Official Protocol Title:	A Randomized Parallel-Group, Placebo-Controlled, Double-Blind, Event-Driven, MultiCenter Pivotal Phase III Clinical Outcome Trial of Efficacy and Safety of the Oral sGC Stimulator Vericiguat in Subjects With Heart Failure With Reduced Ejection Fraction (HFrEF) - VerICiguaT Global Study in Subjects With Heart Failure With Reduced Ejection Fraction (VICTORIA)
NCT number:	NCT02861534
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Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

TITLE:

A Randomized Parallel-Group, Placebo-Controlled, Double-Blind, Event-Driven, Multi-Center Pivotal Phase III Clinical Outcome Trial of Efficacy and Safety of the Oral sGC Stimulator Vericiguat in Subjects With Heart Failure With Reduced Ejection Fraction (HFrEF) - VerICiguaT Global Study in Subjects With Heart Failure With Reduced Ejection Fraction (VICTORIA)

IND NUMBER: 116,743

EudraCT NUMBER: 2016-000671-25

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
4.2.1 5.11 8.1	Rationale for the Trial and Selected Patient Population Clinical Criteria for Early Trial Termination Statistical Analysis Plan Summary	Section updated to indicate that futility analysis will be performed at 75% of CV death events. In addition, CV death assessment has been added to the futility criteria.	Due to a higher than projected number of primary composite events in the trial thus far, the futility analysis as originally proposed would be conducted earlier than planned and would occur at a time when insufficient study follow-up was achieved to enable an adequate futility assessment. The futility analysis is now being revised to ensure that adequate study follow-up will be achieved at the time when the futility analysis is conducted. Also futility criteria on CV death have been added to the futility criteria, to be consistent with the efficacy interim analysis approach.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
8.7.1 8.7.2	Futility Interim Analysis Efficacy Interim Analysis	Futility analysis approach and futility bounds have been revised. Language related to the number of primary endpoint events is revised.	The analysis approach and futility bounds have been updated to take into consideration that more endpoint and longer follow-up data will be available at the time of updated futility analysis compared to the previous approach. Additionally, since the study duration will be driven by the number of CV death events, the expected number of primary endpoint events may differ from the actual observed number of events.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
4.3	Benefit/ Risk	Section updated to indicate that additional details regarding expected adverse reaction terms for subjects participating in this clinical trial are found in the Reference Safety Information included in the IB	To make clear for investigators and sites participating in the trial where reference safety information can be found.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.1.2	Subject Inclusion Criteria	Per inclusion criterion 5, elevated natriuretic peptides are required for study inclusion and minimal natriuretic peptide cut-offs are listed for sinus rhythm and atrial fibrillation. A note was added to this inclusion criterion 5 to indicate selection of the most appropriate natriuretic peptide level cut-off for a given patient should be guided by the investigator's judgment of the impact of the heart rhythm at the time of blood draw on natriuretic peptide levels.	In addition to the severity of heart failure, natriuretic peptide levels can be increased by the presence of atrial fibrillation. Patients with a medical history of atrial fibrillation may fluctuate between sinus rhythm and atrial fibrillation. In these cases, the investigator's medical judgment is required to determine the relevance of the rhythm status near the last measurement on natriuretic peptides in determining the appropriate cut-off for study inclusion.
5.1.3	Subject Exclusion Criteria	Exclusion #5 which states "Has known allergy or sensitivity to any sGC stimulator" has been clarified to indicate that it also applies to subjects that have a prior history of hypersensitivity reaction to the active substance of the investigational product or any of its constituents.	A prior hypersensitivity reaction in exclusion #5 relates to either the active substance of the investigational product or to any of its constituents.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.1.3	Subject Exclusion Criteria	The inclusion/exclusion criteria related to pregnancy have been clarified by stating within Exclusion #26 that subjects who are pregnant or plan to become pregnant during the course of the trial are excluded from the trial.	This clarification has been added to explicitly state that subjects who are pregnant or planning pregnancy should be excluded from the trial.
5.2.1.2 6.0	Dose Modification Trial Flow Chart	Text updated and footnote "y" added to clarify the instances in which the Table 2 dose modification guidance is to be followed.	Table 2 dose modification guidance should be applied at all scheduled and unscheduled visits in which a SBP assessment is performed.
5.7.3	Use in Pregnancy	If a female subject of child-bearing potential becomes pregnant during the study, study treatment will be discontinued; however, follow-up in the trial will continue until study completion. Such a subject would not be removed from the study.	VICTORIA is a double-blinded study; study treatment remains blinded throughout the trial period. A subject discontinued from study treatment should still be followed until study completion.
6.0	Trial Flow Chart	The Study Flow Chart is being revised to indicate that in subjects who discontinue study treatment prematurely, follow-up study visits should occur every 16 weeks from the previous study contact.	This revision provides a consistent approach to follow-up for subjects who prematurely discontinue study therapy.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.0	Trial Flow Chart	Per footnote "o" of the Trial Flow Chart, the local laboratory tests of creatinine (for eGFR calculation) and NT-proBNP or BNP for study eligibility evaluation must be from assessments within 30 days before randomization. The assessments within 30 days before randomization can include recent historical local laboratory assessments available for the patient.	This clarification is being provided to ensure research sites understand that a recent local laboratory assessment available for patients within 30 days before randomization can be used to evaluate the eGFR and NT-proBNP / BNP requirements for the trial.
6.0	Trial Flow Chart	Canadian Cardiovascular Society Functional Classification of Angina (CCSA) added to Trial Flow Chart.	CCSA is to be performed at screening in all subjects with active stable angina.
6.0	Trial Flow Chart	Footnotes "v" and "w" have been revised to indicate that the baseline echocardiogram and cardiac magnetic resonance imaging procedures should be performed prior to study drug administration and may be performed over the course of the screening period.	This update allows additional flexibility in scheduling the baseline imaging procedures for those subjects participating in the Echocardiography and/or Cardiac Magnetic Resonance Imaging substudies.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.0	Trial Flow Chart	Footnote "aa" was added to clarify that Clinical Events Assessment includes an assessment for the occurrence of study endpoints as described in Section 7.3.4.	The purpose of this revision was to clarify the scope of the Clinical Events Assessment and to ensure consistency with Section 7.3.4.
6.0	Trial Flow Chart	Submission of Hospitalization details added as a procedure to be completed for subjects in the United States (US) participating in the Health Economics Outcomes Research analysis.	At US sites participating in the Health Economics Outcomes Research analysis, hospital billing information will be obtained from consenting subjects to inform a cost-effectiveness analysis.
6.0 7.1.3.1 8.2	Trial Flow Chart Laboratory Safety Evaluations Responsibility for In-house Blinding	NT-proBNP blinding will occur after Visit 2 which is the first day of study drug administration.	There is no risk to unblinding to study treatment arm by monitoring NT-proBNP levels on the baseline visit.
6.0 7.1.2.4	Trial Flow Chart 12-Lead Electrocardiogram	Added footnote "x" and updated text to provide additional instructions regarding ECG tracing to sites.	These instructions are being provided to ensure paper tracings are submitted appropriately.
7.1.1.5.1	Prior Medications	Additional guidance provided for the collection of prior medications for subjects entering the trial with an index event defined as IV diuretic use (without hospitalization).	Subjects who enter the trial with an index event defined as IV diuretic use (without hospitalization) are required to record the relevant IV diuretic.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.1.5.2	Concomitant Medications	Reference to the Data Entry Guidelines provided.	Additional instructions regarding recording concomitant medications are provided in the Data Entry Guidelines.
7.1.1.8	Trial Compliance	Additional instructions and clarification regarding sponsor consultation for low treatment compliance provided.	There will be instances in this trial where study drug interruptions will be warranted for subjects as investigators adhere to protocol guidance in Section 5.2.1. This clarification makes clear for the study site, that such study drug interruptions would not require a sponsor consultation and written documentation of collaborative decision on subject management. Additionally, in cases where Sponsor notification is warranted, the updated instructions provided in this section ensure research sites understand the importance of timely notification of poor study drug compliance.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.2.5.2	Pulse Rate	Additional instructions provided regarding the assessment of pulse rate at the randomization visit. This section also clarifies that the mean of three pulse rate assessments is to be obtained.	This clarification is provided to ensure that pulse rate is assessed and recorded correctly.
7.1.4.2 9.3	Blinding/Unblinding Clinical Supplies Disclosure	Updated text to describe who may be unblinded following emergency unblinding and clarifies that the emergency unblinding call center should be used in cases of emergency only.	As management of the participant's care following emergency unblinding requires documentation of the study treatment in the medical record, discovery of the treatment assignment following the unblinding is acceptable if it should occur. This revision will allow greater flexibility when describing who may become unblinded to a single participants treatment following an unblinding.
7.1.4.3	Calibration of Equipment	Updated instructions for calibration of equipment used in the trial.	Textual revision was made to clarify investigator responsibility for calibration and maintenance of trial/study equipment.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.5.1	Screening	Updated text to include the correct abbreviation for left ventricular ejection fraction (LVEF).	Typographical error corrected.
7.1.6.1	Echocardiography and Cardiac Magnetic Resonance Imaging	Revised the description of Echocardiography and Cardiac Magnetic Resonance (CMR) Imaging substudies.	This text clarifies that at participating sites, subjects may consent to echocardiography, CMR, or both if appropriate.
8.1	Statistical Analysis Plan Summary	Clarifying language was added to reconfirm that the total number of subjects with a primary endpoint event may differ from the total number expected based on sample size.	Since the study duration will be driven by the number of CV death events, the expected number of primary endpoint events may differ from the actual observed number of events.
8.4.3	Clinical Endpoints Committee	Title of section changed to Clinical Events Committee.	Title change made for consistency with Section 7.3.4.
8.9	Determination of Sample Size	Language related to the number of primary endpoint events is revised.	Since the study duration will be driven by the number of CV death events, the expected number of primary endpoint events may differ from the actual observed number of events.

1.0 TRIAL SUMMARY

Abbreviated Title	**V**er**IC**igua**T** gl**O**bal study in subjects with heart failure with **R**educed eject**I**on fr**A**ction (VICTORIA)
Sponsor Product Identifiers	MK-1242 Vericiguat
Trial Phase	Phase III
Clinical Indication	Treatment of chronic heart failure with reduced ejection fraction (HFrEF)
Trial Type	Interventional
Type of control	Placebo, on a background of standard of care
Route of administration	Oral
Trial Blinding	Double-blind
Treatment Groups	Vericiguat 10 mg (titrated from 2.5 mg, to 5 mg, and to 10 mg), on a background of standard of care Placebo, on a background of standard of care
Number of trial subjects	Approximately 4872 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 39 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final contact. This is an event-driven trial. After a screening phase of up to 30 days, eligible subjects will be treated until the required number of cardiovascular (CV) death events is observed. The estimated median follow-up duration is approximately 18 months, with a required minimum median follow-up duration of 10 months. After last treatment dose, each subject will be followed for 14 days for adverse event monitoring. All subjects will be followed until study completion to assess for the occurrence of endpoint events.
Randomization Ratio	1:1

A list of abbreviations used in this document can be found in Section 12.6.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, placebo-controlled, parallel-group, multi-center, double-blind, event-driven trial of MK-1242 (vericiguat) in subjects with heart failure with reduced ejection fraction (HFrEF) to be conducted in conformance with Good Clinical Practice (GCP).

Approximately 4872 subjects will be randomized in this trial to evaluate the efficacy and safety of MK-1242 (vericiguat) compared with placebo, on a background of standard of care. After a screening phase of up to 30 days, eligible subjects will be treated until the required number of cardiovascular (CV) death events is observed (estimated median follow-up duration of approximately 18 months). All subjects will be followed until study completion to assess for the occurrence of endpoint events. Clinical outcome events will be adjudicated by an independent clinical events committee (CEC). An independent Data Safety and Monitoring Board (DSMB) will monitor efficacy and safety data.

Subjects will be randomized within 30 days of the screening visit and within 6 months after hospitalization for heart failure or within a time period of up to 3 months if treatment with IV diuretic (without hospitalization) is used as an indicator for heart failure (HF) decompensation. No more than approximately 20% of subjects will be enrolled with an index HF decompensation occurring > 3 months prior to randomization. Enrollment of subjects with estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease (MDRD) equation in the 15 mL/min/1.73 m^2 to 30 mL/min/1.73 m^2 range will be limited to approximately 15% of the total study population. Randomization will be stratified according to region and race as described in Section 5.4.

A starting dose of MK-1242 (vericiguat) 2.5 mg or matching placebo will be initiated at the randomization visit. Subjects will be up-titrated in a blinded fashion to 5 mg and then to the target dose of 10 mg of MK-1242 (vericiguat) or matching placebo using titration criteria based on mean systolic blood pressure (SBP) evaluation and clinical symptoms at 2 week intervals as further described in Section 5.2.1.2. Following the 4-week titration phase, subjects will be evaluated in the clinic every 4 months until study completion. Titration to 10 mg in subjects who have not yet reached the target dose is intended at every visit throughout the study duration based on mean SBP measurement and safety considerations, at the discretion of the investigator (Section 5.2.1.2). After a 10-minute rest in seated position, SBP will be determined by averaging 3 replicate measurements obtained approximately 2 minutes apart. Accurate measurement of blood pressure is essential to dose titration and to detect potential safety issues during the trial. Blood pressure will be monitored in accordance with the instructions provided in the Blood Pressure Measurement Guidance - Section 12.5.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

Formal futility and efficacy interim analyses are planned as described in Section 8.0- Statistical Analysis Plan.

2.2 Trial Diagram

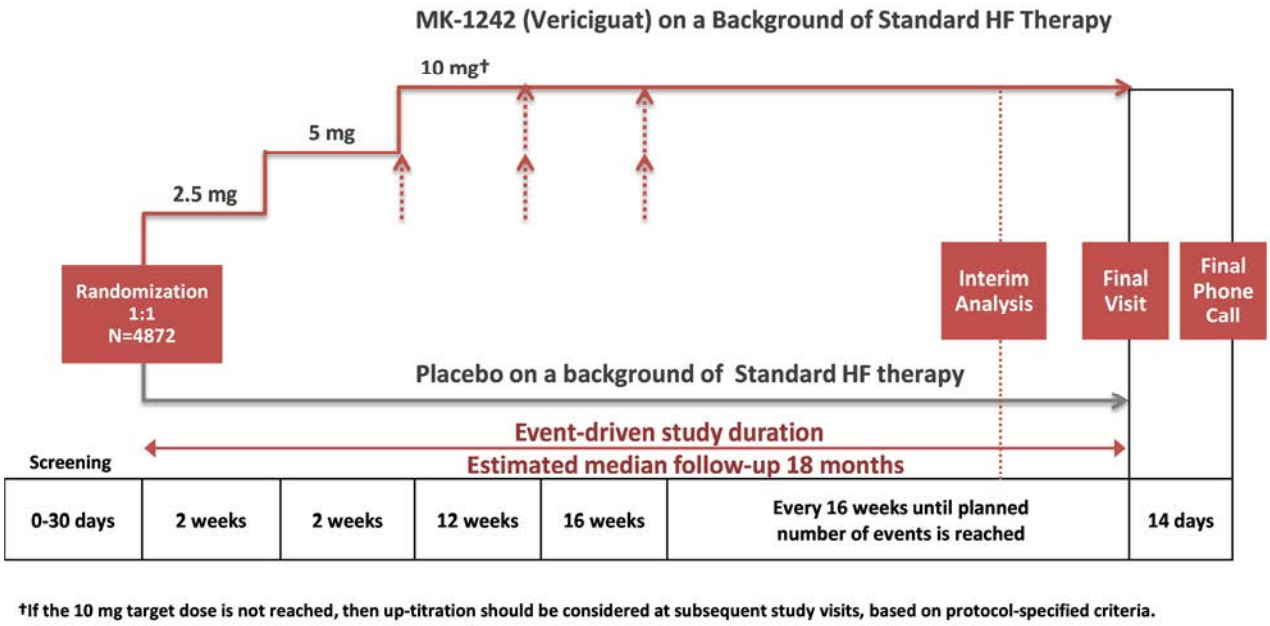

Figure 1 Study Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To evaluate the efficacy of the oral soluble guanylate cyclase (sGC) stimulator MK-1242 (vericiguat) in comparison to placebo on a background of standard of care in increasing the time to first occurrence of the composite of CV death or HF hospitalization in subjects with HFrEF.

