Statistical Analysis Plan

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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Glossary of Abbreviations

Abbreviation	Term
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
aPTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{0-6}	Area the plasma concentration-time curve from time zero to 6 hours
AUC_{0-last}	Area under the plasma concentration-time curve from time zero to the time of last measurable concentration
AUC_{tau}	Area under the plasma concentration-time curve over a dosing interval
[redacted]	[redacted]
BLQ	Below Limit of Quantification
BNP	b-type natriuretic peptide
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
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
CRF	Case Report Form
COVID-19	Coronavirus Disease of 2019
CV	Coefficient of Variation
DMC	Data Monitoring Committee
ECG	Electrocardiogram
FAS	Full Analysis Set
GGT	Gamma-Glutamyl Transferase
IP	Investigational product
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
LLN	Lower Limit of Normal
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention to Treat
MMRM	Mixed model for repeated measures
NT-proBNP	N-terminal pro b-type natriuretic peptide
PD	Pharmacodynamic

Abbreviation	Term
PK	Pharmacokinetic
PKAP	PK Analysis Plan
PP	Per-Protocol
PT	Preferred Term
QTcB	Bazett corrected QT interval
QTcF	Fridericia corrected QT interval
RBC	Red Blood Cells
SAE	Serious AE
SAP	Statistical Analysis Plan
SD	Standard Deviation
SI	International System of Units
SOC	System Organ Class
TFLs	Tables, Figures and Listings
TEAE	Treatment Emergent AEs
t_{max}	Time to reach C_{max}
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO DD	World Health Organization Drug Dictionary

1. Source Documents

The SAP was written based on the following documentation:

Document	Date	Version
Protocol	10 Aug 2022	2.1
eCRF	28 Feb 2023	4.0

2. Protocol Details

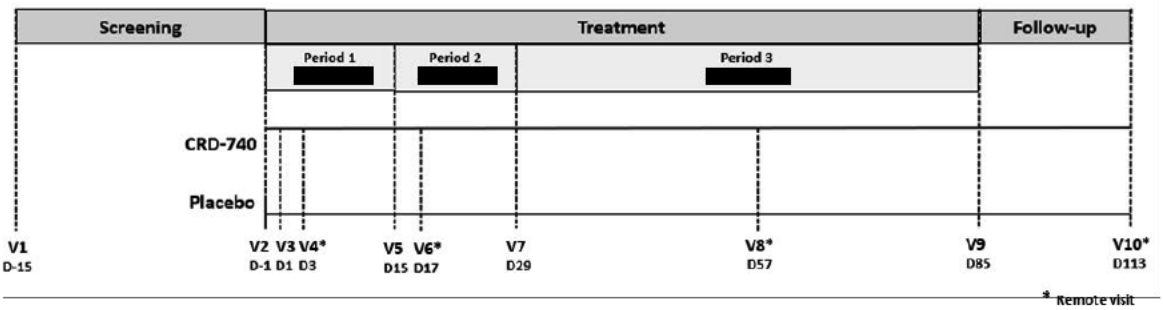
2.1. Overall Study Design

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 Chronic heart failure with reduced ejection fraction (CHFrEF). [redacted]. An independent data monitoring committee (DMC) will oversee the study.

By decision of the Sponsor, and unrelated to safety concerns, Part B of the study will not be conducted.

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).

Figure 1 Study schematic of Part A



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

2.2. Study Objectives

2.2.1. Primary Objectives

Part A:

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

2.2.1.1. Estimands for the Primary Objectives

Estimands for the primary objectives are described in Sections 3.1.1 and 3.1.2 for Part A in this SAP.

2.2.2. Secondary Objectives

Part A:

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

2.2.2.1. Estimands for the Secondary Objectives

Not applicable for Part A.

2.2.3.1. Estimands for the Exploratory Objectives

Not applicable for Part A.

2.3. Sample Size and Power

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 1 below summarizes the Part A sample sizes.

Table 1 Part A, dose ranging, sample sizes, no caps

EF%, Entresto	Randomized (2:1) Treatment	Sample Size
≤40, Yes	CRD-740	⅔ n1
≤40, Yes	Placebo	⅓ n1
≤40, No	CRD-740	⅔ n2
≤40, No	Placebo	⅓ n2
	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

2.4. Primary Variables

2.4.1. Primary Efficacy Variables

Part A:

- Change from baseline in plasma cGMP AUC at Week 4

2.4.2. Primary Safety Variables

Part A:

1. AEs
2. Physical examinations
3. Vital signs
4. 12-lead ECGs
5. Laboratory safety tests (biochemistry, urinalysis, and hematology)

2.5. Secondary Variables

2.5.1. Secondary Efficacy Variables

Part A:

No secondary efficacy variables are defined for Part A of the study.

2.5.2. Secondary Safety Variables

Part A:

No secondary safety variables are defined for Part A of the study.

[redacted]

2.7. Pharmacokinetics Variables

Part A:

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

1. C_{max}
2. Time of C_{max} (t_{max})
3. $AUC_{0\text{-last}}$
4. Area under the plasma concentration-time curve over a dosing interval (AUC_{tau})
5. Apparent total body clearance (CL/F, except for Day 1)

3. Estimand(s)

The ICH[1] E9 (R1) addendum on estimands[2] and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials came into effect on 30 July 2020. This section addresses the construction of estimands for the primary and secondary objectives. Each estimand is defined according to the following five attributes:

1) The **treatment** condition of interest, and as appropriate, the alternative condition to which comparison will be made.
2) The **population** of subjects targeted by the clinical question.
3) The **variable** (or endpoint) to be obtained for each subject that is required to address the clinical question.
4) The clinical question of interest in respect of **other intercurrent events** not covered through the precise specifications of treatment, population and variable.
5) A **population-**level summary for the variable providing a basis for comparison between treatment conditions.

3.1. Part A

3.1.1. Estimands for the primary efficacy objective

The estimand for the primary efficacy objective (assessment of the effect of CRD-740 compared to placebo in plasma cGMP AUC at Week 4 in subjects with CHFrEF) is defined through the 5 attributes described in Sections 3.1.1.1 to 3.1.1.5:

3.1.1.1. Treatment Condition of Interest

The primary treatment condition of interest is CRD-740 dose (either [redacted] or placebo, with or without sacubitril/valsartan, dosed as required.

3.1.1.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is defined through Randomized subjects with CHrEF (EF≤40%) who received at least one dose of CRD-740 or placebo (mITT).

3.1.1.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each subject in the study, the variable to address the clinical question is change from baseline in plasma cGMP AUC at Week 4.

3.1.1.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

Intercurrent events will be handled through a treatment policy and while on treatment strategy. The following intercurrent events are anticipated during the study:

- Discontinuation of treatment
- Subject withdraws consent from further data collection
- Subject lost to follow-up

The following table describes how intercurrent events will be collected and handled within the analysis.

Table 2 Handling of Intercurrent Events for the Primary Efficacy Estimand

Intercurrent event	Data collection and analysis
Discontinuation of treatment	Patients will be followed, and data collected after the intercurrent event will be used in analysis in line with a treatment policy strategy, i.e., disregarding the occurrence of the intercurrent event
Subject withdraws consent from further data collection	Subject who withdraws consent from further data collection will be analyzed by while on treatment strategy: only plasma cGMP values collected before the occurrence of the intercurrent event will be included in the analysis.
Subject lost to follow-up	Subject who is lost to follow-up will be analyzed by while on treatment strategy: only plasma cGMP values collected before the occurrence of the intercurrent event will be included in the analysis.

