

Protocol Title:

Pragmatic Randomized Clinical Trial of Early Dronedaronone versus Usual Care to Change and Improve Outcomes in Persons with First-Detected Atrial Fibrillation (CHANGE AFIB)



Protocol Number: 2.0 –17OCT2022

Amendment Number: 1.0

Compound: Dronedaronone

Brief Title: CHANGE AFIB

Study Phase: Post-market pragmatic clinical trial

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Regulatory Agency Identifier Number(s): NCT05130268

Authors:

This protocol was cowritten by the Duke Clinical Research Institute (DCRI) and the American Heart Association (sponsor). The outline of this template is consistent with the Guidelines for Good Pharmacoepidemiology Practices (GPP), The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist, and International Conference on Harmonisation (ICH) Guidance for Industry, E6 Good Clinical Practice (GCP): Consolidated Guidance.

1. Protocol Synopsis

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| PROTOCOL TITLE | Pragmatic Randomized Clinical Trial of Early Dronedaronone versus Usual Care to Change and Improve Outcomes in Persons with First-Detected Atrial Fibrillation (CHANGE AFIB) |
| PROTOCOL TYPE | Randomized Pragmatic Clinical Trial |
| SPONSOR | American Heart Association |
| STUDY DESIGN | Multicenter, prospective, randomized, open-label clinical trial. |
| STUDY OBJECTIVE | Determine if early treatment with dronedaronone is superior to usual care for the prevention of cardiovascular hospitalization or death from any cause in patients with first-detected atrial fibrillation. |
| STUDY HYPOTHESIS | We hypothesize that earlier administration of a well-tolerated antiarrhythmic drug proven to reduce hospitalization may result in improved cardiovascular outcomes and quality of life in patients with first-detected atrial fibrillation |
| TREATMENT REGIMEN(S) & RANDOMIZATION | Participants will be randomly allocated (1:1) to treatment with dronedaronone on top of usual care versus usual care alone. |
| DURATION OF STUDY PARTICIPATION | Enrollment will occur over approximately 1.5 years, and subjects will be followed for 12 months. |
| NUMBER OF SUBJECTS | 3000 |
| NUMBER OF SITES | Total number: approximately 200 |
| INCLUSION CRITERIA | <ol style="list-style-type: none"> 1. Age \geq21 years 2. First-detected atrial fibrillation (defined as atrial fibrillation diagnosed in the previous 120 days) 3. Acute care encounter for evaluation or treatment of atrial fibrillation, within 120 days.¹ 4. Electrocardiographic documentation of atrial fibrillation. 5. Estimated life expectancy of at least 1 year 6. Patient or legal authorized representative capable of giving signed informed consent, which includes |

¹ Note: Patients can be enrolled from the inpatient setting during this qualifying acute care encounter or afterwards in the outpatient setting, so long as the qualifying acute care event has occurred in the past 120 days. Acute care encounters are defined as a visit to an emergency department, observation unit, or hospital admission.

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| | compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. |
| EXCLUSION CRITERIA | <ol style="list-style-type: none"> 1. Patients with prior or planned treatment with rhythm control, either catheter ablation or chronic (>7 days) antiarrhythmic drug therapy. 2. Prior hospitalization for AF (other than the qualifying event). 3. Planned cardiothoracic surgery. 4. New York Heart Association class III or IV heart failure or a hospitalization for heart failure in the last 4 weeks. 5. Patients with reduced ejection fraction (LVEF $\leq 40\%$). 6. Permanent atrial fibrillation. 7. Ineligible for oral anticoagulation, unless CHA₂DS₂-VASc is less than 3 in women or 2 in men. 8. Bradycardia with a resting heart rate < 50 bpm 9. PR interval >280 msec or 2nd degree or 3rd degree atrioventricular block without a permanent pacemaker/cardiac implanted electronic device. 10. Corrected QT interval ≥ 500 msec. 11. Pregnancy or breast feeding. 12. Severe hepatic impairment in the opinion of the investigator. |
| PRIMARY ENDPOINT | Time to first cardiovascular hospitalization or death from any cause through 12 months from randomization. |
| SECONDARY OUTCOMES | <p>Evaluated through 12 months from randomization</p> <ul style="list-style-type: none"> • WIN Ratio (according to the following hierarchy) <ol style="list-style-type: none"> 1. All-cause mortality 2. Ischemic stroke or systemic embolism 3. Hospitalization for new/worsening diagnosis of heart failure 4. Hospitalization for acute coronary syndrome • Cardiovascular hospitalization • All-cause mortality |
| TERTIARY OUTCOMES | <p>Evaluated through 12 months from randomization</p> <ul style="list-style-type: none"> • Ischemic stroke or systemic embolism • Arrhythmia-related hospitalization • Hospitalization for new/worsening diagnosis of heart failure • AF progression • Cardioversion • Catheter ablation of AF • Days alive and outside of the hospital |

| | |
|----------------------------------|--|
| <p>PATIENT REPORTED OUTCOMES</p> | <ul style="list-style-type: none"> • Change in Atrial Fibrillation Effect on Quality of Life (AFEQT) from baseline to 12 months • Change in Mayo AF-Specific Symptom Inventory (MAFSI) from baseline to 12 months |
| <p>INTERIM ANALYSES</p> | <p>Evaluation of safety and overall endpoint data will be performed every 6 months and evaluated by the data safety and monitoring board. There will be an aggregate analysis of the primary event rate every 6 months (after 500 participants have reached 6-month follow-up). A formal interim analysis for efficacy and futility will be performed after 50% of the anticipated events have occurred.</p> |

Protocol Title: Pragmatic Randomized Clinical Trial of Early Dronedarone versus Usual Care to Change and Improve Outcomes in Persons with First-Detected Atrial Fibrillation

Brief Title: CHANGE AFIB

Rationale: While there are several completed clinical trials that address treatment strategy in patients with symptomatic and recurrent atrial fibrillation (AF), there are no randomized clinical trials that address first-line pharmacologic treatment for first-detected AF. Frequently, these patients are started on an atrioventricular nodal blocking agent (beta-blocker or non-dihydropyridine calcium channel blocker) in addition to oral anticoagulation if their stroke risk is elevated (according to **CHA₂DS₂-VASc**). *We hypothesize that earlier administration of a well-tolerated antiarrhythmic drug proven to reduce hospitalization may result in improved quality of life and cardiovascular outcomes in patients presenting with first-detected AF.*

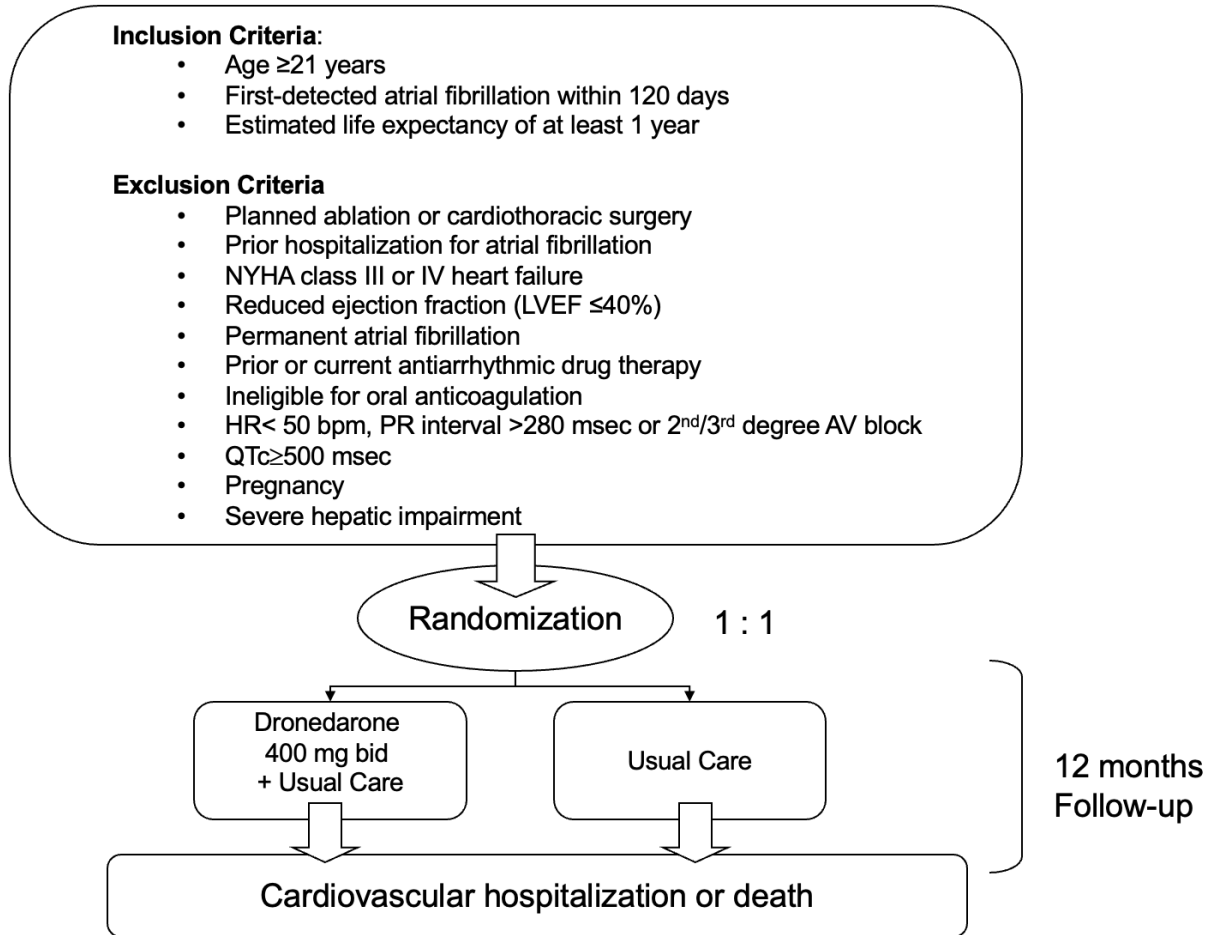
Objectives: Determine if treatment with dronedarone is superior to usual care alone for the prevention of cardiovascular hospitalization or death from any cause in patients with first-detected AF.