Hypothesis: MK-1242 is superior to placebo in increasing the time to first occurrence of the composite of CV death or HF hospitalization in subjects with HFrEF.

The study is considered to have met its primary objective if MK-1242 is superior to placebo in the primary hypothesis testing at the final analysis, or the study is stopped for overwhelming efficacy at the efficacy interim analysis.

3.2 Secondary Objective(s) & Hypothesis(es)

In subjects with HFrEF on a background of standard of care:

(1) **Objective**: To evaluate the efficacy of MK-1242 (vericiguat) in increasing the time to CV death in comparison to placebo.

Hypothesis: MK-1242 (vericiguat) is superior to placebo in increasing the time to CV death.

(2) **Objective**: To evaluate the efficacy of MK-1242 (vericiguat) in increasing the time to first HF hospitalization in comparison to placebo.

Hypothesis: MK-1242 (vericiguat) is superior to placebo in increasing the time to first HF hospitalization.

(3) **Objective**: To evaluate the efficacy of MK-1242 (vericiguat) in increasing the time to total HF hospitalizations (first and recurrent) in comparison to placebo.

Hypothesis: MK-1242 (vericiguat) is superior to placebo in increasing the time to total HF hospitalizations.

(4) **Objective:** To evaluate the efficacy of MK-1242 (vericiguat) in increasing the time to the first occurrence of the composite of all-cause mortality or HF hospitalization in comparison to placebo.

Hypothesis: MK-1242 is superior to placebo in increasing the time to the first occurrence of the composite of all-cause mortality or HF hospitalization.

(5) **Objective**: To evaluate the efficacy of MK-1242 (vericiguat) in increasing the time to all-cause mortality in comparison to placebo.

Hypothesis: MK-1242 is superior to placebo in increasing the time to all-cause mortality.

(6) **Objective:** To evaluate the safety and tolerability of MK-1242 (vericiguat).

3.3 Other Objectives (Exploratory)

In subjects with HFrEF on a background of standard of care:

(1) **Objective:** To evaluate the efficacy of MK-1242 (vericiguat) in comparison to placebo in increasing the time to HF event, defined as composite of HF hospitalization or urgent HF visit (not meeting the criteria for a HF hospitalization).

(2) **Objective:** To evaluate the efficacy of MK-1242 (vericiguat) in comparison to placebo in increasing the time to first CV hospitalization.

(3) **Objective**: To evaluate the efficacy of MK-1242 (vericiguat) in comparison to placebo in reducing the total number of HF hospitalizations.

(4) **Objective:** To evaluate the efficacy of MK-1242 (vericiguat) in comparison to placebo on the change in health-related quality of life summary measures (Kansas City Cardiomyopathy Questionnaire [KCCQ] and EuroQol Group 5-Dimensional [EQ-5D]) from baseline to each measured time point.

(5) **Objective**: To explore the relationship between genetic variation and response to the treatment administered. Variations across the human genome may be analyzed for association with clinical data collected in this study.

(6) **Objective**: To explore relationship between baseline blood biomarker levels and response to treatment and the effect treatment has on established and emerging blood biomarkers.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the latest version of the Investigator's Brochure (IB) for detailed background information on MK-1242 (vericiguat).

4.1.1 Pharmaceutical and Therapeutic Background

Vericiguat is a novel oral soluble guanylate cyclase (sGC) stimulator in development for chronic HF. Bayer and Merck Sharp & Dohme (MSD; Merck & Co. in North America) are developing vericiguat in collaboration and will engage in an academic-pharmaceutical industry partnership with the Canadian VIGOUR Centre (CVC) at the University of Alberta and the Duke Clinical Research Institute (DCRI) to conduct this study.

In patients with HF, endothelial dysfunction and oxidative stress may reduce nitric oxide (NO) bioavailability, resulting in insufficient sGC stimulation and reduced sGC-derived cyclic guanosine monophosphate (cGMP) synthesis. Insufficient sGC activity may be associated with coronary microvascular dysfunction and myocardial derangements in heart failure. This mechanism of cardiac and vascular dysfunction is not directly addressed by currently available therapies. In the presence of relative cGMP deficiency, sGC stimulators offer a novel approach to address the cGMP deficit in chronic HF through a dual mode of action with direct stimulation of sGC as well as enhancement of sGC sensitivity to endogenous NO.

High Mortality and Morbidity Upon Heart Failure Decompensation

Heart failure is a leading cause of cardiovascular (CV) morbidity and mortality and constitutes a major public health problem worldwide. In 51 countries with a population of >900 million represented by the European Society of Cardiology (ESC), there are at least 15 million patients with HF [1]. An estimated 5.1 million patients have HF in the United States (US); the incidence of HF approaches 10 per 1000 population after 65 years of age [2]. The lifetime risk for developing HF is 1 in 5 for men and women [2]. In developed countries, 1–2% of the adult population has HF, with the prevalence rising to ≥10% among persons 70 years of age or older [3].

In patients with chronic HF, the requirement of hospitalization for HF indicates progression of the disease and is associated with substantially worsened prognosis compared to outpatients not hospitalized for HF [4]. Likewise, HF decompensation requiring intravenous (IV) decongestive treatment predicts unfavorable outcomes even in the absence of hospitalization [5]. While neurohumoral antagonists including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs) have been shown to improve outcomes in numerous large-scale HF clinical trials, the prognosis of patients who require hospitalization for HF remains unfavorable despite these treatments [6]. In the Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT), a placebo controlled study that randomized

hemodynamically stable patients recently hospitalized for HF, there was a 17% 1-year mortality rate and a 28% 1-year HF rehospitalization rate in the placebo group despite use of background standard of care therapies [7]. This increased mortality and morbidity in patients with worsening HF on top of standard of care represents a remaining unmet clinical need.

Standard HF treatment is well defined according to guideline recommendations such as American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) and European Society of Cardiology (ESC) Guidelines for the Management of Heart Failure [3] [8]. This includes treatment with ß-blockers, ACE inhibitors, ARBs, MRAs, diuretics, and will also include new recommendations for treatment according to future updates in guidelines. For instance, the recently approved drug sacubitril/valsartan (LCZ-696) has been shown to reduce the risk of CV death and HF hospitalization in patients with chronic HF (New York Heart Association [NYHA] Class II-IV) with reduced ejection fraction when administered in conjunction with other HF therapies, in place of an ACE inhibitor or other ARB (hazard ratio [HR] 0.80; confidence interval [CI] 0.73 to 0.87, $p<0.001$) [9].

Other treatments with less-certain benefits in HFrEF or benefits observed in specific HFrEF subgroups are considered in various guidelines. For instance, in the ACCF/AHA guidelines the combination of hydralazine and isosorbide dinitrate can be used when there is a history of treatment intolerance to an ACE inhibitor or ARB (Class IIa) [8]. Furthermore, the ACCF/AHA guidelines recommend the combination of hydralazine and isosorbide dinitrate for African Americans with NYHA III-IV receiving optimal therapy with ACE inhibitors and beta blockers (Class I). It is important to note that patients taking long-acting nitrates are excluded from the VICTORIA trial. The optimized application of standard therapy following the recommendations of locally relevant scientific guidelines will be expected by the protocol as applied individually at the discretion of the treating investigator in line with individual tolerability.

While disease-modifying treatments reduce the risk of sudden death, they do not abort it. Approximately half of the deaths in HF patients occur suddenly and unexpectedly, mainly due to ventricular arrhythmias. Prevention of sudden cardiac death is an important goal of cardiac device treatment for HF and for this reason implantable cardioverter defibrillators (ICD) have an important role in reducing the risk of death [3] [8]. In the ACCF/AHA guidelines ICD use is a Class I recommendation for primary and secondary prevention after a sufficient optimization of medical therapy in select patients with HFrEF [8]. Cardiac resynchronization therapy via a biventricular pacemaker is known to provide additional benefit when added to conventional therapy in reducing the risk of death from any cause and hospital admission for worsening HF [3] [8]. Cardiac device therapies such as ICDs and biventricular pacemakers should be utilized per local scientific guidelines.

Insufficient Soluble Guanylate Cyclase Signaling is a Target in Heart Failure

The NO-sGC-cGMP pathway is a relevant mechanism in HF that is not targeted by neurohumoral antagonists. Deficiency in sGC-derived cGMP causes myocardial dysfunction and impaired endothelium-dependent vasotone regulation, including in the myocardial microcirculation [10]. Restoration of sufficient sGC–cGMP signaling appears to be an important target in HF. Previous attempts to increase cGMP remain limited. The long-term effects of nitrates and exogenous NO donors are limited by tolerance and they cause endothelial dysfunction, oxidative stress, and release of endothelin-1.

Direct Oral Soluble Guanylate Cyclase Stimulators

A novel class of sGC stimulators directly stimulates the NO receptor sGC with a dual mode of action. They sensitize sGC to endogenous NO by stabilizing the NO-sGC binding and also directly stimulate sGC via a different binding site, independently of NO. Their regional vasoactivity and potential direct myocardial effects are independent of biotransformation and, therefore, could provide an advanced tolerable option to restore cGMP signaling in HF. In the Phase IIb Left ventricular systolic dysfunction associated with Pulmonary Hypertension riociguat Trial (LEPHT, NCT01065454) in patients with systolic HF and secondary pulmonary hypertension, the 3 times daily administered oral sGC stimulator riociguat was well tolerated and improved cardiac index, pulmonary vascular resistance, systemic vascular resistance, and quality of life in addition to standard HF treatment over 16 weeks while not significantly changing systemic BP or mean pulmonary arterial pressure (mPAP) which was the primary endpoint.

Vericiguat, a novel oral sGC stimulator with a similar mechanism of action to riociguat but with a longer half-life that allows for once daily dosing, is currently being developed for the treatment of heart failure.

4.1.2 Pre-clinical and Clinical Trials

Vericiguat has been evaluated in approximately 65 preclinical studies and has been administered to over 500 healthy subjects in 19 completed Phase I studies with single- and multiple-dose administration and approximately 740 heart failure subjects in two Phase IIb studies which studied vericiguat in worsening chronic heart failure subjects with reduced ejection fraction (HFrEF) and with preserved ejection fraction (HFpEF), respectively.

Dose finding in subjects with HFrEF was studied in the Phase IIb SOCRATES-REDUCED study (NCT 0195162). In this 12-week comparison of 4 different dosing strategies with placebo, vericiguat in doses up to 10 mg daily was well tolerated with a clinically significant reduction in N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) levels in the 10 mg target dose arm [11] [12].

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

The worsening of chronic HF in patients despite the use of standard-of-care therapy as indicated by the need for hospitalization or the use of IV diuretics (without hospitalization) is associated with increased morbidity and mortality.

Vericiguat, a sGC stimulator, was studied in a Phase IIb dose-finding study (SOCRATES-REDUCED in subjects with HFrEF [NCT0195162]). In this trial, the highest target dose group demonstrated a reduction in NT-proBNP compared to placebo when added to standard of care. These findings support the rationale for this Phase III clinical outcome trial in HFrEF: VICTORIA Trial.

The VICTORIA trial will evaluate the clinical efficacy of vericiguat on a background of HF standard therapy for subjects with HFrEF [3] [8] and will determine the clinical efficacy of

vericiguat in a pivotal Phase III trial in line with the available guidance on clinical investigation of medicinal products for the treatment of cardiac failure [13].

The primary endpoint of the study is the time-to first occurrence of the composite of CV death or HF hospitalization. This endpoint integrates the cause-specific components CV death and HF hospitalization and is the most frequently used primary endpoint in recent Phase III HFrEF trials. Subjects without a HF hospitalization or CV death at the time of analysis will be censored at the time of a non-CV death or time of last information available for subjects still alive at time of analysis.

A futility interim analysis to assess lack of efficacy is planned at the time when approximately 75% of the planned number of CV death events is observed. The futility analysis will be performed with both the primary endpoint and CV death, and early termination of the study will be considered for lack of efficacy on both the primary composite endpoint and CV death. Additionally, a formal interim efficacy analysis for efficacy is also planned at the time when the futility analysis is performed. Within the pre-specified interim efficacy analysis, the primary purpose is to consider early termination of the study in the presence of substantial impact on both the primary composite endpoint and CV death.

A double-blind, randomized trial design comparing MK-1242 (vericiguat) versus placebo, on a background standard of care, offers an unbiased evaluation of MK-1242 (vericiguat) as a treatment option for this patient population with worsening HF in an international trial.

4.2.2 Rationale for Dose Selection/Regimen/Modification

Dose selection for Phase III is based on results from the Phase IIb study SOCRATES-REDUCED as well as the Phase I program in healthy volunteers.

Data from the Phase I studies show that in healthy volunteers doses up to 10 mg vericiguat are well tolerated. Dose limiting pharmacodynamics effects in Phase I studies at higher doses were associated with orthostatic reactions and syncope (see current version of IB).

In the Phase IIb SOCRATES-REDUCED study, vericiguat doses from 1.25 mg up to a target dose of 10 mg were tested. Vericiguat 1.25 mg was confirmed as a 'no effective dose' with an overall profile comparable to placebo. Vericiguat 2.5 mg was associated with a first dose SBP lowering effect of approximately 3 mmHg (minimally effective dose) and defined as the 'minimally effective dose'. Vericiguat 2.5 mg will be used as the starting dose for all subjects in Phase III. In the highest target dose arm, vericiguat was titrated from a starting dose of 2.5 mg by 2 dose doublings in 2-week intervals up to 10 mg target dose. The blood pressure criterion for up-titration was SBP ≥100 mmHg. The target dose was reached by 72% of subjects receiving vericiguat compared to 75% of subjects sham up-titrated in the placebo group. The main reason for not up-titrating to target per protocol was maintaining dose without any increase when SBP was 90-100 mmHg. Dose decreases were rarely required for SBP <90 mmHg. 10 mg was safe and well tolerated with a clinically meaningful reduction in NT-proBNP and favorable trends in the impact on clinical events.

In conclusion, for vericiguat given on a background of standard of care, a titration regimen starting with 2.5 mg with blood pressure guided up-titration up to 10 mg once daily with 2 dose doublings about every 14 days is expected to cover doses from a minimal

hemodynamically effective starting dose to the maximum clinically favorable dose of 10 mg and is deemed appropriate for the planned Phase III study.

4.2.2.1 Rationale for the Use of Comparator/Placebo

As a novel mechanism, MK-1242 (vericiguat) is being developed for use on a background of standard of care rather than as a replacement for any established mechanisms. To allow a blinded assessment, vericiguat will be compared to a matching placebo. Utilizing placebo as a comparator to the novel sGC stimulator MK-1242 (vericiguat) allows for a representative population receiving standard of care under "real life" conditions.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary efficacy endpoint of the study is the time to first occurrence of the composite of CV death or HF hospitalization. As an integrated measure of HF morbidity and mortality, this endpoint integrates the cause-specific components CV death and HF hospitalization and is the most frequently used primary endpoint in recent phase III HFrEF trials. As secondary efficacy variables, the study will further assess the impact of MK-1242 (vericiguat) on the total number of HF hospitalizations further describing the impact on the patient journey and all cause death as an additional measure of net benefit.