3.1.1.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the Treatment difference (CRD-740 – placebo) in change from baseline in plasma cGMP AUC values at Week 4.

3.1.1.6. Sensitivity Estimators for the Primary Efficacy Estimand

A sensitivity analysis of the primary endpoint will be performed on the Per Protocol Population analysis.

3.1.2. Estimands for the primary safety objective

The estimand for the primary safety objective (assessment of the safety and tolerability of CRD-740 in subjects with CHFrEF, defined as heart failure with EF ≤40%) is defined through the 5 attributes described in Sections 3.1.2.1 to 3.1.2.5:

3.1.2.1. Treatment Condition of Interest

The primary treatment condition of interest is CRD-740 dose ([redacted]) or placebo, with or without sacubitril/valsartan, dosed as required.

3.1.2.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is defined through Subjects with CHFrEF (EF≤40%) who received at least one dose of CRD-740 or placebo.

3.1.2.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each subject in the study, the variables to address the clinical question are AEs, physical examinations, vital signs, 12-lead electrocardiograms and laboratory safety tests (biochemistry, urinalysis, and hematology).

3.1.2.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

Intercurrent events will be handled through a treatment policy and while on treatment strategy. The following intercurrent events are anticipated during the study:

- Discontinuation of treatment
- Subject withdraws consent from further data collection
- Subject lost to follow

The following table describes how intercurrent events will be collected and handled within the analysis.

Table 3 Handling of Intercurrent Events for the Primary Safety Estimand

Intercurrent event	Data collection and analysis
Discontinuation of treatment	Patients will be followed, and data collected after the intercurrent event will be used in analysis in line with a treatment policy strategy, i.e., disregarding the occurrence of the intercurrent event

Intercurrent event	Data collection and analysis
Subject withdraws consent from further data collection	Subject who withdraws consent from further data collection will be analyzed by while on treatment strategy: only safety data collected before the occurrence of the intercurrent event will be included in the analysis.
Subject lost to follow-up	Subject who is lost to follow-up will be analyzed by while on treatment strategy: only safety data collected before the occurrence of the intercurrent event will be included in the analysis.

3.1.2.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by 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.

3.1.2.6. Sensitivity Estimators for the Primary Safety Estimand

No sensitivity analyses will be conducted for primary safety estimand in part A.

4. Analysis Populations

In accordance with ICH E3 and E9[3], the following analysis populations will be used for the analyses.

4.1. All Screened Population

The All Screened Population will include every subject who has signed the informed consent form. The All Screened Population will be used for summaries of disposition and the associated listing.

4.2. Intention to Treat Population

The Intention to Treat Population (ITT) population will consist 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 summaries of disposition, protocol deviations, demographics & baseline characteristics, medical history, and prior/concomitant medications.

4.3. Modified ITT Population

The modified Intention to Treat (mITT) Population will consist 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.

4.4. Per Protocol Population

The Per Protocol Population (PP) will consist 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.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations which may significantly impact the correctness, accuracy, and / or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Section 4.4.1 details the deviations.

4.4.1. Important Protocol Deviations Leading to Exclusion from the PP Population

Deviations from the protocol, as defined in the protocol and / or protocol deviation plan, will be documented by the trial monitors and project management throughout the trial period.

Only those important protocol deviations considered to have a major effect on efficacy will lead to complete exclusion of the patient from the PP Population. For the purposes of this trial, the criteria identified as candidates for important protocol deviations leading to exclusion from the PP Population will be detailed in a separate protocol deviations spreadsheet, as it is considered that the occurrences of any of these criteria might have an important influence on the primary efficacy endpoint. Patients will be assessed purely by comparison of their eCRF data with the defined criteria; protocol waivers will not be taken into consideration (e.g., if a patient younger than 18 enters the trial on a protocol waiver, the patient would still be excluded from the PP Population).

Criteria which require clinical or medical monitoring interpretation will be reviewed prior to database lock. All important protocol deviations leading to exclusion from the PP Population occurring during the trial will be reviewed and approved by Cardurion prior to database lock.

4.5. Week 2 Analysis Population

The Week 2 Analysis Population will consist of all mITT subjects with no important protocol deviations during the first 2 weeks. Subjects will be analyzed according to their randomized treatment. The Week 2 Analysis Population will be used for sensitivity analyses for the interim DMC.

Important protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol that may significantly confound the ability to detect target engagement via pharmacodynamic measures.

4.6. Week 4 Analysis Population

The Week 4 Analysis Population will consist of all mITT subjects with no important protocol deviations during the first 4 weeks. Subjects will be analyzed according to their randomized treatment. The Week 4 Analysis Population will be used for sensitivity analyses for the interim DMC.

Important protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol that may significantly confound the ability to detect target engagement via pharmacodynamic measures.

4.7. Safety Analysis Population (SAF)

The Safety population will consist 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.

4.8. Pharmacokinetics Analysis Population (PK)

The PK population will consist 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. PK Analysis Population subjects are analyzed according to their randomized treatment.

5. Data Handling

5.1. Time Points and Visit Windows

5.1.1. General Definitions

All assessment days will be related to the day of first dose of treatment.

Day 1 is defined as first dose of treatment. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1. Day 0 is not defined.

The date of the first dose of treatment for each subject will be taken from the *Study Drug Administration (Oral)* eCRF page at Visit 3. If the date in this eCRF page is missing, alternatively the date of randomization + 1 will be used.

The date of the last dose of treatment for each subject will be taken from the *End of Treatment* eCRF page. If the date in this eCRF page is missing, alternatively the Completion or discontinuation date of *Disposition – End of Study* eCRF form will be used. If the date is missing because the subject was lost to follow-up, the date of the last visit will be imputed, if appropriate.

5.1.2. Baseline Value and Change from Baseline

Baseline values for the primary efficacy variable in Part A (plasma cGMP) are the plasma cGMP values collected on Day -1 (at 0hr, 1hr, 2hr, 3hr, and 6hr) time-matched to Day 29 values. An $AUC_{0\text{-}6h}$ will also be derived from those values. $AUC_{0\text{-}6h}$ derivation is described in Section 6.6.1. In addition, baseline value for 6-hour urine collection will be the value collected on Day -1.

For all other variables, independently from study Part, **baseline value** is defined as the last non-missing value collected before the first dose of treatment. If assessment is performed on Day 1, it will be considered performed before the first dose intake unless the date/time of assessment confirms that it was performed after the first dose intake.

Change from baseline at Week X will be defined as Week X value – Baseline value.

Change from Week X to Week Y will be defined as Week Y value – Week X value.

5.1.3. Screening Period

For all subjects, the screening period is defined as the period from informed consent to the first dose of treatment. For some variables, data from more than one assessment within the screening period can be collected prior to the first dose of treatment.

5.1.4. Treatment Period

Data collected at Day 1 will be assigned to the Treatment Period unless the time (HH:MM) of data collection and time (HH:MM) of first dose of treatment are both recorded and the data collection time is before the time of first dose of treatment. In this case, the assessment will be assigned to the screening period. If the time (HH:MM) of data collection is not recorded but the protocol and / or eCRF includes an instruction to the effect that all Day 1 assessments are to be performed prior to the first dose of treatment, the data collected at Day 1 will be assigned to the screening period. However, adverse events and medications starting on Day 1, will be assigned to the Treatment Period.