Brief Summary:

While there are several completed clinical trials that address treatment strategy in patients with symptomatic and recurrent AF, there are no randomized clinical trials that address treatment for first-detected AF. In usual care, these patients are often started on an atrioventricular nodal blocking agent (beta-blocker or non-dihydropyridine calcium channel blocker) along with stroke prevention therapy. *We hypothesize that earlier administration of a well-tolerated antiarrhythmic drug proven to reduce hospitalization may result in improved cardiovascular outcomes and quality of life in patients with first-detected AF.*

The purpose of this study is to determine if treatment with dronedarone on top of usual care is superior to usual care alone for the prevention of cardiovascular hospitalization or death from any cause in patients hospitalized with first-detected AF. All patients will be treated with guideline-recommended stroke prevention therapy according to the CHA₂DS₂-VASc score. The treatment follow-up period will be 12 months. There will be two follow-up visits. Consistent with the pragmatic nature of the trial, the 1st follow-up will occur at 6 months (with a window of ±3 months) and the 2nd will occur at 12 months (with a window of ±30 days). Approximately 3000 patients will be enrolled and randomly assigned (1:1) to study intervention. The study intervention will be dronedarone 400 mg twice daily in addition to usual care versus usual care alone.

1.1. Schema



1.2. Schedule of Activities

TRIAL VISIT DATA CAPTURE REQUIREMENTS & SCHEDULE¹

| Trial Visit Data Capture Requirements | <u>Baseline Visit</u> (0-120 days post AFib DX)² | <u>Follow Up Visit 1:</u> 6 Month (± 3 months) | <u>Follow Up Visit 2:</u> 12 Month/End of Study (± 30 days) |
|---|--|---|--|
| Eligibility Confirmation (via Inclusion/Exclusion criteria) | X | | |
| Informed Consent | X ³ | | |
| Randomization | X ⁴ | | |
| First-Detected Atrial Fibrillation Diagnosis Data | X ⁵ | | |
| Index Acute Care Encounter/Hospitalization Data | X ⁵ | | |
| Quality of Life Instruments (AFEQT & MAFSI) | X | | X |
| Medical History Data | X | | |
| Demographic Data | X | | |
| Ejection Fraction Data | X | | |
| Vital Signs Data | X | X | X |
| Clinical Laboratory Data | X | X | X |
| Study Drug Accountability | X ⁶ | X | X |
| Documentation of Cardiac Procedures, if applicable | | X | X |
| Outcomes (Primary, Secondary, & Tertiary) | | X | X |
| Concomitant Medications | X | X | X |
| Adverse Events & Safety Events | X | X | X |

¹This schedule of activities table reflects the collection of data that is being conducted in the course of the patient’s clinical care. This is a pragmatic trial and consistent with the design, there are no diagnostic procedures or laboratory studies required by the protocol. All of the data recorded are data captured in the course of the patient’s clinical care.

²Baseline Visit may occur during the index hospitalization (diagnosis of first-detected atrial fibrillation), or during an outpatient visit occurring within 120 days of diagnosis.

³Consent must occur at the Baseline Visit (time of study enrollment) which may be the index hospitalization or outpatient visit occurring within 120 days of diagnosis.

⁴Randomization to occur at Baseline Visit. Baseline Visit can be the index hospitalization or outpatient visit occurring within 120 days of diagnosis.

⁵Index Hospitalization is defined as an acute care encounter for treatment of atrial fibrillation, defined as a visit to an emergency department, observation unit, or hospital admission.

⁶Confirmation patient has filled and is taking their prescription for study drug, to be conducted within 10 days of Baseline Visit and Randomization.

2. Introduction

2.1. Background & Rationale

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice, accounting for one-third of arrhythmia-related hospitalizations.¹ As many as 1 in 4 people develop AF over their lifetime after the age of 40 years.² The prevalence and burden of AF in the United States is substantial³; the age-adjusted incidence and prevalence has increased over the last 3 decades.^{4,5} Moreover, the number of Americans with AF is expected to increase 150% by 2050.^{4,6-10} The goals of care in the treatment of AF include (1) the management and reduction of risk factors, (2) prevention of tachycardia (rate control), (3) prevention of stroke, and (4) improvement of symptoms. Reduction or elimination of symptoms often requires rhythm control. Historically, randomized clinical trials have not demonstrated a mortality or stroke benefit with a rhythm control versus a rate control strategy.¹¹⁻¹³

Despite the failure of prior randomized clinical trials to demonstrate the superiority of rhythm control, the recent EAST-AFNET 4 trial demonstrated that early introduction of a comprehensive rhythm-control strategy (within one year of diagnosis) is superior to guideline-based usual care in improving cardiovascular (CV) outcomes at a mean follow-up of 5 years.¹⁴ The EAST-AFNET 4 trial found that early rhythm control reduced the primary outcome of CV death, stroke, hospitalization for HF, or acute coronary syndrome (HR 0.79, 96% confidence interval 0.66-0.94, $p = 0.005$). EAST-AFNET 4 also demonstrated a reduction in the risk of stroke with early introduction of rhythm control (HR 0.65, 95% CI 0.44-0.98), a finding that was also observed with dronedarone in the ATHENA trial. In addition, maintenance of sinus rhythm has been associated with improved quality of life and increased exercise capacity in some patients. Outside of clinical trials, a quality-of-life study from the Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation (RECORD-AF) found that rhythm control was associated with better quality of life.¹⁵

There are several antiarrhythmic drugs (AADs) available for rhythm control of AF.¹⁶ Class I antiarrhythmic agents are predominantly limited to younger patients without coronary artery or structural heart disease. Patients with advanced chronic kidney disease, prolonged QT intervals, and/or severe left ventricular hypertrophy should not be treated with sotalol or dofetilide. Even when sotalol or dofetilide can be used, patients are often hesitant to start a medication that requires an inpatient hospitalization for drug loading and laboratory evaluation every 3 months. Amiodarone has been shown to be the most effective AAD for maintaining sinus rhythm in patients with AF;¹⁷⁻¹⁹ however, based on its side effect profile, amiodarone is only recommended as a first-line agent under specific clinical circumstances.¹⁶ Moreover, despite its efficacy, amiodarone has high rates of discontinuation due to frequent adverse events.^{18,20} In addition to its unfavorable side effects, several studies, including those of patients at risk for sudden cardiac death, have demonstrated an association between amiodarone use and higher mortality, as well as lower functional status.²¹⁻²⁴ In contrast to amiodarone, dronedarone is a much better tolerated antiarrhythmic medication.²⁵ In randomized controlled trials, dronedarone has been shown to prevent recurrent AF, improve rate control, and decrease cardiovascular hospitalization in patients with AF.^{26,27}

While there are several completed clinical trials that address treatment strategy in patients with symptomatic and recurrent AF, there are no randomized clinical trials that address treatment for first-detected or new-onset AF. After appropriate evaluation for oral anticoagulation, these patients are often started on an atrioventricular nodal blocking agent (beta-blocker or non-dihydropyridine calcium channel blocker). *We hypothesize that earlier administration of a well-tolerated antiarrhythmic drug proven to reduce hospitalization may result in improved quality of life and cardiovascular outcomes in patients with first-detected AF.*

2.2. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of dronedarone may be found in the investigator's brochure and package insert.