4.2.3.2 Safety Endpoints

Safety assessments will include adverse events (AEs), physical examination findings, and vital signs including pulse rate and blood pressure assessment. Laboratory safety studies will include blood chemistry, hematology, and urine pregnancy testing (performed in women of childbearing potential). Additionally, 12-lead electrocardiograms will be performed.

AEs associated with symptomatic hypotension and syncope are pre-specified safety parameters and will be subject to inferential testing.

4.2.3.3 Pharmacokinetic Endpoints

Pharmacokinetic investigations will be performed to determine systemic exposure to MK-1242 (vericiguat) and its relationship with efficacy. Plasma concentrations of MK-1242 (vericiguat) will be collected at different time points using a sparse sampling approach in all participating subjects to facilitate this analysis.

4.2.3.4 Planned Exploratory Biomarker Research

Planned Genetic Analysis

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

4.2.3.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA specimens collected for future biomedical research during this clinical trial.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Subjects in placebo-controlled clinical trials generally cannot necessarily expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Chronic HF is a major source of morbidity and mortality. Clinical outcomes for patients with chronic HF after hospitalization for HF remain poor, despite contemporary evidence-based therapies. Therefore, drugs are needed that effectively target disease mechanisms not addressed by current standard therapy. Vericiguat has a novel mode of action that targets endothelial dysfunction to improve vasotone regulation and myocardial function, and is expected to fulfill this medical need. Based on its mechanism of action and available preclinical and clinical data, vericiguat has the potential to become a new effective treatment for the proposed patient population by reducing morbidity and mortality and improving quality of life.

In the Phase IIb SOCRATES-REDUCED study, the 10 mg target dose of vericiguat reduced NT-proBNP and was well-tolerated compared to placebo. This target dose was also associated with a numeric reduction in cardiac events. This provides the basis to advance development to an event-driven, appropriately powered Phase III CV mortality and morbidity outcome study in subjects with HFrEF. Anticipated side effects with the use of vericiguat are expected to be well manageable. Based on the existing results, the overall benefit/risk balance is expected to be positive.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the IB and Informed Consent documents. Additional details regarding expected adverse reaction terms for subjects participating in this clinical trial are found in the Reference Safety Information included in the IB.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects aged 18 years or older, with chronic HF (NYHA class II-IV), reduced ejection fraction (<45%), elevated natriuretic peptides, and previous HF decompensation (defined as HF hospitalization or use of IV diuretics for HF [without hospitalization]) will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

2. Be male or female, aged 18 years or older on the day of signing informed consent.

3. Have a history of chronic HF (NYHA class II-IV) on standard therapy before qualifying HF decompensation.

4. Have a previous HF hospitalization within 6 months prior to randomization or IV diuretic treatment for HF (without hospitalization) within 3 months prior to randomization.

   Note: No more than approximately 20% of subjects will be randomized with a qualifying HF hospitalization >3 months prior to randomization.

5. Have brain natriuretic peptide (BNP) or NT-proBNP levels within 30 days prior to randomization as follows:

	NT-proBNP	BNP
Sinus Rhythm	≥ 1000 pg/mL	≥ 300 pg/mL
Atrial Fibrillation	≥ 1600 pg/mL	≥ 500 pg/mL

   Note: BNP cannot be used to determine eligibility for inclusion in subjects on sacubitril/valsartan because sacubitril/valsartan led to ~15% increase in median BNP in the PARADIGM-HF trial [9]. NT-proBNP must be used to confirm eligibility for subjects taking sacubitril/valsartan.

   Note: The most appropriate natriuretic peptide level cut-off should be guided by the investigator's judgment of the impact of the heart rhythm at the time of blood draw on natriuretic peptide levels.

6. Have a left ventricular ejection fraction (LVEF) of <45% assessed within 12 months prior to randomization by any method (most recent measurement must be used to determine eligibility).

7. Meet one of the following criteria:

    a) The subject is a male.

    b) The subject is a female who is not of reproductive potential, defined as a female who either: (1) is postmenopausal (defined as at least 12 months with no menses in women ≥45 years of age); (2) has had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening; OR (3) has a congenital or acquired condition that prevents childbearing.

    c) The subject is a female who is of reproductive potential and agrees to avoid becoming pregnant while receiving study drug and for 14 days after the last dose of study drug by complying with one of the following: (1) practice abstinence[†] from heterosexual activity OR (2) use (or have her partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are[‡]:

        Single method (one of the following is acceptable):

        - Intrauterine device (IUD)
        - Vasectomy of a female subject's male partner
        - Contraceptive rod implanted into the skin

        Combination method (requires use of two of the following):

        - Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
        - Cervical cap with spermicide (nulliparous women only)
        - Contraceptive sponge (nulliparous women only)
        - Male condom or female condom (cannot be used together)
        - Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection.

    [†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

    [‡]If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is clinically unstable at the time of randomization as defined by:

   a. Administration of any intravenous treatment within 24 hours prior to randomization, and/or

   b. Systolic blood pressure (SBP) <100 mmHg or symptomatic hypotension.

2. Has concurrent or anticipated use of long-acting nitrates or NO donors including isosorbide dinitrate, isosorbide 5-mononitrate, pentaerythritol tetranitrate, nicorandil or transdermal nitroglycerin (NTG) patch, and molsidomine.

   Note: Co-administration of short-acting nitrates, i.e., sublingual nitroglycerin spray as indicated for angina attacks, is allowed (See section 5.5.2).

3. Has concurrent use or anticipated use of phosphodiesterase type 5 (PDE5) inhibitors such as vardenafil, tadalafil, and sildenafil.

4. Has concurrent use or anticipated use of a sGC stimulator such as riociguat.

5. Has known allergy or sensitivity to any sGC stimulator.

   Note: Subjects with a known history of hypersensitivity to the active substance of the investigational product or to any of its constituents will be excluded from the trial.

6. Is awaiting heart transplantation (United Network for Organ Sharing Class 1A / 1B or equivalent), receiving continuous IV infusion of an inotrope, or has/anticipates receiving an implanted ventricular assist device.

Cardiac Comorbidity

7. Has primary valvular heart disease requiring surgery or intervention, or is within 3 months after valvular surgery or intervention.

8. Has hypertrophic obstructive cardiomyopathy.

9. Has acute myocarditis, amyloidosis, sarcoidosis, Takotsubo cardiomyopathy.

10. Has post-heart transplant cardiomyopathy.

11. Has tachycardia-induced cardiomyopathy and/or uncontrolled tachyarrhythmia.

12. Has acute coronary syndrome (unstable angina, non-ST elevation myocardial infarction [NSTEMI], or ST elevation myocardial infarction [STEMI]) or coronary revascularization (coronary artery bypass grafting [CABG] or percutaneous coronary intervention [PCI]) within 60 days prior to randomization, or indication for coronary revascularization at time of randomization.

13. Has symptomatic carotid stenosis, transient ischemic attack (TIA) or stroke within 60 days prior to randomization.

14. Has complex congenital heart disease.

15. Has active endocarditis or constrictive pericarditis.

Non-cardiac comorbidity

16. Has an estimated glomerular filtration rate (eGFR) calculated based on the Modification of Diet in Renal Disease (MDRD) equation <15 mL/min/1.73 m^2 or chronic dialysis.

    Note: No more than approximately 15% of subjects will enroll with an eGFR in the 15 mL/min/1.73 m^2 to 30 mL/min/1.73 m^2 range.

17. Has severe hepatic insufficiency such as with hepatic encephalopathy.

18. Has malignancy or other non-cardiac condition limiting life expectancy to <3 years.

19. Requires continuous home oxygen for severe pulmonary disease.

20. Has current alcohol and/or drug abuse.

21. Has participated in another interventional clinical study and treatment with another investigational product ≤30 days prior to randomization or plans to participate in any other trial/investigation during the duration of this study.

22. Has a mental or legal incapacitation and is unable to provide informed consent.

23. Has a medical disorder, condition, or history thereof that in the opinion of the investigator would impair the subject's ability to participate or complete the study.

24. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

25. Has Interstitial Lung Disease.

26. Is pregnant or breastfeeding or plans to become pregnant or to breastfeed during the course of the trial.

5.2 Trial Treatment(s)

The treatment to be used in this trial is outlined below in Table 1.

Table 1 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-1242 (Vericiguat)	2.5 mg	QD	Oral	Starting dose of 2.5 mg, up-titrated to 5 mg and to 10 mg; taken with food (Visit 2 through V_n)	Experimental
MK-1242 (Vericiguat)	5 mg	QD	Oral	Starting dose of 2.5 mg, up-titrated to 5 mg and to 10 mg; taken with food (Visit 3 through V_n)	Experimental
MK-1242 (Vericiguat)	10 mg	QD	Oral	Starting dose of 2.5 mg, up-titrated to 5 mg and to 10 mg; taken with food (Visit 4 through V_n)	Experimental
MK-1242 (Vericiguat) Placebo	Matching placebo for 2.5 mg	QD	Oral	Starting dose of 2.5 mg, up-titrated to 5 mg and to 10 mg; taken with food (Visit 2 through Vn)	Placebo-comparator
MK-1242 (Vericiguat) Placebo	Matching placebo for 5 mg	QD	Oral	Starting dose of 2.5 mg, up-titrated to 5 mg and to 10 mg; taken with food (Visit 3 through Vn)	Placebo-comparator
MK-1242 (Vericiguat) Placebo	Matching placebo for 10 mg	QD	Oral	Starting dose of 2.5 mg, up-titrated to 5 mg and to 10 mg; taken with food (Visit 4 through Vn)	Placebo-comparator

The first dose of trial treatment will be administered at the trial site at Visit 2 (randomization). Subsequent dosing will be performed once daily by the subject (i.e., unsupervised at his/her home) at approximately the same time each day.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

This trial includes a dose titration regimen based on a subject's sitting SBP as described in Section 5.2.1.2.

5.2.1.2 Dose Modification

Subjects will be randomized to a starting dose of MK-1242 vericiguat 2.5 mg or matching placebo. In a blinded manner, the first titration to 5 mg will occur at Visit 3 (14±4 days after randomization) and the second titration to the target dose of 10 mg will occur at Visit 4 (28±4 days after randomization). These titration steps include sham titrations in the placebo arm. Dose modification will depend on mean sitting SBP and the absence of symptoms indicative of hypotension (See Appendix 12.5 - Guidance for Blood Pressure Assessment) before intake of the dose as described in Table 2. Table 2 dose modification guidance should be applied at all scheduled and unscheduled visits in which a SBP assessment is performed.

If the subject does not reach the 10 mg dose step by 28±4 days after randomization, up-titration should be considered at any subsequent visit at the discretion of the investigator according to the SBP criteria in Table 2.

The intention of the protocol is to maintain subjects on the target study drug dose for as long as possible after randomization. However, if in the opinion of the investigator the subject does not tolerate the target dose of study drug, in addition to considering the reduction of the study drug the investigator should consider whether medications not shown to provide an outcome benefit in clinical studies (e.g., various classes and doses of diuretics, calcium channel blockers, or alpha-blockers) can be reduced before reducing the dose of the study drug. For example, in the case of symptoms of orthostatic hypotension the investigator should also consider the volume status and whether there is a necessity to change the dose of diuretics. If such adjustment or discontinuation of concomitant medications that are not associated with an outcome benefit is not possible or does not resolve signs and symptoms of intolerability, the investigator may at any time during the course of the trial reduce the dose or interrupt study treatment in subjects who no longer tolerate the current study drug dose. The doses of disease modifying drugs shown to provide an outcome benefit, such as β-blockers, ACE inhibitors/ARBs, and MRAs, or future standard treatment recommended in the study population, should not be reduced for the sole purpose of facilitating the maintenance of study treatment dosing. In general, every attempt should be made to resume the study treatment upon temporary interruption and reach and maintain the target dose of the study treatment when the investigator feels it is medically appropriate according to Table 2 and Table 3.

Table 2 Systolic Blood Pressure Criteria for Study Treatment Dose Modification

Blood Pressure Assessment	Dose Modification
SBP ≥100 mm Hg AND not on 10 mg target dose	Increase Dose
• SBP ≥100 mm Hg AND on 10 mg target dose **or** • SBP ≥ 90 and <100 mm Hg	Maintain Dose
SBP <90 mm Hg, asymptomatic	• If currently on 5 or 10 mg decrease dose • If currently on 2.5 mg interrupt dose
SBP <90 mm Hg, symptomatic	Interrupt Dose

Dose decrease from 5 or 10 mg doses is possible at any time if the investigator feels this is justified for safety reasons.

Reasons for dose modifications (maintenance, increase, decrease, interruption, or restart) will be collected at all scheduled and unscheduled visits in which a vital signs assessment is performed.

If the subject is not receiving the target dose of 10 mg, up-titration should be considered at any study visit at the discretion of the investigator according to the SBP criteria in Table 2.

5.2.1.2.1 Resumption of Study Treatment after Interruption

Upon interruption of the study drug due to intolerability, intake should be resumed as soon as medically justified at the discretion of the investigator. There is no defined maximum time limit for temporary treatment interruption. In all cases, the reason for study drug interruption or permanent study drug discontinuation must be recorded.

Titration rules following restart of study drug after temporary interruption of study drug are as follows:

- **Interruption During the Titration phase (Day 0 - Day 28)**
  - Restart study drug at a scheduled visit and titrate with intervals as shown in Table 3.
- **Interruption After Day 28**
  - Restart as soon as possible (with an unscheduled visit if required) and titrate according to the instructions provided in Table 2 and Table 3.
  - Subject will then resume the planned visit schedule.
  - Unscheduled clinic and/or phone contacts can be conducted at the discretion of the investigator.

Table 3 Instructions for Resumption of Study Treatment after Interruption due to Intolerability

Dose at Time of Interruption	Length of Interruption	Restart Dose	Dose Level 1st titration (14 days ± 4)	Dose Level 2nd titration (28 days ± 4)
2.5 mg	Any time interval	2.5 mg	5 mg	10 mg
5 mg	Any time interval	2.5 mg	5 mg	10 mg
10 mg	>5 days	2.5 mg	5 mg	10 mg
10 mg	≤5 days	5 mg	10 mg	10 mg

5.2.2 Timing of Dose Administration

Administration is once daily. The study drug should be taken with food. Subjects will be instructed to take study medication at the same time each day.

5.2.3 Trial Blinding

A double-blinding technique with in-house blinding will be used. MK-1242 (vericiguat) and matching placebo will be packaged identically. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to MK-1242 or matching placebo, respectively.

5.4 Stratification

Treatment allocation/randomization will be stratified within the following strata:

- Eastern Europe (plus Israel and South Africa)
- Western Europe
- North America (Black)
- North America (Non-black)
- Latin and South America
- Asia Pacific (including Australia)

The stratification variable race is nested within the region North America. Resulting from the combination of these 2 stratification factors, subjects will be randomized into 6 different strata.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.5.1 Background Standard of Care

Per protocol, all subjects should receive standard HF treatment following locally relevant guidelines such as ACCF/AHA and ESC Guidelines for the Management of Heart Failure recommendations applied individually at the discretion of the treating investigator and in line with individual tolerability [3] [8]. This includes medications such as ß-blockers, ACE inhibitors, ARBs, and MRAs and cardiac device therapies such as ICDs and biventricular pacemakers. Use of treatment expected to be reflected in future recommendations (such as the recently approved combination of sacubitril/valsartan) should be considered.

Any dose adaptation, addition, changed or added route of administration, omission, or cessation of concomitant standard therapy is possible whenever deemed necessary by the investigator in line with guideline-recommended dosing irrespective of blinded dosing of the study drug.