The Treatment Period is defined as the period from the date / time of the first dose of treatment up to and including the date / time of the last dose of treatment.

Treatment period in Part A comprises 3 dosing periods:

Period 1 (dose of [redacted]) from date of the first dose of treatment at [redacted] level till date of the first dose of treatment at [redacted] level;

Period 2 (dose of [redacted]) from date of the first dose of treatment at [redacted] level till day before Visit 7;

Period 3 (dose of [redacted]) from the dose of treatment on Visit 7 till the date of the last dose of treatment.

If subject discontinues during Period 1 or Period 2, the date of the last dose of treatment will be considered as end of the respective period.

5.1.5. Visit Windows

Table 4 Definition of Visit Windows for Efficacy and Safety Assessments provides the relative trial day ranges to be applied to the assessment / sample collection date to derive the analysis visits for analyses of trial assessments.

The following considerations are to be followed when deriving the analysis visit:

- The relative day number of the assessment lies between the lower and upper boundary of the analysis visit window (the boundary values are included)
- Both scheduled and unscheduled assessments are included for visit windowing
- If there are two or more valid assessments for a defined window the following rules will be applied:

- If there are multiple assessments with non-missing assessment results for any specified analysis visit window, the assessment that is closest to the target day of analysis window will be used for analysis
- If there are two or more assessments with non-missing results and the same distance to the planned study day, the assessment prior to the planned study day will be used for analysis.

Table 4 Definition of Visit Windows for Efficacy and Safety Assessments Part A

Visit	Target Day of Visit[a]	Protocol Visit Windows	Analysis Visit Window	Target Day of Analysis Visit	Analysis Visit
Screening (Day -15 to Day -2)	Day –15	Day -15 to Day -2	Day -21 to Day -2	Day –15	Screening
Visit 2, Day -1	Day -1	Day -1			Day -1
Visit 3, Day 1	Day 1	Day 1	Day 1	Day 1	Baseline*
Visit 4, Day 3 (remote)	Day 3	Day ± 1	NA		
Visit 5, Day 15	Day 15	Day ± 2	Day 2 to Day 24	Day 15	Week 2
Visit 6, Day 17 (remote)	Day 17	Day ± 1	NA		
Visit 7, Day 29	Day 29	Day ± 3	Day 25 to Day 43	Day 29	Week 4
Visit 8, Day 57 (remote)	Day 57	Day ± 5	NA		
Visit 9, Day 85	Day 85	Day ± 5	Day 71 to Day 99	Day 85	Week 12
Visit 10, Day 113 (remote)	Day 113	Day – 2/ + 5	NA		

[a] Relative to first dose of treatment
* Except for plasma cGMP and 6-hour urine collection cGMP where baseline is assessed on Day -1. See Section 5.1.2 for details on the baseline definition.
NA= Not Applicable

5.2. Handling of Dropouts, Missing Data, and Outliers

5.2.1. Handling of Missing Efficacy Data

For Part A, missing efficacy data will not be replaced for the primary efficacy analysis.

For sensitivity analysis of the efficacy endpoints in Part A (efficacy endpoints of NT-proBNP, BNP, and urine and plasma cGMP), inference will be done using mixed-effects models repeated-measures[4], which assumes that missing outcomes are missing at random (MAR).

5.2.2. Handling of Missing Safety Data

In general, missing clinical laboratory data, vital signs, and ECG data will not be imputed. Adverse event imputations for missing severity or relationship are given in Section 6.7.2. Unknown or partial medication and AE date imputations are given below and to be used only for the assessment of prior / concomitant status for medications and treatment-emergent status for AEs.

5.2.3. Handling of Partial and Missing Dates for Adverse Events, Prior / Concomitant Medications

Missing or Partial Adverse Event and Prior / Concomitant Medication Start Dates

Missing and / or incomplete dates for medications and AEs are imputed in a manner resulting in the earliest onset or the longest duration during the Treatment Period, whilst ensuring that the start date does not occur after the stop date. The stop date will not be imputed if the medication or AE is "Ongoing". Technically, this will be done as follows:

For a missing / incomplete start date / time the earliest date / time of the following will be imputed:

- The later date of: the earliest possible start date / time, and the date / time of first dose of treatment.
- The latest possible start date / time.
- The latest possible stop date / time.

For a missing / incomplete stop date / time the later date / time of the following will be imputed:

- The earlier date / time of the latest possible stop date / time and the date / time of last dose of treatment.
- The earliest possible stop date / time.
- The earliest possible start date / time.

Here, the earliest possible date / time is defined as:

- The date / time itself if available.
- The date / time of the first day of the month at 00:00hrs, if month and year are available but the day / time is missing.
- The date / time of the first day of the year at 00:00hrs, if year is available but day / time and month are missing.
- 00:00hrs on the day of informed consent, if the date / time is completely missing.

The latest possible date / time is defined as:

- The date / time itself if available.
- The date / time of the last day of the month at 23:59hrs, if month and year are available but the day / time is missing.
- The date / time of the last day of the year at 23:59hrs, if year is available but day / time and month are missing.
- 23:59hrs on the date of last known date on the study for the subject plus one year, if the date / time is completely missing.

5.2.4. Handling of Plasma / Blood / Serum Concentrations that are Below the Lower Limit of Quantification

Plasma / blood / serum concentrations that are below the lower limit of quantification (BLQ) will be handled as follows for descriptive statistics:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.
- Arithmetic mean or median values that are BLQ will be presented as 0.
- If any BLQ results (treated as 0) are in a series of summarized data, geometric mean and coefficient of variation (CV) % of geometric mean will be reported as not calculated (NC).

6. Statistical Methods

6.1. General Principles

All data processing, summarization and analyses will be performed using Labcorp Drug Development's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max), for those subjects with data.

For qualitative variables, the number (n) and percentage (%) of subjects with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Number of subjects in the analysis population will be used as denominator for percentages calculation, unless stated otherwise in TFLs mock shells.

All statistical comparisons will be made using one sided tests at the α=0.025 significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference. All alternative hypotheses will be one-sided.

All laboratory test results will be received from the central laboratories, and the results will be provided in both standard internal (SI) and conventional units. For the TFLs, the results will be summarized or presented in International System of Units (SI) units. Refer to Appendix of the TLFs mock shells for the SI unit corresponding to each laboratory test.
Refer to Appendix of the TLF shells for the precision level in which each laboratory test is reported by the central laboratories.

Specifications for table, figures and data listing formats can be found in the TFL shells specifications for this study. Please refer to "2. General Format Guidelines" section within TFL shells for more details on presentation of results.

6.2. Subject Disposition and Data Sets Analyzed

Subject disposition will be summarized by treatment group, and overall for Part A of the study, where appropriate, for the All Screened Population. The following information will be reported:

- Number of subjects for the following categories:
  - Screened,
  - Treated but not randomized.

