteria, the event should be entered into the online database immediately (i.e., no more than 24 hours after learning of the event).

Any clinical sequelae in association with the overdose should be reported as an AE or SAE along with the overdose. Details of signs or symptoms, clinical management and outcome should be reported, if available.

7.8 Pregnancy

Bucindolol is considered a Pregnancy Category C investigational drug. Bucindolol has not been shown to be teratogenic, but other adverse effects (i.e., developmental delays) have been shown in rats when given at doses as low as 15 mg/kg/day, which is approximately 7 times the human dose.

Pregnancy information for bucindolol is based upon animal studies. Bucindolol hydrochloride did not affect reproduction or fertility in the rat or rabbit; when administered to rabbits during organogenesis it did not affect fetal viability or produce malformations. For more details see the Bucindolol Investigator's Brochure. There are no adequate and well-controlled studies in pregnant women. No pregnancies have been reported in any clinical study conducted with bucindolol.

Similarly, metoprolol tartrate (a drug similar to metoprolol succinate) has been shown to increase post-implantation loss and decrease neonatal survival in rats at doses up to 22 times, on a mg/m^2 basis, the daily dose of 200 mg in a 60-kg patient. Distribution studies in mice confirm exposure to the fetus when metoprolol tartrate is administered to pregnant animals. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies of metoprolol tartrate or metoprolol succinate in pregnant women.

Therefore, females of childbearing potential must have a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Randomization Visit to be eligible for the study. Females of childbearing potential must also agree to use a highly effective contraception for the duration of the trial and for at least 30 days following the last dose of study drug.

All women of childbearing potential should be instructed to notify the Investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study evaluation. While pregnancy in and of itself is not considered to be an SAE, all pregnancies must be reported on the paper Pregnancy Report Form to the CRO Safety Department within 24 hours of the Investigator's knowledge of the pregnancy. Any SAE associated with the pregnancy that occurs to the mother/fetus/child will be recorded on the SAE eCRF within 24 hours of becoming aware of the event (Section 7.3.1). Study drug must be discontinued immediately unless the pregnancy is terminated. Any premature terminations of pregnancy must be reported.

Whenever possible, a pregnancy should be followed by the study site to term, and the status of the mother and child should be reported to the CRO Safety Department after delivery.

7.8.1 Definition of Childbearing Potential and Post-Menopausal

All female patients are considered to be of childbearing potential unless they meet one of the following criteria:

- The patient has been postmenopausal for 12 or more months.
- The patient had a surgical bilateral oophorectomy (with or without hysterectomy) more than 6 weeks prior to randomization.
- The patient had a hysterectomy.

Female patients of reproductive or childbearing potential who are not willing to use a highly effective method of contraception for the duration of the study and for 30 days after the last dose of study drug will be excluded from study participation.

Examples of highly effective contraception include the following:

- Contraceptive pill or transdermal patch
- Single barrier plus spermicide
- Intrauterine device
- Implants for contraception
- Injections for contraception (with prolonged release)
- Hormonal vaginal device
- Sterilization, surgical tubal ligation
- Sole sexual partner consisting of surgically sterilized male partner with appropriate post-surgical documentation of the absence of spermatozoa in the ejaculate
- Same sex partner

8.0 STATISTICAL CONSIDERATIONS

A formal statistical analysis plan (SAP) for the combined Phase 2B/Phase 3 study will be finalized prior to the end of patient follow-up and unblinding of randomized treatment assignments.

8.1 Definitions of Analysis Populations and Endpoint Follow-up Periods

The efficacy analysis will follow the intent-to-treat (ITT) principle and all patients randomized to study treatment will be included regardless of the success of the titration process. As an additional sensitivity analysis, the efficacy endpoint testing will be performed on a protocol-compliant subpopulation. The safety analyses will include those patients which actually received at least one dose of blinded study treatment. The screened population includes any patient who signs informed consent for the study. The screen failure population is a subpopulation of the screened population who are not randomized to study drug for any reason.

Four follow-up periods will be defined for inclusion of each patient's results in endpoint calculations:

- *Drug Titration Period:* Starts on the day of randomized treatment initiation and extends for 6 weeks after randomization.
- *24-week Follow-up Period:* Starts on the day of: 1) the ECG that establishes stable SR; 2) the last ECV attempt for patients who fail to convert to stable SR, or; 3) the Week 0 Visit, for patients in AF/AFL who do not undergo ECV for any reason. Follow-up will be censored at Week 24 for the primary endpoint and all other 24-week endpoints for patients who have not experienced an event by this visit.
- *Total Follow-up Period:* Starts on the same day as the 24-week Follow-up Period initiation and extends until the EOS Visit.
- *Total Study Period:* Starts on the day of randomized treatment initiation and extends until the EOS Visit.

8.2 Study Population Analyses

Screen failure reasons will be tabulated, ordered by frequency.

The distributions of the following characteristics will be contrasted between the randomized treatment groups with descriptive statistics (e.g., mean, standard error, standard deviation, median, minimum, maximum and patient count for continuous variables, and counts with percentages for categorical variables):

- Demographics
- Cardiovascular disease history and AF risk factors
- Physical exam abnormalities
- Baseline results for $CHADS_2$ score, NYHA functional class, vital signs, ECG and laboratory parameters
- Other bucindolol-related genes (i.e., CYP2D6 and α_{2C})
- Final study disposition categories (completed, discontinued due to a non-fatal AE, etc.)
- Treatment exposure, by
  - Patients attaining target dose
  - Length and outcome of titration period
  - Days of double blind treatment by dose and overall
  - Compliance
- Concomitant medication usage at baseline and throughout study
- Protocol deviations

Metrics for several key study procedures will be presented with descriptive statistics by randomized treatment group:

- Type of Medtronic device
- Elapsed days on treatment prior to de novo insertion of Medtronic Reveal ICM
- Elapsed days on treatment prior to ECV
- Outcome of ECV
- Compliance with procedures for upload of Medtronic device results

8.3 Primary Endpoint

The primary endpoint is elapsed time to first event of symptomatic AF/AFL or ACM during the 24-week Follow-up Period. This is a time to event endpoint censored at 24 weeks of follow-up after establishment of stable SR on study drug. The treatment group results will be compared with a log rank statistic for p-value generation and the Cox proportional hazards model will be used for calculation of an estimated hazard ratio and 95% confidence interval. Both calculations will be stratified by the pre-specified randomization strata: HF etiology (ischemic/non-ischemic); LVEF (< 0.35 / ≥ 0.35); type of Medtronic device (Reveal/Non-Reveal/No Device), and; rhythm status at randomization (SR vs. AF/AFL). The analysis methodology will also be applied separately to each component of this compound endpoint (i.e., time to first event of symptomatic AF/AFL and time to ACM).

The following definitions apply to this endpoint:

- Stable SR on study drug is defined as any of the following:
  - SR confirmed ≥ 1 hour after ECV.
  - SR confirmed ≥ 1 hour after spontaneous conversion from AF/AFL.
  - SR confirmed ≥ 1 hour at the Week 0 Visit for patients randomized in SR.
- An AF/AFL event is defined as AF or AFL observed on two consecutive measures separated by at least 10 minutes as assessed by ECG.
- A symptomatic AF/AFL event is defined as an AF/AFL event that is associated with a clinically relevant change in patient-reported symptoms, as determined by the CEC examination of blinded data.

The CEC charter will describe their approach for identifying an AF/AFL event as symptomatic and their approach for identifying the onset date and time of the event.

AF/AFL will be assessed at scheduled clinic visits via 12-lead ECG and via unscheduled ECG whenever a patient experiences a change in symptoms that could potentially be related to AF/AFL. Patients will be

queried at the time of each ECG assessment to determine if they have experienced any change in symptoms that could be potentially related to AF/AFL.

The following scenarios are possible for a small subgroup of patients:

1. Spontaneous conversion to stable SR during titration prior to the planned cardioversion. For these patients, the day of the first ECG assessment that meets the definition of stable SR, as defined above, will be designated as Day 1 of the 24-week Follow-up Period.
2. Failure to attain stable SR because the ECV procedure was not performed due to drop out or any other reason other than those described below. These patients will be included in the analysis as censored on Day 1 of follow-up.
3. Failure to attain stable SR following ECV. These patients will be included in the endpoint calculation as experiencing the event on Day 1 of follow-up.
4. Deaths occurring after randomization and prior to conversion to stable SR will be counted as events on Day 1.
5. A life-threatening AF/AFL event may lead to emergent cardioversion or medical intervention based on a single rhythm assessment. In these cases, the requirement for a second confirmatory rhythm assessment at least 10 minutes after the initial rhythm assessment may not be necessary. Inclusion of these events for the primary endpoint will be determined in a blinded manner by the CEC.

In exploratory analyses, the following covariates as well as the stratification variables and study phase will be included as potentially relevant explanatory variables in the Cox regression models:

1. Baseline NYHA Class
2. $CHADS_2$ Score
3. Gender
4. Race
5. Age
6. Baseline norepinephrine level
7. Baseline heart rate
8. Baseline systolic blood pressure
9. Previous amiodarone use
10. Ablation procedure prior to study
11. For the subset of patients in AF/AFL at randomization, type of rhythm abnormality (paroxysmal AF, persistent AF).
12. For the subset of patients in SR at randomization: the time since last attaining SR, the type of previous rhythm abnormality, and the intervention that ended the previous AF episode.

13. α_{2C} AR polymorphisms (i.e., Del carriers vs. α_{2C} wild type homozygotes).
14. Other clinically significant AF risk factors.

8.4 Secondary Endpoints

The following endpoints will be tested for superiority of bucindolol benefit relative to metoprolol by fixed sequence provided that bucindolol meets the superiority criteria on the primary endpoint. The time to first event endpoints will be analyzed with the same methodology as the primary endpoint with the exception of non-AF rhythm endpoints (e.g., VT/VF, SVT, etc.). For these endpoints, the patients who failed to convert to stable SR will have follow-up results and will therefore not be censored on Day 1 since these events may still be observed. The following statistical analysis methodologies for the study will be described in further detail in the Statistical Analysis Plan.

- Time to first event of AF/AFL (i.e., symptomatic or asymptomatic) or ACM during the 24-week Follow-up Period. A supportive analysis will involve the same analysis methodology applied to each component (i.e., AF, AFL and ACM). Supportive analysis will also be conducted to examine this endpoint and its components for the Total Follow-up Period.
- Proportion of patients with VT, VF, or symptomatic supraventricular tachycardia (SVT) during the 24-week Follow-up Period. Includes VF and symptomatic SVT events of any duration, VT events of ≥ 15 seconds, and VT events that result in appropriate firing of an ICD. This endpoint will be tested with a Cochran-Mantel-Haenszel statistic to control for the four stratification variables. The components will also be examined individually with the same methodology. A supportive analysis will also be conducted to examine this endpoint and its components for the Total Follow-up Period.
- Total number of hospitalization days per patient (all-cause) during the Total Study Period. This count will be normalized for the total number of days of follow-up prior to testing with the Wilcoxon Rank Sum statistic. A supportive analysis for this endpoint will also be conducted that compares patients who are in AF at the EOS Visit and have VRR control to patients who are in AF at the EOS Visit without VRR control. A supportive analysis for this endpoint will also be conducted for the subset of heart-failure related hospitalization days per patient during the Total Study Period.
- Time to first event of AF/AFL (i.e., symptomatic or asymptomatic), HF hospitalization (as assessed by the Investigator), or ACM during the Total Study Period. Supportive analyses will also be performed for the 24-week Follow-up Period only, for each endpoint component, and for each endpoint combination (i.e., AF/AFL+ACM, AF/AFL+HFH, HFH+ACM).