5.5.2 Prohibited Concomitant Medications

Listed below are specific restrictions for concomitant therapy during the course of the trial:

1. Long-acting nitrates or NO donors: co-administration of nitrate preparations with a longer-lasting effect than sublingual nitroglycerin (NTG) such as isosorbide dinitrate and isosorbide 5-mononitrate, pentaerythritol tetranitrate, nicorandil or transdermal NTG patch, or molsidomine is not allowed. In contrast, co-administration of short-acting nitrates, i.e., sublingual NTG spray as indicated for angina attacks, is allowed.

2. PDE5 inhibitors: co-administration of vardenafil, tadalafil, or sildenafil is not allowed.

3. sGC stimulators other than the study drug (such as riociguat) are not allowed during study drug treatment.

Immediate medical attention should be sought in case of hypotension symptoms after the use of short-acting nitrates (allowed) or after the accidental use of long-acting nitrates, PDE5 inhibitors, or non-study treatment sGC stimulators (not allowed).

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should maintain a diet consistent with recommendations in local guidelines, such as the ACCF/AHA and ESC Guidelines for the Management of Heart Failure [3] [8] during the course of the study.

5.7.2 Contraception

Female subjects must agree to avoid becoming pregnant while receiving study drug and for 14 days after the last dose of study drug by complying with one of the following: (1) practice

abstinence† from heterosexual activity OR (2) use (or have her partner use) acceptable contraception during heterosexual activity. Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- Intrauterine device (IUD)
- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection.

† Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡ If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-1242 (vericiguat), study treatment will immediately be discontinued. The subject will continue to be followed for clinical events and vital status until study completion. The pregnancy event will be reported and followed as described in Section 7.2.2-Reporting of Pregnancy and Lactation.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

Table 4 provides reasons why a subject must be discontinued from treatment but may continue to be monitored in the trial, as well as reasons why a subject must be discontinued from treatment and the trial.

Table 4 Discontinuation Scenarios

Reason for Discontinuation Scenario	***Action***
The subject or legal representative (such as a parent or legal guardian) withdraws consent.	Discontinuation from Treatment Investigator to clarify whether subject wishes to withdraw completely from trial (no further contact) or whether subject is willing to be contacted for additional follow-up.
The subject's treatment assignment has been unblinded by the investigator, Merck subsidiary or through the emergency unblinding call center.	Discontinuation from Treatment (should continue to monitor in the trial)
The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial while on study treatment or does not allow the subject to adhere to the requirements of the protocol.	Discontinue from Treatment (should continue to monitor in the trial)
The subject has a confirmed positive serum pregnancy test.	Discontinue from Treatment (should continue to monitor in the trial)

Study drug treatment is intended to continue in all randomized subjects until the final visit, with the goal that subjects are on the target dose of study drug for as long as possible. The study drug will also be continued after any non-fatal potential clinical outcome event, including after HF hospitalizations.

Study drug discontinuation for any reason does not represent withdrawal from the study. Since data on clinical events and vital status are essential to the primary analysis, they must be collected until the end of the study, even if the subject discontinued study drug treatment. Therefore, all efforts will be taken to obtain data on clinical events and vital status until the end of study.

Thus, subjects who permanently discontinue study drug will still be followed for clinical events and vital status until study completion. They should attend all scheduled protocol-defined visits and study procedures as provided in the visit schedule (Section 6.0) just as those who remain on study drug. If the subject does not attend scheduled study visits, follow-up of clinical events specified as endpoints may continue by phone, unless the subject

explicitly withdraws his/her consent to any type of follow-up. In such cases, the phone contact will not be considered a protocol deviation.

At any time a subject's vital status is in question, the investigator should explore all possible options to contact the subjects per local regulations (unless the subject has explicitly withdrawn his/her consent to any type of follow-up). The site must document all attempts to try to contact the subjects in the medical records/source documents. The vital status will be collected for all randomized subjects who have not withdrawn consent, irrespective of completion of study procedures.

In all cases, the reason for temporary interruption or permanent study drug discontinuation must be recorded in the electronic case report form (eCRF) and in the subject's medical records.

Subjects may be allowed to begin treatment/vaccination again if deemed medically appropriate, unless he/she has been unblinded.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

At 75% of the CV death events, a futility interim analysis is planned and the DSMB may recommend early termination of the trial due to the lack of efficacy of vericiguat. Also at 75% of the CV death events, an efficacy interim analysis is planned and the DSMB may recommend early termination of the trial if clear and consistent efficacy is observed for vericiguat.

6.0 TRIAL FLOW CHART

Trial Period	Screening		Treatment								Premature Treatment Discontinuation[f]		
Visit Number/Title:	1 Screen[a]	2 Rand[b]	3	4	5	6	7	Visit$_n$[c]	Final Visit[d]	Final Phone Contact[e]	Discon Visit[g]	Safety Follow-up Visit[h]	Cont. through end of trial[i]
Scheduled Days/Week/Month:	Day -30 to -1	Day 1	Day 14	Day 28	Week 16 (Month 4)	Week 32 (Month 8)	Week 48 (Month 12) and Yearly[j]	Every 16 weeks	At time of Efficacy Cut-off	14 days after Final Visit	At time of permanent treatment discon	14 days from last dose	Every 16 weeks
Scheduling Window Days/Weeks/Months:			±4 days	±4 days	±2 weeks	±2 weeks	±2 weeks	±2 weeks		+1 week		+1 week	±2 weeks
Administrative Procedures													
Informed Consent	X												
Informed Consent for Future Biomedical Research	X												
Informed Consent for Imaging Substudies[v,w]	X												
Demographics & Medical History	X												
Inclusion/Exclusion Criteria	X	X											
Subject Identification Card	X	X											
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X		X	X	X
Treatment Randomization		X											
MK-1242 or Placebo Administration/Dispensing[k]		X	X	X	X	X	X	X					
Clinical Procedures/Assessments													
Height		X											
Weight		X	X	X	X	X	X	X	X		X	X	X
Physical Exam[l]		X					X		X		X		
Electrocardiogram (12 Lead)[x]		X			X				X		X		
Vital Signs (Pulse, BP)[m]	X	X	X	X	X	X	X	X	X		X	X	X
Dose Assessment[y]			X	X	X	X	X	X					
NYHA Classification	X	X	X	X	X	X	X	X	X		X	X	X
CCSA[z]	X												
QOL Questionnaires (KCCQ & EQ-5D)		X		X	X	X	X		X		X	X	
Trial Medication Compliance			X	X	X	X	X	X	X		X		
Clinical Events Assessment[aa]			X	X	X	X	X	X	X	X	X	X	X
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Status[n]										X[n]			
Echocardiogram[v]		X				X							
Cardiac Magnetic Resonance Imaging[w]		X				X							
Submission of Hospitalization Details (US subjects only)[bb]		X	X	X	X	X	X	X	X	X	X	X	X

Trial Period	Screening		Treatment								Premature Treatment Discontinuation[f]		
Visit Number/Title:	1 Screen[a]	2 Rand[b]	3	4	5	6	7	$Visit_n$[c]	Final Visit [d]	Final Phone Contact[e]	Discon Visit[g]	Safety Follow-up Visit [h]	Cont. through end of trial[i]
Scheduled Days/Week/Month:	Day -30 to -1	Day 1	Day 14	Day 28	Week 16 (Month 4)	Week 32 (Month 8)	Week 48 (Month 12) and Yearly[j]	Every 16 weeks	At time of Efficacy Cut-off	14 days after Final Visit	At time of permanent treatment discon	14 days from last dose	Every 16 weeks
Scheduling Window Days/Weeks/Months:			±4 days	±4 days	±2 weeks	±2 weeks	±2 weeks	±2 weeks		+1 week		+1 week	±2 weeks
Local Laboratory Assessments													
Creatinine (calculation of eGFR[o])	X												
BNP/NT-proBNP[o]	X												
Central Laboratory Assessments													
NT-proBNP[p]		X			X	X	X		X[u]		X		
Hematology		X			X	X	X		X[u]		X	X	
Chemistry		X			X	X	X		X[u]		X	X	
Liver Function Tests		X			X	X	X		X[u]		X	X	
Hemoglobin $A1_c$[q]		X			X	X	X		X[u]		X		
Urine Pregnancy Test[r]		X			X	X	X	X	X[u]		X		
Blood for Genetic Analysis[s]		X											
Blood for PK evaluation[t]		X			X		X		X[u]		X		
Blood for Biomarkers		X			X	X			X[u]		X		

a. Screening can start as early as at time of hospitalization or upon intravenous diuretic treatment for heart failure.
b. Screening visit and Randomization (Visit 2) can occur on the same day if the subject is clinically stable as defined as having not received IV treatment for > 24 hours and having SBP ≥ 100 mmHg. In this case, all procedures specified for Visit 2 must be done after informed consent is given and will replace screening visit procedures.
c. V_n: Starting from Visit 7 (Week 48) all subsequent visits will be scheduled at 16 ±2 week intervals until study completion is reached.
d. The Final visit will be conducted for all subjects (including those who prematurely discontinued study treatment) when the planned number of CV death events is reached and the efficacy cut-off is announced by the Sponsor.
e. All subjects will be contacted by phone within 14 days (+ 1 week) of the Final visit to assess for clinical events, adverse events, and vital status (if applicable).
f. Premature treatment discontinuation visits are relevant to subjects who **permanently** discontinue study treatment. These visits do not apply to subjects who temporarily interrupt study treatment.
g. Discontinuation visits will be conducted at the time of permanent treatment discontinuation for the collection of clinical events, adverse events, and other procedures listed.
h. In-clinic safety follow-up visit required for all subjects who permanently discontinue study treatment prematurely. Visit to be conducted within 14 days (+ 1 week) after last dose study treatment.
i. Subjects who permanently discontinue treatment prematurely will continue in-clinic visits every 16 weeks, including the Final Visit and Final Phone Contact.
j. Procedures completed at Week 48 and at each yearly visit until study completion.
k. Dose assessment based on criteria described in Section 5.2.1.2.
l. Complete physical exam completed at Visit 2. Directed physical exams to be completed at Week 48 (Visit 7), subsequent Yearly visits, and the Premature Discontinuation Visit and/or Final Visit.
m. Three measurements, each approximately 2 min apart. Visit 2: Prior to and at 2 ±0.5h post study-drug dosing; $Visit_n$ until Final visit: vital sign measurement is only needed prior to study drug dosing. Blood Pressure and pulse rate measurements should be performed as described in Appendix 12.5
n. This assessment can be performed at any point in the trial when vital status is in question.
o. Local laboratory creatinine and NT-proBNP or BNP within 30 days before randomization will be entered in eCRF to confirm eligibility. The creatinine assessed at this time will be used to calculate eGFR by MDRD equation. Recent historical local laboratory assessments may be used provided these assessments were obtained within 30 days before randomization.
p. NT-proBNP measurements assessed by the central lab will be blinded after Visit 2.
q. Hemoglobin A1c to be evaluated in diabetic subjects only.
r. In case of positive urine pregnancy test, a confirmatory serum test will be done. A negative result is required for randomization.
s. Refer to section 7.1.3.4 for sample collection information.
t. In case the PK sample at the specified visits cannot be obtained at a specified time point, the sample can be taken at the subsequent visits within the year of treatment. Exact collection date/time of the

Trial Period	Screening		Treatment								Premature Treatment Discontinuation[f]		
Visit Number/Title:	1 Screen[a]	2 Rand[b]	3	4	5	6	7	Visit$_n$[c]	Final Visit [d]	Final Phone Contact[e]	Discon Visit[g]	Safety Follow-up Visit [h]	Cont. through end of trial[i]
Scheduled Days/Week/Month:	Day -30 to -1	Day 1	Day 14	Day 28	Week 16 (Month 4)	Week 32 (Month 8)	Week 48 (Month 12) and Yearly[j]	Every 16 weeks	At time of Efficacy Cut-off	14 days after Final Visit	At time of permanent treatment discon	14 days from last dose	Every 16 weeks
Scheduling Window Days/Weeks/Months:			±4 days	±4 days	±2 weeks	±2 weeks	±2 weeks	±2 weeks		+1 week		+1 week	±2 weeks

PK samples and date/time of last study drug intake (either at home on the day before the sample or at site) must be documented.

u. Not applicable for subjects who prematurely discontinue from study treatment.

v. At sites participating in the imaging substudies, subjects may elect to participate in an echocardiography substudy as described in Section 7.1.6.1. The baseline echocardiogram should be performed prior to study drug administration and may be performed over the course of the screening period.

w. At sites participating in the imaging substudies, subjects may elect to participate in a cardiac magnetic resonance imaging substudy as described in Section 7.1.6.1. The baseline cardiac magnetic resonance imaging should be performed prior to study drug administration and may be performed over the course of the screening period.

x. At each scheduled ECG assessment, sites should print 2 original paper tracings. One original paper tracing should be maintained in subject files and second original paper tracing should be mailed to the core ECG vendor (batched once monthly).

y. Dose assessment to be performed at all scheduled and unscheduled visits when BP is assessed.

z. Performed only in subjects with a medical history of active stable angina.

aa. Clinical Events Assessment includes an assessment for the occurrence of study endpoint events as described in Sec. 7.3.4.

bb. At US sites participating in the Health Economics Outcomes Research analysis, hospital billing information will be obtained to inform a cost-effectiveness analysis.

Abbreviations: CCSA = Canadian Cardiovascular Society Functional Classification of Angina EQ-5D = EuroQol Group 5-dimension, 5-level questionnaire; KCCQ= Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association; ECG = electrocardiogram; BP = blood pressure; NT-proBNP = N-terminal brain natriuretic peptide; PK=pharmacokinetics; QoL=quality of Life; eGFR=estimated Glomerular Filtration Rate; US = United States

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, and record prior medication taken by the subject 30 days before starting the trial. For subjects entering the trial with an index event defined as IV diuretic use (without hospitalization) per inclusion criterion 4, sites should report the diuretic administered within the required 3 month timeframe with the route of administration reported as intravenous.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial as instructed in the Data Entry Guidelines.

7.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

7.1.1.8 Trial Compliance

Subjects will be directed to bring any used and unused bottles to each visit. The investigator must maintain a complete and current accountability record for the blinded investigational product.

Study drug will be dispensed at each visit starting at Visit 2. Compliance with blinded trial medication will be assessed by tablet counts of returned medication. To facilitate this, subjects must be instructed to return all of the study drug packaging including unused study drug and empty packaging.

Any discrepancies between actual and expected amount of returned study medication must be discussed with the subject at the time of the visit, and any explanation must be documented in the source records.

Interruptions from the protocol specified treatment compliance <80% require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Sponsor consultation and written documentation of collaborative decision on subject management is not required if reason for <80% compliance is due to protocol specified (Section 5.2.1) interruptions per dose modification scheme, investigator discretion, and/or adverse event. Such instances of <80% compliance will not be considered a protocol deviation.

Consultation should occur in a timely manner upon site learning of poor study drug compliance. While awaiting Sponsor feedback, the research site should conduct patient counseling regarding importance of study drug adherence, and the investigator can dispense study drug after such counseling, if in their medical judgment, the patient is able to comply moving forward with study treatment instructions

Administration of trial medication will be witnessed by the investigator and/or trial staff at the randomization visit only.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Height

Height will be measured without shoes, using a stadiometer or other appropriate device.

7.1.2.2 Weight

Body weight will be measured using a standardized scale at each of the pre-defined time points outlined in the Trial Flow Chart – Section 6.0.

7.1.2.3 Physical Examinations

The investigator or qualified designee will perform a full physical exam at the time of randomization. Clinically significant abnormal findings should be recorded as medical history.

Directed physical exams with a focus on cardiovascular assessment will be performed at the yearly visits and at the Premature Discontinuation Visit and/or Final Visit.

