Protocol

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Clinical Study to Assess the Effectiveness of CRD-740 in Subjects with Chronic Heart Failure

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SPONSOR APPROVAL

I have read the following and approve:

[redacted] _____ _____
Date
Executive Director, Clinical Research

INVESTIGATOR AGREEMENT

I have read the following protocol and agree to conduct the study as described herein.

[Name, Qualification(s)] Principal Investigator	Date

SYNOPSIS

Title of study: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Clinical Study to Assess the Effectiveness of CRD-740 in Subjects with Chronic Heart Failure

Indication: Chronic heart failure

Number of study centers: Approximately 100 sites globally

Development phase: 2

Objectives:

Part A

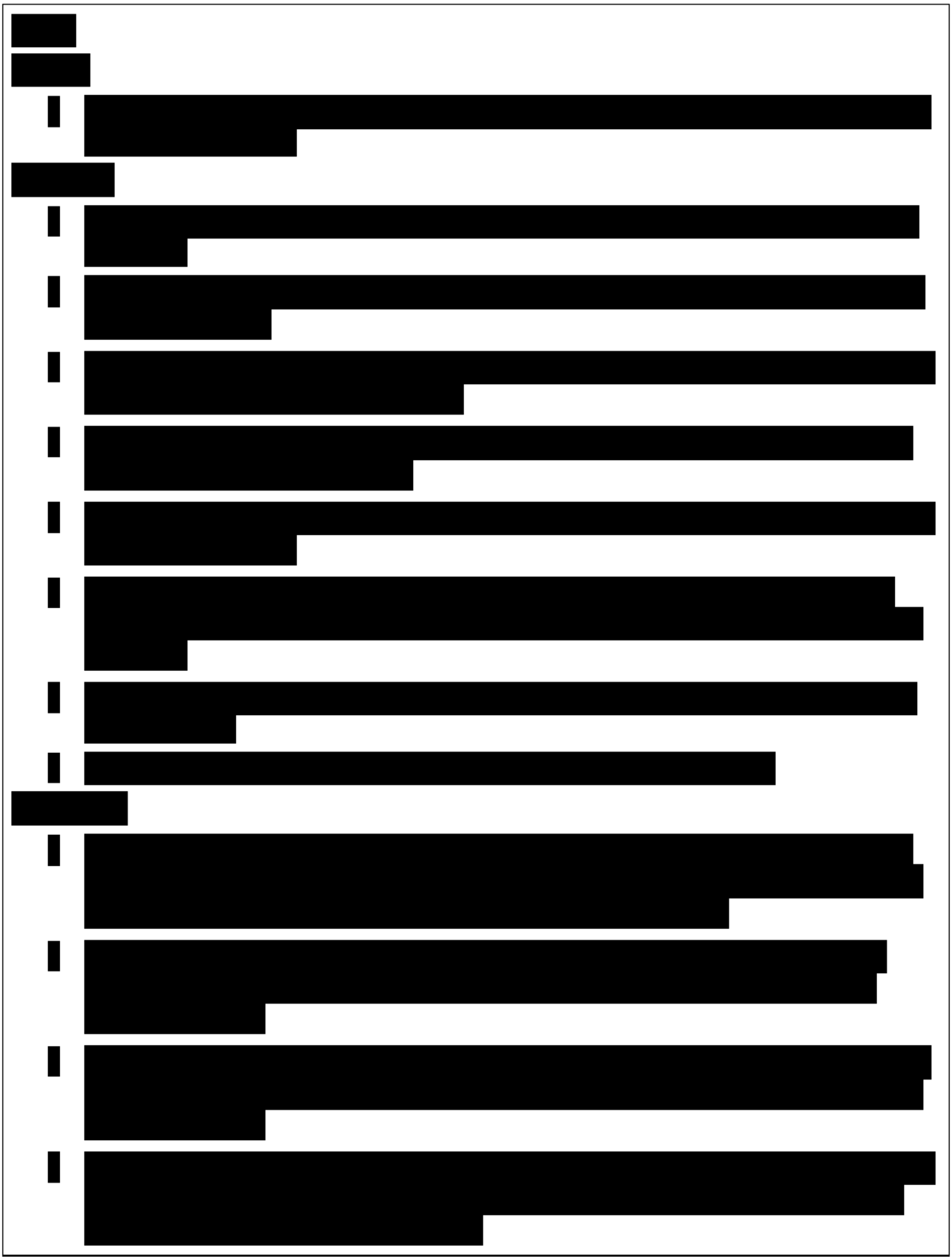
Primary

- To assess the safety and tolerability of CRD-740 in subjects with chronic heart failure with reduced ejection fraction (CHFrEF), defined as heart failure (HF) with ejection fraction (EF) ≤40%.
- To assess the effect of CRD-740 compared to placebo in plasma cyclic guanosine monophosphate (cGMP) at Week 4 in subjects with CHFrEF.

Secondary

- To assess the pharmacokinetics (PK) of CRD-740 in subjects with CHFrEF.

[redacted]



- [redacted]

Methodology/Study design:

This is a Phase 2, two-part, seamless, randomized, double-blind, placebo-controlled, parallel group clinical study. Part A is a dose ranging study in a group of subjects with CHFrEF. Part B is a proof-of-concept study in subjects with either CHFrEF or chronic heart failure with preserved ejection fraction (CHFpEF).

In Part A, eligible subjects with CHFrEF will be randomized to either CRD-740 or placebo in a 2:1 ratio. Subjects will start Period 1 at a dose of CRD-740 [redacted] or matching placebo. Subjects will remain in Period 1 for 2 weeks. At Day 15, subjects enter Period 2 and are dosed at CRD-740 [redacted] or matching placebo. Subjects will continue in Period 2 for 2 weeks. At Day 29, subjects enter Period 3 and continue CRD-740 [redacted] or matching placebo. Subjects will continue in Period 3 for 8 weeks to complete a total of 12 weeks of CRD-740 or matching placebo. Safety and tolerability will be continuously assessed. A post-study visit will occur at Week 16. Part A will evaluate the effectiveness of CRD-740 in the overall population of subjects with CHFrEF, and possibly in the 2 subgroups defined by sacubitril/valsartan (Entresto) use (yes, no), depending on the number of subjects in each stratum. Randomization will be stratified on Entresto use (yes vs no).

[redacted]

Endpoints

Primary efficacy

Part A

- The change from baseline (Day -1) in plasma cGMP at Week 4.

[redacted]

Primary safety

Part A only

- Adverse events (AEs)
- Physical examinations
- Vital signs
- 12-lead electrocardiograms (ECGs)
- Laboratory safety tests (biochemistry, urinalysis, and hematology)

[redacted]

[redacted]

Pharmacokinetics

Part A

The pharmacokinetic (PK) endpoints are the following PK parameters of CRD-740:

- Maximum observed plasma concentration (C_{max})
- Time to reach C_{max} (t_{max})
- Area under the plasma concentration-time curve from time zero to the time of last measurable concentration ($AUC_{0\text{-}last}$)

- Area under the plasma concentration-time curve over a dosing interval (AUC_{tau})
- Apparent total body clearance (CL/F, except for Day 1)
- Accumulation ratio for AUC_{tau} [Racc(AUC_{tau})] and for C_{max} [Racc(C_{max})]

[redacted]

Independent data monitoring committee

An independent DMC will be established at the beginning of the study. The DMC will be responsible for ensuring the safety of study subjects, study integrity, and validity of study results. The DMC will review study results from Part A and make a non-binding dose recommendation for Part B to the sponsor's representative. The DMC members will not be involved in any day-to-day study decisions and will remain independent from the study team. The DMC will review safety and efficacy data to make recommendations concerning study continuation, modification, and termination based on ongoing study data. The DMC will operate according to a DMC charter, which will describe the DMC's membership, roles, and responsibilities.

Number of subjects (planned):

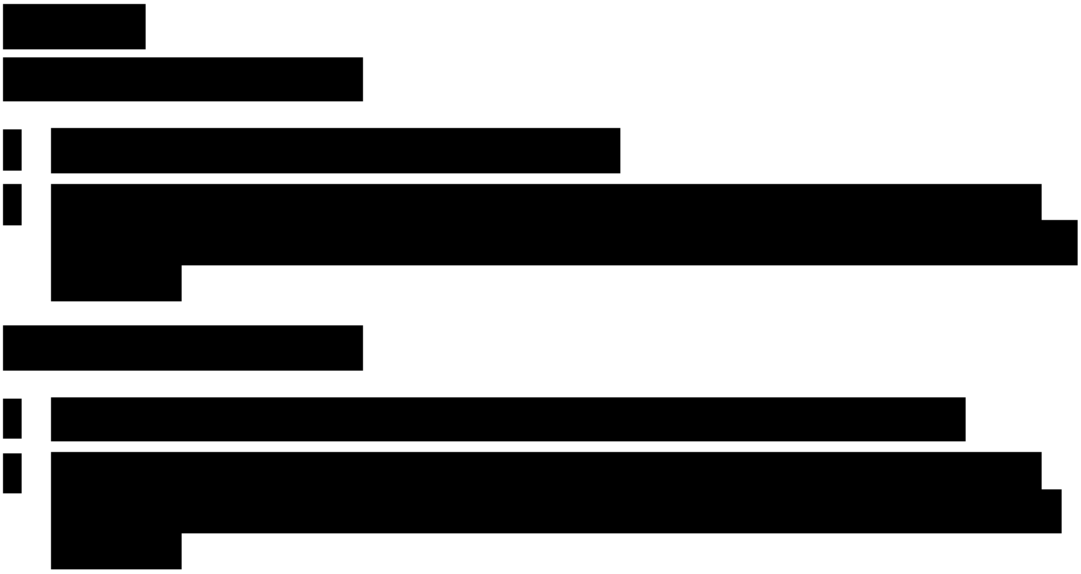
In Part A, approximately 60 subjects with CHFrEF will be included.

[redacted]

Criteria for inclusion:

1. Able to understand and comply with all study procedures, understand the risks involved in the study, and provide written informed consent.
2. Adult male or female subjects ≥18 years of age, at screening.
3. Subject has evidence in medical history supporting a diagnosis of clinical HF syndrome, New York Heart Association functional class II – III, with the duration of at least 6 months prior to screening. The HF syndrome is defined by documentation of 1 or more of the following:
   - Dyspnea, paroxysmal nocturnal dyspnea;
   - Reduced exercise capacity, extended recovery after exercising;
   - Fatigue;
   - Peripheral edema (lower leg, ankle); or
   - Hospitalization or emergency department visit for HF requiring intravenous diuresis within the past 6 months.

4. For Part A:
   - EF ≤40% by echocardiography at screening.
   - NT-proBNP level ≥600 pg/ml at screening. Subjects with atrial fibrillation or flutter at screening are required to have an NT-proBNP level of ≥1000 pg/mL at screening.