2.2.1. Risk Assessment

Dronedarone is approved by the Food and Drug Administration to reduce the risk of hospitalization for AF in patients with paroxysmal or persistent AF. The efficacy and safety of dronedarone 400 mg twice daily was evaluated in five controlled studies, ATHENA, ANDROMEDA, EURIDIS, ADONIS, and DAFNE, involving more than 6,000 patients with AF, including more than 3200 patients who received dronedarone.²⁶⁻³¹ As with any therapeutic agent, there are known risks with dronedarone therapy. These risks include hepatic injury, heart failure exacerbation, increased exposure to digoxin (2.5 fold increase), increased plasma concentration of tacrolimus, sirolimus, and other CYP 3A substrates, and very rare instances of pulmonary toxicity. The risks of dronedarone are felt to be outweighed by its benefits. The guideline recommendations provided by the European Society of Cardiology and AHA/ACC/HRS are commensurate with this risk benefit assessment.^{32, 33}

2.2.2. Benefit Assessment

While there are no completed randomized clinical trials to guide selection or initiation of rhythm control therapies in patients with first-detected AF, there are recent trials that suggest benefit with both dronedarone antiarrhythmic therapy and early-initiation of rhythm control in persons with AF. The recent EAST-AFNET 4 trial demonstrated that early introduction of a comprehensive rhythm-control strategy (within one year of diagnosis) is superior to usual guideline-recommended care in improving cardiovascular (CV) outcomes at 5 years.¹⁴ The median time from new-onset AF to randomization in the EAST-AFNET4 trial was 36 days. The trial found that early rhythm control reduced the primary outcome of CV death, stroke, hospitalization for HF, or acute coronary syndrome (HR 0.79, 95% confidence interval 0.66-0.94, $p = 0.005$). EAST-AFNET 4 also demonstrated a reduction in the risk of stroke with early introduction of rhythm control (HR 0.65, 95% CI 0.44-0.98), a finding that was also observed with dronedarone in the ATHENA trial. Thus, we hypothesize that early initiation of dronedarone in patients with new-onset AF will lead to a reduction in CV hospitalization or death.

3. Objectives and Endpoints

| Objectives | Endpoints |
|---|--|
| Primary | |
| Determine if treatment with dronedarone on top of usual care is superior to usual care for the prevention of cardiovascular hospitalization or death from any cause in patients with first-detected AF. | <ul style="list-style-type: none"> • Time to cardiovascular hospitalization or death from any cause within 12 months of randomization. |
| Secondary | |
| To assess the efficacy of treatment with dronedarone on top of usual care compared to usual care for the following outcomes occurring within 12 months of randomization: | <ol style="list-style-type: none"> 1. WIN Ratio (according to the following hierarchy) <ol style="list-style-type: none"> a. All-cause mortality b. Ischemic stroke or systemic embolism c. Hospitalization for new/worsening diagnosis of heart failure d. Hospitalization for acute coronary syndrome 2. Cardiovascular hospitalization 3. All-cause mortality |
| Tertiary | |

| | |
|---|--|
| <p>To assess the efficacy of treatment with dronedarone on top of usual care compared to usual care for the following outcomes occurring within 12 months of randomization:</p> | <ul style="list-style-type: none"> • Ischemic stroke or systemic embolism • Arrhythmia-related hospitalization • Hospitalization for new or worsening heart failure • AF progression • Cardioversion • Catheter ablation of AF • Days alive and out of the hospital |
| <p>Patient Reported Outcomes</p> | |
| | <ul style="list-style-type: none"> • Change in Atrial Fibrillation Effect on Quality of Life (AFEQT) from baseline to 12 months • Change in Mayo AF-Specific Symptom Inventory (MAFSI) from baseline to 12 months |

Primary Outcome:

The primary study outcome is the first occurrence of unplanned CV hospitalization or death from any cause within 12 months of randomization. All unplanned hospitalizations (i.e. admission with an overnight stay in an acute care healthcare facility/hospital) for cardiovascular causes will

be considered a cardiovascular hospitalization. Similar to the ATHENA trial, the pre-specified causes of cardiovascular hospitalization will be defined as shown in Table 1.³⁴

Table 1. Main Causes for Cardiovascular Hospitalization*

- Atherosclerosis related (cardiac, neurologic, or peripheral) hospitalization
- Myocardial infarction/acute coronary syndrome
- Stable angina pectoris or atypical chest pain
- Syncope/near-syncope
- Transient ischemic attack or stroke
- Atrial fibrillation, atrial flutter, atrial tachycardia, or any other supraventricular arrhythmia
- Ventricular arrhythmia
- Cardiovascular surgery, LVAD implantation, or cardiac transplantation
- Implantation of a permanent pacemaker, hemodynamic monitor, loop monitor, implantable cardioverter defibrillator, cardiac resynchronization device, or any other cardiac implanted electronic device
- Implantation of a left atrial appendage closure device
- Percutaneous coronary, cerebrovascular, valvular, or peripheral intervention
- Blood-pressure related hospitalization (hypotension, hypertension, or shock)
- Cardiovascular infection
- Major bleeding requiring hospitalization
- Pulmonary embolism or deep venous thrombosis
- New or worsening heart failure, including pulmonary edema or dyspnea of cardiac etiology

*This list represents the most frequent or main causes but is not exhaustive. Other documented causes of cardiovascular hospitalization will be included.

Secondary Outcomes:

1. **WIN Ratio:** The WIN ratio will be the key secondary endpoint.³⁵ Among the randomized patients, every patient in the dronedarone arm will be compared with every patient in the usual care arm. Within each pair of patients, the component outcomes will be compared in descending order of importance until one of the patients in the pair demonstrates a better outcome compared with the other. For the purpose of this trial the hierarchy of component outcomes are shown in **Table 2**. The components in the WIN ratio hierarchy are similar to the endpoints considered in the recent EAST-AFNET4 trial.

Table 2. Hierarchy of Outcomes for the WIN Ratio

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| <ol style="list-style-type: none"> 1. All-cause mortality 2. Ischemic stroke or systemic embolism 3. Hospitalization for new/worsening diagnosis of heart failure 4. Hospitalization for acute coronary syndrome |
|--|

2. **Cardiovascular Hospitalizations:** Given the importance of CV hospitalization as an outcome³⁶ from a clinical perspective, patient perspective, and economic perspective³⁷, there will be two analyses of CV hospitalization. The key secondary endpoint will be time to first unplanned CV hospitalization (similar to the component of the primary endpoint). However, a second exploratory analysis of unplanned cardiovascular hospitalization using a method to account for repeated events (Anderson-Gill extension) will also be performed.
3. **All-cause mortality.** The final secondary endpoint of interest is all-cause mortality. For descriptive purposes, deaths will be categorized by the site investigators according to the following categories: cardiovascular and non-cardiovascular. Cardiovascular deaths will be further classified into arrhythmic vs non-arrhythmic according the modified Hinkle-Thaler criteria, as used in several landmark cardiovascular trials. Patients who are well and (1) have a witnessed sudden collapse or (2) those found dead, but known to be alive and well in the previous 24 hours (e.g. no signs or symptoms of cardiorespiratory distress) will be defined as having arrhythmic death.³⁸

Tertiary Outcomes:

- **Ischemic Stroke or Systemic Embolism:** The occurrence of ischemic stroke will be defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Symptoms or signs must persist ≥ 24 hours, unless the stroke is documented by CT, MRI or autopsy, in which case the duration of symptoms/signs may be less than 24 hours. Stroke may be classified as ischemic (including hemorrhagic transformation of ischemic stroke), hemorrhagic, or undetermined. Systemic embolism will be defined as acute arterial insufficiency or occlusion of the extremities or any non-CNS organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanism (e.g., trauma, atherosclerosis, or instrumentation).³⁹
- **Arrhythmia-Related Hospitalization** will be defined as any unplanned hospitalization (i.e. admission with an overnight stay in an acute care healthcare facility/hospital) due to any tachy- or brady-arrhythmia.