- Proportion of patients with adequate ventricular rate control in the setting of AF/AFL. These patients will be identified by the CEC and the condition will be defined by (a) a ventricular response rate (VRR) between 40 and 80 beats per minute at rest on the last tracing demonstrating AF/AFL during the 24-week Follow-up Period and (b) the absence of symptoms associated with bradycardia. This endpoint will be tested with a Cochran-Mantel-Haenszel statistic to control for the four stratification variables. A supportive analysis will also be performed to evaluate this endpoint at the time of study drug discontinuation.

8.5 Tertiary Endpoints

- Time to first event of VT/VF or ACM during the Total Follow-up Period. Includes VF events of any duration, VT events of ≥ 15 seconds, and VT events that result in appropriate firing of an ICD.
- Time to first event of AF/AFL (i.e., symptomatic or asymptomatic), CV-related hospitalization (as assessed by the Investigator), or ACM during the Total Study Period. Supportive analyses will also be performed for the 24-week Follow-up Period only, for each endpoint component, and for each endpoint combination (i.e., AF/AFL+ACM, AF/AFL+CVH, CVH+ACM). Proportion of patients with stroke or systemic embolism during the Total Follow-up Period. This endpoint will be tested with a Cochran-Mantel-Haenszel statistic to control for the four stratification variables. The components will also be examined individually with the same methodology. Stroke is defined as a focal neurologic deficit from a non-traumatic ischemic, hemorrhagic, or uncertain cause lasting at least 24 hours (as assessed by the Investigator).
- Total number of new or worsening symptoms reported on the AFSQ during the 24-week Follow-up Period. Supportive analyses will also be conducted to examine symptoms reported prior to recurrence of AF/AFL and symptoms reported in periods of SR during the 24-week Follow-up Period.
- Proportion of patients who convert from AF/AFL to stable SR (i.e., spontaneously or post-ECV) and enter the 24-week Follow-up Period. This endpoint will be tested with a Cochran-Mantel-Haenszel statistic to control for the four stratification variables. Supportive analyses will also be conducted to individually examine spontaneous conversion to stable SR that leads to avoidance of protocol-scheduled ECV and the establishment of stable SR at the time of the initial protocol-scheduled ECV procedure. A supportive analysis will also be conducted to examine this endpoint for the Total Follow-up Period.

- Total number of ECV procedures per patient during the Total Study Period. This count will be normalized for the total number of days of follow-up prior to testing with the Wilcoxon Rank Sum statistic.
- Total number of persistent AF/AFL episodes per patient during the 24-week Follow-up Period. Persistent AF/AFL is defined as AF/AFL observed on two consecutive ECG assessments separated by > 7 days. This count will be normalized for the total number of days of follow-up prior to testing with the Wilcoxon Rank Sum Statistic. Supportive analyses will also examine the time to first event of persistent AF/AFL and the proportion of patients at the end of follow-up who are in a state of persistent AF/AFL. This endpoint and both supportive analyses will also be evaluated for the Total Follow-up Period.
- Proportion of patients at Week 24 who are receiving study drug and have not had an AF/AFL event. This endpoint will be tested with a Cochran-Mantel-Haenszel statistic to control for the four stratification variables.
- Change in NT-proBNP, assessed relative to baseline. Change from baseline will be tested for greater reduction in the bucindolol treatment group with the Wilcoxon Rank Sum test because of the historically high lack of normality of this measure.
- Change in norepinephrine, assessed relative to baseline.
- The EQ-5D questionnaire has 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and each is self-rated by the patient as no problems, some problems, or severe problems. The bucindolol treatment group will be tested for superior response using a Cochran-Mantel-Haenszel statistic to control for the four stratification variables.
- Population PK analysis. Details of this analysis will be prespecified in a separate analysis plan.
- Pharmacoeconomic modeling of healthcare utilization. Details of this analysis will be prespecified in a separate analysis plan.

8.6 Safety Endpoints

The results for the following safety endpoints will be compared with descriptive statistics between the treatment groups for all patients receiving study treatment. All results collected from first dose of study drug to within 14 days of the last dose for each patient will be included in the assessments of safety unless otherwise stated. Exploratory analyses will also examine polymorphisms in other bucindolol-related genes (i.e., α_{2C} AR and CYP2D6) and their relationship to the safety endpoints.

- Incidence of ACM during the Total Study Period. This will also be tabulated for the Total Follow-up Period. A supportive analysis for this endpoint will also be conducted to examine the

association of VRR control with mortality using the final heart rate measurement available for each patient (comparisons will be within the treatment groups).

- Incidence of ACM, CV-related hospitalization (as assessed by the Investigator), or withdrawal of study drug due to an AE during the Drug Titration Period. The components will also be examined individually.
- Incidence of heart block during the Total Study Period. Defined as third degree heart block, second degree heart block requiring pacemaker implantation, or symptomatic second degree heart block as determined by the CEC.
- Incidence and severity of treatment-emergent AEs/SAEs over time during the Total Study Period.
- Incidence of neoplasm-related AEs during the Total Study Period. The AEs of special interest will be tabulated according to the following characteristics:
    - Development of treatment-emergent neoplastic conditions.
    - Progression or worsening of pre-study neoplastic conditions.
    - Progression or worsening of treatment-emergent neoplastic conditions.
- Change from baseline in clinical laboratory tests over time during the Total Study Period. Also for clinical laboratory tests, the numbers and percentages of patients with values exceeding the bounds of normal ranges.
- Change from baseline in vital signs and weight over time during the Total Study Period.
- Change from baseline in quantitative ECG parameters (i.e., QTc, QRS, PR and HR).
- Proportion of patients attaining target study drug dose during the Drug Titration Period. Supportive analyses will also be performed for the subpopulations receiving and not receiving previous β-blocker therapy at randomization.