- Number and percentage of subjects for the following categories:
  - Randomized,
  - Treated,
  - Not Treated,
  - Discontinued the study treatment,
  - Reasons for study treatment discontinuation
  - Completed the study,
  - Ongoing in the study,
  - Discontinued the Study,
  - Reasons for study discontinuation.
- Number and percentages of subjects completing period 1, completing period 2 and completing period 3 (applicable for Part A only)
- Number and percentage of subjects included in, and excluded from, each study population together with the reasons for exclusion from the respective analysis population (this will be summarized for ITT population);
- Number and percentage of subjects who met / did not meet all eligibility criteria, together with the criteria not met;
- Number and percentage of subjects who failed screening prior to randomization, including the primary reason for screen failure;
- Number and percentage of subjects at each site (this will be summarized for ITT population);
- Number and percentage of subjects by stratification factors (this will be summarized for ITT population). Each stratification variable will be presented by the stratum collected in Interactive web-based response system (IWRS) and the stratum collected in the eCRF (if available).

In Part A of this study, a subject will be considered to have completed the study if he/she has answered "Yes" to question "Did the subject complete the study" on *Disposition – End of Study* form in eCRF. A subject will be considered as having discontinued the study if the question is answered "No". Otherwise, the subject will be considered as ongoing study.

A subject will be considered to have discontinued the study treatment if reason of discontinuation is provided on *End of Treatment* eCRF form.

A listing of all subjects with their treatment and study completion status, including the respective reasons for treatment and study discontinuation will be presented for the ITT.

A listing of all screen failed subjects with their reasons for screen failure will be presented for the All Screened Population. A separate listing of subjects who failed at least one inclusion /

exclusion criteria including a text description of the criterion failed will be presented for the All Screened Population.

A listing of all randomized subjects with their randomization details, including first dose date and time, and actual treatment received will be presented for the ITT.

A listing of all subjects excluded from at least one analysis population will be presented for the All Screened Population.

6.3. Protocol Deviations

All important protocol deviations will be summarized for the ITT by treatment group and overall for Part A of the study as described below:

- The number of unique subjects with at least one important protocol deviation as well as the number of subjects in each important protocol deviation category will be presented by default descriptive summary statistics for categorical variables.

A listing of all subjects with one or more important protocol deviations will be presented for the ITT. In addition, a listing of the subjects affected by Coronavirus Disease of 2019 (COVID-19) and the type of COVID-19 disruption will be provided for the ITT.

6.4. Demographic and Other Baseline Characteristics

6.4.1. Demographic Characteristics

Demographic characteristics will be summarized for the ITT by treatment group and overall for Part A of the study as described below. All missing data will be presented as part of a missing category, if appropriate. Standard descriptive statistics will be presented for the continuous variables of:

- Age (years)
- Height (cm) at baseline
- Weight (kg) at baseline
- Body mass index (kg/m^2) at baseline
  [calculated as (body weight / $height^2$) where weight is in kg and height is in m] and presented to one decimal precision

Total counts and percentages of subjects will be presented for the categorical variables of:

- Age group (years):
  - ≤ 65
  - > 65
- Sex (Male/Female)
- Reproductive system status (Childbearing potential, menopause status) – for females only
- Race

- Ethnicity (Hispanic or Latino/Not Hispanic or Latino / Unknown)

In addition, a summary table presenting the number of subjects by geographical location (EU member state, Non-EU country, by each EU member state/Non-EU country) and overall for Part A. A further breakdown by age group and sex by geographical location may also be presented.

Countries will be retrieved from the 3 first digits of subject id as detailed in Table 5.

Table 5 Country and geographical locations from Subject number

Country	Range of the 3 first digits	Location
Bulgaria	101-149	EU member state
Canada	151-199	Non EU country
Czech Republic	201-249	EU member state
Hungary	251-299	EU member state
Israel	301-349	Non EU country
Italy	351-399	EU member state
Poland	401-449	EU member state
Slovakia	501-549	EU member state
United Kingdom	551-599	Non EU country
United States of America	601-649	Non EU country

Demographic characteristics will be listed for the ITT.

6.4.2. Baseline Characteristics

Baseline characteristics will be summarized by treatment group and overall for Part A as described below. All missing data will be presented as part of a missing category, if appropriate.

Total counts and percentages of subjects will be presented for the categorical variables of:

- Echocardiogram performed during screening (Yes/No)
- EF group
  - $\leq 40\%$
  - $> 40\%$

Standard descriptive statistics will be presented for the continuous variables of:

- EF (%) by EF subgroup ($\leq 40\%$ / $> 40\%$)

Baseline characteristics will be listed for the ITT population.

6.4.3. Medical History

Medical history is defined as any condition, with the exception of the study indication, that the subject may have had prior to enrollment in the study, including any chronic conditions diagnosed prior to entry in the study. See section 5.2.3 for imputation of missing or partial dates for medical history.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [version 24.1 or a later version if updated during the study] and will be presented by System Organ Class (SOC) and Preferred Term (PT). The SOCs and PTs are to be sorted by Internationally Agreed order SOCs and descending PTs in the overall column.

Medical history records will be summarized for the ITT population by treatment group and overall for Part A of the study as follows:

- The number and percentage of subjects with at least one medical history record will be presented.
- The number and percentage of subjects with at least one medical history record within each primary SOC and PT will be presented. The summary will be sorted using the internationally agreed order for SOC and using descending order of overall numerical counts for PT. Where terms tie, these will be sorted alphabetically.

Medical history records will be listed by-subject and within-subject by medical history start date for the ITT population.

6.4.4. Prior and Concomitant Medications

All medications will be coded using the WHO Drug Global Dictionary, Format B3 [Version SEP 2021 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken prior to screening with a stop date and time prior to the start of the Treatment Period.
- Concomitant medications are those with a start date and time on or after the start of the Treatment Period, or those with a start date and time before the start of the Treatment Period and either a stop date and time on or the start of the Treatment Period, or are ongoing at the end of the study.

See Section 5.2.3 for imputation of missing or partial dates for medication.

Prior and concomitant medications will be summarized separately for the ITT population by treatment group and overall for Part A of the study as follows:

- The number and percentage of subjects with at least one prior / concomitant medication will be presented.
- The number and percentage of subjects with at least one prior / concomitant medication within each Anatomical Group (ATC Level 1), Therapeutic Subgroup (ATC Level 2), and preferred term will be presented. The summary will be sorted using numerical counts by descending order of Anatomical Group, then descending order of Therapeutic Subgroup, then descending order of preferred term in the total column. Where groups or terms tie these will be sorted alphabetically.