- **Hospitalization for new or worsening heart failure** will be defined as any unplanned hospitalization (i.e. admission with an overnight stay in an acute care healthcare facility/hospital) due to a new diagnosis or worsening symptomatic heart failure.
- **AF Progression** will be defined as the transition from (a) paroxysmal to persistent or (b) persistent to permanent AF.⁴⁰
- **Cardioversion** (either pharmacologic or electrical) with or without transesophageal echocardiographic guidance will be a tertiary endpoint.
- **Ablation of AF** including catheter ablation, surgical ablation, or hybrid (endocardial and epicardial ablation) ablation will be a tertiary endpoint.
- **Days Alive and Out of the Hospital.** Days alive and out of the hospital (DAOH, also referred to as “home time”) is an emerging clinical trial endpoint that is both pragmatic and patient centered.⁴¹ It is highly correlated with traditional time-to-event mortality and hospitalization outcomes.⁴²

Patient reported outcomes. The inclusion of patient reported outcomes in clinical trials is widely recommended, including in the study of interventions for AF.^{39, 43, 44} Patient reported quality of life will be defined according to the two prespecified AF-related quality of life instruments: (1) the Atrial Fibrillation Effect on Quality of Life (AFEQT) and (2) the Mayo AF-Specific Symptom Inventory (MAFSI).⁴⁵

- a. The AFEQT⁴⁶ is a 21-item, AF-specific health-related QOL questionnaire that assesses the impact of AF on patient-reported quality of life. The AFEQT includes a summary score (calculated from 18 of the questions) and subscale scores in three domains: symptoms, daily activities, and treatment concern. The summary and subscale scores range from 0 (corresponds to complete AF-related disability) to 100 (no AF-related disability). A change of 5 or more points in the AFEQT has been identified as a benchmark for a clinically meaningful difference in an individual patient.⁴⁷ Changes from baseline will be assessed overall as well as the proportion of patients in each treatment group who improved their AFEQT scores (12-month value minus baseline value) by ≥ 5 , ≥ 10 , ≥ 15 , and ≥ 20 points. We will also conduct an analysis examining patterns of quality of life at baseline and 12 months by severity levels. AFEQT scores at baseline and 12 months will be divided into categories: severely impaired from AF (scores < 70), mildly to moderately impaired (scores 70-89), and minimally impaired/asymptomatic (scores ≥ 90).⁴⁸
- b. The MAFSI was developed as a modification and update of the AF Symptom Checklist.⁴⁹ The trial will use a modified MAFSI⁵⁰ questionnaire comprised of a 10-item AF symptom checklist that asks about both the frequency and severity of each symptom. The frequency of symptoms is recorded as 0 (never), 1 (rarely), 2 (sometimes), 3 (often), or 4 (always). These responses are summed for a total Frequency Score that ranges from 0 (no AF symptoms) to 40 (worst score). Similarly, MAFSI Severity Scores are recorded as 1 (mild), 2 (moderate), or 3 (extreme). Severity scores are summed and range from 0 (no AF symptoms) to 30 (most severe AF symptoms). For an individual patient, a clinically meaningful change in the MAFSI has not previously been established and therefore will be considered to be about $\frac{1}{4}$ of the pooled baseline standard deviation (SD), or 1.6 points for the Frequency Score and 1.3 points for the Severity Score.⁴⁵ We will

also conduct a responder analysis for the MAFSI Frequency Score (>9, 4-9, and <4 to indicate severely symptomatic, mild to moderately symptomatic, and minimally symptomatic).⁴⁵

The AFEQT and MAFSI will be collected on the trial case report form and will be administered by site coordinators at baseline and the 12-month follow-up visit.

4. Study Design

4.1. Overall Design

Dronedaronone is approved by the Food and Drug Administration to reduce the risk of CV hospitalization in patients with AF or atrial flutter. However, it is unknown if dronedaronone (or any antiarrhythmic medication) can reduce CV hospitalization or death in patients with first-detected AF. This trial has been designed to address this important question. In order to facilitate the trial enrollment, data collection, and generalizability to clinical practice, the CHANGE AFIB study has been designed as an open-label pragmatic clinical trial nested within the Get With The Guidelines (GWTG) Atrial Fibrillation registry. At present the overall GWTG program is being implemented in over 2,300 hospitals across the U.S. and is comprised of over 9 million patient records, with an estimated 650,000 new patient records entered per year. The trial will utilize the existing GWTG registry network, data collection architecture, and experience to facilitate both enrollment and conduct of the trial.

The comparator arm will be “usual care.” Thus, this study will compare usual care plus dronedaronone versus usual care alone. While usual care often varies from center to center, usual care typically consists of an atrioventricular blocking agent (beta-blocker, non-dihydropyridine calcium channel blocker, or digoxin) without an antiarrhythmic drug.[†] As dronedaronone has anti-adrenergic rate controlling properties, a low dose of beta-blocker or calcium-channel blocker is recommended in the USPI when starting dronedaronone. In the dronedaronone arm concomitant digoxin use will be contraindicated due to P-gp interaction based upon data from the PALLAS trial.^{29, 51} All patients will receive oral anticoagulation for stroke prevention according to current guideline recommendations.³³

CHANGE AFIB will leverage several critical advantages as a pragmatic clinical trial.⁵² Data collection will be integrated into the Get With The Guidelines AFIB registry.^{53, 54} The use of the GWTG-AFIB registry will also enhance subject recruitment and ensure the enrollment of a diverse group of patients. The randomized intervention will be compared with usual care thus further enhancing generalizability. Follow-up visits will be minimized to reduce patient burden. Moreover, follow-up visits will have “windows” to accommodate variation in follow-up intervals at different centers.

[†] Orally administered antiarrhythmic drugs for the treatment of atrial fibrillation include Vaughan-Williams class I and III medications, including flecainide, propafenone, sotalol, dofetilide, dronedaronone, and amiodaronone. Note, beta-blockers (class II) and non-dihydropyridine calcium channel blockers (class IV) are not membrane active antiarrhythmic medications.

4.2. Justification for Study Drug Intervention and Dose

Dronedarone is a non-iodinated benzofuran similar to amiodarone but is not associated with thyroid or pulmonary toxicity in randomized clinical trials or post-marketing observational studies.^{55, 56} Dronedarone has electrophysiological characteristics spanning all 4 Vaughan-Williams anti-arrhythmic classes, with primarily class III effects. Initial trials suggested that dronedarone prolonged the time to recurrence of AF and reduced cardiovascular death and hospitalization.^{26, 27}

The landmark ATHENA trial evaluated the efficacy and safety of dronedarone in patients with atrial arrhythmias (atrial fibrillation or atrial flutter). This trial did not include patients with a recent history of NYHA class IV heart failure or recent hospitalization for decompensated heart failure (<4 weeks). Approximately 30% of the ATHENA population had NYHA class I-III heart failure. ATHENA demonstrated that dronedarone 400 mg twice daily (in combination with background therapy) reduced the combined endpoint of CV hospitalization or death from any cause by 24% ($p < 0.001$) compared with placebo. Of course, the ATHENA trial was not conducted in the special population of patients with a new diagnosis of AF. There are no randomized trials or guideline recommendations for antiarrhythmic therapy at the time of first-detected AF. A subgroup analysis from the ATHENA trial suggests that optimal outcomes may be achieved in those patients with shorter duration of AF (time from diagnosis).⁵⁷ Similar observations have also been made in patients undergoing other forms of rhythm control, including catheter ablation.⁵⁸ In this trial, patients with first-detected AF will be randomized to dronedarone on top of usual care versus usual care alone. Patients randomized to the intervention arm will be prescribed and treated with Dronedarone 400 mg bid. This dose has been chosen as it is the Food and Drug Administration approved dose as well as the dose recommended in current international guidelines.^{26, 33} Dronedarone has also been shown to be an effective rate control agent as well. In the ERATO study, treatment with dronedarone 400 mg twice daily led to a mean reduction of 24.5 beat/min in patients with permanent AF when compared with placebo. In the EURIDIS/ADONIS studies the mean difference in patients with paroxysmal/persistent AF during AF recurrence was 14 beats/min.²⁷ Moreover, the dronedarone treated patients experienced improved rate control without any reduction in exercise tolerance as measured by maximal exercise.⁵⁹

5. Study Population

- Eligible patients enrolled in GWTG-AFIB who provide informed consent will undergo randomization in a 1:1 fashion, to dronedarone on top of usual care or usual care alone.

5.1. Inclusion Criteria

Participants are eligible to be included in the study if the following apply:

1. Age 21 years or older.
2. First-detected atrial fibrillation (defined as atrial fibrillation diagnosed in the previous 120 days)
3. Acute care encounter for evaluation or treatment of atrial fibrillation, within 120 days.[‡]
4. Electrocardiographic documentation of atrial fibrillation.
5. Estimated life expectancy of at least 1 year
6. Patient or legal authorized representative capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Patients with prior or planned treatment with rhythm control, either catheter ablation or chronic (>7 days) antiarrhythmic drug therapy.[§]
2. Prior hospitalization for atrial fibrillation (other than the qualifying event).
3. Planned cardiothoracic surgery
4. New York Heart Association class III or IV heart failure or a hospitalization for heart failure in the last 4 weeks
5. Patients with reduced ejection fraction (LVEF \leq 40%)
6. Permanent atrial fibrillation
7. Ineligible for oral anticoagulation, unless CHA₂DS₂-VASc is less than 3 in women or 2 in men.
8. Bradycardia with a resting heart rate < 50 bpm
9. PR interval >280 msec or 2nd degree or 3rd degree atrioventricular block without a permanent pacemaker/cardiac implanted electronic device.
10. Corrected QT interval \geq 500 msec.
11. Pregnancy or breast feeding
12. Severe hepatic impairment in the opinion of the investigator

[‡] Note: Patients can be enrolled from the inpatient setting during this qualifying acute care encounter or afterwards in the outpatient setting, so long as the qualifying acute care event has occurred in the past 120 days. Acute care encounters are defined as a visit to an emergency department, observation unit, or hospital admission.