5. Stable doses of guideline-directed heart failure therapy for a minimum of 4 weeks prior to screening that has been individually optimized according to standard practice guidelines and no addition of guideline-directed heart failure therapy within 3 months of screening. Treatment of HF should include standard of care therapies, such as a beta-blocker and a Renin-Angiotensin-Aldosterone System inhibitor (angiotensin-converting enzyme [ACE]-inhibitor, angiotensin II receptor blocker [ARB]) or combination ARB and neprilysin inhibitor therapy (sacubitril/valsartan [Entresto®]), mineralocorticoid receptor antagonists (MRAs), sodium-glucose transport protein 2 (SGLT-2)-inhibitors, diuretics, or other standard therapies based on practice guidelines and individual subject tolerability.
6. Women of childbearing potential may be considered for enrollment if they are not pregnant, not breastfeeding, do not plan to become pregnant during the study, and are taking appropriate contraception as defined in Inclusion Criterion #7. Women are considered to be of childbearing potential unless they meet at least 1 of the 2 following criteria:
   a. They have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at a minimum of 1 menstrual cycle prior to signing the informed consent form; or
   b. They are post-menopausal: for women ≥55 years of age, defined as ≥1 year since their last menstrual period, or for women <55 years of age, defined as ≥1 year since their last menstrual period and have a follicle-stimulating hormone level in post-menopausal range.

7. Women of childbearing potential must use a double contraception method including a highly effective method of birth control from screening up to 1 month after the last dose. Accepted double contraception methods include the use of intrauterine device or hormonal contraception in addition to 1 of the following contraceptive options: (1) condom; or (2) diaphragm or cervical/vault cap. Female subjects who are monogamous with male partners who have had a documented vasectomy is also an accepted method of birth control.
8. Male subjects with female partners of child bearing potential must agree to use highly effective contraceptive measures from the screening visit through 3 months after the last dose of study medication. Highly effective contraceptive measures include documented vasectomy, abstaining from sexual intercourse, double-barrier method (e.g., male using a condom and female using a diaphragm or cervical cap), or barrier plus hormonal contraception (e.g., male using a condom and female using hormonal contraception or intrauterine device). As there may be a risk of drug being secreted in the ejaculate, male subjects (including men who have had vasectomies) whose partners are currently pregnant should use barrier methods for the duration of the study and for 3 months after the last dose of study medication. Male subjects with female partners that are confirmed as post-menopausal are not required to use contraceptive measures.

Exclusion criteria:

1. [redacted]
2. Recent HF exacerbation defined by hospitalization or requirement for intravenous diuretics within 60 days of screening.
3. Symptomatic hypotension or uncontrolled hypertension (multiple readings with systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg) at the screening or baseline visit.
4. History of seizure disorder or subjects considered to be at increased risk for seizures.
5. Any ECG abnormality that, in the judgment of the investigator, poses a risk to subject safety or impact the validity of study results.
6. Subjects with planned interventions (e.g., percutaneous coronary intervention, devices) etc. occurring during their involvement in this study.
7. Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or other major cardiovascular surgery or carotid angioplasty within 60 days of screening.
8. Subjects with clinical suspicion of infiltrative cardiomyopathy (e.g., amyloid, sarcoid), hypertrophic cardiomyopathy (obstructive or non-obstructive), or HF secondary to severe valvular disease, active myocarditis, active pericarditis, or clinically significant congenital heart disease.
9. Prior or planned orthotopic heart transplantation.
10. Presence of or plan for mechanical circulatory support.
11. Chronic treatment with phosphodiesterase (PDE)-5 inhibitors (e.g., Viagra, Cialis, Revatio, and Adcirca).

12. Estimated glomerular filtration rate <30 mL/min/1.73m^2 as measured by the simplified Modification of Diet in Renal Disease formula at screening.
13. Hepatic impairment at screening defined as alanine aminotransferase/aspartate aminotransferase >3 x upper limit of normal (ULN) and/or total bilirubin >2 x ULN.
14. Concomitant use of a drug that is a known, strong inhibitor or inducer of cytochrome P450 3A4 (CYP3A4).
15. Concurrent participation in other clinical studies or receiving other investigational treatments within 30 days of randomization or within 5 half-lives of the other investigational treatment, whichever is longer.
16. In the judgment of the investigator, a history of alcohol or drug abuse which would interfere with the subject's ability to adhere with protocol requirements.
17. Has evidence of clinically significant cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, neurologic, oncologic, pulmonary, psychiatric, or renal disease or any other condition which, in the judgment of the investigator, is not explained by the diagnosis of HF and would jeopardize the safety of the subject or impact the validity of study results.
18. History of malignancy, except subjects who have been disease-free for >5 years prior to screening or subjects whose only malignancy has been successfully treated basal or squamous cell skin carcinoma.
19. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin laboratory test.
20. Women of childbearing potential, as defined in Inclusion Criterion #6, unless they are using contraception as defined in Inclusion Criterion #7.

Investigational product, dosage, and mode of administration:

CRD-740 tablets for oral administration will be provided in 2 tablet strengths [redacted]) with 2 different matching placebo tablets (1 placebo tablet matching the image of the CRD-740 [redacted] tablet and 1 placebo tablet matching the image of the CRD-740 15-mg tablet). Subjects will receive CRD-740 [redacted] or matching placebo or CRD-740 [redacted] or matching placebo.

In both Part A and Part B of this study, site pharmacists will be blinded to treatment allocation and will dispense a sufficient quantity of CRD-740 or matching placebo tablets for the subject to self-administer on an out-patient basis.

Duration of subject participation in study:

In each of Part A and Part B of this study, the study duration is expected to be approximately 4 months (including safety follow-up).

Statistical Methods:

Analysis Populations

Intention to Treat (ITT): The ITT population consists of all randomized subjects. Subjects will be analyzed according to their randomized treatment, regardless of actual treatment received, treatment compliance, or treatment duration. The ITT population will be used for sensitivity analyses.

Modified ITT (mITT): The mITT population consists of all randomized subjects who received at least one dose of CRD-740 or placebo. Subjects will be analyzed according to their randomized treatment, regardless of actual treatment received, treatment compliance, or treatment duration. The mITT population will be used as the primary efficacy population.

Safety: The Safety population consists of all subjects who received at least one dose of CRD-740 or placebo. Subjects will be analyzed according to the treatment first received. The Safety population will be used as the primary safety population.

Pharmacokinetic: The PK population consists of all subjects who received at least one dose of CRD-740 and have no protocol deviations that are considered to impact the PK results.

Per protocol (PP): The PP population consists of all mITT subjects with no important protocol deviations. Subjects will be analyzed according to their randomized treatment. The PP population will be used for sensitivity analyses.

Primary Efficacy Analyses

Part A: The primary endpoint, the change from baseline (Day -1) in plasma cGMP at Week 4, will be compared between CRD-740 and placebo in the mITT population using an analysis of covariance (ANCOVA) model with categorical terms for treatment (2 levels), and Entresto (2 levels), and continuous terms for EF, and baseline plasma cGMP. CRD-740 will be analyzed as one treatment group even though CRD-740 consists of two weeks of treatment with CRD-740 [redacted], followed by 2 weeks of treatment with CRD-740 [redacted] The least square means of the change from baseline for each treatment group, along with the 95% confidence intervals (CI), and the least square mean treatment difference and the associated 95% CI for this difference will come from the ANCOVA model.

[redacted]

[redacted]

Safety

All safety data will be summarized by dose and the incidence of AEs will be presented by system organ class and preferred term according to the Medical Dictionary of Regulatory Activities, relationship to the test article, and severity. Descriptive statistics of clinical laboratory results and vital signs and the change from baseline will be presented, as will a summary of clinically notable values.

Pharmacokinetics

PK parameters will be calculated with plasma concentrations of CRD-740 in Part A using non-compartmental methods. [redacted]

All plasma concentrations of CRD-740 will be summarized by study part, dose, visiting day, and time-points. PK will be summarized for Part A by dose and visiting day.

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Abbreviations	Definitions
ACE	angiotensin-converting enzyme
AE	adverse event
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
ARB	angiotensin II receptor blocker
$AUC_{0\text{-last}}$	area under the plasma concentration-time curve from time zero to the time of last measurable concentration
$AUC_{0\text{-8h}}$	area under the plasma concentration-time curve from time zero to 8 hours
AUC_{ss}	steady-state area under the plasma concentration-time curve
AUC_{tau}	area under the plasma concentration-time curve over a dosing interval
[redacted]	[redacted]
BNP	b-type natriuretic peptide
CFR	Code of Federal Regulations
cGMP	cyclic guanosine monophosphate
CHF	chronic heart failure
CHFpEF	chronic heart failure with preserved ejection fraction
CHFrEF	chronic heart failure with reduced ejection fraction
CI	confidence interval
CL/F	apparent total body clearance
C_{max}	maximum observed plasma concentration
CNP	c-type natriuretic peptide
CRO	contract research organization
CSA	clinical study agreement
CSF	cerebrospinal fluid
CYP3A4	cytochrome P450 3A4
DMC	data monitoring committee
EAE	emergent adverse event
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture

Abbreviations	Definitions
EF	ejection fraction
GCP	Good Clinical Practice
GC-B	guanylate cyclase type B receptor
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
ICF	informed consent form
ICH	International Council for Harmonisation
IC_{50}	half maximal inhibitory concentration
IMP	investigational medicinal product
INR	international normalized ratio
IRB	institutional review board
ITT	Intention to Treat
IWRS	interactive web-based response system
KCCQ-23	Kansas City Cardiomyopathy Questionnaire-23
KCCQ-23-CS	KCCQ-23 clinical summary score
KCCQ-23-OS	KCCQ-23 overall summary score
mITT	modified Intention to Treat
MMRM	mixed model for repeated measures
NO	nitric oxide
NP	natriuretic pathway
NT-proBNP	N-terminal pro b-type natriuretic peptide
OS	Overall Score
PDE	phosphodiesterase
PK	pharmacokinetic(s)
PKGI	protein kinase GI
PP	per protocol
PT	prothrombin time
Racc(AUCtau)	accumulation ratio for AUCtau
Racc(C_{max})	accumulation ratio for C_{max}
SAE	serious adverse event
SAP	statistical analysis plan
sGC	soluble guanylate cyclase

Abbreviations	Definitions
SGLT-2	sodium-glucose transport protein 2
TAC	transaortic constriction
t_{max}	time to reach C_{max}
ULN	upper limit of normal

1. INTRODUCTION

CRD-740 is phosphodiesterase (PDE)-9 inhibitor being investigated for the treatment of chronic heart failure (CHF). Refer to the investigator's brochure [1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of this investigational medicinal product (IMP).

1.1. Background and Study Rationale

Both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) are major health problems with a significant impact on morbidity, mortality, quality of life, and healthcare costs. They are leading global causes of hospitalizations, and despite treatment advances, 5-year mortality rates remain approximately 50% within 5 years of first diagnosis. New therapeutics that reduce morbidity and mortality in heart failure (HF) are needed.