7.1.2.4 12-Lead Electrocardiogram

Electrocardiograms (ECG) will be obtained as described in the Trial Flow Chart-Section 6.0.

- Subjects will refrain from nicotine-containing products and/or ingesting caffeine for at least 30 minutes preceding the procedure.

- 12-lead ECGs should be performed after the subject has rested quietly for approximately 10 minutes.

Record ECG with a paper speed of 25 mm/sec. Ensure standard calibration is performed and provide record of a calibration mark indicating the equivalence of 1mV signal to 10 mm vertical deflection on the ECG. The same ECG machine should be used at all time points for an individual subject.

At each scheduled ECG assessment, sites should print 2 original paper tracings. One original paper tracing should be maintained in subject files and the second original paper tracing should be mailed to the core ECG vendor (batched once monthly).

These ECGs will be used to assess the impact of study drug on electrocardiographic changes such as heart rate and repolarization.

7.1.2.5 Vital Signs

Vital sign measurements include a triplicate measurement of sitting blood pressure and pulse rate. Site personnel should use the same blood pressure measuring device throughout the study for each subject. Other procedures should not be performed during the time of the blood pressure and pulse rate measurements. Detailed information regarding BP monitoring is located in Appendix 12.5.

7.1.2.5.1 Blood Pressure Assessment

Blood pressure assessment is to be completed after the subject has been seated for a 10-minute rest. Whenever possible, BP measurements should be obtained using the same arm, same BP monitoring device, and same examiner at each visit. Systolic and diastolic blood pressures will be determined by averaging 3 replicate measurements obtained approximately 2 minutes apart. At the randomization visit, blood pressure assessment will also be completed 2 ± 0.5 hour after dose is administered.

7.1.2.5.2 Pulse Rate

Pulse rate is to be assessed after the subject has been seated for a 10 minute rest. The pulse rate will be determined by averaging 3 replicate measurements obtained approximately 2 minutes apart.

Assessment of pulse rate can be manual (rather than using an automated device); however, when done manually, pulse rate must be measured in the brachial/radial artery for at least 30 seconds.

At the randomization visit, pulse rate will also be completed 2 ± 0.5 hour after dose is administered.

7.1.2.6 Quality of Life Measures

7.1.2.6.1 Kansas City Cardiomyopathy Questionnaire

The KCCQ is a 23-item, self-administered questionnaire intended for the quantification of HF patients' perspectives of how their disease impacts their lives. The questionnaire requires, on average, 5 to 8 minutes for completion. The KCCQ measures the impact of patients' heart failure, or its treatment, on 7 distinct domains using a 2-week recall period: symptom frequency, symptom burden, physical limitation, health perceptions, social limitations, self-efficacy and symptom stability. The KCCQ domains of self-efficacy and symptom stability will be reported but are not considered in the efficacy assessment as they address patient knowledge and recent changes in symptoms respectively.

In addition, there are 3 summary scores; a total symptom scale that combines the symptom frequency and the symptom burden scores, a clinical summary scale that combines the total frequency and physical limitation scores to replicate the NYHA Classification, and an overall summary score that includes the Total Symptom, Physical Limitation, Social Limitation and Quality of Life scores. The clinical summary score and its components address the most relevant concepts for the heart failure patients, showing good correlation with improvement following HF hospitalization.

The questionnaire is available in over 40 translations with established validity, reliability, and responsiveness. In cases when a validated translation is needed and not available for a specific language, subjects who speak that language will be exempt from the requirement to complete the questionnaire.

7.1.2.6.2 EuroQol Group 5-Dimensional, 5-level Questionnaire

The EQ-5D is a questionnaire used to assess current health status as reported by patients, consisting of 5 domain questions and one visual analogue scale (VAS) response. The domain questions assess, mobility, self-care, usual activities, pain/discomfort, anxiety/depression, with 5-level Likert response options; no problems, slight problems, moderate problems, severe problems, and extreme problems. Summary scores will be calculated from the 5 domain scores according to scoring instructions from the EuroQol group and the EQ-5D-5L value sets for the United States and for Europe.

The EQ VAS records patient self-rated health on a 20 cm vertical, VAS with endpoints labeled 'the best health you can imagine' and 'the worst health you can imagine' and is scored on a 0 to 100 scale.

The questionnaire is available in over 60 translations with established validity, reliability, and responsiveness. In cases when a validated translation is needed and not available for a specific language, subjects who speak that language will be exempt from the requirement to complete the questionnaire.

7.1.2.7 Vital Status Assessment

Vital status is collected at the Final Phone Contact. This assessment can also be performed at any point in the trial when vital status is in question, unless subject has specifically withdrawn consent for further follow-up.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood volumes drawn/collected by visit and by sample type per subject can be found in Section 12.4.

7.1.3.1 Laboratory Safety Evaluations

Laboratory tests are specified in Table 5.

NT-proBNP measurements assessed by the central lab will be blinded after Visit 2.

Table 5 Laboratory Tests

Hematology	Chemistry	Other
Hematocrit (Hct)	Alanine aminotransferase (ALT)	Hemoglobin A1c (HbA1c) in Diabetic subjects
Hemoglobin (Hb)	Albumin (serum)	N-terminal pro-Brain Natriuretic Peptide (NT-proBNP)
Mean corpuscular volume (MCV)	Alkaline phosphatase	Serum β-human chorionic gonadotropin†
Mean corpuscular hemoglobin (MCH)	Aspartate aminotransferase (AST)	
Mean corpuscular hemoglobin concentration (MCHC)	Bicarbonate	
Platelet count	Bilirubin (Total)	
Red blood cells (RBC)	Blood glucose	
Red cell distribution width (RDW)	Blood urea nitrogen (BUN)	
Reticulocytes	Calcium	
White blood cells (WBC)	Chloride	
	Creatinine	
	Gamma glutamyl transferase (GGT)	
	Potassium (K)	
.	Sodium (Na)	
	Uric acid	

† Serum β-human chorionic gonadotropin only to be conducted in the event urine pregnancy test is positive

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

For the investigation of systemic exposure to vericiguat and its relationship with efficacy, the plasma concentrations of vericiguat will be determined at different time points using a sparse sampling approach in all participating subjects.

Blood samples will be collected at the time points indicated in Section 6.0-Study Flow Chart. PK samples obtained at additional time points based on the investigator's discretion will not qualify as a protocol deviation and will be analyzed. Deviations from the specified time points will be documented and taken into account when calculating the PK parameters. Date and time of the PK sample collection and date and time of last study drug intake (either at home on the day before the sample or at site) must be documented.

Details about the collection, processing, storage and shipment of samples will be provided separately.

Pharmacokinetics and, if applicable, pharmacokinetics/pharmacodynamics (PK/PD) modeling using population approaches to describe vericiguat PK including potential influence of relevant subject covariables (e.g., age, gender, body weight, etc.) or potentially to relate parameters of clinical safety and efficacy response with vericiguat plasma concentrations will be investigated under a separate detailed PK/PD evaluation and analysis plan.

7.1.3.3 Biomarker Investigations

Biomarker investigations will examine the impact of vericiguat on HF disease progression and identify candidate biomarkers that may predict drug response to the treatment.

Biomarker blood samples will be collected at the time points indicated in Section 6.0-Study Flow Chart.

In the event the biomarker sample at the specified visit is not obtained, the sample can be taken at a subsequent visit within the year of treatment.

Details on the collection, processing, storage and shipment of biomarker samples will be provided in a separate laboratory manual and results of the biomarker analyses will be reported separately.

Investigators will not receive the results of analyses during the study, and no alerts will be sent.

7.1.3.4 Planned Genetic Analysis Sample Collection

This genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the operations/laboratory manual.

7.1.3.5 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

DNA For future research.

Refer to Section 7.1.3.4 for further description of the Future Biomedical Research sample.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the Premature Treatment Discontinuation visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.2 Blinding/Unblinding

STUDY TREATMENT IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE SUBJECT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND THE SUBJECT UNLESS NECESSARY.

For emergency situations where the investigator or sub-investigator needs to identify the drug used by a subject and/or the dosage administered he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. The emergency unblinding call center will make a record promptly however, the investigator or sub-investigator must enter the intensity of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed. Subjects whose treatment assignment has been unblinded must be discontinued from study drug.

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to continue to be monitored in the trial.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant. Subjects whose treatment assignment has been unblinded (by the investigator, Merck subsidiary, or through the emergency unblinding call center) must be discontinued from study drug.

7.1.4.3 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical trial that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Screening

Up to 30 days prior to treatment allocation/randomization, potential subjects will be evaluated to determine whether they fulfill the entry requirements as set forth in Section 5.1. If subject is outside of the 30-day screening period and would like to be rescreened, then screening procedures may be repeated after consultation with the Sponsor and re-signing the ICF. At screening, a signed written informed consent must be available. All subsequent procedures will be done after the informed consent is signed.

Procedures for the Screening visit can be performed over several days. Alternatively, the screening visit and randomization visit can take place on the same day and subjects can be randomized during this visit if all required tests for eligibility criteria are available.

The screening visit can start from hospitalization (or upon IV diuretic treatment for HF without hospitalization) and no more than 30 days before randomization (Visit 2).

Additionally, evidence of a LVEF <45% within 12 months prior to randomization by any method (most recent measurement must be used) must be provided. The investigator is asked to ensure that the assessment of the LVEF represents the status at the time of study enrollment, so if clinically warranted, the investigator is encouraged to repeat the EF assessment.

Subjects who sign the ICF and, who for any reason (e.g., failure to satisfy the selection criteria), do not continue on to randomization will be considered a screen failure.

7.1.5.2 Treatment Period

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.2.1 Randomization Visit

At the randomization visit (within 30 days after the screening visit started, and up to 6 months after hospitalization or 3 months after IV therapy for HF without hospitalization), subjects who fulfill all inclusion/exclusion criteria will be randomized to either MK-1242 (vericiguat) or placebo on a background of standard of care HF treatment.

As noted above, the Screening visit and the Randomization visit can occur on the same day, if all required tests for eligibility criteria are available at screening visit.

All procedures and assessments specified for this visit will be done after screening visit procedures are performed.

7.1.5.2.2 Unscheduled Visits

In the event a subject requires an unscheduled visit for dose modification, the following assessments will be performed:

- Adverse events
- Dose assessment
- Clinical events
- Concomitant medication: record any new or ongoing medication or changes in dosage
- Blood pressure and pulse rate (3 measurements, each approximately 2 minutes apart) prior to study drug dosing

Upon interruption of the study drug due to intolerability, intake should be resumed as soon as medically justified to the discretion of the investigator as described in Section 5.2.1.2.

Investigators should make every attempt to resume study drug treatment in all subjects after interruption of study drug as soon as medically justified.

7.1.5.2.3 Final Visit

The Final visit will be conducted for all subjects when the planned number of CV death events is reached and the efficacy cut-off is announced by the Sponsor.

If applicable, subjects will continue study treatment until this visit, and will be asked to stop taking study drug medication at this visit. Those subjects who prematurely discontinued study drug treatment are still required to attend the Final visit for collection of clinical events and all other procedures listed in the study flow chart.

7.1.5.2.4 Final Phone Contact

All subjects will be contacted by phone within 14 days (+ 1 week) of the Final visit to assess for clinical events, adverse events and vital status (if applicable).

7.1.5.3 Premature Treatment Discontinuation

7.1.5.3.1 Premature Treatment Discontinuation Visit

A premature treatment discontinuation visit will be conducted at the time of treatment discontinuation for the collection of clinical events, adverse events, and other procedures listed in Section 6.0

7.1.5.3.2 Safety follow-up Visit

An in-clinic safety follow-up visit will be conducted for all subjects who discontinue study drug prematurely. This visit will be conducted within 14 days + 1 week after last dose of study treatment. Subjects who discontinue treatment prematurely will continue to attend all protocol specified visits and perform all procedures stipulated in that visit, including the Final visit, except in case the subject specifically withdrew consent for further follow-up and no additional information is permitted to be collected. If the subject does not attend the study visit, a telephone contact for collection of protocol defined endpoint events should occur. In such cases, the phone contact will not be considered a protocol deviation.

7.1.6 Other Ancillary Studies

7.1.6.1 Echocardiography and Cardiac Magnetic Resonance Imaging

At sites participating in the Echocardiography Imaging substudy, approximately 938 subjects may consent to undergo echocardiography at randomization and Month 8.

At sites participating in the Cardiac Magnetic Resonance (CMR) Imaging substudy, approximately 180 subjects without contraindications for magnetic resonance imaging assessment may consent to CMR imaging at randomization and Month 8.

Subjects are not required to participate in the echocardiography or CMR imaging substudy in order to participate in the main trial. In addition, subjects must provide separate informed consent in order to participate in these substudies.

Additional details will be specified in separate Site Imaging Procedure Manuals and Imaging Substudy Analysis Plans.

7.1.6.2 Health Economics Outcomes Research

The Health Economics Outcomes Research (HEOR) analysis has a pre-specified analytical plan focusing on healthcare resource use parameters as well as patient-reported outcome assessments. For the United States population, hospital billing information will be obtained to inform a United States cost-effectiveness analysis.

Additional details regarding the HEOR analysis will be provided in a separate manual.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is defined as any occasion when the subject has taken (accidentally or intentionally) any dose higher than the maximal target dose prescribed in the protocol.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a non-serious adverse event, unless other serious criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious adverse event using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 6 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

2. symptomatic hypotension. Subjects will be monitored for symptomatic hypotension. The DSMB will monitor with special attention to the relationship to baseline BP. While all hypotension AEs will be captured, only symptomatic hypotension is considered an event of clinical interest.

3. syncope.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Potential pre-specified efficacy endpoints will be submitted for adjudication to an independent CEC (see Section 7.3.4). This will include all-cause mortality, including cardiovascular and non-cardiovascular death.

The following events will not be subject to expedited reporting/unblinding by the Sponsor to investigators, Ethics Committees/IRBs, and regulatory agencies, regardless of causality, unless and until the event is reviewed by the CEC and found not to meet the specified criteria in the CEC charter for the following endpoint types:

- Cardiovascular Death
- Cardiovascular hospitalizations
- Urgent Heart Failure Visit

Fatal events that are adjudicated to be non-cardiovascular deaths by the CEC will require an independent Merck company causality assessment and will be subject to expedited reporting, where required by local legislation, when there is evidence suggesting a causal relationship between vericiguat and the event.

If an event submitted for adjudication is determined by the CEC not to meet the endpoint criteria in the CEC charter, the event will then be subject to expedited reporting (as appropriate, based upon both investigator and Merck company causality assessment of drug relationship, as required by local legislation).

Note that all of these events, including confirmed adjudicated cardiovascular events, will be reviewed and monitored by an external DSMB unblinded to treatment as part of the overall assessment of safety and efficacy for vericiguat. Based upon their regular review of unblinded safety results, the DSMB is empowered by the DSMB charter to make recommendations with regard to trial conduct to assure the continuing appropriate safety of the subjects participating in the study.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 6. The investigator's assessment of causality is required for each adverse event. Refer to Table 6 for instructions in evaluating adverse events.

Table 6 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Overdose, although not serious per ICH definition, whether accidental or intentional, with or without an accompanying adverse event/serious adverse event, is reportable to the Sponsor within 24 hours to meet certain local requirements.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Executive Committee

The executive committee (EC) provides scientific leadership of the VICTORIA study. As described in the EC charter, the EC consists of the following individuals:

- Executive Committee Chair
- Co-principal investigators
- Independent academic scientific leaders
- Clinical leaders from the Canadian VIGOUR Centre
- Clinical leaders from the Duke Clinical Research Institute
- Sponsor Senior Management

The EC will be responsible for all scientific aspects of the study, maintaining effective and independent scientific oversight, and will ensure that study execution and management are of the highest quality. The EC will convene regularly to discuss and report on ongoing supervision of the study. The EC serves as the publications committee and is responsible for oversight of all public and scientific communications and publications. On decisions regarding early termination of the trial, the EC will receive recommendations from the DSMB and then the EC will provide recommendations to the Sponsor, who has final decision making rights.