[§] Acute use of an antiarrhythmic drug in the hospital is not exclusionary. For the purpose of this trial, prior antiarrhythmic drug therapy is defined as chronic antiarrhythmic drug therapy (>7 days).

6. Study Intervention, Usual Care, and Concomitant Therapy

The study intervention will be treatment with oral dronedarone 400 mg twice daily in addition to usual care. The comparator arm will be usual care alone. Usual care will be defined as best-practice, guideline-directed therapy of AF, including but not limited to (a) stroke prevention therapy, (b) rate-control, and (c) treatment of risk factors. More specifically, oral anticoagulation in those men with a CHA₂DS₋₂VASc score of 2 or greater or women with a CHA₂DS₋₂VASc score of 3 or greater, rate control, and treatment of concomitant cardiovascular conditions (e.g. coronary artery disease or heart failure) will be required in all trial participants. As defined in the protocol, those randomized to the dronedarone arm will be prescribed 400 mg oral dronedarone twice daily. Similar to the approach in the EAST trial, those randomized to usual care alone will initially be treated without rhythm-control therapy¹⁴, however rhythm-control therapy (except dronedarone) may be initiated during follow-up in the usual care arm to ameliorate AF-related symptoms despite adequate rate-control therapy per current guideline recommendations. In the dronedarone arm concomitant digoxin use is contraindicated due to P-gp interaction based upon data from the PALLAS trial.²⁹

6.1. Measures to Minimize Bias: Randomization

This is an open-label study; however, the specific intervention to be taken by an enrolled participant will be randomly assigned. Participants will be randomly assigned 1:1 to dronedarone on top of usual care or usual care alone. Randomization will be created with a random block size. All participants will be centrally assigned to randomized study intervention using an interactive web response system (IWRS). The site will contact the IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form, if required. Potential bias will be reduced by the use of central randomization. Site staff and participants will not know the randomized sequence of treatment assignment prior to enrollment. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

6.2. Study Intervention Compliance

The intervention will be prescribed by the treating physician. Study drug will not be supplied as part of the study. Insurance coverage for dronedarone will be verified as part of the study evaluation and screening process. Participants in the intervention arm will be contacted within 10 days of randomization to verify that they have filled and started taking their prescription for dronedarone. Participants will self-administer the study intervention at home and compliance will be assessed at each visit. There is one guideline-recommended therapeutic dose of dronedarone. Any deviation(s) from the prescribed dosage regimen should be recorded. At the end of the study, the patient's physicians will determine whether to stop or continue dronedarone.

6.3. Concomitant Treatment

Concomitant drug therapy will be recorded in the case report form at baseline and all follow-up periods. In the dronedarone arm concomitant digoxin use is contraindicated due to P-gp interaction based upon data from the PALLAS trial.²⁹ Observational data have observed a small increased risk of bleeding in patients treated with dronedarone and direct acting oral anticoagulants, however, there is no apparent increased risk of intracranial bleeding.⁶⁰

Cardioversion (pharmacologic or electrical) is not an exclusion and is permitted throughout the trial. Patients who are planned or scheduled to undergo catheter ablation during screening or at the baseline visit are not eligible. Following enrollment, if a patient experiences escalation of symptoms or refractory symptoms, escalation of rhythm control interventions, including catheter ablation, can be considered if deemed necessary by the patient's treating physician.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the schedule of activities for the last participant in the study. A participant is considered to have completed the study if he/she has completed all periods of the study including the last study visit at 12 months, or if deceased during the follow-up period.

Patients should not be discontinued when they experience a primary endpoint event. They should continue in the trial until the end of study visit at the end of follow-up. The study intervention therapy should be continued unless deemed otherwise by the treating physician or if the patient requires initiation of a different antiarrhythmic medication.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study until they complete 12-month follow-up/final visit.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon. The participant will be permanently discontinued from the study intervention and the study at that time. If the participant withdraws consent for disclosure of future information, any data collection before withdrawal of consent can be used.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he/she fails to complete the final 12 month visit and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, [3] telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is

determined as deceased, this will be documented and the participant will not be considered lost to follow-up.

8. Study Assessments and Procedures

Patient eligibility will be evaluated. Eligible patients who express interest in participating and express informed consent will undergo enrollment and randomization. Patients can be enrolled in the inpatient setting during their qualifying acute care encounter or afterwards in the outpatient setting so long as their new-onset atrial fibrillation and acute care visit were in the prior 120 days. At the baseline encounter (enrollment and randomization) data on the inclusion and exclusion criteria will be recorded in REDCap and the randomization module in REDCap will assign a treatment arm if participant meets all inclusion and exclusion criteria. The GWTG-AFIB registry data and additional data on the patient's medical and cardiovascular history will be recorded in the Get With The Guidelines CHANGE AFIB case report form. There are no special laboratory testing procedures or interventional procedures required by the protocol other than the randomized treatment. All data, including electrocardiographic, echocardiographic, laboratory, and other baseline data will be obtained as part of the participant's usual care. The two quality-of-life measures will be recorded at baseline and the 12 month follow-up visit as well as previously detailed.

There are two pre-specified follow-up encounters. The first will occur at 6 months with an eligibility window between 3 and 9 months. This encounter can be either in-person or a virtual assessment. At the 6-month visit, the 6-month follow-up form will be completed in the Get With The Guideline CHANGE AFIB case report form. The second pre-specified encounter will be the final follow-up encounter at 12 months (window of ± 30 days). Similar to the 6 month encounter, the final visit can be either in-person or a virtual assessment. At this final follow-up visit, the final visit module will be completed in the Get With The Guideline CHANGE AFIB case report form. Participants will also complete the final quality-of-life assessments at this same encounter. Patients who withdraw early or experience mortality will also have the final follow-up form completed.

8.1. Outcomes Assessments

Planned timepoints for all assessments are provided in the assessment table. Get With The Guidelines (GWTG) has several quality control assessments. Bi-annual data quality reports are provided by Duke Clinical Research Institute, which highlight the health of the GWTG data set, levels of element completion, and any areas of inconsistency. GWTG has an annual audit process, where a random sample of hospitals are selected for chart re-abstraction to independently assess data quality. GWTG sites are trained on the detailed data definitions provided to sites. Sites will be familiar and comfortable with the level of detail provided in the data definitions for various CHANGE AFIB endpoints. A nationwide audit was conducted among 147 hospitals and results were published in the *American Heart Journal* validating the health and reliability of the GWTG data set.⁶¹

8.1.1. Pregnancy

Women of reproductive age should use measures to prevent pregnancy during the study. Nevertheless, in case of pregnancy, the sponsor and coordinating center should be notified

immediately. Follow-up of the pregnancy will be mandatory until the outcome has been determined. Pregnancy will be recorded as an adverse event in all cases and dronedarone should be immediately discontinued. Pregnancy will be considered a severe adverse event only if it fulfills the severe adverse event criteria.

8.2. Adverse Events (AEs) Serious Adverse Events (SAEs), and Other Safety Reporting

All participating centers will receive adequate training regarding pharmacovigilance specifications and reporting of adverse events among patients taking dronedarone as part of their onboarding process. Participating centers will be responsible to inform Sanofi of any complaints on the Product to Sanofi PV at 1-800-633-1610 immediately, but in any event within three (3) business days, after becoming aware of the complaint. Any additional documentation of these cases will be conducted by Sanofi U.S. PV. Due to the pragmatic nature of the Study, all Adverse Events should be reported by the individual facilities, as instructed by current regulations, to Sanofi PV at 1-800-633-1610.