8.7 Optional Substudies

- DNA Bank, with collection at time of screening for patients who agree to participate in the substudy.
- AFB for patients who agree to participate in the substudy.
    - AFB is defined as the amount of time per day that a patient is in AF/AFL, as measured by a Medtronic implanted device.
    - The primary AFB endpoint will be measured through the Week 24 Visit. It will be a time to first event analysis, with an AF/AFL event defined as at least 6 hours of AFB in a single day. It will be analyzed with the same methodology as the primary endpoint.

- AFB will also be presented as hours/day with descriptive statistics and graphical displays.
- Additional analyses will examine all available AFB data, including VRR during periods of AF/AFL as collected by implanted Medtronic devices.

8.8 Power and Sample Size

In a previous study involving post-ECV follow-up, the AF event rate in successfully converted patients who were subsequently treated for approximately 6 months with metoprolol was 52%. This study included both HF and non-HF/LV dysfunction patients and the average LVEF was 49%. In a second study with a similar design and patient population (i.e., post-ECV follow-up of HF and non-HF/LV dysfunction patients), the 6 month event rate was 46% in the group of patients treated with bisoprolol. In the EURIDIS and ADONIS studies, which primarily enrolled non-HF/LV dysfunction patients in SR who had experienced at least one episode of AF in the preceding 3 months, the 6 month event rate was approximately 54% in patients who received dronedarone, compared to 65% for patients receiving placebo.[37] Because enrollment in the current study is limited to a HFREF population, it can be assumed that the AF event rate will be higher than these previously published studies. This study also considers failure to achieve normal SR post-ECV (expected to be 5-10%) and ACM (expected to be 1-2%) as events for the primary endpoint.

Power level estimates for the primary endpoint given a variety of metoprolol event rate and treatment benefit assumptions appear below. In particular, assuming an event rate of 60% at 6 months in the metoprolol group and a bucindolol effect size of 25%, a 620-patient study (310 patients in each group) with at least 330 accrued endpoint events would have 98% power to achieve a p-value ≤ 0.050 and a 90% power to achieve a p-value ≤ 0.01. Therefore, the study design should be sufficient to test the hypothesis that bucindolol is superior to metoprolol for the prevention of symptomatic AF/AFL in HFREF patients with the $\beta_1$389Arg/Arg genotype. Further evaluation of sample size will be performed via an interim analysis conducted by the DSMB during Phase 3 (Section 8.9).

Table 10: Power for Primary Endpoint: 620 Patients and Alpha = 0.01

Metoprolol Group Event Rate	Treatment Benefit of Bucindolol					
	15%	20%	25%	30%	35%	40%
50%	26%	49%	74%	91%	98%	99%
52.5%	29%	54%	79%	93%	99%	99%
55%	32%	59%	83%	96%	99%	99%
57.5%	36%	65%	87%	97%	99%	99%
60%	40%	70%	90%	98%	99%	99%

Table 11: Power for Primary Endpoint: 620 Patients and Alpha = 0.05

Metoprolol Group Event Rate	Treatment Benefit of Bucindolol					
	15%	20%	25%	30%	35%	40%
50%	48%	73%	90%	98%	99%	99%
52.5%	52%	77%	92%	99%	99%	99%
55%	56%	80%	94%	99%	99%	99%
57.5%	60%	84%	96%	99%	99%	99%
60%	65%	87%	98%	99%	99%	99%

8.9 Interim Analyses

Blinded safety data (e.g., group A and group B) will be summarized for inspection by the DSMB and will be reviewed at regular intervals. The DSMB Chair will also monitor a subset of safety data at periodic intervals during the study (e.g., monthly). If a clinically significant imbalance in the groups is observed at any time, the DSMB Chair may request an unblinded analysis.

In addition to these routine safety reviews, an interim analysis of unblinded data will be conducted by the DSMB for the purpose of ruling out futility for meeting the Phase 3 primary endpoint. The DSMB will determine the timing of the interim analysis based on pre-specified thresholds for patient enrollment. If the DSMB determines there is absence of futility, acceptable safety, and pre-trial assumptions regarding the endpoint event rate and other factors are correct, the trial will proceed to Phase 3.

A second interim analysis will be conducted by the DSMB during Phase 3 to assess the absence of futility and whether an expansion of the total sample size is warranted. The DSMB may also make suggestions to the Steering Committee for adjustment in sample size based on other factors (e.g., event rate, discontinuation rate, etc.) or other modifications to the protocol that would improve trial conduct. Further details of the Phase 2B and Phase 3 interim analyses are available in the DSMB charter.

8.10 Significance

At the end of Phase 3, the alpha level for the primary endpoint will be reduced to 0.04989 to adjust for the Phase 2B ($\alpha = 0.00001$) and Phase 3 ($\alpha = 0.0001$) interim analyses.

8.11 Deviation Reporting

All patients with protocol deviations will be included in the ITT analyses; a limited per-protocol analysis will be performed separately. During study initiation, sites will receive instructions on the reporting of protocol deviations or violations. In addition, sites will be responsible for reporting such occurrences to their respective IRB/IEC as required. If protocol deviations and/or violations during monitoring visits are observed, education of the offending sites will occur and repeat offenders may be suspended from

enrolling additional patients. Differences in protocol deviations/violations between treatment groups will be analyzed.

9.0 RESPONSIBILITIES

9.1 Trial Conduct

9.1.1 Ethical Considerations

This study will be conducted according to US (FDA regulations 21CFR312 for IND studies) and international standards (ICH E6) Good Clinical Practices. Applicable local government regulations will also be followed.