The cyclic guanosine monophosphate (cGMP)/protein kinase GI (PKGI) signaling pathway plays a critical role in cardiovascular pathophysiology. PKGI activation inhibits cardiac hypertrophy and remodeling and, therefore, is a rational target for potential new therapies in the treatment of HF [2]. In the cardiomyocyte, signaling through the cGMP/PKGI pathway is achieved via 4 hormones; nitric oxide (NO) and 3 natriuretic peptides (atrial natriuretic peptide, b-type natriuretic peptide [BNP], and c-type natriuretic peptide [CNP]) acting through 3 receptors located in different subcellular regions [3]. NO acts through the soluble guanylate cyclase (sGC) receptor located in the cytoplasm whereas CNP acts through the guanylate cyclase type B receptor (GC-B) located in the cell membrane. NO and CNP are secreted by the endothelial cells. Atrial natriuretic peptide and BNP are produced within the cardiomyocyte and act through the guanylate cyclase type A receptor (GC-A) which spans the plasma membrane. Stimulation of guanylate cyclase results in the conversion of guanosine triphosphate to cGMP.

cGMP is a second messenger molecule that transduces NO- and natriuretic-peptide-coupled signaling, stimulating phosphorylation changes by protein kinase G. cGMP generally has a protective function on the heart, attenuating adverse remodeling [3]. The breakdown or hydrolysis of cGMP can occur under the action of 2 enzymes, PDE-5 and PDE-9. PDE-5 acts primarily in the vasculature and its inhibitors have been shown to be beneficial in both erectile dysfunction and pulmonary arterial hypertension; however, the role of PDE-5 in the myocardium is uncertain. The IMP, CRD-740, is a PDE-9 inhibitor.

In pilot pharmacology studies in a mouse model of HF (transaortic constriction [TAC] model), both PDE-5 and PDE-9 were shown to be capable of reversing remodeling effects commonly found in HF. PDE-9 was also identified as the PDE that controls NO independent cGMP generated by the natriuretic peptide receptor signaling pathway [4].

In studies done in the presence of an inhibitor of the NO-sGC pathway, L-NAME (which inhibits NO production by NO synthase and therefore, activation of the sGC), removal of the effects of PDE-5 and the NO-sGC pathway revealed that PDE-9 inhibition was independently efficacious in preventing HF. The increased oxidative stress and reactive oxygen species commonly present in cardiovascular disease result in uncoupling of NO synthase and low levels of bioavailable NO

may be one explanation for the lack of efficacy observed with PDE-5 inhibition in treating HF patients.

The demonstration that PDE-9 regulates signaling through the NO-independent natriuretic peptide GC-A receptor pathway identifies this enzyme as an important target to explore in clinical studies of HF to optimize signaling through the beneficial natriuretic peptide receptor pathway. The importance of the natriuretic peptide receptor signaling pathway in CHF with both reduced (CHFrEF) and preserved ejection fraction (CHFpEF) has been demonstrated and validated by the clinical studies of sacubitril/valsartan (ENTRESTRO®) and the importance of this drug in treating human HF is now well-established based on data from the controlled clinical studies PARADIGM-HF [5] and PARAGON-HF [6]. However, the sacubitril approach to enhancing signaling through the natriuretic peptide receptor pathway is expected to be a less efficacious approach to increasing natriuretic peptide receptor signaling than inhibition of PDE-9 because PDE-9 is downstream of the activated receptor and degrades the amplified signal distal to the receptor itself. Recent data from human myocardial samples indicate that PDE-9 is up-regulated in HF patients, particularly in those with CHFpEF, further emphasizing the limiting effect of PDE-9 on cGMP signaling in HF and the potential to enhance cGMP activity via PDE-9 inhibition [7].

A small molecule PDE-9 inhibitor was demonstrated to ameliorate the increase in left ventricular mass in a mouse model of cardiac pressure overload caused by trans-aortic constriction. CRD-740 [redacted] was also studied by the same investigators and was found to significantly reduce left ventricular mass and improve left ventricular function after trans-aortic constriction (data on file). Cardurion has studied a previous PDE-9 inhibitor candidate, CRD-733, in both the mouse trans-aortic constriction HF model and in patients with HFrEF and HFpEF. Consistent with the data from Lee and colleagues, CRD-733 reversed the increase in left ventricular mass and wall thickness that occurred after trans-aortic constriction in mice [4]. CRD-733 also lowered intracardiac pressure and improved left ventricular function [8]. In patients with CHFrEF and CHFpEF, CRD-733 increased levels of plasma cGMP, consistent with target engagement in HF patients and consistent with up-regulation of PDE-9 in this population.

[redacted] The studies include data on safety, tolerability, pharmacodynamics, and pharmacokinetics (PK) of the CRD-740 molecule.

1.2. Benefit-risk Assessment

CRD-740 has been generally well tolerated in all clinical studies to date. [redacted]

[redacted]

additionally dizziness in the 25 mg every 12 hours group. A total of 6 serious adverse events [redacted]

[redacted]

In conclusion, no major safety concerns were detected for CRD-740 to date. [redacted]

Considering the excellent safety profile of CRD-740 described above and given the beneficial effects of natriuretic peptide signaling, the demonstration that PDE-9 activity is increased in HF (which would attenuate these effects), and the beneficial effects of a PDE-9 inhibitor seen in the mouse TAC model of HF, there is a strong rationale for studying a PDE-9 inhibitor such as CRD-740 in patients with HF. The HF populations that will be enrolled in this Phase 2 study will include both CHFpEF and CHFrEF subjects.

2. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

2.1. Objectives

Part A:

Primary:

- To assess the safety and tolerability of CRD-740 in subjects with CHFrEF, defined as HF with ejection fraction (EF) ≤40%.
- To assess the effect of CRD-740 compared to placebo in plasma cGMP at Week 4 in subjects with CHFrEF.

Secondary:

- To assess the PK of CRD-740 in subjects with CHFrEF.

[redacted]

- To assess the effect of CRD-740 compared to placebo on plasma cGMP to NT-proBNP [redacted]

2.2. Endpoints

2.2.1. Primary Efficacy

Part A:

- The change from baseline (Day -1) in plasma cGMP at Week 4.

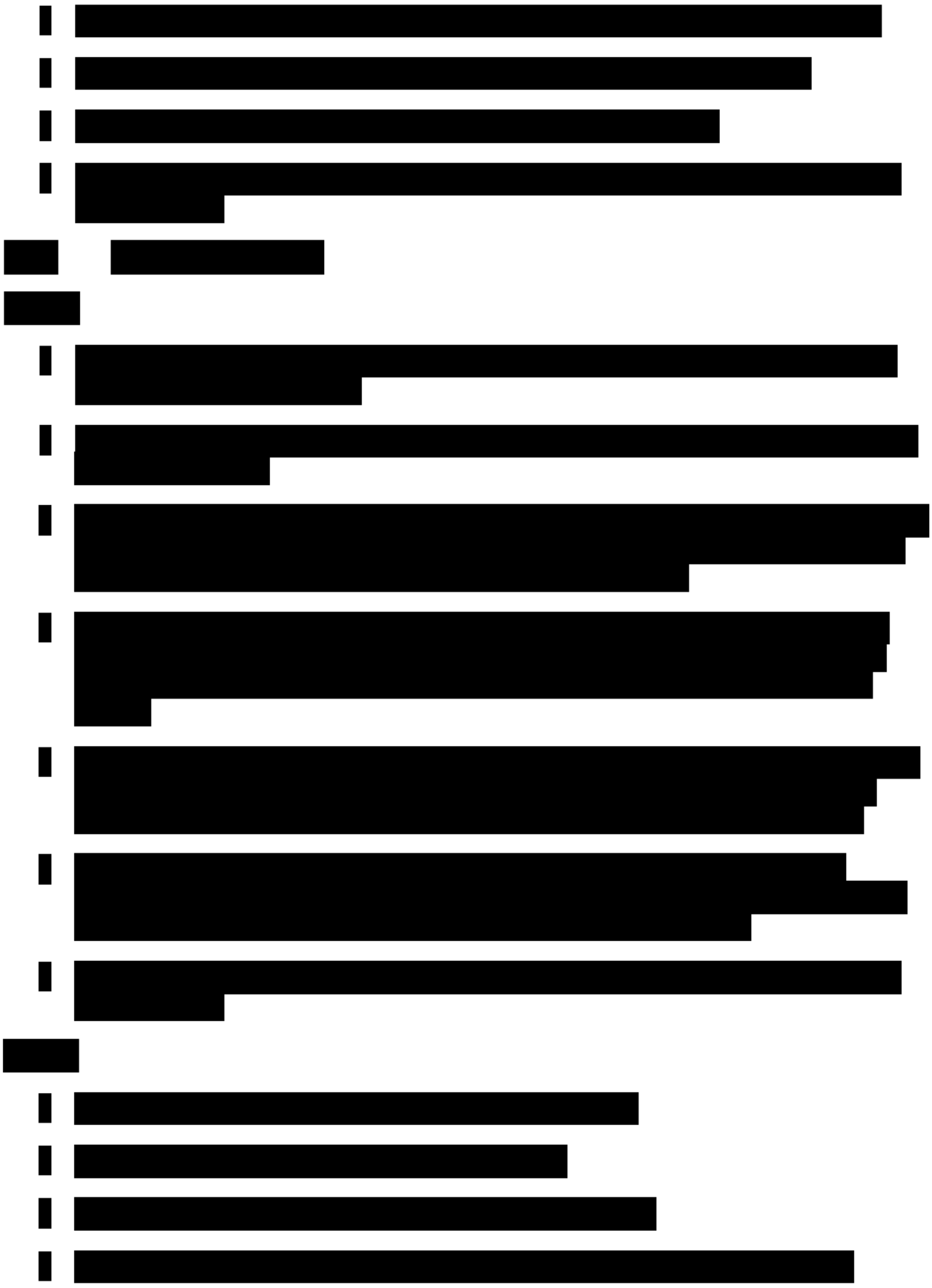
[redacted]

2.2.2. Primary Safety

Part A only:

- AEs
- Physical examinations
- Vital signs
- 12-lead ECGs
- Laboratory safety tests (biochemistry, urinalysis, and hematology)

[redacted]



[redacted]

2.2.6. Pharmacokinetics

Part A:

The PK endpoints are the following PK parameters of CRD-740:

- C_{max}
- Time to reach C_{max} (t_{max})
- $AUC_{0\text{-last}}$
- Area under the plasma concentration-time curve over a dosing interval (AUC_{tau})
- Apparent total body clearance (CL/F, except for Day 1)
- Accumulation ratio for AUC_{tau} [Racc(AUC_{tau})] and for C_{max} [Racc(C_{max})]

[redacted]