7.3.2 National Leader Committee

The primary role of the National Leader Committee is to serve as the interface between the Executive Committee and the study sites for the VICTORIA trial and to facilitate the progress of the study at the regional level. The National Leader Committee is composed of Country Leads selected by the Executive Committee from investigators in each country with appropriate clinical trial experience. National Leader Committee members should participate with their local site in VICTORIA to ensure adequate direct experience with the trial.

7.3.3 Data Safety Monitoring Board

To supplement the routine trial monitoring outlined in this protocol, an external Data Safety Monitoring Board (DSMB) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DSMB must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DSMB will make recommendations to the EC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DSMB will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.7 - Interim Analyses) and recommend to the EC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DSMB reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DSMB. The DSMB will monitor the trial at an appropriate frequency, as described in the detailed DSMB charter. The DSMB will also make recommendations to the Sponsor regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

A DSMB recommendation will be communicated to the Sponsor as agreed to in the Collaboration agreement.

7.3.4 Clinical Events Committee

A Clinical Events Committee (CEC) will evaluate the following events for the purposes of confirming them according to the criteria in Section 8.0 – Statistical Analysis Plan, as well as evaluating the presence of confounding factors.

1) Death
2) Cardiovascular Hospitalizations
3) Urgent Heart Failure Visit

All personnel involved in the adjudication process will remain blinded to treatment allocation throughout the trial. Specific details regarding endpoint definitions can be found in the CEC Charter.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. PK/PD endpoints and analysis approaches will be described in a separate detailed PK/PD evaluation and analysis plan.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2 to 8.10.

Study Design Overview	A randomized parallel-group, placebo-controlled, double-blind, event-driven, multi-center phase III clinical outcome trial of efficacy and safety of the oral sGC stimulator Vericiguat in subjects with heart failure with reduced ejection fraction (HFrEF)
Treatment Assignment	*Randomization method*: Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to MK-1242 (vericiguat) or matching placebo, respectively. *Stratification method*: Treatment allocation/randomization will be stratified in the following strata: a. Eastern Europe plus Israel and South Africa b. Western Europe c. North America (Black) d. North America (Non-black) e. Latin and South America f. Asia Pacific (including Australia)
Analysis Populations	Primary Efficacy Analysis: ITT population. Secondary Efficacy Analysis: ITT population Safety: All subjects as treated (ASaT)
Primary Endpoint(s)	Time to the first occurrence of the composite endpoint of CV death or HF hospitalization.
Secondary Endpoints	Time to CV death Time to first HF hospitalization Time to total HF hospitalizations (first and recurrent) Time to the composite of all-cause mortality or HF hospitalization Time to all-cause mortality
Statistical Methods for Key Efficacy	The analysis of the primary endpoint will be performed with a one-sided log-rank test, stratified by the same strata that are considered for randomization, to test if the time to first composite of CV death or HF hospitalization is prolonged in the vericiguat treatment group compared to placebo. The same one-sided stratified log-rank test will be used to test if the time-to first HF hospitalization, time-to CV death, time-to all-cause mortality, and time to the composite of all-cause mortality and HF hospitalization is prolonged in the vericiguat treatment group compared to placebo. The time-to total HF hospitalization will be tested with an Andersen-Gill model to compare the vericiguat treatment group to placebo. The overall study-wise type I error rate will be controlled at 0.025 (one-sided).

Statistical Methods for Key Safety Analyses	95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the unstratified Miettinen and Nurminen method. In addition, p-values will be provided for Tier 1 safety endpoints.
Interim Analyses	One interim analysis for efficacy is planned at the time when approximately 75% (587) of the planned number of CV death events are observed and the median follow up time is at least 10 months. At the interim analysis, both the primary composite endpoint of time to CV death or HF hospitalization and its component time to CV death will be tested. The study can only be terminated early for success if both the primary endpoint and the CV death component are statistically significant based on the nominal significance level used for the interim analysis. At the same time as the interim analysis for efficacy, a futility analysis will be performed with the option to terminate the study early if it is determined at the time of analysis that the study is unlikely to demonstrate the efficacy of vericiguat on the primary endpoint and CV death. An unblinded Data Safety Monitoring Board (DSMB) will assess the unblinded results of the interim analysis and may recommend early study termination for overwhelming efficacy or futility.
Multiplicity	The secondary endpoints will be separated into two families. The first family consists of the components of the primary endpoint, CV death and HF hospitalization, and the second family consists of total HF hospitalization, composite of all-cause mortality or HF hospitalization, and all-cause mortality. CV death and HF hospitalization will be tested only if the primary composite endpoint is significant and will be tested in parallel with multiplicity adjusted for the interim analysis only. Other secondary endpoints will be tested using a hierarchical testing approach.
Sample Size and Power	The sample size calculation is driven by the CV death component of the composite primary endpoint. For the CV death component, the expected event rate in the comparator group after 12 months is 11%. The relative risk reduction with vericiguat is assumed to be 20% for both CV death and primary endpoint, relating to a HR of 0.8. Using the log-rank test, a sample size of 4872 subjects and a total of 782 CV deaths will be required to achieve 80% power. With this sample size, it is expected that 1561 subjects with a primary endpoint event will be observed and there will approximately be 98% power for primary hypothesis testing. However, since the study duration will be driven by the number of CV death events, the expected number of primary endpoint events may differ from the actual observed number of primary endpoint events.

8.2 RESPONSIBILITY FOR ANALYSES/IN-HOUSE BLINDING

The statistical analyses of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

This study will be conducted as a double-blind study under in-house treatment blinding procedures. The central laboratory values for NT-pro BNP will also be blinded after Visit 2. The official, final database will not be unblinded until medical/scientific review has been performed, protocol violators have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an interactive voice response system (IVRS).

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0 – Objectives & Hypotheses

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

8.4.1 Efficacy Endpoints

Primary Endpoint

The primary endpoint of the study is the time to the first occurrence of the composite endpoint of CV death or HF hospitalizations. Subjects without a HF hospitalization or CV death at the time of analysis will be censored at time of non-CV death or time of last information available during the pre-specified follow-up period for subjects still alive at time of analysis. Only clinical events confirmed by CEC will be used to define the primary endpoint.

Secondary Endpoints

The secondary study endpoints are:

- Components of the primary composite endpoint:
  - Time to CV death
  - Time to first HF hospitalization
- Time to total HF hospitalizations (first and recurrent)
- Time to first occurrence of the composite of all-cause mortality or HF hospitalization
- Time to all-cause mortality

Exploratory Endpoints

The following endpoints will be considered outside of the testing procedure and considered as exploratory endpoints:

- Time to first HF event, defined as composite of HF hospitalization or urgent HF visit (not meeting the criteria for a HF hospitalization).
- Time to first CV hospitalization
- Total number of HF hospitalizations
- Change from baseline in health-related quality of life measures (KCCQ and EQ-5D)

8.4.2 Safety Endpoints

Safety measurements are described in Section 7.0 – Trial Procedures

8.4.3 Clinical Events Committee (CEC)

A clinical events committee (CEC) will be created to review and adjudicate each suspected clinical endpoint event without unblinding treatment. The CEC will comprise qualified members, who are not investigators in the study and not otherwise directly associated with the sponsor. The CEC members will remain blinded to treatment throughout the adjudication process and the study. The adjudication guidance and clinical endpoint event definitions will be described in detail in the CEC charter. Only clinical endpoint events adjudicated by the CEC will be used in the final efficacy and safety analyses.

Analysis of CEC adjudicated clinical events not already pre-specified as the primary, secondary or exploratory endpoints will be described in the supplemental Statistical Analysis Plan (sSAP).

8.5 Analysis Population

The primary endpoint analysis will use the Intention-to-Treat (ITT) population. The ITT population includes all randomized subjects. The subjects will be analyzed according to the planned treatment. Subjects without any post-randomization information will be censored at Day 1.

The ITT population will also be used for the secondary and exploratory efficacy endpoints analyses. The subjects will be analyzed according to the planned treatment. Subjects without any post-randomization information will be censored at Day 1 for time to event endpoints.

The All-Subjects-as-Treated (ASaT) population will be used for safety analyses. The ASaT population includes all subjects who have taken at least one dose of study drug (vericiguat or placebo). All subjects will be analyzed according to the actual treatment received. Any subjects in ASaT who received both placebo and vericiguat during the study by mistake will be analyzed according to the planned treatment.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

Efficacy results will be deemed to be statistically significant after consideration of the Type I error control strategy as described in Sections 8.7 and 8.8. A brief summary of analysis

approaches for the primary and secondary efficacy endpoints are described in Table 7. Nominal p-values will be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

Analysis of Primary Endpoint

The analysis of the primary efficacy endpoint will follow the intention-to treat principle and will be performed in the ITT population, comprised of subjects randomized. Subjects will be analyzed as randomized. The analysis of the primary endpoint will be based on results from adjudication and will test if the time to the first occurrence of the composite endpoint is prolonged in the MK-1242 (vericiguat) treatment group. Randomized subjects without any HF hospitalization or CV death event at the time of analysis will be censored at their last available information or the date of their non-CV death.

The analysis will be performed with a one-sided log-rank test, stratified by the same six strata by region and race that are considered for randomization, testing the following null hypothesis:

H_0: $S_{Vericiguat}(t) = S_{Placebo}(t)$ for all time points $t \geq 0$.

The alternative hypothesis will be:

H_1: $S_{Vericiguat}(t) > S_{Placebo}(t)$ for at least one time point $t \geq 0$ and

$S_{Vericiguat}(t) \geq S_{Placebo}(t)$ for all time points $t \geq 0$.

$S_{Vericiguat}$ denotes the (event-free) survival function of the vericiguat treatment group and $S_{Placebo}$ denotes the (event free) survival function of the placebo treatment group.

The overall study-wise one-sided type I error rate will be controlled at 0.025. The following decision rule to test the null hypothesis will be applied:

If the z-value from the one-sided stratified log-rank test (for the difference $S_{Vericiguat}$ - $S_{Placebo}$) is larger than the critical quantile from the standard normal distribution ($z_{1-\alpha}$, with α being the nominal significance level at the respective interim or final analysis), the null hypothesis will be rejected in favor of the alternative hypothesis.

Kaplan-Meier estimates of the primary composite endpoint (95% confidence interval) survival curves will be presented for each treatment group. Hazard ratio, relative risk reduction and corresponding 95% confidence intervals will be estimated based on a Cox proportional hazards model stratified by the same factors as used for the primary efficacy analysis.

The number and proportion of subjects with a CV death or HF hospitalization event will be provided by treatment group. In addition, rates per 100 patient-years will be provided.

Analysis of Secondary Endpoints

Analogous to the analysis of the primary endpoint, the analysis of the secondary efficacy endpoints will be performed under the intention to treat principle. All subjects randomized will be included in the analysis. Subjects will be analyzed as randomized.

A one-sided stratified log-rank test similar to the one used for the primary efficacy endpoint will be used to test if the time to first HF hospitalization, time to CV death, time to all-cause mortality, and time to first occurrence of the composite of all-cause mortality or HF hospitalization is prolonged in the vericiguat treatment group compared to placebo.

The time-to total HF hospitalization will be tested with an Andersen-Gill model [14] to compare the vericiguat treatment group to placebo. The Anderson-Gill model is an extension of the Cox proportional hazards model, where the hazard for the kth event, i.e. including both first and recurrent, for a subject i at time t, is given by

$$h_{ik}(t) = h0(t) \exp(\beta Tx),$$

with h0(t) being the baseline hazard and x the vector of covariates for subject i.

Treatment group and the stratification factors used for randomization will be included in the model as fixed effects. Robust standard errors will be used to account for correlations of event times within a subject [15] [16].

The following null hypothesis will be compared with the alternative hypothesis:

H0: $HR_{Vericiguat/Placebo} = 1$

H1: $HR_{Vericiguat/Placebo} < 1$

Superiority of MK-1242 (vericiguat) over placebo in prolonging the time to total HF hospitalization will be concluded, if the upper limit of the confidence interval of the hazard ratio is below 1 with the confidence level matching the nominal alpha level used for testing at the interim or final analysis. Estimates of treatment comparisons and effect size including 95% confidence intervals will be provided based on the fitted model.

In addition, time to total HF hospitalizations and CV death will be analyzed using the Wei, Lin, Weissfeld (WLW) method [17], and details will appear in the supplemental SAP.

Missing Data

Subjects who prematurely withdraw from study treatment will be followed for further data collection. As long as the subject does not withdraw consent for any further data collection, every effort will be made to collect at least data on the components of the primary endpoint up to the last safety phone call which occurs two weeks after the final study visit. Subjects are requested to attend the protocol specified study visits. If a subject does not attend the regular study visits, the investigator will contact the subject via telephone to collect at least data for the primary endpoint.

Due to this follow up approach, it is expected that the amount of missing data will be only minor, as most subjects will be followed up until trial termination.

For the primary analysis, subjects without any HF hospitalization or CV death event at the time of analysis will be censored at their last available information or the date of their non-CV death. The censoring mechanism is assumed to be non-informative.

Supportive analyses will be performed to assess the impact of a potential informative censoring and missing data, and details will be described in the supplemental statistical analysis plan.

Table 7 Primary Analysis Strategy for Efficacy Variables

Endpoint/Variable	Statistical Method†	Analysis Population	Missing Data Approach
Primary Hypothesis:			
Time to first occurrence of the composite endpoint of CV death or HF hospitalization	Stratified Log-Rank Test	ITT	Censored at the last available information
Secondary Endpoints:			
Time to the first occurrence of CV death	Stratified Log-Rank Test	ITT	Censored at last known alive date
Time to the first occurrence of HF hospitalization	Stratified Log-Rank Test	ITT	Censored at the last available information
Time to total HF hospitalizations (including the first and recurrent events)	Andersen-Gill model ‡	ITT	Censored at the last available information
Time to first occurrence of the composite of all-cause mortality or HF hospitalization	Stratified Log-Rank Test	ITT	Censored at last available information
Time to all-cause mortality	Stratified Log-Rank Test	ITT	Censored at last known alive date

† Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization will be used as stratification factors for analysis.
‡ Treatment group and the stratification factors used for randomization will be included in the model as fixed effects.

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, and vital signs.

The analysis of safety results will follow a tiered approach (Table 8). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse events of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the unstratified Miettinen and Nurminen method.

Adverse events (specific terms as well as system organ class terms) and predefined limits of change in laboratory and vital signs that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed.

Membership in Tier 2 requires that at least 4 subjects in at least one treatment group exhibit the event; all other adverse events and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse events and predefined limits of change.

Continuous measures such as changes from baseline in laboratory and vital signs that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format. In addition, summary statistics for the difference between treatment groups will also be provided, along with nominal p-values for between-group differences. Mean change from baseline over time will be plotted with the corresponding standard errors.

Table 8 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	• Syncope • Symptomatic hypotension	X	X	X
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any AE leading to death		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs, SOCs, or PDLCs‡ (incidence ≥4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCs‡ (incidence <4 of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, Vital Signs)			X

† Adverse Event references refer to both Clinical and Laboratory AEs.

‡ Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.

Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis testing will be performed on these characteristics. The number and percentage of subjects randomized and the primary reason

for discontinuation will be displayed. Demographic variables (e.g., age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analysis

8.7.1 Futility Interim Analysis

A futility interim analysis to assess lack of efficacy is planned at the time when approximately 75% (587) of the planned number of CV death events are observed, and is projected to take place approximately 33 months after the start of the study. The futility analysis, to be performed at the same time as the interim efficacy analysis (see Section 8.7.2, Efficacy Interim Analysis), will be performed with both the primary composite endpoint and CV death. The futility boundary will be based on the point estimate of hazard ratio (vericiguat/placebo). A point estimate of hazard ratio above 0.95 for the primary endpoint and a point estimate of hazard ratio above 1.0 for CV death, simultaneously, will be considered meeting the futility criteria. Based on simulation analysis, the impact of this futility analysis approach on the overall study power is negligible. Under the null hypothesis with true hazard ratio equal to 1 (no treatment effect) for CV death and for the primary endpoint, the probability of stopping the study for futility is approximately 47%. If the true effect size is 20% (hazard ratio of 0.80) as projected for CV death and for the primary endpoint, the probability of stopping for futility is less than 0.1%. An unblinded DSMB will assess the results of the futility interim analysis and may recommend early study termination for futility.

8.7.2 Efficacy Interim Analysis

An efficacy interim analysis is also planned at the same time of futility analysis when approximately 75% of the planned number of CV death events are observed. Based on the assumptions from the sample size calculation, the interim analysis will take place approximately 33 months after start of the study, shortly after all subjects have been accrued. To ensure that the study has accumulated adequate follow up for safety assessment when stopped for positive efficacy results, the timing of the efficacy interim analysis should also ensure that the median follow up time is at least 10 months. Under the assumption of an 11% 12-month placebo event rate for CV death, the median follow-up time when 75% of CV death events have been observed is expected to be approximately 375 days. Approximately 51% of the subjects will have follow-up time of at least 12 months, 38% of at least 15 months, and 26% of at least 18 months. The median treatment duration will be 340 days.

If the observed CV death event rate is substantially higher than anticipated and thus median follow-up time is less than 10 month when 75% of the planned number of CV events has occurred, the efficacy interim analysis will be delayed until 10 months of median follow up is achieved. In this case, the futility analysis will also be delayed and will be performed at the same time as the interim efficacy analysis. Under an extreme scenario of a much higher than anticipated event rate, the efficacy interim analysis may become unnecessary if the timing for the efficacy IA falls too close to the final analysis. The decision to adjust the timing of the efficacy interim analysis or to cancel the efficacy interim analysis under a higher than expected event rate will be made by the blinded Sponsor team.

At the efficacy interim analysis, the primary endpoint and the secondary endpoint of time to CV death will be tested. The study can only be terminated early for success if both the primary endpoint and the CV death endpoint are statistically significant based on the pre-specified interim analysis boundaries. The testing approach controls the overall alpha-level between the primary endpoint and CV death.

The Hwang, Shih and DeCani (γ=-6.5) alpha spending function will be used for the efficacy interim analysis to assess superiority of MK-1242 (vericiguat). The spending function can be expressed as

$$f(t) = \alpha\left(\frac{1-e^{-\gamma t}}{1-e^{-\gamma}}\right),$$

with *t* denoting the percentage of information included at the respective interim analysis.

With this alpha spending approach, the nominal significance level will be approximately 0.0049 (one-sided) at the interim analysis and 0.0242 at the final analysis, respectively. This testing approach controls the one-sided alpha between the efficacy interim analysis and final analysis at 0.025. The corresponding observed hazard ratio for the stopping boundary is approximately 0.81 for CV death at the efficacy interim analysis.

The actual α to be spent at the efficacy interim analysis and final analysis will be precisely determined using the number of actually observed primary outcome events and the alpha spending function defined as above.

At the time of the interim analysis, approximately 587 CV death events and approximately 1171 (may vary depending on the actual event rate) primary endpoint events are expected. A one-sided stratified log-rank test will be used to assess if vericiguat prolongs the time to primary composite endpoint event compared with placebo. The same nominal significance level as used for the primary composite endpoint will also be used for the analysis of the CV death component.

If the study can be stopped early for success, the nominal one-sided significance level of approximately 0.0049 for the primary endpoint and CV death will be applied to other secondary endpoints as well.

If the study cannot be stopped early for success, the CV death component will be analyzed at the final analysis time point as one of the secondary endpoints.

An unblinded DSMB will assess the results of the interim analysis and may recommend early study termination if the interim analysis shows clear and consistent benefit of vericiguat as guided by the above described alpha-spending approach.

If the DSMB recommendation leads to termination of the study at the interim analysis due to efficacy, all subjects will be called in to their final visit. The complete analysis will be based on the entire data collected until the study completion, i.e. it will also include data collected after the cut-off for the interim analysis.

Table 9 summarizes the timing, number of events, endpoint, and the efficacy and futility bounds at each of the interim analysis and at the final analysis.

Table 9 Summaries of the Interim and Final Analyses

Analysis	Key Endpoint(s)	Target Number of Events	Anticipated Time From Study Start	Statistical Testing Criteria
Futility Interim Analysis	Primary Endpoint Time to CV Death	587 CV Death† (75% of planned number of events)	Month 33†	A point estimate of HR>0.95 for the primary endpoint and a point estimate of HR>1.0 for CV death for futility
Efficacy Interim Analysis	Primary Endpoint, Time to CV Death	587 CV Deaths† (75% of planned number of events)	Month 33†	P<0.0049 (one-sided) on both endpoints for efficacy, corresponding to an observed HR<0.81 for Time to CV Death
Final Analysis	Primary Endpoint, Secondary Endpoints	782 CV deaths†	Month 39†	P<0.0242 (one-sided) for statistical significance, using the pre-specified multiplicity adjustment approach (Section 8.8)
†Median follow up time of 10 months are also required.				

8.8 Multiplicity Adjustment

The study-wise one-sided alpha level will be controlled at 0.025 for the test of the primary endpoint. Multiplicity due to the interim analysis at 75% of planned CV death events will be controlled using a Hwang, Shih and DeCani (γ=-6.5) alpha spending function as described in section 8.7.

The secondary endpoints will be separated into two families. The first family consists of the components of the primary endpoint, time to CV death and time to first HF hospitalization.

The second family will consist of the endpoints of time to total HF hospitalization, time to all-cause mortality, and time to first occurrence of composite of HF hospitalization or all-cause mortality. The endpoints from the second family will be tested hierarchically and at the same time be adjusted for the interim analysis, thereby maintaining the study-wise alpha level. These secondary endpoints will only be tested if both the primary composite endpoint and CV death are significant at the interim analysis, or if the primary composite endpoint alone is significant at the final analysis. Total HF hospitalization will be tested first, and only if this is significant, the composite of all-cause mortality and HF hospitalization will be tested afterwards. All-cause mortality will be tested only if both of the above endpoints are tested significant (see Figure 2 for the procedure at the final analysis).

At the interim analysis, if the study is stopped early for efficacy due to success on the primary composite endpoint and separately the CV death component, then the HF hospitalization component will be tested at the same alpha level as the CV death component. In addition, the family of secondary endpoints will be tested in a sequential manner using the same alpha as the primary composite endpoint.

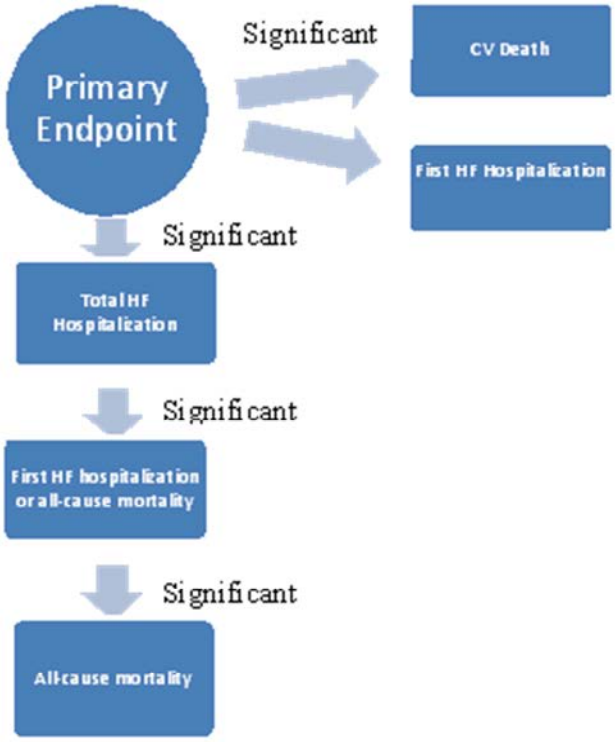

Figure 2 Testing of Primary and Secondary Endpoints

8.9 Determination of Sample Size

The sample size estimation is based on a 1:1 randomization and a study-wise one-sided significance level of 0.025. In accordance with the planned interim analysis, the nominal one-sided significance level will be 0.0242 at the final analysis. A conservative approach of power calculation based only on the final analysis is used.

The study will be an event-driven study. It is planned to accrue subjects during 30 months and have a follow-up of 9 months after the last subject is included in the study. This leads to total study duration of 39 months. It is assumed that setting up of all sites will take approximately 12 months, assuming a quadratic ramp-up function for subject accrual.

The primary analysis will be performed in the ITT population. Every effort will be made to follow-up subjects that prematurely stop study medication to collect at least information for the primary endpoint (i.e. information on hospitalizations and death).

It is assumed that 2% of subjects per year will prematurely stop study medication and either object to further follow-up or be lost to follow-up, despite efforts to contact them. In addition, it is assumed that approximately 10% per year of subjects will stop study treatment and can be followed up off treatment for the primary endpoint. When a subject in the placebo group stops treatment prematurely, it is assumed that the hazard for CV death and HF hospitalization does not change, as the subject is expected to continue with standard heart failure therapy. For vericiguat subjects stopping treatment prematurely, it is assumed that they switch to the hazard of the placebo group, as they henceforth will switch back to

standard heart failure therapy. These effects will dilute the observed treatment effect when the ITT analysis approach is used. The sample size calculations are adjusted for this dilution.

The sample size calculation is driven by the CV death component of the composite primary endpoint. For the CV death component, the expected event rate in the comparator group after 12 months is 11%. The relative risk reduction with vericiguat is assumed to be 20%, relating to a HR of 0.8. Using the log-rank test, a sample size of 4872 subjects and a total of 782 CEC confirmed CV deaths will be required to achieve 80% power.

For the comparator arm, the event rate of the composite endpoint, i.e. first HF hospitalization or CV death, is expected to be 23% after 12 months. The relative risk reduction with vericiguat is assumed to be 20%, relating to a HR of 0.8. With a sample size of 4872 subjects, it is expected to observe 1561 subjects with a composite endpoint event and expected power of approximately 98%. The time point of final analysis will be based on the number of CV deaths, and the total number of subjects with primary endpoint event may vary depending on the actual event rate in the study.

If the study is not stopped early for success, the median follow-up time (including off-treatment times) is expected to be approximately 532 days. Approximately 74% of the subjects will have follow up time of at least 12 months, 60% of at least 15 months, and 47% of at least 18 months. The median treatment duration will be approximately 480 days.

If the CV death event rate is much higher than anticipated such that the median follow up time is less than 10 months when 782 CV death events have been observed, the study will continue until a median follow up time of 10 months has been achieved.

Expected event rate and relative risk reduction

The assumed comparator event rates refer to the placebo arm of the ASTRONAUT study population with stabilized worsening chronic HFrEF on standard therapy for HFrEF. The event rate of these patients with worsening chronic HFrEF requiring hospitalization is extrapolated to those receiving IV diuretic treatment for worsening HF because outpatient management of worsening HF was reported to portend a similarly high risk of death compared to inpatient HF events, and may be equally sensitive to the effects of therapy [5].

The estimated annual event rate for the primary endpoint and for CV mortality in the control (standard of care) arm was based on the ASTRONAUT study in patients with stabilized worsening chronic HFrEF on standard HF therapy that was conducted between 2009 and 2012 [7]. Both trials recruit from similar geographic regions (North America, Latin America, Eastern Europe, Western Europe, and Asia/Pacific). In the ASTRONAUT trial, Asia/Pacific had the greatest representation with 32% of the trial population. Otherwise there was a fairly equal distribution across the regions, and the intent in VICTORIA is also to have equal distribution across regions. Other key differences in the ASTRONAUT patient population include a lower LVEF cutpoint (≤40%), the lack of atrial fibrillation-specific natriuretic peptide cutpoints, the lack of inclusion of IV diuretic use without hospitalization as an enrichment criteria, and the lack of sacubitril/valsartan as a background standard of care therapy. The rate of a first event of either CV death or HF hospitalization was 37% at 12 months, and 17% for CV mortality as single endpoint [7].

Because the timeframe for inclusion will be 6 months in the planned study, opposed to inclusion within a median of 5 days after stabilization after hospitalization for an acute HF decompensation in ASTRONAUT [7], a more conservative expected annual event rate of 11% CV mortality and 23% annual event rate for the composite of CV death and HF hospitalization is chosen for sample size calculation. Since elevated levels of NT-proBNP are mandated by the protocol as a second enrichment factor in addition to the initial decompensation, and since event rates in patients enrolled after the median time after CV hospitalization in EMPHASIS-HF (83.4 % patients had been previously hospitalized for CV reasons within 6 months of the study, with ≈50 % of them hospitalized because of HF [18] [19] were only slightly lower than those in patients enrolled before the median, no greater reduction in assumed event rates is estimated.

We consider a 20% relative risk ratio (RRR), corresponding to a hazard ratio of 0.8, in the primary composite of CV death and HF hospitalization as a clinically relevant treatment effect in the planned high-risk population. With an assumed annual event rate of 23%, the absolute reduction by 4.6 percentage points results in a number needed to treat (NNT) of 22 to prevent 1 event per year. A 20% RRR in in CV mortality is considered as clinically relevant treatment effect. With an assumed annual event rate of 11%, the absolute reduction of 2.2 percentage points results in a NNT of 45 to prevent one CV death per year.

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints will be estimated and plotted within each category of the following classification variables in all subjects:

- Age (<65 years vs. ≥65 years)
- Sex (Female vs. Male)
- Geographic region (Eastern Europe / Western Europe / North America / Latin and South America / Asia Pacific)
- Index event (IV diuretic within 3 months of randomization / Hospitalization within 3 months of randomization / Hospitalization 3 to 6 months prior to randomization)
- eGFR at randomization (between 15 and 30 mL/min/1.73 m^2 vs. above 30 mL/min/1.73 m^2)
- NYHA class at baseline (II/III/IV)
- Use of sacubitril/valsartan at baseline
- Baseline NT-pro BNP (by Quartiles)
- Baseline ejection fraction (<35% vs. ≥35%)
- Race (Caucasian / Black / Asian / Other)
- Race in North America only (Black vs. Non-black)

In addition to the above subgroup analyses by baseline factors, if it is observed or anticipated that the background standard care treatment evolves over time during the course of the study,

analysis to assess the consistency of the treatment effect of MK-1242 under different background therapies will be performed. Details of the analysis approach will be pre-specified in the supplemental Statistical Analysis Plan (sSAP).

8.11 Compliance (Medication Adherence)

Compliance for study treatment will be collected during the study as described in 7.1.1.8. Deviation from protocol-directed administration will be summarized at the end of the study.

8.12 Extent of Exposure

The extent of exposure will be summarized as the duration of study treatment. Furthermore, exposure summary based on dosage and dose titration will also be provided.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 10.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 10 Product Descriptions

Product Name & Potency	Dosage Form
MK-1242 2.5 mg	Tablet
MK-1242 5 mg	Tablet
MK-1242 10 mg	Tablet
MK-1242 2.5 mg Placebo	Tablet
MK-1242 5 mg Placebo	Tablet
MK-1242 10 mg Placebo	Tablet

All placebos were created by the Sponsor to match the active product.

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive blinded bottles. No kitting is required.