Prior medications and concomitant medications will be listed separately for the ITT population. In the listings the relative start and stop day of prior / concomitant medication use will be calculated relative to the first dose date and time of treatment and will be presented for those subjects who received at least one dose of treatment. If the concomitant medication is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

6.4.5. Prohibited Concomitant Therapy

Prohibited concomitant therapies are defined as he following drugs taken by subjects from the time of ICF signing onwards:

- PDE-5 inhibitors (ATC codes G04BE03 and G04BE08)
- Known strong inhibitors CYP3A4:
    - Atazanavir (J05AE08)
    - Ceritinib (L01ED02)
    - Clarithromycin (J01FA09)
    - Cobicistat and cobicistat-containing coformulations (V03AX03, J05AR14, J05AR15)
    - Darunavir (J05AE10, J05AR22, J05AR26)
    - Idelalisib (L01EM01)
    - Indinavir (J05AE02)
    - Itraconazole (J02AC02)
    - Ketoconazole (D01AC08, D01AC08, H02CA03, J02AB02)
    - Levoketoconazole
    - Lonafarnib (A16AX20)
    - Lopinavir (J05AR10)
    - Mifepristone (G03XB01, G03XB51)
    - Nefazodone (N06AX06)
    - Nelfinavir (J05AE04)
    - Ombitasvir-paritaprevir-ritonavir (J05AP53)

  - Ombitasvir-paritaprevir-ritonavir plus dasabuvir (J05AP52)
  - Posaconazole (J02AC04)
  - Ritonavir and ritonavir-containing coformulations (J05AR10, J05AR23, J05AR26, J05AR10, J05AP53, J05AP53)
  - Saquinavir (J05AE01)
  - Telithromycin (J01FA15)
  - Tucatinib (L01EH03)
  - Voriconazole (J02AC03)
- Known strong inducers of CYP3A4:
  - Apalutamide (L02BB05)
  - Carbamazepine (N03AF01)
  - Enzalutamide (L02BB04)
  - Fosphenytoin (N03AB05)
  - Lumacaftor (R07AX30)
  - Lumacaftor-ivacaftor (R07AX30)
  - Mitotane (L01XX23)
  - Phenobarbital (N03AA02)
  - Phenytoin (N03AB02, N03AB05, N03AB04, N03AB54, N03AB52)
  - Primidone (N03AA03)
  - Rifampin (rifampicin) (J04AB02, J04AM02, J04AM05, J04AM07, 04AM06)

Prohibited concomitant therapy will be listed for the ITT population.

6.5. Measurements of Treatment Compliance

Treatment compliance is defined as the number of tablets that were actually taken relative to the number of tablets that should have been taken as per the protocol for the duration of actual treatment exposure.

In general, the percentage compliance, assessed by tablet count, will be calculated as follows:

$$\textit{Compliance (\%)} = \frac{\textit{Number of tablets dispensed} - \textit{Number of tablets returned}}{\textit{Number of days on treatment} \times 2 \times \textit{Number of tablets/dose}} \times 100\%$$

Number of tablets per dose is [redacted] mg dosing.

Number of days on treatment will be calculated as follows:

(last dose date of treatment - first dose date of treatment) + 1

The calculated percentage compliance will be categorized as:

- < 80% compliance
- ≥ 80% to ≤ 125% compliance
- > 125% compliance

Compliance will be summarized for the SAF by treatment group and overall for Part A of the study as follows:

- Percent compliance will be presented by default summary statistics.
- Number and percentage of subjects within each of the compliance categories will be presented. Any subjects with missing data will be presented as part of a "Missing" category.

In addition, for part A, compliance by period (period 1, period 2, period 3 and pooled periods 2 and 3) will be calculated using the same formula with the denominator (number of days on treatment) corresponding to the number of days within each period. Compliance by period will be summarized in the same way as overall compliance.

Treatment compliance will be listed together with exposure for the SAF. Missing data will not be imputed and only original data for those fields (for example, date fields) will be presented in the listing together with derived variables such as the calculated compliance (%) and exposure duration.

6.6. Efficacy Analysis

Efficacy assessments will undergo visit windowing procedure as described in Section 5.1.5 and will be analyzed using analysis visits.

6.6.1. Primary Efficacy Analysis

Part A:

The primary endpoint is the change from baseline in plasma cGMP AUC at Week 4. Blood samples for cGMP are collected at Visit 2, Visit 3, Visit 5 and Visit 7 on specific timepoints (pre-dose, 1 hr, 2 hr, 3 hr, 6 hr post dose). AUC_{0-6} will be derived from those timepoints at each visit using the linear trapezoidal rule[5].

The change in plasma cGMP AUC_{0-6} will be compared between CRD-740 and placebo in the mITT population using an analysis of covariance (ANCOVA) model with fixed factors for treatment (2 levels), and Entresto use at baseline (2 levels), and covariates for baseline EF, and baseline plasma cGMP AUC.

The analysis will be repeated on the change from baseline in plasma cGMP AUC at Week 2.

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.

Observed values and absolute change from baseline at each analysis visit for plasma cGMP AUC will be summarized by treatment group using default summary statistics for continuous variables on the mITT population.

Absolute change from baseline at each analysis visit for plasma cGMP AUC will be plotted by treatment group using mean and standard error for continuous variables on the mITT population.

cGMP data will be listed for mITT population.

6.6.2. Sensitivity Analysis for the Primary Efficacy Endpoints

Part A

The following sensitivity analyses of the primary efficacy endpoint will be performed:

- Primary analysis will be repeated on the PP population.
- Primary analysis will be repeated on the Week 2 Analysis population. This analysis will be performed for interim DMC purposes only.
- Primary analysis will be repeated on the Week 4 Analysis population. This analysis will be performed for interim DMC purposes only.
- Change from baseline in log-transformed plasma cGMP AUC over time will be analyzed in the mITT population using a mixed model for repeated measures (MMRM) including treatment, post-baseline visit (Visits 3, 5 and 7), Entresto use, treatment-by-visit interaction, treatment-by-Entresto interaction, visit-by-Entresto use interaction, and baseline EF as a covariate with random effects for subject, intercept, and slope. The covariance structure will be unstructured. No imputation of missing data will be performed. The least-square means of log (plasma cGMP AUC) and associated two-sided 95% CI for each treatment, the estimated least square mean treatment differences (on the log scale), and corresponding two-sided 95% CI coming from the MMRM will be given for all visits.
- The MMRM analysis described above will be conducted on raw plasma cGMP AUC in the mITT population.

6.6.3. Secondary Efficacy Analysis

Part A

Not applicable.

6.6.4. Sensitivity Analyses for the Secondary Efficacy Endpoints

No sensitivity analyses will be conducted for secondary efficacy endpoints in Part A.

6.6.5. Subgroup Analysis

Not applicable.

[redacted]

[redacted]

[redacted]

6.7. Safety Analysis

6.7.1. Extent of Exposure

Duration of exposure will be defined in week as:
Exposure (weeks) = ([date of last dose – date of first dose]) / 7

The calculated exposure duration of exposure will be categorized for Part A as:

- Less or equal than 2 weeks
- > 2 weeks to 4 weeks
- > 4 weeks to 12 weeks

- > 12 weeks

Duration of exposure will be summarized in two ways for the SAF by treatment group and overall for Part A of the study.

- Descriptive statistics will be presented for duration of exposure.
- Number and percentage of subjects within each of the exposure categories will be presented.

A listing of overall treatment exposure data, including the first and last dates of treatment will be presented together with compliance for the SAF. Further, study treatment administration data will be listed for the SAF.