2.3. Estimands

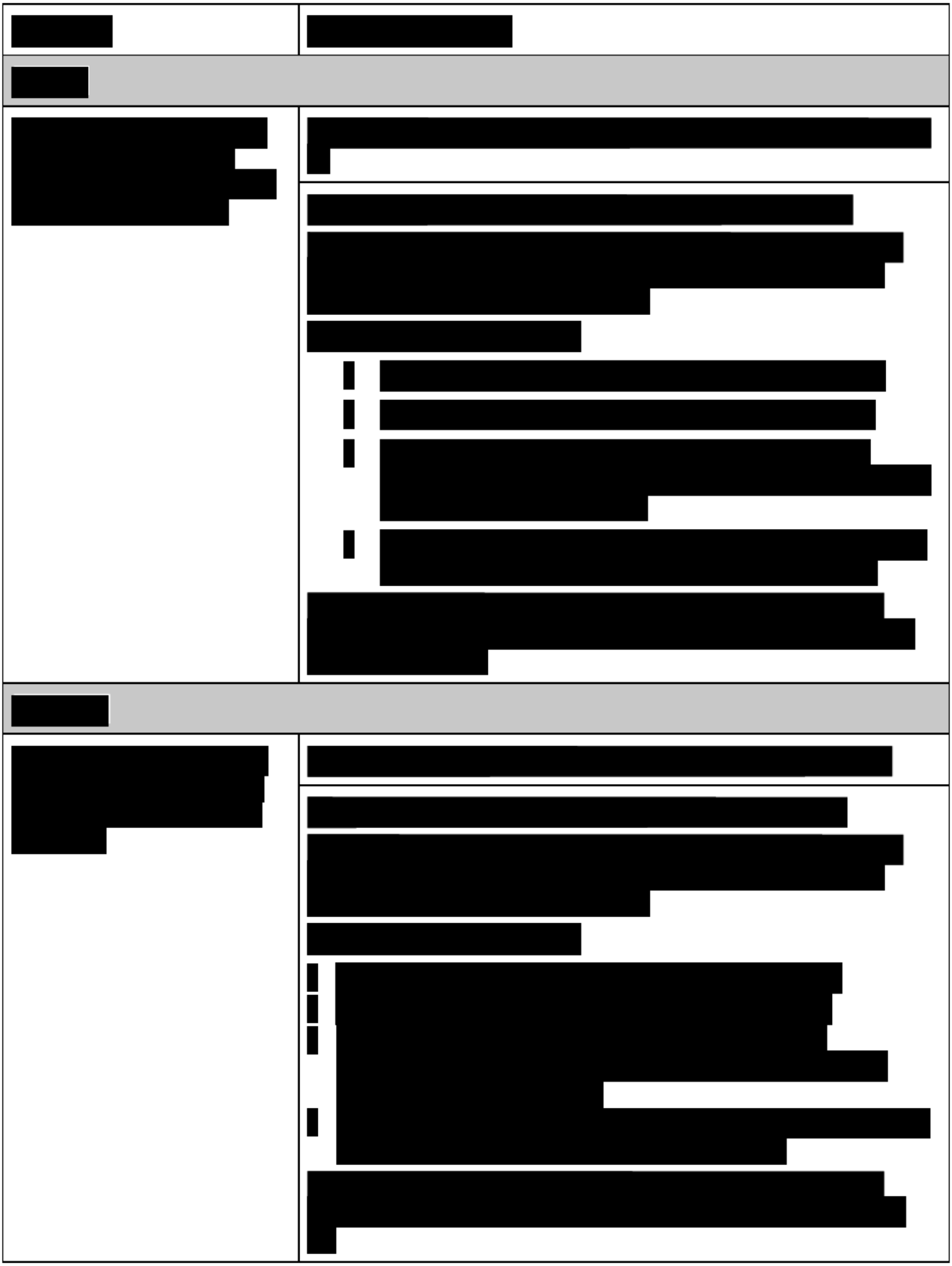
The ICH [9] E9 (R1) addendum on estimands [10] and sensitivity analysis in clinical studies analysis in clinical studies to the guideline on statistical principles for clinical studies became effective on 30 July 2020. Table 1 [redacted] address the construction of estimands for the primary objectives for Part A [redacted]

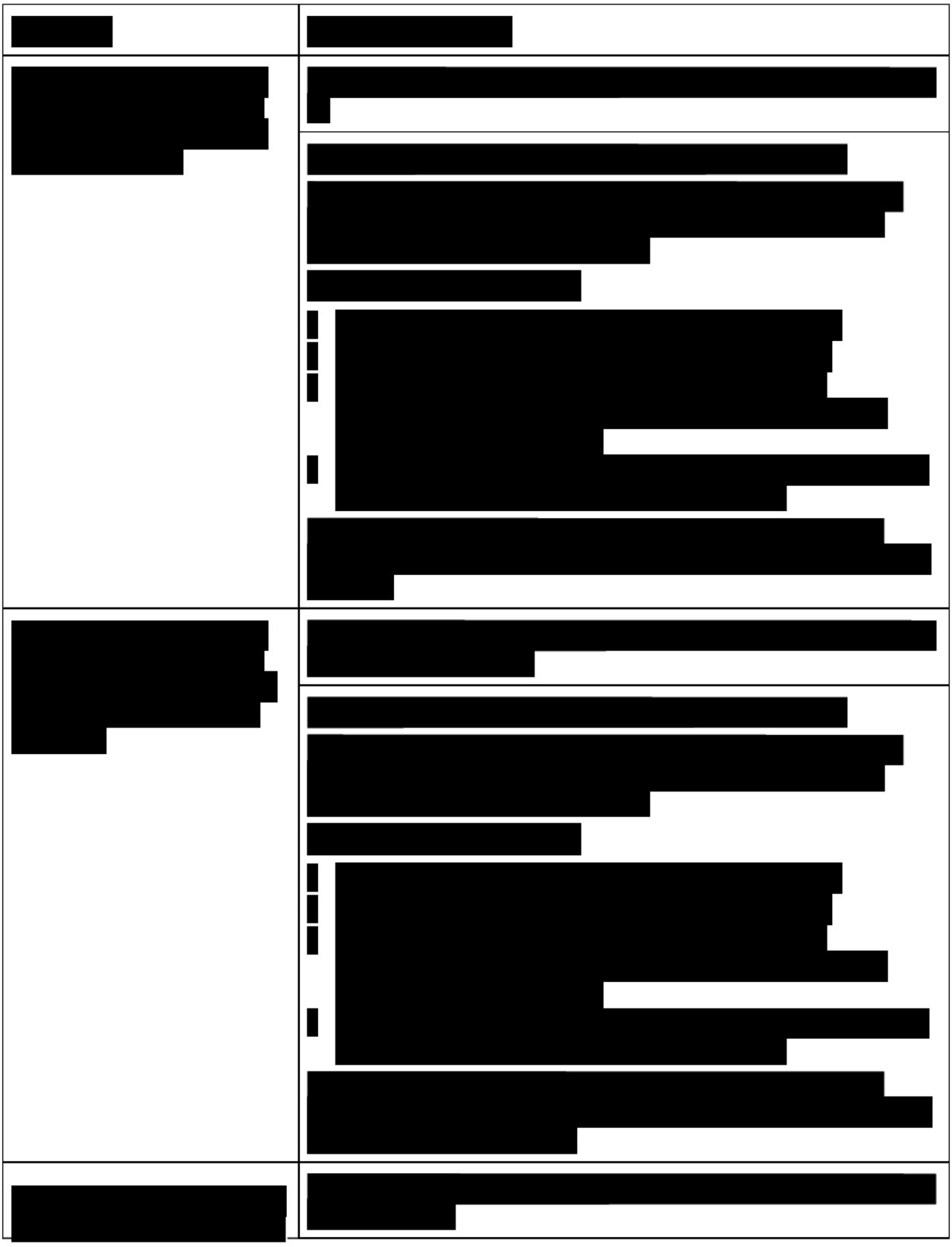
Table 1: Estimands for primary objectives for Part A

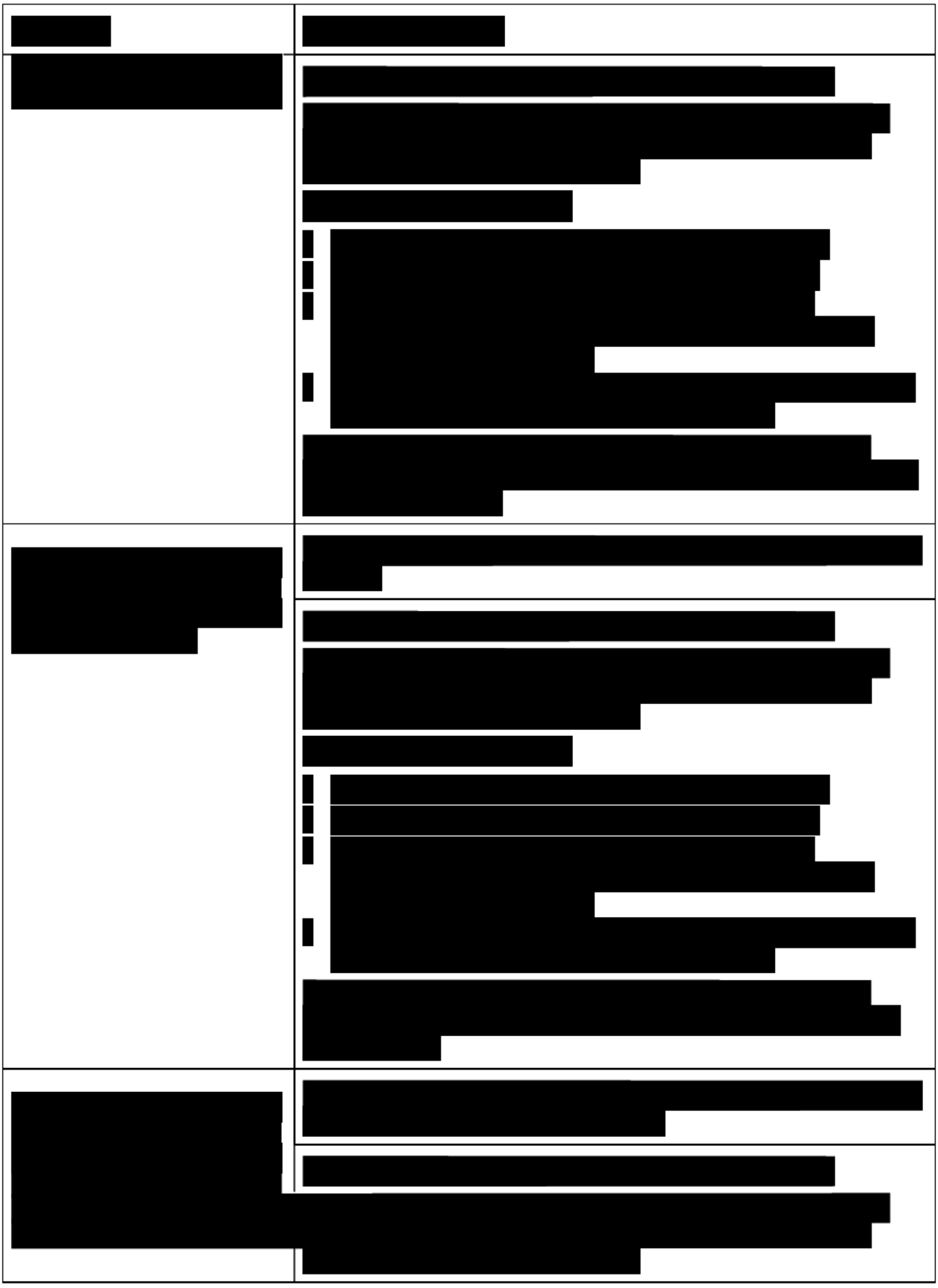
Objectives	Estimands/Endpoints
Primary	
To assess the effect of CRD-740 compared to placebo in plasma cGMP at Week 4 in subjects with CHFrEF.	**Endpoint**: The change from baseline (Day -1) in plasma cGMP at Week 4
	Population: Randomized subjects with CHrEF (EF≤40%) who received at least one dose of CRD-740 or placebo (mITT) **Treatment**: CRD-740 dose [redacted] or placebo, with or without sacubitril/valsartan, dosed as required. **Intercurrent Event Strategy**: • Discontinuation of treatment (Treatment policy strategy) • Subject withdraws consent from further data collection (While on treatment strategy) • Subject lost to follow-up (While on treatment strategy) **Population Level Summary**: Treatment difference (CRD-740 – placebo) in change from baseline in plasma cGMP values at Week 4.
To assess the safety and tolerability of CRD-740 in subjects with CHFrEF, defined as heart failure with EF ≤40%.	**Endpoint**: AEs, physical examinations, vital signs, 12-lead electrocardiograms, laboratory safety tests (biochemistry, urinalysis, and hematology)
	Population: Subjects with CHFrEF (EF≤40%) who received at least one dose of CRD-740 or placebo **Treatment**: CRD-740 dose [redacted] or placebo, with or without sacubitril/valsartan, dosed as required. **Intercurrent Event Strategy**: • Discontinuation of treatment (Treatment policy strategy) • Subject withdraws consent from further data collection (While on treatment strategy) • Subject lost to follow-up (While on treatment strategy) **Population Level Summary**: The proportion of subjects who experience any AE, the proportion of subjects who experience any SAE and the exposure-adjusted incidence rates for AE and SAE in each treatment and dose level group.

