STATISTICAL ANALYSIS PLAN

Cardiol 100-002

Impact of C**AR**diolRxTM on Myo**C**ardial Recovery in patients wit**H** Acut**E** Myoca**R**ditis – A double-blind, placebo-controlled trial (**ARCHER**)

Protocol Number:	Cardiol 100-002
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Sponsor:	Cardiol Therapeutics Inc. 2265 Upper Middle Road East Suite 602 Oakville, ON, L6H 0G5, Canada
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ABBREVIATIONS

Abbreviation	Definition
#	Number
a.m	Morning
AE	Adverse Event
ALT	Alanine Aminotransferase
AMI	Myocardial Infarction
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
b.i.d	Twice a Day
BDRM	Blind Data Review Meeting
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CBD	Cannabidiol
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMR	Cardiac Magnetic Resonance Imaging
CS	Clinical Summary Score (KCCQ Score)
C-SSRS	Columbia Suicide Severity Rating Scale
cTn	Cardiac Troponin Test
CYP2C19	Cytochrome P450 2C19
CYP3A4	Cytochrome P450 3A4
ECG	Electrocardiogram
ECV	Extracellular Volume
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EMB	Endomyocardial Biopsy

Abbreviation	Definition
eSOCDAT	Electronic-Source Consultation Data Acquisition Tool
FSH	Follicle Stimulating Hormone
g	Gram
GLS	Global Longitudinal Strain
HCT	Hematocrit
HF	Heart Failure
HGB	Hemoglobin
hr	Hour
hs-CRP	High Sensitivity C Reactive Protein
hs-troponin	High Sensitivity Troponin
ICD	Implantable Cardioverter-Defibrillator
ICU	Intensive Care Unit
IL-1 beta	Interleukin 1-Beta
IL-6	Interleukin 6
IL-10	Interleukin 10
IL-18	Interleukin 18
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
ITT	Intention-to-treat
IU/L	International Unit per Liter
KCCQ	Kansas City Cardiomyopathy Questionnaire
kg	Kilogram
kg/m²	Kilogram per Square Meter
LAESV	Left Atrial End-Systolic Volume
LGE	Late Gadolinium Enhancement
LLOQ	Low Limit of Quantification
LV	Left Ventricular
LVAD	Left Ventricular Assist Device
LVEDV	Left Ventricular End-Diastolic Volume
LVEF	Left Ventricular Ejection Fraction

Abbreviation	Definition
LVESV	Left Ventricular End-Systolic Volume
MedDRA	Medial Dictionary For Regulatory Activities
mg	Milligram
mg/kg	Milligram per Kilogram
min	Minute
mITT	Modified Intention-to-treat
mIU/mL	Milli-International Units per Milliliter
mL	Milliliter
mL/min/1.73m^2	Milliliter per Minute per 1.73 Square Meter
mmHg	Millimeters of Mercury
msec	Milliseconds
ng/L	Nanogram per Liter
NT-proBNP	N-terminal pro B-type naturetic peptide
NYHA	New York Heart Association
OS	Overall Summary Score (KCCQ Score)
p.m	Afternoon
PCI	Percutaneous Coronary Intervention
PL	Physical Limitation (KCCQ Score)
QL	Quality of Life (KCCQ Score)
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SB	Symptom Burden (KCCQ Score)
SD	Standard Deviation
SE	Self-Efficacy (KCCQ Score)
SF	Symptom Frequency (KCCQ Score)
SL	Social Limitation (KCCQ Score)
SOC	System Organ Class
SS	Symptom Stability (KCCQ Score)
sVCAM-1	Soluble Vascular Cell Adhesion Molecule-1

Abbreviation	Definition
TEAE	Treatment - Emergent Adverse Events
TGF-beta	Transforming Growth Factor Beta
TIA	Transient Ischemic Attack
TNF-alpha	Tumor Necrosis Factor Alpha
TS	Total Symptom Score (KCCQ Score)
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

DOCUMENT REVISION HISTORY

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1.0	09-May-2025		Initial Release	Sophie de Brouwer, Emilie Perrin

1 INTRODUCTION

1.1 Background

This statistical analysis plan (SAP) describes the statistical methods for the analyses of the Cardiol 100-002 trial titled “Impact of CardiolRxTM on Myocardial Recovery in Acute Myocarditis – A double-blind, placebo-controlled trial” (‘’ARCHER’’). The SAP was prepared using Protocols listed on page 1 of this document but taking into consideration, as appropriate, protocol version 3.4 for the two patients who were randomized under this protocol version. The ARCHER SAP was finalized prior to the final database lock and unblinding.

2 OVERALL STUDY DESIGN, OBJECTIVES AND OUTCOMES

2.1 Study design

Cardiol 100-002 was designed as a multi-center, double-blind, randomized, placebo-controlled, parallel group trial. The trial protocol planned that approximately 100 patients would be enrolled.

2.2 Study objectives

The primary and secondary objectives were to evaluate the effect of treatment with CardiolRx^{TM} on myocardial recovery in patients who were diagnosed with acute myocarditis.