Prior clinical trials and observational data have demonstrated that individuals taking dronedarone have higher rates of diarrhea (9% vs 6% in ATHENA), bradycardia (3% versus 1% in ATHENA), QT-interval prolongation** (28% vs 19%) and cutaneous rash (5% versus 3%) than patients taking placebo. The case report form will query and document the occurrence of these and other adverse/safety events of interest as shown in **Table 3**.

| Table 3. Pre-specified Safety Events of Interest |
|--|
| Symptomatic bradycardia |
| 2 nd or 3 rd degree atrioventricular block |
| Pacemaker implantation |
| QT prolongation |
| Cutaneous rash |
| Hepatic injury. <i>Hepatic injury will be defined AST or ALT greater than 3x the upper limit of normal or clinical findings of hepatic insufficiency (jaundice, ascites, etc).</i> |
| New-onset heart failure (Note that this event is also an efficacy endpoint) |
| Heart failure hospitalization (Note that this event is also an efficacy endpoint) |

** QT prolongation was defined as QTc Bazett >450 msec in males or >470 msec in females.

Ventricular arrhythmia (including sustained ventricular tachycardia or nonsustained polymorphic VT/torsades)

Major bleeding. *Note Major bleeding will be defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria: 1) Fatal bleeding, and/or 2) Symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), and/or 3) Bleeding causing a fall in hemoglobin level of 20 g L⁻¹ (1.24 mmol L⁻¹) or more, or leading to transfusion of two or more units of whole blood or red cells.*⁶²

Initiation of dronedarone is contraindicated in patients with severe heart failure (NYHA class IV) or NYHA Class II - III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic in the prior 4 weeks. Similar patients in the ANDROMEDA trial receiving dronedarone were observed to have a greater than 2-fold increase in mortality compared to placebo.³⁰ Accordingly, patients with NYHA class III and IV heart failure or any individual with a heart failure hospitalization in the last 4 weeks will be excluded from the trial. Additionally, any patients with an ejection fraction less than or equal to 40% will be excluded from the trial. The trial will document hospitalization for new or worsening heart failure during the follow-up period. It is important to note that dronedarone competes with creatinine for the renal tubular cation transport pathway, inhibiting tubular secretion of creatinine by approximately 18% and subsequently increasing serum creatinine without affecting renal function. This is of importance when considering down-titration/discontinuation of ACE/ARBs.

9. Statistical Considerations

The statistical analysis plan will be finalized before the first data and safety monitoring board (DSMB) meeting with blinded review of data, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary efficacy endpoints, patient reported outcomes, and key safety outcomes.

9.1. Statistical Hypotheses

The primary efficacy objective is to determine if treatment with dronedarone on top of usual care is superior to usual care for the prevention of unplanned cardiovascular hospitalization or death from any cause within 12 months of randomization in patients with first-detected atrial fibrillation.

- The null hypothesis is that the hazard rate of first unplanned cardiovascular hospitalization or death from any cause through 12 months of follow-up in the dronedarone + usual care arm is not different from the hazard rate in the usual care arm.

Key secondary efficacy objectives are to assess the efficacy of treatment with dronedarone on top of usual care versus usual care on

- WIN Ratio
- Time to first unplanned CV hospitalization
- All-cause mortality

There will also be a **patient reported outcomes** study. Patient reported change in quality of life at 12 months compared to baseline, assessed by the AFEQT and by the MAFSI AF-related quality of life questionnaires.

The key safety objective is to characterize the incidence of specific safety events of interest in patients taking dronedarone versus usual care (defined in **Table 3**).

9.1.1. Multiplicity Adjustment

Formal statistical hypothesis testing will be restricted to the primary objective and the win ratio (the first secondary objective). Type I error (one-sided $\alpha=0.025$) will be controlled for these objectives using the gatekeeping testing strategy adapted from Maurer & Bretz (2013),⁶³ accounting for one unblinded interim analysis. The details of multiplicity adjustment are described in Section 9.4 below.

9.2. Analysis Sets

| Population | Description |
|-----------------------|--|
| Intent-to-treat (ITT) | <ul style="list-style-type: none"> • All randomized participants will be included in the analyses according to the intervention arm they were assigned, |

| Population | Description |
|---|---|
| | regardless of treatment initiation, discontinuation or switching. |
| On treatment population and on-treatment period | <ul style="list-style-type: none"> All randomized participants who took the assigned treatment will be included in the analyses according to the intervention arm they were assigned until they switch or discontinue the assigned treatment regimen. Follow-up will be censored 5 days after treatment switching or discontinuation, i.e. all events occurring until 5 days after discontinuation or switching to the other treatment group will be attributed to the randomized group and all events occurring later than 5 days after discontinuation or switching will be censored. Participants in the usual care arm who start dronedarone drug therapy will be considered to have switched treatment regimen. Participants in the dronedarone arm who temporarily suspend or are non-adherent with dronedarone for >14 consecutive days will be considered to have discontinued treatment. |

9.3. Statistical Analyses

9.3.1. General Considerations

- A detailed Statistical Analysis Plan (SAP) will be developed and contained in a separate document. Study population details including the number randomized to each treatment arm, the number completing the study, and lost to follow-up will be described. Baseline participant characteristics will be summarized as means, standard deviations, medians, and/or 25th, 75th percentiles for continuous variables, and as counts and percentages for categorical variables. Unless otherwise stated, tests of hypotheses about the efficacy of dronedarone will be one sided ($\alpha=0.025$) and effect estimates will be presented with nominal 95% confidence intervals (CI).

9.3.2. Primary Efficacy Estimand Analysis

| | |
|---|---|
| Question of Interest | Does the treatment with dronedarone on top of usual care reduce cardiovascular hospitalization or death from any cause in patients with first-detected atrial fibrillation without heart failure compared to usual care alone? |
| Objective Description / Study Population | Primary objective of the study / All randomized participants |
| Endpoint | Time from randomization to the first occurrence of unplanned cardiovascular hospitalization or death from any cause within 12 months of randomization |
| Intercurrent Events | Early study withdrawal or lost-to-follow-up: follow-up will be censored at the last date when patient event status was known. Analysis will assume that censoring is non-informative. All other intercurrent events will be ignored in these analyses. |
| Population Summary | Hazard ratio estimate based on a Cox proportional hazards model. Values below 1.0 suggest benefit from the treatment with dronedarone and usual care versus usual care alone. |

The Cox proportional hazards model will be fit for time to first event with the treatment group as exposure variable. The treatment effect will be presented as a hazard ratio (dronedarone on top of usual care vs. usual care) and a 95% CI and P-value.

9.3.3. Key Secondary Efficacy Estimand Analysis

9.3.3.1. WIN Ratio

| | |
|---|--|
| Question of Interest | To assess the efficacy of treatment with dronedarone on top of usual care versus usual care on adverse outcomes in patients with first-detected AF. |
| Objective Description / Study Population | Key secondary objective of the study / All randomized participants |
| Endpoint | Multivariate endpoint consisting of the measures listed in Table 2 |
| Intercurrent Events | All other intercurrent events will be ignored in these analyses. |
| Population Summary | Win ratio estimate. Values above 1.0 suggest benefit from the treatment with dronedarone and usual care versus usual care alone |

Unmatched win ratio model according to Finkelstein and Schoenfeld method (1999) compares every patient on the dronedarone arm with every patient in the usual care arm, noting 'winner',

‘loser’, or ‘tied’ for each comparison. For each pair, the component outcomes will be compared in descending order of importance until one of the patients in the pair demonstrates a better outcome compared with the other. The hierarchy of component outcomes are shown in **Table 2**. For example, the dronedarone arm is a ‘winner’ or ‘loser’ according to who had an all-cause death first. If that is unknown, then whether they are labelled a ‘winner’ or ‘loser’ depends on who had an ischemic stroke or systemic embolism first, except all-cause mortality. In a similar way using the rest of hierarchy of outcomes, decide a ‘winner’ or ‘loser’. Otherwise, they are considered tied. The win ratio is the total number of dronedarone arm winners divided by the total number of dronedarone arm losers. A 95% CI and P-value will be obtained by Luo’s method (2015).⁶⁴ Statistical significance will be determined using the multiplicity adjustment methods described below in **Table 4**.

9.3.3.2. Cardiovascular Hospitalization

| | |
|---|---|
| Question of Interest | To assess the efficacy of treatment with dronedarone on top of usual care versus usual care on the rate of first occurrence of unplanned cardiovascular hospitalization in patients with first-detected AF. |
| Objective Description / Study Population | Key secondary objective of the study / All randomized participants |
| Endpoint | Main analysis: Time from randomization to the first occurrence of unplanned cardiovascular hospitalization within 12 months of randomization. Exploratory analysis: Overall rate of all recurrent cardiovascular hospitalization events within 12 months of randomization. |
| Intercurrent Events | Death – follow-up will be censored at date of death. Hazard ratio for cardiovascular hospitalization will be estimated among participants still alive and in follow-up. Early study withdrawal or lost-to-follow-up – follow-up will be censored at the last date when patient event status was known. Analysis will assume that censoring is non-informative. All other intercurrent events will be ignored in these analyses. |
| Population Summary | Main analysis: Hazard ratio estimate based on a Cox proportional hazards model for time to first event. Exploratory analysis: Hazard ratio estimate based on a proportional intensity model developed by Anderson & Gill (1982) using all recurrent events. Hazard Ratio values below 1.0 suggest benefit from the treatment with dronedarone and usual care versus usual care alone |

For the main analysis the Cox proportional hazards model will be fit for time to first event with the treatment group as exposure variable. Follow-up will be censored early if death occurs prior to cardiovascular hospitalization. The treatment effect will be presented as a cause-specific hazard ratio (dronedarone on top of usual care vs. usual care) and a nominal 95% CI.