Abbreviations: AE = adverse event; cGMP = cyclic guanosine monophosphate; CHFrEF = chronic heart failure with reduced ejection fraction; EF = ejection fraction; mITT = modified Intention to Treat; SAE = serious adverse event

[redacted]







[redacted]	[redacted]
	[redacted]

Abbreviations: BNP = b-type natriuretic peptide; cGMP = cyclic guanosine monophosphate; CHF = chronic heart failure; CI = confidence interval; EF = ejection fraction; KCCQ-23-CS = Kansas City Cardiomyopathy Questionnaire-23 clinical summary score; LS = least square; mITT = modified Intention to Treat; MMRM = mixed model for repeated measures; NT-proBNP = N-terminal pro b-type natriuretic peptide

3. INVESTIGATION PLAN

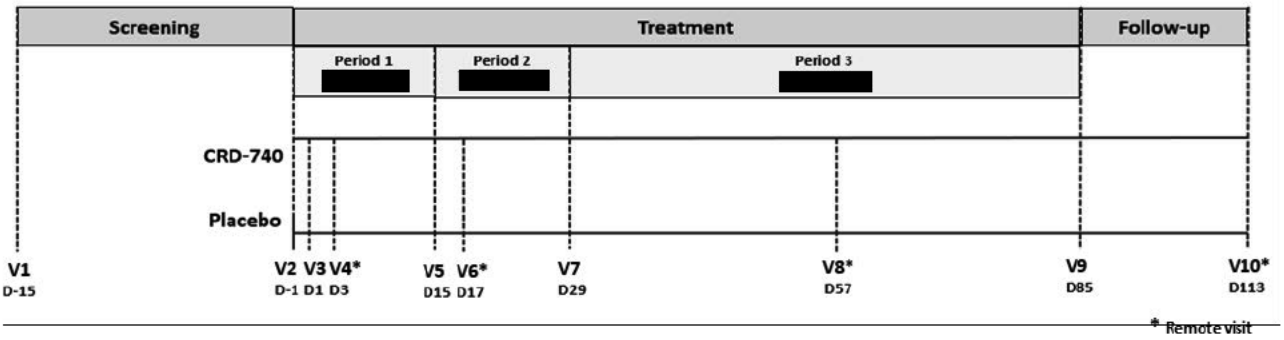
3.1. Overall Study Design and Plan Description

This is a Phase 2, two-part, seamless, randomized, double-blind, placebo-controlled, parallel group clinical study. Part A is a dose ranging study in a group of subjects with CHFrEF. [redacted] An independent data monitoring committee (DMC) will oversee the study (please refer to Appendix 3 for details).

In Part A, eligible subjects with CHFrEF will be randomized to either CRD-740 or placebo in a 2:1 ratio. As shown in Figure 1, subjects will start Period 1 at a dose of CRD-740 [redacted] or matching placebo. Subjects will remain in Period 1 for 2 weeks. At Day 15, subjects enter Period 2 and are dosed at CRD-740 [redacted] or matching placebo. Subjects will continue in Period 2 for 2 weeks. At Day 29, subjects enter Period 3 and continue CRD-740 [redacted] or matching placebo. Subjects will continue in Period 3 for 8 weeks to complete a total of 12 weeks of CRD-740 or matching placebo. Safety and tolerability will be continuously assessed. A post-study visit will occur at Week 16. Part A will evaluate the effectiveness of CRD-740 in the overall population of subjects with CHFrEF, and possibly in the 2 subgroups defined by sacubitril/valsartan (Entresto) use (yes, no), depending on the number of subjects in each stratum. Randomization will be stratified on Entresto use (yes vs no).

[redacted]

Figure 1: Study schematic of Part A



Abbreviations: D = Day; [redacted] V = Visit

[redacted]

3.2. End of Study Definition

In both Part A and Part B of this study, a subject is considered to have completed the study if he/she has completed the Week 16 visit.

The end of the study is defined as the date of the last visit of the last subject in the study.

3.3. Selection of Doses in the Study

In Part A, subjects randomized to CRD-740 will receive CRD-740 [redacted] or matching placebo orally [redacted] for 2 weeks and CRD-740 [redacted] or matching placebo orally [redacted] for 10 weeks.

[redacted]

This clinical study will test doses of CRD-740 that have been previously tested safely in humans.

[redacted]

[redacted] The maximum planned dose in this clinical study is [redacted], which is expected to provide a mean C_{max} of [redacted]

While it is not definitively known what the minimum percentage of enzyme inhibition is needed to demonstrate effectiveness of CRD-740 in HF, nonclinical data and clinical data support that an exposure above the half maximal inhibitory concentration (IC_{50}) for PDE-9 will be required. The dose regimens of [redacted] of CRD-740 are expected to achieve exposures above the IC_{50} for PDE-9, providing margins above the IC_{50} that thoroughly explore the effect of PDE-9 inhibition while remaining well below a 10-fold margin to the no observed adverse effect level.

4. SELECTION OF STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the screening visit unless otherwise stated:

1. Able to understand and comply with all study procedures, understand the risks involved in the study, and provide written informed consent.

2. Adult male or female subjects ≥18 years of age, at screening.

3. Subject has evidence in medical history supporting a diagnosis of clinical HF syndrome, New York Heart Association functional class II – III, with the duration of at least 6 months prior to screening. The HF syndrome is defined by documentation of 1 or more of the following:

   - Dyspnea, paroxysmal nocturnal dyspnea;
   - Reduced exercise capacity, extended recovery after exercising;
   - Fatigue;
   - Peripheral edema (lower leg, ankle); or
   - Hospitalization or emergency department visit for HF requiring intravenous diuresis within the past 6 months.

4. For Part A:

   - EF ≤40% by echocardiography at screening.
   - NT-proBNP level ≥600 pg/ml at screening. Subjects with atrial fibrillation or flutter at screening are required to have an NT-proBNP level of ≥1000 pg/mL at screening.

[redacted]

[redacted]

5. Stable doses of guideline-directed heart failure therapy for a minimum of 4 weeks prior to screening that has been individually optimized according to standard practice guidelines and no addition of guideline-directed heart failure therapy within 3 months of screening. Treatment of HF should include standard of care therapies, such as a beta-blocker and a Renin-Angiotensin-Aldosterone System inhibitor (angiotensin-converting enzyme [ACE]-inhibitor, angiotensin II receptor blocker [ARB]) or combination ARB and neprilysin inhibitor therapy (sacubitril/valsartan [Entresto®]), mineralocorticoid receptor antagonists (MRAs), sodium-glucose transport protein 2 (SGLT-2)-inhibitors, diuretics, or other standard therapies based on practice guidelines and individual subject tolerability.

6. Women of childbearing potential may be considered for enrollment if they are not pregnant, not breastfeeding, do not plan to become pregnant during the study, and are taking appropriate contraception as defined in Inclusion Criterion #7. Women are considered to be of childbearing potential unless they meet at least 1 of the 2 following criteria:

    a. They have had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at a minimum of 1 menstrual cycle prior to signing the informed consent form (ICF); or

    b. They are post-menopausal: for women ≥55 years of age, defined as ≥1 year since their last menstrual period, or for women <55 years of age, defined as ≥1 year since their last menstrual period and have a follicle-stimulating hormone level in post-menopausal range.

7. Women of childbearing potential must use a double contraception method including a highly effective method of birth control from screening up to 1 month after the last dose. Accepted double contraception methods include the use of intrauterine device or hormonal contraception in addition to 1 of the following contraceptive options: (1) condom; or (2) diaphragm or cervical/vault cap. Female subjects who are monogamous with male partners who have had a documented vasectomy is also an accepted method of birth control.

8. Male subjects with female partners of child-bearing potential must agree to use highly effective contraceptive measures from the screening visit through 3 months after the last dose of study medication. Highly effective contraceptive measures include documented vasectomy, abstaining from sexual intercourse, double-barrier method (e.g., male using a condom and female using a diaphragm or cervical cap), or barrier plus hormonal contraception (e.g., male using a condom and female using hormonal contraception or intrauterine device). As there may be a risk of drug being secreted in the ejaculate, male subjects (including men who have had vasectomies) whose partners are currently pregnant should use barrier methods for the duration of the study and for 3 months after the last dose of study medication. Male subjects with female partners that are confirmed as post-menopausal are not required to use contraceptive measures.

4.2. Exclusion Criteria

Subjects will be excluded from the study if they satisfy any of the following criteria at the screening visit unless otherwise stated:

[redacted]

2. Recent HF exacerbation defined by hospitalization or requirement for intravenous diuretics within 60 days of screening.

3. Symptomatic hypotension or uncontrolled hypertension (multiple readings with systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg) at the screening or baseline visit.

4. History of seizure disorder, or subjects considered to be at increased risk for seizures.

5. Any ECG abnormality that, in the judgment of the investigator, poses a risk to subject safety or impact the validity of study results.

6. Subjects with planned interventions (e.g., percutaneous coronary intervention, devices) etc. occurring during their involvement in this study.

7. Acute coronary syndrome, stroke, transient ischemic attack, cardiac, carotid or other major cardiovascular surgery or carotid angioplasty within 60 days of screening.

8. Subjects with clinical suspicion of infiltrative cardiomyopathy (e.g., amyloid, sarcoid), hypertrophic cardiomyopathy (obstructive or non-obstructive), or HF secondary to severe valvular disease, active myocarditis, active pericarditis, or clinically significant congenital heart disease.