6.7.2. Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary [version 24.1 or a later version if updated during the study] and classified as either pre-treatment AEs or treatment–emergent AEs (TEAEs) as follows:

- Pre-treatment AEs are events that start prior to the start of the Treatment Period.
- TEAEs are either events with start date and time after the first study treatment administration or events with start date and time prior to the first study treatment administration whose severity worsening or becoming serious after the start of the Treatment Period.
- The relationship between a TEAE and treatment is assessed as related, or not related. A treatment-related TEAE will be defined as a TEAE considered by the investigator as related to treatment or unknown / missing relationship to treatment.
- The severity of and AE is assessed as Mild / Moderate / Severe according to the investigator. Severe TEAEs are defined as TEAEs assessed as being “Severe” and includes those events where the severity is missing.
- TEAEs leading to discontinuation of study are defined as TEAEs where “Required Withdrawal from study” is indicated as other action taken on AE eCRF form.
- TEAEs leading to discontinuation of study treatment are defined as TEAEs where “Drug Withdrawn” is indicated as action taken with study treatment on AE eCRF form
- TEAEs leading to dose interruption are defined as TEAEs where “Drug Interrupted” is indicated as action taken on AE eCRF form

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 by the sum of the at-risk times. For a subject who does not have that particular AE or SAE, the at risk time is the exposure time in each period in years. For a subject who does have

that particular AE or SAE, the at risk time is the exposure time until the event occurs 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 will be summarized by treatment group and overall by dose period (Period 1, Period 2, Period 3, pooled Period 2 and Period 3, and overall) for Part A in the SAF.

- An overview of TEAEs including the number and percentage of subjects with at least one of each mentioned TEAE type:
  - Any TEAE
    - Leading to discontinuation of study
    - Leading to discontinuation of study treatment
    - Leading to death
    - Mild
    - Moderate
    - Severe
  - Any study treatment related TEAE
    - Leading to discontinuation of study
    - Leading to discontinuation of study treatment
    - Leading to death
  - Any serious TEAE
    - Leading to discontinuation of study
    - Leading to discontinuation of study treatment
    - Leading to death
  - Any serious study treatment related TEAE
    - Leading to discontinuation of study
    - Leading to discontinuation of study treatment
    - Leading to death

- The number and percentage of subjects reporting each TEAE and the count of number of events will be summarized by SOC and PT for the following types of TEAEs:
  - All TEAEs
  - TEAEs Leading to Discontinuation of Study Treatment
  - TEAEs Leading to Dose interruption
  - TEAEs Leading to Study Withdrawal
  - TEAEs Leading to Death
  - TEAEs by Maximum Severity
  - TEAEs by Relationship to Treatment
  - TEAEs by Relationship and Maximum Severity
  - Study Treatment related TEAEs
  - Study Treatment Related TEAEs Leading to Discontinuation of Study Treatment

  - Study Treatment related TEAEs Leading to Death
  - Serious TEAEs
  - Serious TEAEs Leading to Discontinuation of Study Treatment
  - Serious TEAEs Leading to Dose Interruption
  - Serious TEAEs Leading to Study Withdrawal
  - Serious TEAEs Leading to Death
  - Study Treatment Related Serious TEAEs
  - Study Treatment Related Serious TEAEs Leading to Discontinuation of Study Treatment
  - Study Treatment Related Serious TEAEs Leading to Death
  - Study Treatment Related Serious TEAEs Leading to Study Withdrawal
- The number and percentage of subjects who died will be summarized by the primary reason of death (if available)

In the above summaries, subjects with more than one TEAE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one TEAE within a particular PT are counted only once for that PT.

For summaries by maximum severity, subjects with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe TEAE within that SOC or PT.

Summaries by SOCs and PTs will be sorted by SOCs by their Internationally Agreed Order (MedDRA) and PTs within SOC by descending order of total incidence. Where preferred terms tie PTs will be sorted alphabetically.

No statistical comparisons of AEs between treatment groups will be performed.

All AE data will be listed and Pre-treatment AEs and TEAEs will be presented together. Treatment-emergence status will be flagged in the listing. The listing will present the relative start and stop day of the AE calculated relative to the first dose of treatment and will be presented for those subjects who received at least one dose of treatment. If the AE is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

In addition, the following listings will be presented:

- Listing of Deaths
- Listing of Serious TEAEs
- Listing of Severe TEAEs
- Listing of AEs Leading to Interruption of Study Treatment
- Listing of AEs Leading to Discontinuation of Study Treatment
- Listing of AEs Leading to Study Withdrawal

6.7.3. Laboratory Evaluations

Data for the following hematology, biochemistry, urinalysis and coagulation analytes received from central laboratory are to be measured at the scheduled time points indicated in the study flowchart.

Table 7 Laboratory Tests

Hematology Test (SI unit)	Serum Chemistry Test (SI unit)	Coagulation (SI unit)	Urinalysis	Pregnancy Test
• Hematocrit (%) • Hemoglobin (g/L) • Mean corpuscular hemoglobin (MCH)(fmol) • Mean corpuscular hemoglobin concentration (MCHC) (mmol/L) • Mean corpuscular volume (MCV) (fL) • Platelet count (10^9/L) • Red Blood Cell Count (RBC) (10^{12}/L) • White Blood Cell (WBC) Count (10^9/L) • Differential WBC (10^9/L and %) o Neutrophils o Lymphocytes o Eosinophils o Basophils o Monocytes	• Albumin (g/L) • Alkaline phosphatase (ALP) (U/L) • Alanine aminotransferase (ALT) (U/L) • Aspartate aminotransferase (AST) (U/L) • Blood urea nitrogen (BUN) • Calcium (mmol/L) • Chloride (mmol/L) • Creatinine* (mmol/L) • Direct Bilirubin (mmol/L) (only in patients with bilirubin >2×ULN) • Gamma-Glutamyltransferase (GGT) (U/L) • Glucose (mmol/L) • Indirect Bilirubin (mmol/L) (only in patients with bilirubin >2×ULN) • Phosphorus (mmol/L) • Potassium (mmol/L) • Sodium (mmol/L) • Total Bilirubin (mmol/L) • Total CO_2 - Bicarbonate (mmol/L)	<u>Coagulation:</u> • Activated partial thromboplastin time (aPTT) (sec) • Prothrombin time (PT) (sec) • INR	<u>Macroscopic panel:</u> • Color and appearance • Ph • Specific gravity • Bilirubin • Glucose • Ketones • Leukocytes • Nitrites • Occult blood • Proteins <u>Microscopic panel:</u> • Red blood Cell Count • White Blood Cell Count	<u>For women of childbearing potential only:</u> • Serum pregnancy test • Urine pregnancy test

* 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.

In accordance with the baseline value definition in Section 5.1.3, the absolute change from baseline will be derived as follows:

Absolute change (unit) = (post-baseline value – baseline value)

All laboratory data will be reported in SI units. All quantitative laboratory test values at each assessed timepoints will be compared with the relevant reference range in SI units and categorized as:

- Low: Below the lower limit of the reference range.
- Normal: Within the reference range (upper and lower limits included).
- High: Above the upper limit of the reference range.

For summaries which present worst value with respect to the reference range at the subject level, low and high are each chosen in preference to normal values. For parameters with both low and high reference ranges, subjects who have assessments within both low and high ranges will be counted within each category for worst value summary tables.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory values will be assigned toxicity grades, when available, using criteria based on the NCI CTCAE version 5.0 scale[6]. For summaries which present worst CTCAE value at the subject level higher grades are used in preference to lower grades.