This protocol and any amendments will be submitted to the IRB/IEC for formal approval to conduct the study. The decision of the IRB/IEC concerning the conduct of the study will be made in writing to the Investigator.

All patients for this study will be provided a consent form describing this study and providing sufficient information for patients to make an informed decision about their participation in the study. The consent form will be submitted with the protocol for review and approval by the IRB/IEC. The formal consent of a patient, using the IRB/IEC-approved consent form, will be obtained before that patient is submitted to any study procedure. The patient or a legally acceptable surrogate must sign the consent form, and the Investigator-designated research professional obtaining the consent.

9.1.2 Conflict of Interest Policy

Investigators and participants in this study should have no significant conflict of interest with respect to financial holdings in companies that may benefit from the results of this study. Full disclosure of all ties to pharmaceutical and device manufacturers will be required as stipulated by FDA regulations and ICH guidelines. The Executive Committee (Section 9.1.4) will determine if a significant conflict of interest exists and will make recommendations about courses of action.

9.1.3 Quality Control and Quality Assurance

The clinical performance of the study will be monitored according to ICH Good Clinical Practice (GCP) guidelines by means of on-site visits, remote monitoring, telephone calls and regular inspection of the case report forms with sufficient frequency to assess the following: patient enrollment; compliance with the protocol procedures; the completeness and exactness of data entered in the eCRFs; verification against original source documents; and occurrence of AEs. Monitoring visits are to be conducted by appropriate staff as designated by the Sponsor (e.g., the CRO). Data verification will be accomplished by comparing eCRFs to the source documents (e.g., medical files, laboratory printouts, etc.).

9.1.4 Steering Committee

The Steering Committee oversees all aspects of the study and during the trial will remain blinded to treatment group results. The Steering Committee has the authority to propose protocol amendments to the Sponsor based on its monitoring of the progress of the trial, including reports or recommendations received from the DSMB.

The Steering Committee will be responsible for the design of the final protocol and any substudies, as well as the publication of trial results. The Steering Committee will meet regularly to monitor the progress of the study using blinded tabulations based on all patients (i.e., the Steering Committee will not receive the blinded 'Group A' and 'Group B' reports provided to the DSMB). Based on recommendation from the DSMB, the Steering Committee has the authority to stop the trial for unexpected safety reasons.

The Steering Committee will establish committees to develop procedures and report their recommendations to the full Steering Committee for approval. An Executive Committee, a subset of the Steering Committee that includes the Steering Committee Chair, will develop the meeting agendas and make recommendations for consideration by the Steering Committee. The Executive Committee will provide study direction between meetings of the Steering Committee. A Publication Committee appointed by the Steering Committee will review all publications following the guidelines (Section 9.5) and report its recommendations to the Steering Committee. Additional Committees may be added by the Steering Committee during the course of the trial.

Chairpersons of the committees will be appointed by the Steering Committee. For voting, each Steering Committee member shall have a single vote, and no clinical investigation site shall have more than one vote.

9.1.5 Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be established with a charter and standard operating procedures designed to follow FDA Guidance on the Establishment and Operation of Clinical Trial Data Monitoring. The DSMB will be comprised of experts in relevant biomedical fields such as electrophysiology, cardiology and biostatistics. The members will have no direct relationship to the study, or to the Sponsor. The DSMB Chair and committee members will be selected by the Sponsor and the Steering Committee; either can nominate DSMB members with approval by the other. Once established, the DSMB will operate independently of the Steering Committee and the Sponsor.

The DSMB will review the protocols of the main study and substudies during the planning phase. Thereafter it will periodically monitor the progress, data, outcomes, toxicity, safety and other confidential data. The DSMB Chair will also monitor a subset of safety data at periodic intervals during the study (e.g., monthly). For these monitoring activities, the DSMB will be provided with tabulations by blinded

group (e.g., Group A versus Group B). The DSMB may choose to examine specific unblinded data if they identify a significant imbalance of clinical concern in the blinded group analysis. Based on these monitoring activities, the DSMB is empowered to recommend to the Steering Committee any change in the design of the study required to ensure the safety of the enrolled patients and the scientific integrity of the trial.

In addition to these routine safety reviews, a Phase 2B interim analysis of unblinded data will be conducted by the DSMB primarily for the purpose of ruling out futility for meeting the Phase 3 primary endpoint. If the trial proceeds to Phase 3, a second interim analysis will be conducted by the DSMB to determine the absence of futility and to assess whether an expansion of the Phase 3 sample size is warranted. The DSMB will determine the timing of these interim analyses based on pre-specified thresholds for patient enrollment and will ensure that the endpoint event count is consistent with protocol assumptions. Further details of the Phase 2B and Phase 3 interim analyses are available in the DSMB charter.

9.1.6 Clinical Events Committee

A Clinical Events Committee (CEC) will be established with a charter and standard operating procedures. The CEC is an independently appointed panel of experts in relevant biomedical fields such as electrophysiology and cardiology, who are not participating in this trial and will not be affiliated with the Sponsor. The CEC members, who are selected by the CRO and approved by the Sponsor and Steering Committee, will be convened to review the study specific endpoints and is charged with the development of specific criteria used for the adjudication of clinical events.

At the onset of the trial, the CEC will establish rules outlining the minimum amount of data required and the algorithms to be followed in order to classify a clinical event. The rules will be documented in the CEC charter. All members of the CEC will be blinded to the patient treatment assignment.

The CRO will compile all clinical event packets when the necessary data is available from the trial sites and provide to the CEC. The CEC will meet based on event accrual rate to review and adjudicate all clinical events for which the required minimum data is available, including evaluation of all pertinent ECG data.

Criteria for adjudication, procedures, data flow, and the meeting schedule are described in a separate CEC charter maintained by the Sponsor and the CEC.