9. Prior or planned orthotopic heart transplantation.

10. Presence of or plan for mechanical circulatory support.

11. Chronic treatment with PDE-5 inhibitors (e.g., Viagra, Cialis, Revatio, and Adcirca).

12. Estimated glomerular filtration rate <30 mL/min/1.73m^2 as measured by the simplified Modification of Diet in Renal Disease formula at screening.

13. Hepatic impairment at screening defined as alanine aminotransferase/aspartate aminotransferase >3 x upper limit of normal (ULN) and/or total bilirubin >2 x ULN.

14. Concomitant use of a drug that is a known, strong inhibitor or inducer of cytochrome P450 3A4 (CYP3A4).

15. Concurrent participation in other clinical studies or receiving other investigational treatments within 30 days of randomization or within 5 half-lives of the other investigational treatment, whichever is longer.

16. In the judgment of the investigator, a history of alcohol or drug abuse which would interfere with the subject's ability to adhere with protocol requirements.

17. Has evidence of clinically significant cardiovascular, endocrine, gastrointestinal, hematologic, hepatic, immunologic, neurologic, oncologic, pulmonary, psychiatric, or renal disease or any other condition which, in the judgment of the investigator, is not explained by the diagnosis of HF and would jeopardize the safety of the subject or impact the validity of study results.

18. History of malignancy, except subjects who have been disease-free for >5 years prior to screening or subjects whose only malignancy has been successfully treated basal or squamous cell skin carcinoma.

19. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin laboratory test.

20. Women of childbearing potential, as defined in Inclusion Criterion #6, unless they are using contraception as defined in Inclusion Criterion #7.

4.3. Discontinuation Criteria

4.3.1. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently entered in the study because of failure to meet the inclusion/exclusion criteria, or any other reason. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

4.3.2. Re-screening

Subjects who do not meet the criteria for participation in this study may be re-screened once if the reason for the original screen failure is believed not to be present again during the subsequent screening. Re-screened subjects will be assigned a new subject number.

4.3.3. Temporary or Permanent Discontinuation of Study Treatment

In rare instances, it may be necessary for a subject to temporarily interrupt or permanently discontinue the study drug. If a subject requires temporary interruption of the study drug, the study team should consult with the study medical monitor and sponsor. In this study, every attempt will be made to prevent missing data and to obtain complete follow-up of all subjects for the study duration. Investigators will be trained to minimize full withdrawals wherever possible. Subjects who permanently discontinue the study drug are not required to withdraw from the study. These subjects will be encouraged to remain in the study and asked to conduct the remaining study visits as outlined in the protocol.

4.3.4. Subject Discontinuation/Withdrawal from the Study

Subjects may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. However, every effort should be made to retain the subject in the study. The reasons for subjects not completing the study will be recorded.

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. Additionally, subjects may request destruction of any samples taken and not tested. The investigator must document this in the site study records and notify the sponsor or its designee.

Subjects who withdraw from the study will be asked to complete final study procedures (Visit 9 for Part A [redacted]) as described in the Schedule of Assessments (Appendix 4). All (S)AEs that are ongoing at the time of withdrawal will be followed up for 28 days, or until resolution or stabilization.

4.3.5. Lost to Follow-up

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

The following actions must be taken if a subject fails to attend a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow-up, the investigator or his/her designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

4.3.6. Replacement Procedures

Subjects who withdraw from the study will not be replaced.

4.4. Study Termination

The sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed. Reasons for study termination may include, but are not limited to:

- AEs unknown to date (i.e., not previously reported in any similar investigational study drug clinical study with respect to their nature, severity, and/or duration)

- Increased frequency and/or severity and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined at check-in as baseline signs and symptoms)

- Medical or ethical reasons affecting the continued performance of the study

- Difficulties in the recruitment of subjects

- Cancelation of drug development.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a study site by the sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the institutional review board/ethics committee or local health authorities, the sponsor's procedures, or Good Clinical Practice guidelines

- Inadequate recruitment of subjects by the investigator.

5. STUDY TREATMENTS

5.1. Treatments Administered

The investigational product of this study is CRD-740 tablets for oral administration provided in 2 tablet strengths [redacted]. The control of this study is 2 different matching placebo tablets (1 placebo tablet matching the image of the CRD-740 [redacted] tablet and 1 placebo tablet matching the image of the CRD-740 [redacted]). The matching placebo tablets are identical in color, size, and shape to the active tablets.

In Part A of this study, subjects will receive CRD-740 [redacted] or matching placebo in Period 1 for 2 weeks and CRD-740 [redacted] or matching placebo in Periods 2 and 3 for 10 weeks. In Part A, on the days of Visit 5 and Visit 7, subjects will be instructed NOT to take their dose of study drug before the pre-dose blood and urine sampling. Subjects will not take the study drug at Visit 9. They will be instructed to take the study drug up through the day before Visit 9.

[redacted]

In both Part A and Part B of this study, subjects will be instructed to take their study drug orally [redacted] at the same times each day, whenever possible.

5.2. Preparation, Storage, Handling, and Accountability

The study drug will be supplied by the sponsor or its designee. The packaging of the [redacted] CRD-740 and matching placebo dose will be clearly differentiated from that of the [redacted] CRD-740 and matching placebo dose. However, for each dose level, CRD-740 and its matching placebo are labeled in a double-blind fashion.

The investigator or his/her designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before the use of the study drug.

All study drug must be maintained at room temperature in a locked, secure, environmentally controlled, and monitored (manual or automated) location at the site with access limited to the investigator and authorized site staff.

Only subjects enrolled in the study may receive the study drug. At the study visits in Parts A or B of this study, as summarized in the Schedule of Assessments (Appendix 4), site pharmacists will be blinded to treatment allocation and will dispense a sufficient quantity of CRD-740 or matching placebo tablets for the subject to self-administer on an out-patient basis. Subjects will be instructed to follow the provided instructions to take the study drug.

At the study visits in both Part A and Part B of this study, as summarized in the Schedule of Assessments (Appendix 4), subjects will be asked to return all used and unused drug supply containers. Returned study drug should not be re-dispensed to the subjects.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

5.3. Method of Treatment Assignment

All subjects will be centrally randomized using an interactive web-based response system (IWRS). Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site. On Day -1 of Part A of this study, eligible subjects will be randomly assigned to either CRD-740 or placebo in a 2:1 ratio using the IWRS. [redacted] Randomization will be stratified in Part A on Entresto use (yes vs no) [redacted]

The investigator or his/her designee will obtain the randomization number assigned to a subject by accessing the IWRS after confirming that the subject meets all inclusion criteria and does not meet any of the exclusion criteria.

5.3.1. Dose Modification

No dose modification other than the protocol-specified dose escalation will be permitted.

5.4. Blinding and Blind-Breaking Procedures

This is a double-blind study. On Day -1 of Part A, eligible subjects will be randomly assigned to either CRD-740 or placebo in a 2:1 ratio. [redacted] Both investigators and subjects will remain blinded to each subject's assigned study drug throughout the course of the study.

The following controls will be employed to maintain the double-blind status of the study:

- For each dose, CRD-740 tablets and their matching placebo tablets will be supplied in identical packaging and will be identical in color, smell, taste, and appearance.
- The investigator and other members of staff involved with the study will remain blinded to the treatment randomization code.
- The site pharmacists responsible for the dispensation of the study drug are blinded to treatment allocation.

If it becomes necessary to break the code during the study, the date, time, and reason will be recorded in the subject's source data. Under such circumstances, subjects will be withdrawn from the study; dosing of CRD-740 or matching placebo will be stopped, and end of treatment procedures will be conducted with documented AE related to the unblinding reason.

The IWRS will be programmed with blind-breaking instructions. The study blind may be broken if, in the opinion of the investigator, it is in the subject's best interest to know the study drug assignment. If possible, the sponsor must be notified before the blind is broken unless identification of the study drug is required for a medical emergency in which the knowledge of the specific blinded study drug will affect the immediate management of the subject's condition (e.g., antidote is available). In this case, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study treatment records, if any, at the site(s) to verify that randomization/dispensing has been done accurately.

5.5. Treatment Compliance

The study drug will be dispensed at the study visits in Parts A and B of this study, as summarized in the Schedule of Assessments (Appendix 4). Subjects will be instructed to follow the provided instructions to take the study drug.

At the study visits in Parts A and B of this study, as summarized in the Schedule of Assessments (Appendix 4), subjects will be asked to return all used and unused drug supply containers.

Accountability and subject compliance will be assessed by maintaining adequate drug dispensing and returning records.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of ICF signing onwards must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Any medications, excluding those mentioned in Section 6.1.1, may be given concomitantly as needed for the subject's welfare for treatment of comorbid conditions or potential AEs.

At each visit in this study, the study staff will review use of concomitant medications with the subject and will record entries in the eCRF.

6.1.1. Prohibited Concomitant Therapy

Subjects may not be on the following drugs from the time of ICF signing onwards:

- PDE-5 inhibitors (e.g., Viagra, Cialis, Revatio, and Adcirca)
- Known strong inhibitors or inducers of CYP3A4.

6.1.2. Contraception

6.1.2.1. Female Subjects

Female subjects of childbearing potential, as defined in Inclusion Criterion #6, will be required to follow contraception requirements as defined in Inclusion Criterion #7.

6.1.2.2. Male Subjects

Male subjects with female partners of child-bearing potential, or female partners who are pregnant will be required to follow contraception requirements as defined in Inclusion Criterion #8.

6.1.2.3. Sexual Abstinence and Same-sex Relationships

Subjects who practice true abstinence, which must be due to the subject's lifestyle choice (i.e., the subject should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (e.g., calendar, ovulation, symptothermal,

post-ovulation methods) and withdrawal are not acceptable methods of contraception. If a subject who is abstinent at the time of signing the ICF becomes sexually active, they must agree to use contraception as described previously.

For subjects who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a subject who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, they must agree to use contraception as described previously.

7. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Assessments (Appendix 4). Adherence to the study design requirements, including those specified in the Schedule of Assessments (Appendix 4), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure (Section 4.3.1), as applicable.

All laboratory tests in this study will be performed at a central laboratory.

The maximum amount of blood collected from each subject over the duration of the study will be in line with local regulations. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Please refer to the study-specific safety guidance documents for detailed safety requirements of this study.

7.1. Efficacy Assessments

[redacted]

7.1.4. Plasma cGMP

Plasma cGMP will be assessed at the time-points specified in the Schedule of Assessments (Appendix 4).

7.1.5. Urinary cGMP

In Part A of this study only, urinary cGMP (6-hour urine collection and spot urine) will be assessed at the time-points specified in the Schedule of Assessments (Appendix 4).

7.2. Safety and Tolerability Assessments

7.2.1. Adverse Events

AE definitions and assignment of severity and causality are detailed in Appendix 1.

AEs will be elicited from the subject (or, when appropriate, from a caregiver, surrogate, or the subject's legally authorized representative) by the study site staff using a non-leading question such as "How are you feeling today?" or "Have you had any health concerns since your last visit?" Subjects will be encouraged to voluntarily report AEs occurring at any time during the study. AEs will be recorded in the eCRF.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study drug or the study, or that caused the subject to discontinue the study drug or study. For all AEs, the investigator must pursue and obtain information to determine the causality and outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to the sponsor or its designee.