Parameters whose grade can be derived are detailed in Table 8 CTCAE gradingTable 8:

Table 8 CTCAE grading

Parameter	Value	CTCAE Term
Hematology		
Hemoglobin	Low	Anemia
	High	Hemoglobin increased
WBC	Low	White blood cells decreased
	High	Leucocytosis
Neutrophils (absolute)	Low	Neutrophil count decreased
Lymphocytes (absolute)	Low	Lymphocyte count decreased
	High	Lymphocyte count increased
Platelet	Low	Platelet count decreased
Blood chemistry		
Sodium	Low	Hyponatremia
	High	Hypernatremia
Potassium	Low	Hypokalemia
	High	Hyperkalemia
Total Bilirubin	High	Blood bilirubin increased
ALT	High	Alanine aminotransferase increased
AST	High	Aspartate aminotransferase increased
ALP	High	Alkaline phosphatase increased
Glucose	Low	Hypoglycemia
	High	Hyperglycemia
GGT	High	GGT increased
Albumin	Low	Hypoalbuminemia
Creatinine	High	Creatinine increased
Bicarbonate	Low	Blood bicarbonate decreased

Laboratory data will be summarized by default descriptive summary statistics for continuous and categorical variables by treatment group and overall by dose period (Period 1, Period 2, Period 3, pooled Period 2 and Period 3, and overall) for Part A in the SAF as follows:

- Observed values and change from baseline at each assessed timepoint for each standard continuous laboratory parameter;
- Number and percentage of subjects with categorized shift (low, normal and high) values relative to the reference range at baseline compared to each post-baseline timepoint standard continuous laboratory hematology and chemistry parameter;
- Number and percentage of subjects with worst post-baseline NCI-CTCAE toxicity values;
- Number and percentage of subjects with categorized shift NCI-CTCAE toxicity values at baseline compared to each post-baseline timepoint.

In addition, box plots of AST, ALT, Total Bilirubin and Creatinine values at baseline and each post-baseline visit will be generated for the SAF.

Listings of all clinical laboratory data including derived percentage change from baseline will be provided for the SAF. Within each listing, laboratory values outside the normal ranges will be flagged as either high or low.

In addition, a listing of hematology and serum chemistry parameters of toxicity grade 2 and above will be provided.

6.7.4. Vital Signs

The analyses described below will be conducted for the following vital signs assessments respectively:

- systolic blood pressure (mmHg);
- diastolic blood pressure (mmHg);
- pulse rate (bpm);
- weight (kg);
- respiration rate (breaths / min);
- body temperature (°C).

The following will be summarized by treatment group and overall by dose period (Period 1, Period 2, Period 3, pooled Period 2 and Period 3, and overall) for Part A in the SAF:

- Observed values and change from baseline at each assessed timepoint for each standard vital sign parameter using default summary statistics for continuous variables;

Box plots of systolic blood pressure and diastolic blood pressure values at baseline and each post-baseline visit will be generated for the SAF.

A listing of all vital signs data including derived change from baseline will be provided for the SAF.

6.7.5. Electrocardiograms

The following electrocardiogram (ECG) assessments will be taken during the study:

- An overall investigator assessment classified as normal, abnormal, not clinically significant / abnormal, clinically significant
- Heart rate (bpm);
- RR interval (msec);
- PR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- QTcB (msec);
- QTcF (msec);

The maximum post-baseline QTcF / QTcB values will be classified in accordance with the ICH E14[7], Boundaries as presented in Table 9.

Table 9 QTcF / QTcB Interval ICH E14 Boundaries

QTcF / QTcB Interval	Criteria (msec)
Observed QTcF / QTcB interval	<=450 msec >450 msec >480 msec >500 msec
Change from baseline in QTcF / QTcB interval	<=30 >30 to <= 60 msec >60 msec

The ECG findings will be summarized by treatment group and overall by dose period (Period 1, Period 2, Period 3, pooled Period 2 and Period 3, and overall) for Part A in the SAF as follows:

- Observed values and change from baseline at each assessed timepoint for each ECG parameter using default summary statistics for continuous variables;
- The ECG overall assessment as reported by the investigator will be summarized at each assessed timepoint by providing number and percentage of subjects within each assessment category;
- A categorical summary of QTcF / QTcB classification according to ICH E14 boundaries will be provided using counts and percentages for baseline and maximum

post-baseline value.

Box plots of QTcF at baseline and each post-baseline visit will be generated for the SAF. A listing of all ECG data including derived change from baseline will be provided for the SAF.

6.7.6. Physical Examination

Abnormalities identified from physical examination are recorded in the eCRF as Medical History or AEs as appropriate and will be listed and summarized as such [See Sections 6.4.3 (Medical History) and 6.7.2 (Adverse Events)].

For each physical examination body system, the number and percentage of subjects with abnormalities at baseline and at each assessed timepoint will be summarized by treatment group and overall by dose period (Period 1, Period 2, Period 3, pooled Period 2 and Period 3, and overall) for Part A in the SAF.

Physical examination findings (normal / abnormal) and details of abnormalities will be listed for each subject at each assessed timepoint in the SAF.

6.7.7. Interim Analysis and Data Monitoring

No interim analysis (blinded or unblinded) will be performed.

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. 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.

At each of the DMC meetings, the DMC will assess whether the safety profile of the Investigational Product (IP) is acceptable to allow the current trial to continue without adjustment.

The DMC can make recommendations based on safety considerations at the DMC meetings that take place while subjects are still undergoing treatment.

For all meetings, the DMC will be provided with the following data to assess the safety of the IP:

1. Summary of subject enrollment (Section 6.2)
2. Subject disposition (Section 6.2)
3. Demographics and baseline characteristics (Sections 6.4.1 and 6.4.2)
4. Prior and concomitant medications (Section 6.4.4)
5. Treatment exposure data (Section 6.7.1)
6. Safety profile (TEAEs, treatment-related TEAEs, serious TEAEs, TEAEs leading to study withdrawal, TEAEs of severe intensity, laboratory values of at least grade 2 toxicity) (Sections 6.7.2 and 6.7.3)
7. Deaths (Section 6.7.2)
8. Clinical laboratory results (Section 6.7.3)
9. Other safety information (vital sign measurements, ECG results, questionnaires) (Sections 6.7.4, 6.7.5, 6.7.6)
10. Subjects randomized and not meeting eligibility criteria (Section 6.2)
11. PK analysis (Section 6.8)

The DMC can recommend stopping the trial or modifying the trial design if there are significant concerns regarding the safety profile of the IP.

Efficacy analysis data will also be provided:

For Part A:

1. The change from baseline in plasma cGMP AUC at Week 2 and Week 4 (Section 6.6.1)
2. The change in NT-proBNP from baseline to Week 2, to Week 4, and to Week 12 (Section 6.6.6.1)
3. The change in BNP from baseline to Week 2, to Week 4, and to Week 12 (Section 6.6.6.1)
4. The change in plasma, spot urine, and 6-hour urine collection cGMP from baseline to Week 2, to Week 4, and to Week 12 (Section 6.6.6.2)
5. The change from baseline at Week 12 in the KCCQ-23-CS, KCCQ-23-OS, and 7 domains: physical limitation, symptom stability, symptom frequency, symptom burden, quality of life, self-efficacy, and social limitation (Section 6.6.6.4)
6. The proportion of subjects with ≥5-point improvement from baseline in the KCCQ-23-CS (Section 6.6.6.4)

The list of tables and listings provided for each safety data review will be a subset of the global TFL shells from the trial: the ones that are provided for the DMC will be flagged.

The DMC will not perform any formal (based on conditional probability) futility assessment.