For the exploratory analysis a generalization of the Cox model to handle recurrent events, developed by Anderson & Gill (1982), with robust standard errors to account for individual patients' heterogeneity. Even though the Anderson-Gill approach assumes independence between all observed event times irrespective whether these event times correspond to the same patient or to different patients, this approach will be the analysis method for the total number of events of cardiovascular hospitalization. The treatment effect will be presented as a hazard ratio (dronedarone on top of usual care vs. usual care) and a nominal 95% CI.

9.3.3.3. All-cause Mortality

| | |
|---|--|
| Question of Interest | To assess the efficacy of treatment with dronedarone on top of usual care versus usual care on the rate of all-cause mortality in patients with first-detected atrial fibrillation |
| Objective Description / Study Population | Key secondary objective of the study / All randomized participants |
| Endpoint | Time from randomization to death within 12 months of randomization |
| Intercurrent Events | Early study withdrawal or lost-to-follow-up – follow-up will be censored at the last date when patient event status was known. Analysis will assume that censoring is non-informative. All other intercurrent events will be ignored in these analyses. |
| Population Summary | Hazard ratio estimate based on a Cox proportional hazards model. Values below 1.0 suggest benefit from the treatment with dronedarone and usual care versus usual care alone |

The Cox proportional hazards model will be fit for time to death with the treatment group as exposure variable. The treatment effect will be presented as a hazard ratio (dronedarone and usual care vs. usual care) and a nominal 95% CI.

9.3.4. Tertiary Efficacy Endpoints Analysis

Analysis methods for the tertiary efficacy endpoints will be provided in the statistical analysis plan.

9.3.5. Patient reported outcomes (12-month change in quality of life)

| | |
|---|--|
| Question of Interest | To estimate the effect of treatment with dronedarone versus usual care on 12-month change in patient reported quality of life in patients with first-detected AF. |
| Objective Description / Study Population | Patient reported outcomes study / All randomized participants who did not die during follow-up |
| Endpoints | 12-month change in quality of life compared to baseline, assessed by AFEQT Overall Score and by MAFSI Total Severity score. |
| Intercurrent Events | Death – 12-month change in quality of life will be assessed in participants who were alive at the 12-month follow-up assessment. Early study withdrawal, lost-to-follow-up, or missing assessment – analysis will assume that missing data due to withdrawal, lost-to-follow-up or other reasons is not informative conditional on patient demographics, heart failure status, time since AF diagnosis, and baseline value of quality of life assessments. Analysis will adjust for missing data using inverse probability weighting. |
| Population Summary | Difference in mean change from baseline between dronedarone versus usual care, estimated using analysis of covariance. For the AFEQT, a mean difference greater than zero suggests benefit from treatment with dronedarone versus usual care alone. For the MAFSI, a mean difference less than zero suggests benefit from treatment with dronedarone versus usual care alone. |

This objective will be assessed using Analysis of Covariance (ANCOVA) with the 12-month change in quality of life (12-month score – baseline score) as response variable, treatment group as exposure, and baseline score as covariates. Inverse probability weighting will be used to adjust for missing data. The treatment effect will be presented as the difference between mean 12-month change (dronedarone and usual care vs. usual care) and a nominal 95% CI.

9.3.6. Safety Analyses

All safety analysis will be performed in the on-treatment (OT) population during the on-treatment period. A linearized event rate for each safety endpoint (see Section 8.2) for each treatment group will be calculated as percentage per patient year, and the approximate 95% CI for the difference of linearized event rates will be calculated as

$$\left(\frac{r_D}{T_D} - \frac{r_U}{T_U} \right) \pm 1.96 \sqrt{\frac{r_D}{T_D^2} + \frac{r_U}{T_U^2}}$$

where subscript D and U denote the dronedarone and usual care arms, respectively, and r is the total number of occurrences of the safety outcome, and T is the total patient time (years).⁶⁵

9.3.7. Other Analyses

On treatment analysis of efficacy endpoints

As sensitivity analyses, the primary and key secondary objectives will be tested using the OT population during the on-treatment period.

Pre-Specified Subgroups of Interest

Subgroup analyses for the primary outcome will be performed to assess whether the therapeutic effect is consistent across all patients, or whether it varies according to specific patient characteristics. These analyses will focus on whether the relative therapeutic effect differs according to the following baseline variables:

- Age (<70 years vs. ≥ 70 years)
- Sex (male vs. female)
- Race (white vs. racial minorities)
- AF type (paroxysmal vs. persistent, or long-standing persistent)
- Left atrial dimension (<50 mm versus ≥ 50 mm)
- AF duration (<30 days versus ≥ 30 days)
- Structural heart disease (present vs. absent)
- Hypertension (present vs. absent)
- Chronic kidney disease (estimated eGFR ≤ 60 vs. > 60 ml/min)
- CHA₂DS₂-VASc score (0-1 vs. ≥ 2 excluding sex)
- Sleep Apnea (present vs. absent)
- BMI (<30 vs. ≥ 30)
- Heart failure vs no heart failure
- Left ventricular ejection fraction (LVEF) (41-55 vs. > 55)

Cox proportional hazards regression modeling will be used to assess whether treatment effect is heterogeneous across pre-specified subgroups. For each subgroup analysis, the Cox proportional hazards model will be fit for time to first event including the subgroup as a stratification factor, and the treatment group and interaction between treatment and subgroup as covariates. The treatment effect within each subgroup level will be presented as a hazard ratio (dronedarone on top of usual care vs. usual care) and a 95% CI. Heterogeneity will be assessed by presenting the interaction P-value, using a two-sided test.

9.4. Data Safety & Monitoring Board & Interim Analysis

There will be a Data and Safety Monitoring Board (DSMB) in this pragmatic clinical trial. The DSMB will be an independent group of experts that advises the principal investigator, steering committee, and study investigators. The DSMB will consist of one statistician and two clinicians with expertise in clinical trials and in the management of AF. The members of the DSMB will serve in an individual capacity and provide their expertise and recommendations.

The DSMB will meet approximately every 6 months to monitor the recruitment and conduct of trial, data quality and timeliness, the distribution of therapies within the study groups, the occurrence of safety and other events selected to their discretion during the course of the trial. The DSMB chair will receive a quarterly report between two regular meetings.

Since the event rate of the primary outcome is closely associated with the statistical study power, a blinded sample size and power analysis based on the overall event rate will be included in the regular DSMB report. Recommendations for the sample size adjustment by DSMB will be made before the interim analysis based on trying to maintain $\geq 85\%$ power for the primary outcome and allow to increase as much as 35% but no reduction.

If a clinically significant imbalance in efficacy or safety events between the groups is observed at any time, the DSMB Chair may request an unblinded analysis. Similarly, if the DSMB identifies any other concerns, the Chair can call a separate meeting. A DSMB charter providing operating procedures and responsibilities will be discussed, drafted, and implemented by the DSMB and an unblinded statistician.

In addition to these routine safety reviews, an interim analysis for efficacy and futility of the primary objective is planned at approximately 50% of total information, i.e. when 50% of the expected total number of events (approximately 733 events, see **Table 4** below) are collected. The Lan-DeMets spending function similar to the O'Brien-Fleming boundaries will be used to monitor the efficacy of the primary outcome as a guide for the DSMB. See **Table 4** for the details of these procedures. This spending function is conservative in that priority is given to preserving power for the final analysis with the use of stringent stopping rules early in the study. For futility, conditional power will be calculated under originally hypothesized hazard ratio, the null hypothesis and the observed trend at the interim analysis and will be compared with 10%. The futility stopping rules will be considered non-binding by the DSMB in their review of interim data.

If the primary endpoint is declared to be statistically significant in the favorable direction at a one-sided alpha level of 0.025, win ratio as the first key secondary endpoint will be tested according to an OBF-like boundary. See **Table 4** for the details of these procedures.

Table 4. Significance level for the primary endpoint and win ratio

| | At the interim analysis at 50% | At the final analysis | One-sided nominal significance level |
|--|---------------------------------------|------------------------------|---|
| One-sided significance level for the primary hypothesis | 0.0153 | 0.0245 | 0.025 |
| One-sided significance level for win ratio if the primary endpoint is declared significant | 0.0153 | 0.0245 | 0.025 |

The Steering Committee will approve the timing of all interim analyses proposed by the DSMB. 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 continue as planned.