7.2.2. Reporting Serious Adverse Events

Please refer to the study-specific safety guidance documents for the appropriate methods for the reporting and handling of SAEs.

7.2.3. Pregnancy

If a female subject becomes pregnant during the study, the study drug must be discontinued immediately. During the study, pregnancy events should be reported and will be followed until conclusion. Please refer to the study-specific safety guidance documents for details.

7.2.4. Laboratory Safety Tests

At the time-points specified in the Schedule of Assessments (Appendix 4) and at all unscheduled visits as applicable, blood and urine samples will be collected for laboratory safety tests, including hematology, biochemistry, coagulation, and urinalysis. Please refer to Appendix 2 for the analytes of each laboratory test. Clinically significant laboratory abnormalities, in the opinion of the investigator, should be reported as AEs.

7.2.5. Vital Signs

Vital signs, including heart rate, blood pressure (systolic and diastolic), respiratory rate, and temperature will be measured at the time-points specified in the Schedule of Assessments (Appendix 4) and at all unscheduled visits as applicable. Vital sign measurements will be recorded with the subject in a seated position and after the subject has been resting for at least 5 minutes. All measurements will be performed singly. For any abnormal vital sign finding, further assessment should be performed as deemed necessary by the investigator. In case of re-screening, all vital sign parameters will be rechecked as described above.

7.2.6. Physical Examination

Physical examination will include assessment of heart, lung, extremities, body weight, and height. Height will only be assessed at screening. Body weight will be assessed at screening and on Day 85 (Visit 9 of Part A [redacted]). All the other assessments will be performed at the time-points specified in the Schedule of Assessments (Appendix 4) and at all unscheduled visits as applicable. Clinically significant changes from the initial physical findings at screening observed in subsequent visits will be considered AEs and will be documented on the AE section of the eCRF.

7.2.7. 12-lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes at the time-points specified in the Schedule of Assessments (Appendix 4) and at all unscheduled visits as applicable.

7.3. Pharmacokinetic Analysis

7.3.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples for analysis of CRD-740 concentrations will be collected by venipuncture at the time-points specified in the Schedule of Assessments (Appendix 4). Procedures for collection, processing, and shipping of PK blood samples will be detailed in the laboratory manual. PK samples will be assessed at a central laboratory.

7.3.2. Analytical Methodology

Plasma concentration of CRD-740 will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in the bioanalytical report.

8. SAMPLE SIZE AND DATA ANALYSES

8.1. Determination of Sample Size

In Part A, approximately 60 subjects with CHFrEF will be included.

The sample size was not determined by power calculations but by considerations to provide a reasonable number of subjects to assess the study objectives. Table 3 below summarizes the Part A sample sizes.

Table 3: Part A, dose ranging, sample sizes, no caps

EF%, Entresto	Randomized (2:1) Treatment	Sample Size
≤40, Yes	CRD-740	$\frac{2}{3}$ n_1
≤40, Yes	Placebo	$\frac{1}{3}$ n_1
≤40, No	CRD-740	$\frac{2}{3}$ n_2
≤40, No	Placebo	$\frac{1}{3}$ n_2
	Total N	60

Note: $n_1 + n_2 = 60$, where n_1 and n_2 are unknown and random; they denote the number of CHFrEF subjects with and without Entresto use, respectively. Randomization will be stratified on Entresto use (yes, no) and employ a 2:1 randomization ratio (CRD-740 : Placebo) within each stratum.

Abbreviations: CHFrEF = chronic heart failure with reduced ejection fraction; EF = ejection fraction

In Part B, approximately 600 subjects are planned to be included with approximately 300 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.2. Analysis Populations

The following analysis populations will be included for this study:

Intention to Treat (ITT): The ITT population consists of all randomized subjects. Subjects will be analyzed according to their randomized treatment, regardless of actual treatment received, treatment compliance, or treatment duration. The ITT population will be used for sensitivity analyses.

Modified ITT (mITT): The mITT population consists of all randomized subjects who received at least one dose of CRD-740 or placebo. Subjects will be analyzed according to their randomized treatment, regardless of actual treatment received, treatment compliance, or treatment duration. The mITT population will be used as the primary efficacy population.

Safety: The Safety population consists of all subjects who received at least one dose of CRD-740 or placebo. Subjects will be analyzed according to the treatment first received. The Safety population will be used as the primary safety population.

Pharmacokinetic: The PK population consists of all subjects who received at least one dose of CRD-740 and have no protocol deviations that are considered to impact the PK results.

Per protocol (PP): The PP population consists of all mITT subjects with no important protocol deviations. Subjects will be analyzed according to their randomized treatment. The PP population will be used for sensitivity analyses.

8.3. General Considerations

In general, data will be summarized with descriptive statistics for continuous endpoints, and frequency and percentage for categorical endpoints, unless otherwise specified. Percentages by

categories will be based on the number of subjects with no missing data (i.e., will add up to 100%).

Baseline will be defined as the last non-missing observation prior to first treatment intake, unless otherwise specified.

[redacted]

8.4. Efficacy Analysis

8.4.1. Primary Efficacy Outcome Measures

Part A

The primary endpoint is the change from baseline (Day -1) in plasma cGMP at Week 4. It will be compared between CRD-740 and placebo in the mITT population using an analysis of covariance (ANCOVA) model with categorical terms for treatment (2 levels), and Entresto (2 levels), and continuous terms for EF, and baseline plasma cGMP.

CRD-740 will be analyzed as one treatment group even though CRD-740 consists of two weeks of treatment with CRD-40[redacted], followed by two weeks of treatment with CRD-740[redacted]

The least square means of the change from baseline for each treatment group, along with the 95% confidence intervals (CI), and the least square mean treatment difference and the associated 95% CI for this difference will come from the ANCOVA model.

[redacted]

[redacted]

8.4.2. Secondary Efficacy Outcome Measures

Part A

Not Applicable.

[redacted]

[redacted]

8.5. Safety Analysis

All safety data will be summarized, by treatment group and dose period (Period 1, Period 2, Period 3, pooled Period 2 and Period 3, and overall) for Part A and by treatment group for Part B in the Safety Data Set.

For Part A, the primary safety analysis will be performed by reporting the exposure-adjusted incidence rates in subject-years for AE and SAE defined as the number of subjects with that particular AE or SAE within a system organ class or preferred term during the relevant period divided the sum of the at-risk times. The total at risk time is the sum of exposure time in each period in years. The adjusted incidence rates will be presented by system organ class and preferred term for Period 1, and separately for Periods 2 and 3 combined. The Hodges-Lehmann methodology will be used to estimate the within-subject point and interval treatment difference.

Adverse events

For both Part A and Part B, global incidence of emergent adverse events (EAE) (i.e., all events occurring, worsening or becoming serious after the first study treatment intake) will be given by system organ class and preferred term according to the Medical Dictionary of Regulatory Activities.

The same description will be performed for serious EAE, severe EAE, treatment related EAE, and EAE leading to study drug withdrawal.

AEs leading to death will also be summarized.

Vital signs / Physical examination

For both Part A and Part B, descriptive statistics will be performed on observed values at each visit and on each change and relative change from baseline.

Box plots will be produced for some pre-selected vital signs.

ECG abnormalities

For both Part A and Part B, quantitative routine 12-lead ECG results will be summarized on observed values at each visit and on each change and relative change from baseline.

Box plots will be produced for some pre-selected ECGs.

12-lead ECG data interpretations and quantitative values will be listed.

Laboratory tests

For both Part A and Part B, descriptive statistics will be performed on observed values at each visit and on each change and relative change from baseline.

The number and percentage of subjects having a value out of reference laboratory range (respectively out of potentially clinically significant range) will also be provided.

Box plots will be produced for some pre-selected lab parameters.

8.6. Pharmacokinetic Analysis

PK parameters will be calculated with plasma concentrations of CRD-740 in Part A using non-compartmental methods. Details of PK data handling, analysis methodology, and reporting will be included in the SAP.

All plasma concentrations of CRD-740 will be summarized by study part, dose, visiting day, and time-points. PK parameters will be summarized for Part A by dose and visiting day.

9. REFERENCES

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10. APPENDICES

Appendix 1 – Adverse Event Definitions

Definitions

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. This includes the following:

- Any clinically significant worsening of a pre-existing condition.
- Any recurrence of a pre-existing condition.
- An AE occurring from overdose of a sponsor study drug whether accidental or intentional (i.e., a dose higher than that prescribed by a health care professional for clinical reasons).
- An AE occurring from abuse of a sponsor study drug (i.e., use for non-clinical reasons).
- An AE that has been associated with the discontinuation of the use of a sponsor study drug.

Note: A procedure is not an AE, but the reason for a procedure may be an AE.

A pre-existing condition is a clinical condition (including a condition being treated) that is diagnosed before the subject signs the informed consent form and that is documented as part of the subject's medical history.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a treatment-emergent AE. An AE is considered to be treatment-emergent if (1) it is not present when the active phase of the study begins and is not a chronic condition that is part of the subject's medical history, or (2) it is present at the start of the active phase of the study or as part of the subject's medical history, but the severity or frequency increases during the active phase. The active phase of the study begins at the time of the first dose of the study drug. The active phase of the study ends at the follow-up visit.

Reporting of Adverse Events

At each visit, the investigator, or delegate, will determine whether or not any AEs have occurred. Non-leading questions such as "How are you feeling today?" or "Have you had any health concerns since your last visit?" should be used to elicit the subject (or, when appropriate, from a caregiver, surrogate, or the subject's legally authorized representative) to report any possible AEs. If any AEs have occurred, they will be recorded in the AE section of the electronic case report form (eCRF) and in the subject's source documents. If known, the diagnosis should be recorded, in preference to listing the individual signs and symptoms.

AE reporting begins from the time of informed consent and ends 28 days after the last dose of study drug.

Assessment of Severity

The investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- **Severe**: Interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Drug

The investigator will make a determination of the relationship of the AE to the study drug using a binary system according to the following guidelines:

- **Related**: There is a reasonable possibility that the drug causes the AE.
- **Not related**: There is no reasonable possibility that the drug causes the AE.

Action Taken for Adverse Events

The investigator or his/her designee will record the action taken for the AE in the eCRF. Actions taken will include:

- **Dose not changed**: The medication schedule was not changed.
- **Drug interrupted**: The medication schedule was modified by temporarily terminating the prescribed regimen of medication.
- **Drug withdrawn**: The medication schedule was modified through termination of the prescribed regimen of medication.
- **Not applicable**
- **Unknown**

Follow-up of Adverse Events

All AEs or serious adverse events (SAEs) that are ongoing at the time of discontinuation, or that develop prior to the final follow-up visit, will be followed for 28 days, or until resolution or stabilization.

Adverse Drug Reactions

All noxious and unintended responses to an investigational medicinal product (IMP; i.e., where a causal relationship between an IMP and an AE is a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., investigator's brochure for an unapproved IMP).

Serious Adverse Events

An SAE is any AE occurring at any dose that meets 1 or more of the following criteria:

- Results in death
- Is life threatening (see below)
- Requires subject hospitalization or prolongation of an existing hospitalization (see below)
- Results in a persistent or significant disability or incapacity (see below)
- Results in a congenital anomaly or birth defect
- Results in an important medical event (see below).