6.8. Pharmacokinetic Analysis

A listing of PK blood sample collection times and Plasma concentrations will be presented for CRD-740 by study part for all subjects for the Pharmacokinetics Analysis Set.
Plasma concentrations of CRD-740 will be summarized by study part, dose, visiting day, and time-points using descriptive statistics.

See Section 5.2.4 for the handling of Plasma concentrations that are BLQ.

6.8.1. PK Parameters in Part A

The following PK parameters will be determined where possible from the plasma concentrations of CRD-740 on Day 1 ([redacted]), Day 15 ([redacted]) and Day 29 ([redacted]) using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.1 or higher):

Table 10 PK parameters

Parameter	Units[a]	Definition
C_{max}	ng/mL	maximum observed plasma concentration
t_{max}	h	Time to reach C_{max}
$AUC_{0\text{-}last}$ [b]	h*ng/mL	Area under the plasma concentration-time curve from time zero to the time of last measurable concentration
$AUC_{0\text{-}6}$ [b]	h*ng/mL	Area under the plasma concentration-time curve from time zero to 6 hours postdose
AUC_{tau} [b c]	h*ng/mL	Area under the plasma concentration-time curve over a dosing interval (Only Day 29)
CL/F	mL/h/kg	Apparent total body clearance (Only Day 29)

The dosing interval τ is 12 hours.
a Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] Area under the concentration-time curve will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations (linear up/log down rule).
[c] AUC_{tau} calculated by substitution of 12 h timepojnt with predose concentration under assumption of steady state.
[d] Accumulation ratios calculated by dose normalization under assumption of linear PK.

Additional PK parameters may be determined where appropriate.

Pharmacokinetic analysis will be carried out where possible using actual dose administered (*m*g) and actual postdose blood sampling times. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

The parameters C_{max} and t_{max} will be obtained directly from the concentration-time profiles. If C_{max} occurs at more than 1 timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

6.8.1.1. Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only 3 consecutive concentrations, at least 1 should follow C_{max}.

6.8.1.2. Criteria for Handling Concentrations Below the Limit of Quantification or Missing Concentrations for Pharmacokinetic Analysis

Plasma concentrations below the limit of quantification (BLQ) will be assigned a value of 0 before the first measurable concentration and thereafter BLQ concentrations will be treated as missing. The following rules apply to the specific situations defined below:

- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are considered to be a true characteristic of the profile of the drug.
- If a predose plasma concentration is missing, it will be set to 0 by default within Phoenix WinNonlin for the first dosing day.

6.8.1.3. Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude the value from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in the CSR.

Any quantifiable predose concentration value on the first dosing day will be considered anomalous and set to missing for the PK analysis. This will be set to 0 by default in Phoenix WinNonlin.

6.8.1.4. Presentation of Pharmacokinetic Data

If the actual time of sample collection deviates by more than protocol window the plasma blood concentration may be flagged and excluded from the summary statistics at discretion of Pharmacokineticist.

Individual concentrations deemed to be anomalous will be flagged in the listings and excluded from the summary statistics.

PK parameters will be reported to 3 significant figures. Summary statistics will be presented for all PK parameters with the following exception:

- Geometric mean and coefficient of variation will not be calculated for t_{max}

All PK concentrations and parameters will be listed for the Pharmacokinetics Analysis Set.

Summary tables, mean (+ standard deviation [SD]) figures, overlaying individual figures, and individual figures dose level and by PK profile (Day 1, Week 2 and Week 4) and time postdose will be provided for plasma PK concentrations. All figures will be produced on both linear and semi-logarithmic scales.

Summary tables dose level and by PK profile (Day 1, Week 2 and Week 4) will be provided for all PK parameters, with the exception of regression-related PK parameters.

Additional PK outputs may be presented if appropriate.

In addition, for parameters C_{max} and AUC, the geometric means, the geometric mean CV% and the 95% CI of geometric means will be provided.

The geometric mean CV% will be calculated according to the following formula: $100 \times \text{sqrt}(\exp(s^2) - 1)$, where s^2 is the observed variance on the natural log-scale. The geometric mean and its 95% CI will be obtained by exponentiating the mean and 95% CI of the mean on the natural log-scale

Scatter plots will be also performed presenting changes from baseline in plasma cGMP (time-matched 1-hour, 2-hour, 3-hour and 6-hour), cGMP AUC and 6-hour urine collection cGMP versus CRD-740 concentrations (2-hour concentration for cGMP AUC and 6-hour urine cGMP, and time-matched concentration for plasma cGMP) by dose period (Period 1, Period 2, Period 3, pooled Period 2 and Period 3) and overall on the Pharmacokinetics Analysis Set, including Pearson and Spearman correlation coefficient values

7. Changes in the Conduct of the Study or Planned Analysis

Baseline calculation for cGMP (that is collected at several timepoints) in Part A has been defined using time-matched values and using AUC_{0-6}.

Baseline calculation for spot urine cGMP in Part A has been defined as the last non-missing value collected before the first dose of treatment rather than the Day -1 value noted in the protocol.

Analysis (ANCOVA) of change from baseline in cGMP AUC at Week 2 has been added for Part A.

Racc(AUC_{0-6}) and Racc(C_{max}) have been removed from PK endpoints and parameters to analyse, as only approximations of these parameters can be retrieved: AUC_{tau} can only be calculated on Day 29, hence we would have to base accumulation ratio on AUC_{0-6}. In addition, there are different doses between day 29 and Day 1 which is problematic for the calculation. Only a dose adjustement could be used (if the compound displays linear PK over dose) to provide approximate Racc parameters.

Any deviations from the approved SAP will be described and justified in the CSR.

8. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary / Reason for Changes
Version 1.0, Final, 17MAY2023	Final version, updated according to comments on 6th draft
Version 0.6, Sponsor Draft. 10MAY2023	Sixth draft, updated according to comments on 5th draft
Version 0.5, Sponsor Draft, 20MAY2022	Fifth draft, updated according to comments on 4th draft
Version 0.4, Sponsor Draft, 12APR2022	Fourth draft, updated according to 3rd draft of TFL shells
Version 0.3, Sponsor Draft, 31MAR2022	Third draft including sponsor's comments and comments from PK team
Version 0.2, Sponsor Draft, 22MAR2022	Second draft including sponsor's comments
Version 0.1, Sponsor Draft, 02MAR2022	First sponsor version after internal review
Version 0.1, Internal Draft, 18FEB2022	Not applicable; the first version

9. References

[1]ICH. *Statistical Principles for Clinical Trials*, Guideline E9, 1998. Available at https://database.ich.org/sites/default/files/E9_Guideline.pdf

[2]ICH. *Addendum on Estimands and Sensitivity Analysis in Clinical Trials*, Guideline E9(R1). Available at https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

[3]ICH. *Structure and Content of Clinical Study Reports*, Guideline E3, 1995. Available at https://database.ich.org/sites/default/files/E3_Guideline.pdf

[4]Brown H and Prescott R. *Applied Mixed Models in Medicine*. John Wiley & sons (Chichester), 1999.

[5]*Katz D, D'Argenio DZ. Experimental design for estimating integrals by numerical quadrature, with application to pharmacokinetic studies.* Biometrics. *1983;39:621–628.*

[6]*Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Available at* https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_60

[7]ICH. *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.* 12 May 2005. Available at https://database.ich.org/sites/default/files/E14_Guideline.pdf