9.5. Sample Size Determination

- With a planned accrual time of 1.5 years, a fixed follow-up period of 1 year, an assumed lost to follow up of 20% before 12 months (assuming exponential distribution for time-to-censoring), a two-sample log-rank test with two-sided alpha of 0.05, a cumulative incidence function (CIF) of 30% at 12 months in the usual care arm, an assumed hazard ratio of 0.79, one interim analysis using the Lan-DeMets spending function similar to the O'Brien-Fleming boundaries, a planned sample size of 3000 patients (1500 patient per arm) provides approximately 89% study power as shown in the following table:

Table 5. Study power and number of events with 3000 patients
Estimated by Markov chain Monte Carlo simulations with 10,000 iterations

| Hazard Ratio (Dronedarone vs. Usual care) | 0.78 | 0.79 | 0.80 |
|---|------|------|------|
| Nominal Power | 0.92 | 0.89 | 0.86 |
| Total number of events | 730 | 733 | 737 |

- The study will be conducted at sites participating in the GWTG-AFIB Registry. Some sites will be centers that are established GWTG-AFIB sites and others will be recruited to participate in GWTG-AFIB for the purpose of this study. We will attempt achieve a total of up to 200 sites. There have been more than 40,000 patients included in the GWTG-AFIB Registry. For the purpose of this pragmatic trial, patients will be approached during their first admission with first-detected AF. Preliminary query of the GWTG-AFIB database suggests that greater than 1400 patients were enrolled each year in GWTG with new-onset AF and no heart failure. Using the Jan 2020 GWTG-AFIB data harvest, there were a total of 8,192 patients meeting the inclusion/exclusion criteria (see Table 6). As we plan to include sites beyond GWTG-AFIB sites, we plan to enrol 3000 patients in 18 months.

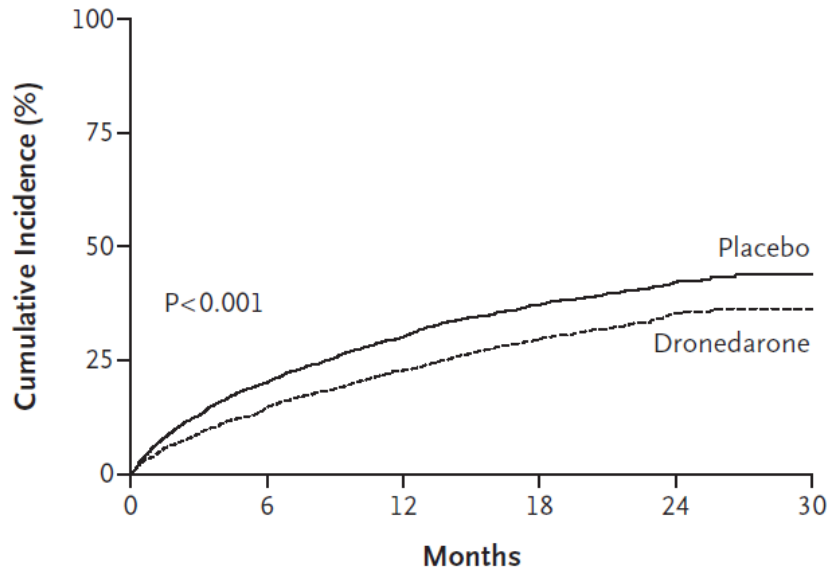
Table 6. Distribution of Admissions for GWTG-AFIB Registry Patients

| Admission Year | Frequency (patients) | Percent | Cumulative Frequency (patients) | Cumulative Percent |
|----------------|----------------------|---------|---------------------------------|--------------------|
| 2013 | 65 | 0.79% | 65 | 0.79% |
| 2014 | 390 | 4.76% | 455 | 5.55% |
| 2015 | 1229 | 15.00% | 1684 | 20.56% |
| 2016 | 1429 | 17.44% | 3113 | 38.00% |
| 2017 | 1750 | 21.36% | 4863 | 59.36% |
| 2018 | 1871 | 22.84% | 6734 | 82.20% |
| 2019 | 1458 | 17.80% | 8192 | 100.00% |

In the ATHENA trial a post-hoc analysis was conducted that analyzed events according to the duration of AF history.²⁶ Using event rates in the placebo and dronedarone arms among patients with a duration of AF history <3 months (45% of the ATHENA study cohort), the expected hazard ratio for dronedarone vs. placebo was ~0.79 for the primary endpoint of CV hospitalization or death evaluated through 12 months of follow-up. The event accumulation in

placebo arm through 12 months in the ATHENA trial was CIF% of approximately 10%, 20%, 25%, and 30% at 3, 6, 9, and 12 months, respectively, as shown in **Figure 1**.²⁶ The estimated sample size by various statistical power and hazard ratio are shown in **Table 7**. To account for one interim analysis using the Lan-DeMets spending function similar to the O’Brien-Fleming boundaries, the estimated sample size should be inflated by 1.01.⁶⁶ Therefore, the study will enroll approximately 3000 patients.

Figure 1. Event accumulation in placebo arm through 12 months in the ATHENA trial



| No. at Risk | | | | | | | |
|---------------|------|------|------|------|-----|---|--|
| Placebo | 2327 | 1858 | 1625 | 1072 | 385 | 3 | |
| Dronedaronone | 2301 | 1963 | 1776 | 1177 | 403 | 2 | |

Table 7. Total sample size estimated with 20% attrition by 12 months, two-sided log-rank test, alpha=0.05, placebo CIF curve like ATHENA (30% with event by 12 months)

| Nominal Power | Hazard Ratio (Dronedaronone vs. Placebo) | | | | | |
|---------------|--|------|------|------|-------------|------|
| | 0.75 | 0.76 | 0.77 | 0.78 | 0.79 | 0.80 |
| 0.85 | 1794 | 1960 | 2148 | 2364 | 2612 | 2898 |
| 0.86 | 1848 | 2018 | 2212 | 2434 | 2688 | 2984 |
| 0.87 | 1904 | 2080 | 2280 | 2508 | 2770 | 3074 |
| 0.88 | 1964 | 2146 | 2352 | 2588 | 2858 | 3172 |
| 0.89 | 2030 | 2216 | 2430 | 2674 | 2954 | 3278 |
| 0.90 | 2100 | 2294 | 2514 | 2766 | 3056 | 3392 |

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
 - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
 - Applicable ICH Good Clinical Practice (GCP) guidelines
 - Applicable laws and regulations
- The protocol, protocol amendments, ICF, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
 - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
 - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations.

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Electronic Informed Consent (eIC) may be used to either supplement or replace paper-based informed consent processes.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

- A copy of the ICF(s) must be provided to the participant or their legally authorized representative.

10.1.3. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in Get With The Guidelines AFIB.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.4. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study/Site Termination

- The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor.
- Study sites will be closed upon study completion.
- A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.
- The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators and the IECs/IRBs of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.5. Registry Organization and Leadership

Duke University and Duke Clinical Research Institute (DCRI) along with the sponsor (American Heart Association) will be responsible for the CHANGE AFIB trial and its design,

implementation, and leadership. A Steering Committee that includes representatives from cardiology, electrophysiology, biostatisticians and clinical trialists will govern the operations of the trial. The Scientific Advisory Committee consists of Executive Co-Chairmen, an Executive Committee, and a Steering Committee.

Steering Committee

The Steering Committee will include prominent US thought leaders in clinical trial conduct, experts in the evaluation and management of atrial fibrillation, and the study leadership. An appropriately qualified representative from Sanofi will have a voting seat on the Steering Committee. The Steering Committee will be responsible for the scientific leadership of the CHANGE AFIB Trial. The Steering Committee will be led by the study Chair.

10.1.6. Intended Use of Information and Publication

Data generated from the study will be published. The Steering Committee will also serve as the Publication Committee and shall oversee the publication of study data. The Publication Committee will function as an independent body of scientific and medical experts acting to fulfill the study sites' obligations to the study participants, and shall act to facilitate, encourage, and coordinate complete and accurate dissemination of the results of the study.

All manuscripts approved by the Publication Committee shall conform to the Uniform Requirements for Manuscript Submitted to Biomedical Journals, including, but not limited to the standards for authorship.

- The steering committee will submit all manuscripts or abstracts to the American Heart Association, Duke Clinical Research Institute, and Sanofi for approval before submission. This allows all organizations to provide comments and ensure accuracy of any included statements.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

There are no required laboratory tests for the purpose of this trial, however, laboratory data that is conducted in the course of usual care will be collected in the case report forms.

Regarding potential guidance in the event of hepatic injury: ALT [or AST] $>3 \times$ upper limit of normal (ULN) and total bilirubin $>2 \times$ ULN ($> 35\%$ direct bilirubin) OR ALT [or AST] $>3 \times$ ULN and international normalized ratio (INR) > 1.5 (if INR measured) may indicate severe liver injury (Hy's law), and must be reported in an expedited manner.

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