9.1.7 Clinical Research Organization

A Clinical Research Organization (CRO) will be utilized to manage database creation and maintenance, and generation of blinded data analyses for trial monitoring. Unless stated elsewhere, all CRO study

personnel will remain blinded to treatment assignment until the final patient visit has been completed, all outstanding data queries are resolved and the database is considered locked.

An unblinded statistician at the CRO will have access to the randomization schedule and will only provide that schedule to a limited number of entities involved in study drug packaging and distribution, as well as those required for safety reporting. The CRO or its designee will generate all unblinded interim analyses pre-specified in the protocol. The CRO will also provide blinded pooled data to the Steering Committee for the evaluation of event rate and other study design considerations. Final study analyses will be conducted by the CRO and/or the Sponsor after the database has been locked and the study has been unblinded.

9.2 Investigator Responsibilities

9.2.1 Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with the principles of the ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study patient.

The Sponsor and Investigators will follow requirements as set forth in the U.S. Code of Federal Regulations (CFR), 21CFR Parts 50, 54, 56, and 312 and the ICH E6 GCP Consolidated Guidance. Investigator responsibilities are set out in Section 4 of the E6 Guideline. Sponsor responsibilities are set out in Section 5 of the E6 ICH Guideline.

Since this is a "covered" clinical trial, the Investigator will ensure that 21CFR Part 54, 1998, is adhered to; a "covered" clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that Investigators and all sub-Investigators must provide documentation of their financial interest or arrangements with the Sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the Investigator and any sub-Investigator. The Investigator and Sub-Investigator agree to notify the Sponsor of any change in reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last patient has completed the protocol-defined activities.

This study is also subject to and will be conducted in accordance with 21CFR Part 320 "Retention of Bioavailability and Bioequivalence Testing Samples."

9.2.2 Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the Investigator to an IRB/IEC. Approval from the IRB/IEC must be obtained before starting the study and should be documented in a letter to the Investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

All documents subject to review during the study, including, but not limited to, any modifications made to the protocol after receipt of IRB/IEC approval and SAE safety reports must also be submitted to the committee for review and/or approval prior to implementation (if applicable).

If requested as part of the written application to the IRB/IEC, the Investigator should provide the committee with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the study, the Investigator should supply an updated copy to the committee.

9.2.3 Informed Consent

The Investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The Investigator must utilize an IRB/IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

9.2.4 Confidentiality

The Investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC, or laboratory. The Investigator must keep a patient identification log showing codes, names, and addresses for all patients screened and for all patients participating in the trial.

The Investigator agrees that all information received from the Sponsor, including but not limited to the Investigator Brochure, this protocol, eCRFs, the study drug, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The

Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.2.5 Study Files and Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: 1) Investigator's study file, and 2) patient clinical source documents.

The Investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant letters, etc.

All clinical study documents must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements or an agreement with the Sponsor. The Investigator must notify the Sponsor before destroying any clinical study records.

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained in storage by the Sponsor for a period up to 15 years for purposes of this study.

9.2.6 Case Report Forms

For each patient, an eCRF must be completed and signed by the Principal Investigator within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study (even during a pre-randomization Screening Period if an eCRF was initiated). If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

All protocol required data will be collected in a case report form or via electronic means. A list of systems used to create, modify, maintain, archive, retrieve, or transmit data will be maintained by the Sponsor or their designee.

9.2.7 Drug Accountability

The Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition) and patient dispensing records and returned or destroyed study product. Dispensing records will document quantities received from the Sponsor or its representative and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction in order to ensure that it complies with Sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study, if appropriate, as directed by the site's monitor. During or at the end of the study (as appropriate by site), following acceptable final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the Sponsor's requirements for disposal, arrangements will be made between the site and the Sponsor or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

9.2.8 Inspections

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor or its representatives, to the IRB/IEC, or to regulatory authority or health authority inspectors.

9.2.9 Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. All deviations from the protocol must be noted by the Investigator and may result in retraining of study personnel and/or discontinuation of site participation. All patients who miss a scheduled visit must be contacted via phone to confirm continued participation in the study.

9.3 Sponsor Responsibilities

9.3.1 Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by the Sponsor. All protocol modifications must be submitted to the IRB/IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/IEC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC and the Investigator must await approval before implementing the changes. The Sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

If, in the judgment of the IRB/IEC, the Investigator, and/or the Sponsor, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a study participant, the currently approved written ICF will require similar modification. In such cases, informed consent will be renewed for patients randomized in the study before implementing protocol changes.

9.3.2 Clinical Study Reports

A clinical study report will be prepared and provided to regulatory agencies. The Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

9.4 Joint Investigator/Sponsor Responsibilities

9.4.1 Access to Information for Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the Investigator’s source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

9.4.2 Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the Sponsor may conduct inspections or audits of the clinical study. If the Investigator is notified of an inspection by a regulatory authority, the Investigator agrees to notify the designated Sponsor representative immediately. The Investigator agrees to provide to representatives of a regulatory agency or the Sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.4.3 Study Discontinuation

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the patients' interests.

9.5 Publication Committee

A Publication Committee will review all publications following the guidelines given below and report its recommendations to the Steering Committee. The Publications Committee will be comprised of the Principal Investigator, the Chair and the Co-Chair of the Steering Committee, and a Sponsor representative. The Publication Committee Chair will be selected by the Steering Committee.

9.5.1 Data Analysis and Release of Results

The scientific integrity of the study requires that the data from all clinical sites be analyzed and reported study-wide. Thus, an individual center or group of centers may not independently report data. All presentations and publications must protect the integrity of the major objectives of the study; data that would release endpoint results will not be presented prior to the release of the main study results. The timing of presentation of any data and the venue in which the data are presented will be subject to the review and approval of the Steering Committee.

9.5.2 Review Process

Each paper, abstract, or presentation of previously unreported data from the trial must be submitted to the Publication Committee for review of scientific merit and appropriateness for submission or presentation.