9.3 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment/randomization schedule for the study to unblind subjects and to unmask study treatment identity. The emergency unblinding call center should only be used in cases of emergency (see Section 7.1.4.2). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask study treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded to treatment assignment. Subjects whose treatment assignment has been unblinded (by the investigator, Merck subsidiary, or through the emergency unblinding call center) must be discontinued from study drug.

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to continue to be monitored in the trial.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign

treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the

Sponsor and agrees not to submit any information about this trial or its results to those registries.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that

are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

11.0 LIST OF REFERENCES

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.5 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated

mailbox (clinical.specimen.management@merck.com) and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available

through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

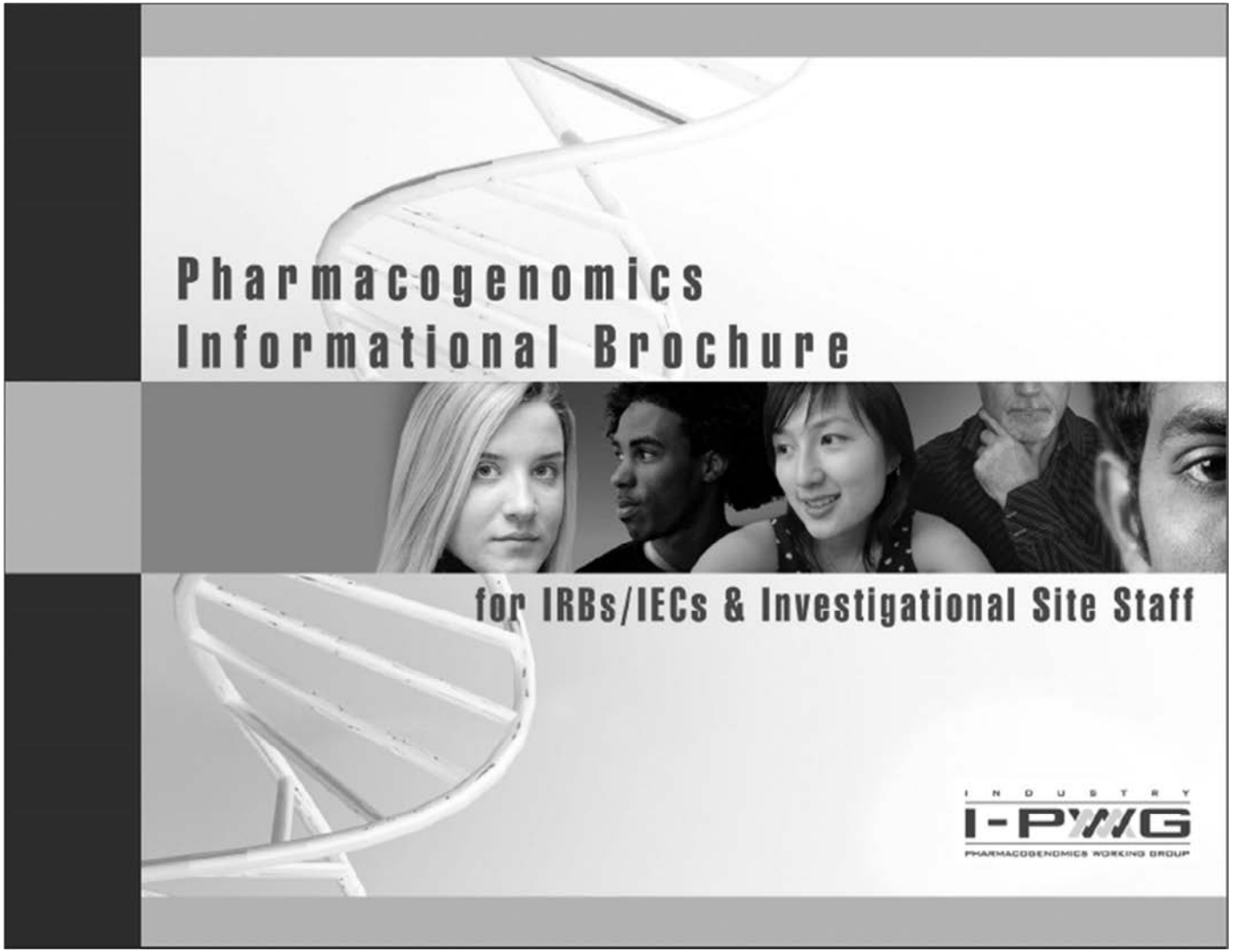
12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

12.3 Pharmacogenetics Informational Brochure for IRBs/IECs & Investigational Site Staff



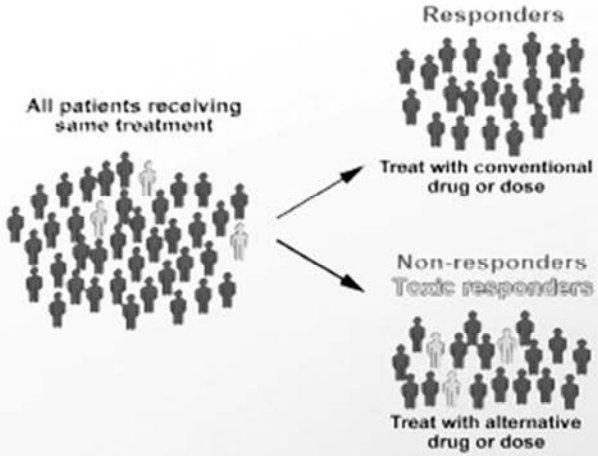
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid** (**DNA**). DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

Pharmacogenomics (PGx) is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA[1], and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.



Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

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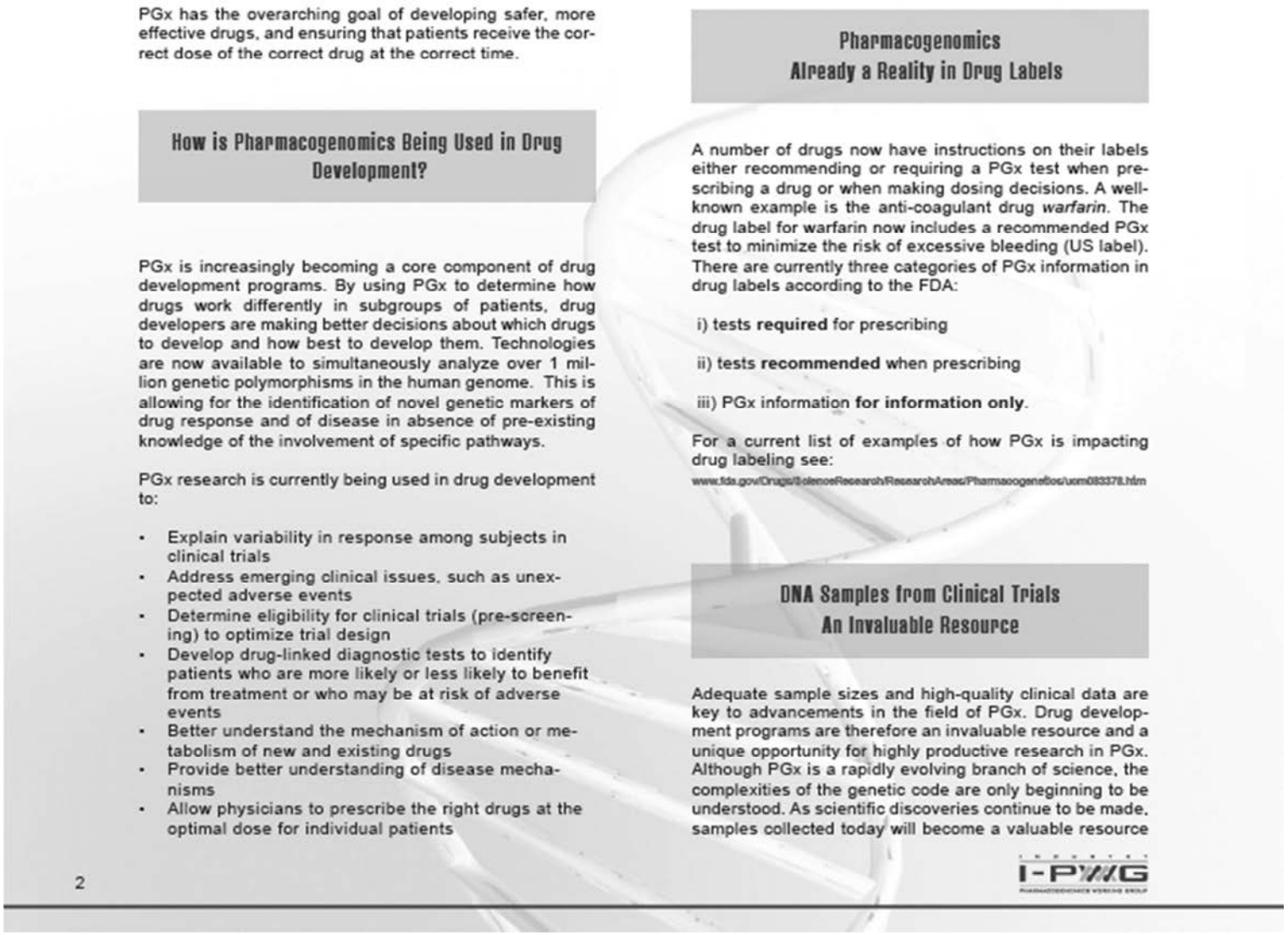
PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.
How is Pharmacogenomics Being Used in Drug Development?
PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.
PGx research is currently being used in drug development to:
• Explain variability in response among subjects in clinical trials
• Address emerging clinical issues, such as unexpected adverse events
• Determine eligibility for clinical trials (pre-screening) to optimize trial design
• Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
• Better understand the mechanism of action or metabolism of new and existing drugs
• Provide better understanding of disease mechanisms
• Allow physicians to prescribe the right drugs at the optimal dose for individual patients
2
Pharmacogenomics Already a Reality in Drug Labels
A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug warfarin. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:
i) tests required for prescribing
ii) tests recommended when prescribing
iii) PGx information for information only.
For a current list of examples of how PGx is impacting drug labeling see:
www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
DNA Samples from Clinical Trials An Invaluable Resource
Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource
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for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies[2]. These elements build upon existing basic elements of informed consent for clinical research on human subjects[3].

Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006[4].

Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

i) Sample Labeling

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15[1]. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)[1]. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

3

Table adapted from ICH Guidance E15

Sample Coding Category		Link Between Subject's Personal Identifiers and Genomic Biomarker Data	Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (Direct) Allows for Subjects to be Identified	Yes	Yes	Similar to General Healthcare Confidentiality and Privacy
Coded	Single	Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key)	Yes	Yes	Standard for Clinical Research
	Double	Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys)	Yes	Yes	Added Privacy and Confidentiality Protection over Single Code
Anonymized		No Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted	No	No	Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted
Anonymous		No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified	No	No	Genomic Data and Samples Never Linked to Subject

ii) Separation of Data and Restricted Access

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form[2].

4

I-PWG

iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)[5, 6] serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: http://www.i-pwg.org

Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: http://www.i-pwg.org. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[19].

Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: http://www.i-pwg.org.

What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: http://www.i-pwg.org.

5

Glossary

Identified Data and Samples: Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). The use of identified data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

Coded Data and Samples: Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.

Single-Coded Data and Samples: are usually labeled with a single specific code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

Double-Coded (De-identified) Data and Samples: are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code.

Anonymized Data and Samples: Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification.

Anonymous Data and Samples: Anonymous data and samples are never labeled with personal identifiers when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

6

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I-PWG

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7

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12.4 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

Trial Visit/ Cycle/etc:	Screen-ing Visit	Rand Visits 2	Treatment Visit 5 Week 16	Treatment Visit 6 Week 32	Treatment Visits 7 Week 48 and Yearly Visits	Every 16 week visits	Discon Visit	Safety Follow-up Visit	Final Visit
Blood Parameter	**Approximate Blood Volume (mL)**								
Hematology		2	2	2	2		2	2	2[c]
Serum/Plasma Chemistry (including liver function tests)		6	6	6	6		6	6	6[c]
Serum β-Human Chorionic Gonadotropin (β-hCG)[a]		Included with the Chemistry Sample	Included with the Chemistry Sample	Included with the Chemistry Sample	Included with the Chemistry Sample	2			
NT-proBNP		2	2	2	2		2		2[c]
Local NT-proBNP/BNP	2								
Local Creatinine	2								
Hemoglobin A1c[b]		2	2	2	2		2		2[c]
Blood for Planned Genetic Analysis		8.5							
Pharmacokinetic Sample		6	6		6		6		6[c]
Blood for Biomarkers		12	12	12			12		12[c]
Expected Total (mL)	4	38.5	30	24	18	2	30	8	30

a. For female subjects of child bearing potential only.
b. Sample obtained in subjects with diabetes mellitus only.
c. Not applicable for subjects who prematurely discontinue.

12.5 Blood Pressure Measurement Guidance

Accurate measurement of blood pressure is essential to guide dose titration management and to detect potential safety signals during the trial.

A number of factors related to the subject can cause significant deviations in measured blood pressure. These include room temperature, exercise, alcohol or nicotine consumption, positioning of the arm, muscle tension, bladder distension, talking, and background noise.

Blood Pressure and Pulse Rate should be measured under the following conditions:

- Measurement of Pulse Rate and Blood Pressure must be conducted after 10 minute resting period with subject comfortably seated in a chair with the legs uncrossed and the back and arm supported. Measurements should not be made while the subject is on an examining table. The subject should be instructed to relax as much as possible and to not talk during the measurement procedure
- The examiner should ensure that the middle of the cuff on the upper arm is at the level of the right atrium (the mid-point of the sternum).
- The subject should be asked to remove all clothing that covers the location of cuff placement.
- The same examiner should assess the subject at all subsequent visits and use the same device under same external conditions.
- The protocol requires 3 measurements – approximately 2 min apart. Please record the time, positioning and arm used for each measurement

12.6 List of Abbreviations

Abbreviation	Meaning
ACCF	American College of Cardiology Foundation
ACE	Angiotensin Converting Enzyme
AE	Adverse Event
AHA	American Heart Association
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ARB	Angiotensin Receptor Blocker
ARO	Academic Research Organization
BNP	Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Grafting
CCSA	Canadian Cardiovascular Society Functional Classification of Angina
CEC	Clinical Events Committee
cGMP	cyclic Guanosine Monophosphate
CI	Confidence Interval
CMR	Cardiac Magnetic Resonance
CRT	Cardiac Resynchronization Therapy
CVC	Canadian VIGOUR Centre
CV	Cardiovascular
DCRI	Duke Clinical Research Institute
DSMB	Data Safety Monitoring Board
ECI	Events of Clinical Interest
eCRF	electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
EQ-5D	EuroQol Group 5-Dimensional
ESC	European Society of Cardiology
GCP	Good Clinical Practice
HEOR	Health Economics Outcomes Research
HFpEF	Heart Failure with preserved Ejection Fraction
HF	Heart failure
HFrEF	Heart Failure with reduced Ejection Fraction
HR	Hazard Ratio
IB	Investigator's Brochure
ICD	Implantable Cardioverter-Defibrillators
ICF	Informed Consent Form
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left Ventricular Ejection Fraction
MDRD	Modification of Diet in Renal Disease
MRA	Mineralocorticoid Receptor Antagonist
NNT	Number Needed to Treat
NO	Nitric Oxide
NTG	Nitroglycerin
NT-proBNP	N-terminal pro-Brain Natriuretic Peptide
NYHA	New York Heart Association
PDE5	Phosphodiesterase type 5
RRR	Relative Risk Ratio
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure

Abbreviation	Meaning
sGC	soluble Guanylate Cyclase
SoC	Standard of Care
TIA	Transient Ischemic Attack

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	