Additionally, important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not require hospitalization, or development of drug dependency or drug abuse.

A ***life-threatening AE*** is any AE that places the subject at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening, even though drug-induced hepatitis of a more severe nature can be fatal. Hospitalization is to be considered only as an overnight admission.

Hospitalization or prolongation of a hospitalization is a criterion for considering an AE to be serious. In the absence of an AE, the participating investigator should not report hospitalization or prolongation of hospitalization. This is the case in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.

- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study center (e.g., stent removal after surgery). This should be recorded in the study file.

- Hospitalization for survey visits or annual physicals fall in the same category.

In addition, a hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the study).

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions (i.e., the AE resulted in a significant, persistent, or permanent change, impairment, damage, or disruption in the subject's bodily function/structure, physical activities, or quality of life).

Medical and scientific judgment should be exercised in deciding whether a case is serious in those situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability, or incapacity. These include events that may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. Such events should usually be considered as serious.

Appendix 2 – Clinical Laboratory Evaluations

The following clinical laboratory analytes will be assessed:

Biochemistry:	**Hematology (CBC):**
Albumin	Hematocrit
ALP	Hemoglobin
ALT	MCH
AST	MCHC
BUN	MCV
Calcium	Platelet count
Chloride	RBC count
Creatinine*	WBC count
Direct bilirubin	WBC differential
GGT	(% & absolute):
Glucose	Basophils
Indirect bilirubin	Eosinophils
Phosphorus	Lymphocytes
Potassium	Monocytes
Sodium	Neutrophils
Total bilirubin	
Total CO_2 (measured as bicarbonate)	**For Females of Childbearing Potential Only:**
	Serum Pregnancy Test
Urinalysis:	Urine Pregnancy Test
Color and appearance	
pH and specific gravity	**Coagulation:**
Bilirubin	aPTT
Glucose	PT
Ketones	INR
Leukocytes	
Nitrite	
Occult blood	
Protein	
Microscopic (including RBC and WBC)	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; aPTT: activated partial thromboplastin time; BUN = blood urea nitrogen; CBC = complete blood count; CO_2 = carbon dioxide; GGT = gamma glutamyl transferase; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PT = prothrombin time; RBC = red blood cell; WBC = white blood cell

* Estimated glomerular filtration rate, as measured by the simplified Modification of Diet in Renal Disease formula, will be derived based on the level of creatinine.

Appendix 3 – Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

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

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

The protocol, protocol amendments, informed consent form (ICF), investigator's brochure, and other relevant documents (e.g., advertisements) must be submitted to an institutional review board (IRB)/ethics committee (EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

- Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the investigator or his/her designee, that their participation is voluntary and they are free to withdraw from the study at any

time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/EC or study center, where applicable. The subject will be given a copy of the signed ICF, and the original will be maintained with the subject's records.

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

Subject Data Protection

Subjects will be assigned a unique identifier and will not be identified by name in electronic case report forms (eCRFs), study-related forms, study reports, or any related publications. Subject and investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or investigators will be redacted according to applicable laws and regulations.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject. The subject must also be informed that his/her medical records may be examined by sponsor or contract research organization (CRO) auditors or other authorized personnel appointed by the **s**ponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

Independent Data Monitoring Committee

An independent data monitoring committee (DMC) will be established at the beginning of the study. The DMC will be responsible for ensuring the safety of study subjects, study integrity, and validity of study results. The DMC will review study results from Part A and make a non-binding dose recommendation for Part B to the sponsor's representative. The DMC members will not be involved in any day-to-day study decisions and will remain independent from the study team. The DMC will review safety and efficacy data to make recommendations concerning study continuation, modification, and termination based on ongoing study data. The DMC will operate according to a DMC charter, which will describe the DMC's membership, roles, and responsibilities.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The investigator or his/her designee agrees not to disclose such information in any way without prior written permission from the sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All subject data relating to the study will be recorded on eCRFs unless directly transmitted to the sponsor or its designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

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

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

- The sponsor or its designee is responsible for the data management of this study including quality checking of the data. Pre-defined, agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in the data management plan.

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

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in accordance with 21 CFR 312.62(c) (US site) or in the study site archive for at least 5 years after the end of the study (UK site) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Investigator Documentation Responsibilities

All individual, subject-specific study data will be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion. All data generated from external sources (e.g., central laboratory) and transmitted to the sponsor or its designee electronically will be integrated with the subject's eCRF data in accordance with the data management plan.

An eCRF must be completed for each subject who signs an ICF and undergoes any screening procedures, according to the eCRF completion instructions. The sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the

accuracy of the electronic data. The investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the investigator reviewed and approved the data on the eCRF, the data queries, and the site notifications.

Publications

If on completion of the study the data warrant publication, the investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process shall occur:

The institution and investigator shall not publish or present data from an individual study center until the complete multicenter study has been presented in full or for 2 years after the termination of the multicenter study, whichever occurs first. Subsequent publications must refer to the multicenter findings. Thereafter, if the investigator expects to participate in the publication of data generated from this site, the institution and investigator shall submit reports, abstracts, manuscripts, and/or other presentation materials to the sponsor for review before submission for publication or presentation. The sponsor shall have 60 days to respond with any requested revisions, including (without limitation) the deletion of confidential information. The investigator shall act in good faith upon requested revisions, except the investigator shall delete any confidential information from such proposed publications. The investigator shall delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 4 – Schedule of Assessments

1. Schedule of Assessments for Part A

Visit	1	2	3	4 (remote[o])	5	6 (remote[o])	7	8 (remote[o])	9	10 (remote[o])
Assessment [a]	**Screening [b] (Day -15 to Day -2)**	**Day -1**	**Day 1**	**Day 3 (±1 day)**	**Day 15 (Week 2) (±2 days)**	**Day 17 (±1 day)**	**Day 29 (Week 4) (+3 days)**	**Day 57 (Week 8) (±5 days)**	**Day 85 or ET (Week 12) (±5 days)**	**Day 113 (Week 16) (-2/+5 days)**
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographic data	X									
Medical history	X									
Serum pregnancy test [c]	X									
Urine pregnancy test [c]			X		X		X		X	
FSH [d]	X									
Vital signs [e]	X		X		X		X		X	
Physical examination [f]	X		X		X		X		X	
12-lead ECG [g]	X		X		X		X		X	
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]			[redacted]		[redacted]		[redacted]		[redacted]	
Randomization		X								
Coagulation panel (aPTT, PT, INR)	X									
Laboratory safety tests [i]	X		X	X	X	X	X	X	X	
Study drug administration [j]			X	X	X	X	X	X		

Visit	1	2	3	4 (remote[o])	5	6 (remote[o])	7	8 (remote[o])	9	10 (remote[o])
Assessment [a]	**Screening [b] (Day -15 to Day -2)**	**Day -1**	**Day 1**	**Day 3 (±1 day)**	**Day 15 (Week 2) (±2 days)**	**Day 17 (±1 day)**	**Day 29 (Week 4) (+3 days)**	**Day 57 (Week 8) (±5 days)**	**Day 85 or ET (Week 12) (±5 days)**	**Day 113 (Week 16) (-2/+5 days)**
Drug accountability			X		X		X		X	
Dose escalation					X					
AE recording	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Blood sample for drug assay (PK)			X [k] (pre-dose, 1 hr, 2 hr, 3 hr, 6 hr post dose)		X [k] (pre-dose, 1 hr, 2 hr, 3 hr, 6 hr post dose)		X [k] (pre-dose, 1 hr, 2 hr, 3 hr, 6 hr post dose)		X	
Blood sample for cGMP assay (target engagement)		X [k] (0hr, 1 hr, 2 hr, 3 hr, 6 hr)	X [k] (pre-dose, 1 hr, 2 hr, 3 hr, 6 hr post dose)		X [k] (pre-dose, 1 hr, 2 hr, 3 hr, 6 hr post dose)		X [k] (pre-dose, 1 hr, 2 hr, 3 hr, 6 hr post dose)		X	
Spot urine sample for cGMP		X	X		X		X		X	
6 hr urine collection for cGMP		X	X		X		X			
Echocardiogram	X									
[redacted]										
Dispense study drug			X [m]		X [m]		X [m]			
Return study drug					X [n]		X [n]		X [n]	

Abbreviations: AE = adverse event; aPTT: activated partial thromboplastin time; [redacted] cGMP = cyclic guanosine monophosphate; ECG = electrocardiogram; ET = end of trial; FSH = follicle-stimulating hormone; hr = hour; INR = international normalized ratio; [redacted] PK = pharmacokinetics; PT = prothrombin time

a. All assessments will be performed pre-dose unless otherwise specified.

b. All screening laboratory tests should ideally be performed on Day -15 to ensure eligibility assessment completed during screening window. In rare situations, if the laboratory reporting is delayed due to unforeseen circumstances (e.g., transit delays, lost sample, or outstanding queries), up to 21 days of screening will be accepted.

c. Women of childbearing potential only.

d. FSH will only be measured for women <55 years of age who have not had a menstrual period for ≥12 months at screening.

e. Vital signs, including heart rate, blood pressure (systolic and diastolic), respiratory rate, and temperature, will be measured at the time-points specified in the above table and at all unscheduled visits as applicable. Vital sign measurements will be recorded with the subject in a seated position and after the subject has been resting for at least 5 minutes. All measurements will be performed singly. For any abnormal vital sign finding, further assessment should be performed as deemed necessary by the investigator. In case of re-screening, all vital sign parameters will be rechecked as described above.

f. Physical examination will include assessment of heart, lung, extremities, body weight, and height. Height will only be assessed at screening. Body weight will be assessed at screening and at Visit 9. All the other assessments will be performed at all the applicable time-points and at all unscheduled visits as applicable.

g. Resting 12-lead ECGs will be recorded at the time-points specified in the above table and at all unscheduled visits as applicable. Resting 12-lead ECGs will be recorded after the subject has been supine and at rest for at least 5 minutes.

h. The blood sample will be collected 12-24 hours after last dose of study drug.

i. Laboratory safety tests will include biochemistry, urinalysis, and hematology. Please refer to Appendix 2 for the specific analytes of each test. Laboratory safety tests will be performed at the time-points specified in the above table and at all unscheduled visits as applicable. All laboratory safety tests will be analyzed at a central laboratory.

j. On the days of Visit 5 and Visit 7, subjects will be instructed NOT to take their dose of study drug before the pre-dose blood and urine sampling. Subjects will not take the study drug at Visit 9. They will be instructed to take the study drug through the day before Visit 9.

k. A time window of ±15 minutes applies to the time-points of 1 hour, 2 hours, 3 hours, and 6 hours.

[redacted]

m. Site pharmacists blinded to treatment allocation will dispense the study drug for subjects to self-administer on an out-patient basis. Subjects will be instructed to follow the provided instructions to take the study drug.

n. Subjects to return all used and unused drug supply containers.

o. If a subject refuses to have labs collected remotely, or a country/site's policy does not permit a 3rd party to collect blood draws off site, the subject will be allowed to have their visit conducted at the site instead.