Slides or posters containing data from the trial should be submitted to the Publications Committee before their initial presentation. All submissions should be made at least two weeks before the presentation or the abstract deadline. The committee may recommend changes to the authors and will submit its recommendations to the Steering Committee for approval. The final determination about whether or not a particular analysis represents a primary outcome will be made by the Steering Committee.

9.5.3 Authorship: Primary Outcome Paper

Authorship on primary outcome manuscripts will be "The Trial Investigators". For such manuscripts, there will be an appendix containing the names of the various organizational units and their Principal Investigators and Coordinators. Members of the DSMB and contributing Sponsor personnel will also be included in these manuscripts.

9.5.4 Authorship: Other Study Papers, Abstracts and Presentations

All studies other than those designated “primary outcome” fall into this category. Papers or abstracts resulting from these studies will have named authorship of individuals involved, ending with the phrase "and the Trial Investigators". Suitability of authorship will be subject to approval by the Publications Committee. Papers will either have an appendix with the names of the organizational units and their Principal and Co-Investigators, or a reference to a methods or primary outcome paper with such a list. The Publications Committee must review all papers and abstracts prior to being submitted for publication.

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11.0 APPENDICES

Appendix 1 Study Personnel Information

Sponsor:	ARCA biopharma, Inc. 11080 CirclePoint Road, Suite 140 Westminster, CO 80020 Phone: 720-940-2100
Data Coordinating Center:	Duke Clinical Research Institute 2400 Pratt Street, Durham, NC 27705 Principal Investigator: Jonathan Piccini, MD Phone: 919-668-8700
SAE/Safety Monitor:	Duke Clinical Research Institute 2400 Pratt Street, Durham, NC 27705 Medical Monitor: Karen Alexander, MD Phone: 919-668-8624 or 866-668-7799 (toll free) Email: dcrisafetysurveillance@dm.duke.edu
Central Laboratory	LabCorp Clinical Trials 4307 Emperor Blvd. Suite 200 Durham, NC 27703

Appendix 2 Investigator Signature Page

ARCA BIOPHARMA, INC.

11080 CIRCLEPOINT ROAD, SUITE 140

WESTMINSTER, CO 80020

STUDY ACKNOWLEDGMENT

GENETIC-AF – A **Gen**otype-Directed Comparative **E**ffectiveness **Tri**al of Bu**c**indolol and Toprol-XL for Prevention of Symptomatic **A**trial **F**ibrillation/Atrial Flutter in Patients with Heart Failure

Version 4.0 29 January 2016

This protocol has been approved by ARCA biopharma, Inc. The following signature documents this approval.

2/3/16

Christopher Dufton, PhD
Vice-President, Clinical Development

Investigator Statement

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by ARCA biopharma, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Print)	Principal Investigator Name (Signature)
Site Number	Date

Appendix 3 Abbreviations and Definition of Terms

Abbreviation	Definition
ACM	all-cause mortality
AE	adverse event
AF	atrial fibrillation
AFB	atrial fibrillation burden
AFL	atrial flutter
AFSQ	AF symptoms questionnaire
AR	adrenergic receptor
BEST	Beta Blocker Evaluation of Survival Trial
BID	twice daily
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHF	chronic heart failure
CONMED	concomitant medication
CRO	contract research organization
CRT	cardiac resynchronization therapy
CV	cardiovascular
CVH	cardiovascular hospitalization
CVM	cardiovascular mortality
DNA	deoxyribonucleic acid
DSMB	data and safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
ECV	electrical cardioversion
EOS	end of study
EOT	end of treatment
EP	electrophysiology
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HF	heart failure
HFREF	heart failure with reduced left ventricle ejection fraction
ICD	implantable cardioverter-defibrillator
ICF	informed consent form
ICH	International Conference on Harmonisation
ICM	insertable cardiac monitor

IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ratio
IPG	implantable pulse generator
IRB	Institutional Review Board
ITT	intent to treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LV	left ventricle
LVEF	left ventricle ejection fraction
MDR	Medical Device Reports
NSAID	nonsteroidal anti-inflammatory drug
NT-proBNP	n-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
PK	pharmacokinetic
PTCA	percutaneous transluminal coronary angioplasty
PVC	polyvinylchloride
QD	once daily
SAE	serious adverse event
SR	sinus rhythm
SVT	supraventricular tachycardia
TTM	transtelephonic monitor
VF	ventricular flutter
VRR	ventricular response rate
VT	ventricular tachycardia

Appendix 4 Schedule of Assessments

	Screen Period		24-week Follow-Up Period (Week)													Treatment Extension Period		
	Screen Visit	**Rand Visit**	**0[1]**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**EXT Visit[2]**	**EOT Visit[3]**	**EOS Visit[4]**
Visit window	-	-	-	2d	2d	2d	2d	2d	2d	2d	2d	2d	2d	2d	2d	4d	-	-
Informed consent	X																	
Medical history	X																	
Inclusion/exclusion criteria	X	X																
Physical exam		X																
Device implant[5]		X																
Device interrogation[6]		X							X						X	X	X	X
NYHA class assessment		X							X						X	X	X	X
Electrical cardioversion			X															
12-lead ECG[7]		X	X	X	X		X		X		X		X		X	X	X	X
Telephone contact[8]						X		X		X		X		X				
AF symptoms questionnaire[9]		X	X[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D questionnaire		X							X						X			
Clinical events assessment		X	X	X	X		X		X		X		X		X	X	X	X
$B_1$389 AR genotype	X																	
α_2c AR/CYP2D6 genotype[11]		X																
Optional DNA bank[11]		X																
Chemistry/hematology	X				X				X						X	X	X	X
NT-proBNP[12]		X			X				X						X			
Plasma norepinephrine		X			X				X						X			
Population PK[13]			X[14]		X				X									
Pregnancy test[15]	X	X																
Coagulation status[16]		X	X	X	X		X		X		X		X		X	X	X	X
Vital signs and weight	X	X	X	X	X		X		X		X		X		X	X	X	X
AE collection		X	X	X	X		X		X		X		X		X	X	X	X
Concomitant medications	X	X	X	X	X		X		X		X		X		X	X	X	X
Study drug collect/dispense		X	X		X		X		X		X		X		X	X	X	X

[1]Up-titration of study drug during the Drug Lead-in Period (i.e., after randomization and prior to the Week 0 Visit) will be managed via unscheduled Drug Titration Visits to provide flexibility for optimal patient management (Section 6.1.2.1). Study drug collections/dispensation is the only required procedure for these visits; however, if any unscheduled procedures and/or safety evaluations are performed, they must be entered into the eCRFs.
[2]Extension Visit: Clinic visits will be every 12 weeks after the Week 24 Visit.
[3]End of Treatment Visit: Only required for patients who prematurely discontinue study drug who will continue to participate in the study. These patients should complete the EOT Visit prior to discontinuation of study drug (if possible) and then remain in the study and complete all remaining visits. Patients who wish to discontinue study drug and study participation should complete all assessments described for the EOS Visit.
[4]End of Study Visit: Phase 3 follow-up will continue until a total of at least 330 primary endpoint events have been observed. After this event, all patients will complete the 24-week Follow-up Period or return to the clinic for an EOS Visit if already in the Treatment Extension Period.
[5]Patients who agree to have a Medtronic device inserted may do so at the Randomization Visit or at any time prior to the start of the 24-week Follow-up Period.
[6]Devices interrogated via the Medtronic Carelink Programmer and uploaded to the Medtronic Clinical Transfer Site.
[7]A 12-lead ECG is not required at the Screening Visit; however, if one if collected during this visit the results should be entered into the Screening ECG eCRF. Two 12-lead ECGs are required at the Week 0 Visit.
[8]Schedule telephone contacts to administer the AFSQ and determine if the patient has experienced any new or worsening symptoms that could potentially be related to AF/AFL (Section 6.1.4.2). If the Investigator suspects that a new AF/AFL event has occurred between scheduled clinic visits (i.e., a change in rhythm from SR to AF/AFL), the patient will be instructed to return to the clinic within 3 business days for further assessments (Section 6.1.4.2).
[9]AFSQ must be collected prior to ECG at clinic visits (Section 6.2.6).
[10]At the Week 0 Visit the AFSQ will be collected prior to the ECV procedure and a second AFSQ will be administered the following day for those patients achieving stable SR post-ECV. The second AFSQ assessment can be performed via telephone, if necessary. For patients in SR who do not require ECV at this visit, the AFSQ will be collected prior to the first ECG assessment only.
[11]Samples should be collected prior to first dose of study drug for randomized patients only.
[12]Whenever possible, NT-proBNP should also be collected at the time of an AF/AFL event.
[13]Study drug must be withheld on the morning of these visits until the Population PK sample is collected. If possible, a trough blood sample should also be obtained prior to discontinuation of study drug for any patient who experiences a SAE leading to permanent discontinuation of study drug.
[14]Population PK sample at Week 0 is only required for patient who spontaneously converts from AF/AFL to SR prior to the protocol-specified ECV procedure.
[15]Women of childbearing potential only. Serum pregnancy test at Screening Visit and urine pregnancy test at the Randomization Visit (Section 6.2.8).
[16]Local labs used to monitor coagulation status per standard of care. Local lab results will not be collected but coagulation status relative to normal limits will be collected via eCRFs.

Appendix 5 EQ-5D Questionnaire

A. Administrative Information

1. Date of questionnaire completion _____

B. EQ-5D

1. Mobility:

- ☐ I have no problems in walking about.
- ☐ I have some problems in walking about.
- ☐ I am confined to bed.

2. Self-care:

- ☐ I have no problems with self-care.
- ☐ I have some problems washing or dressing myself.
- ☐ I am unable to wash or dress myself.

3. Usual Activities (e.g. work, study, housework, family or leisure activities):

- ☐ I have no problems with performing my usual activities.
- ☐ I have some problems with performing my usual activities.
- ☐ I am unable to perform my usual activities.

4. Pain/discomfort:

- ☐ I have no pain or discomfort.
- ☐ I have moderate pain or discomfort.
- ☐ I have extreme pain or discomfort.

5. Anxiety/depression:

- ☐ I am not anxious or depressed.
- ☐ I am moderately anxious or depressed.
- ☐ I am extremely anxious or depressed.

Appendix 6 AF Symptoms Questionnaire

1. Since your last clinic visit, have you experienced any of the following:
   a) Heart palpitations (pounding, racing or irregular heart beat)? [Yes/No]
   b) Shortness of breath? [Yes/No]
   c) Chest pain or pressure? [Yes/No]
   d) Fatigue or tiredness? [Yes/No]
   e) Weakness or problems exercising? [Yes/No]
   f) Lightheadedness, dizziness or fainting? [Yes/No]
   g) Confusion/trouble concentrating? [Yes/No]
   h) Sweating unrelated to physical activity? [Yes/No]
   i) Weight gain greater than 2 pounds? [Yes/No]
   j) Swelling of both legs and/or feet? [Yes/No]

2. Which symptom do you consider the predominant or worst symptom?
   [choose only one from above, or 'NA' if no symptom experienced]

3. For questions 1a-j, if "yes" collect the following:
   a) How frequently have you experienced this symptom? [rarely, sometimes, often, always]
   b) How would you rate the intensity/discomfort of this symptom? [mild, moderate, severe]
   c) When did you first experience this symptom during this reporting period? [MM/DD/YYYY]
   d) When did you last experience this symptom during this reporting period? [MM/DD/YYYY]