2.3 Study endpoints as defined in the study protocol

2.3.1 Primary efficacy endpoint

The primary efficacy outcome of this study was comprised of two primary endpoints, i.e., the difference in the means between the active and the placebo groups of (a) extracellular volume (ECV) and (b) global longitudinal strain (GLS), as measured by CMR, at 12 weeks post randomization.

2.3.2 Secondary efficacy endpoints

The secondary efficacy outcome was the difference between the active and the placebo groups in the mean LVEF, as measured by CMR, at 12 weeks post randomization.

2.3.3 Other efficacy endpoints foreseen in the study protocol include

a. Survival, free from major event: cardiac transplant, LVAD, hospitalization for HF 12 weeks post randomization
b. Change in CMR parameters from baseline to 12 weeks post randomization: LVEF, ECV, GLS, LVEDV, LVESV, LAESV, LV mass, LGE, degree of edema
c. Change in NYHA classification from baseline to 12 weeks post randomization
d. Change in KCCQ from baseline to 12 weeks post randomization
e. Time to resolution of clinical symptoms, including chest pain, arrhythmias, shortness of breath (will not be analysed)
f. Time to normalization of hs-troponin, NT-proBNP and inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10, IL-18) and endothelial markers (sVCAM-1, TGF-beta [beta 1 and beta 2])
g. Change in hs-troponin, NT-proBNP and inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10, IL-18) and endothelial markers (sVCAM-1, TGF-beta [beta 1 and beta 2]) from baseline to week 12
h. Time to normalization of ECG abnormalities (will not be analysed)

2.3.4 Safety objective/endpoints

The primary safety objective was to demonstrate that administration of CardioIRx™ in the proposed doses in this patient population is safe.

Safety endpoints include the number of AEs and SAEs, clinically significant changes in ECG findings, clinically significant changes (from baseline) in the C-SSRS as well as clinically significant changes in laboratory assay, including liver function assays, and INR over the entire study period.

3 SAMPLE SIZE AND POWER

Please refer to section 11.1 of the study protocol version 4.X

4 STUDY POPULATION

4.1 Inclusion criteria

Per protocol version 4.0, the following inclusion criteria had to be met for patients:

1. Males and females 18 years of age or older

2. Diagnosed with acute myocarditis including:
    a. Clinical criteria (symptoms of chest pain, arrhythmia or shortness of breath, or history of viral-like illness), preferably followed by elevated troponin ***PLUS***
    b. CMR diagnosis: (Lake Louise Criteria, Appendix 17.4 of this protocol) within 10 days prior to randomization ***OR***
    c. Endomyocardial biopsy showing either cellular inflammation and/or immunohistochemistry consistent with inflammation
3. Male subjects with partners of childbearing potential who have had a vasectomy or are willing to use double barrier contraception methods during the conduct of the study and for 2 months after the last dose of study drug.
4. Women of childbearing potential willing to use an acceptable method of contraception starting with study drug administration and for a minimum of 2 months after study completion. Otherwise, women must be postmenopausal (at least 1 y absence of vaginal bleeding or spotting and confirmed by follicle stimulating hormone [FSH] ≥40 mIU/mL [or ≥ 40 IU/L] if less than 2 y postmenopausal) or be surgically sterile. The following reliable methods of contraception are: parenteral contraceptives, oral contraceptives, patch contraceptives, implantable hormonal contraceptives, intrauterine device or system, surgical sterilization (hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy), tubal ligation/occlusion, vasectomized partner, or sexual abstinence, if this is the subject's current practice. Periodic abstinence, i.e., calendar, symptothermal, or post-ovulation methods are not an acceptable form of contraception for this study. These methods of contraception also apply to female partners of male subjects

4.2 Exclusion criteria

Patients meeting any of the following criteria were not eligible to participate:

1. Coronary artery disease (CAD) defined as a stenosis greater than 50% in a major epicardial coronary artery
2. Severe valvular heart disease
3. Inability to safely undergo CMR including administration of gadolinium
4. Estimated glomerular filtration rate (eGFR) < 30 ml/min

5. Elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 times the upper limit of normal (ULN) or ALT or AST >3x ULN plus bilirubin >2x ULN.
6. Sepsis, defined as documented bacteremia at the time of presentation or other documented active infection.
7. Severe left ventricular (LV) dysfunction requiring inotropic support, left ventricular assist device (LVAD) or other circulatory assist devices, or urgent need for transplantation
8. Documented biopsy evidence of giant cell or eosinophilic myocarditis
9. Prior history of sustained ventricular arrhythmia
10. Acute coronary syndrome within 30 days
11. Percutaneous coronary intervention within 30 days
12. History of QT interval prolongation or QTc interval > 500 msec
13. Treated with strong inducers CYP3A4 or CYP2C19, as listed in Appendix 17.8
14. Treated with digoxin and/or type 1 or 3 antiarrhythmics
15. Current participation in any research study involving investigational drugs or devices
16. Inability or unwillingness to give informed consent
17. Ongoing drug or alcohol abuse
18. Women who are pregnant or breastfeeding
19. Current diagnosis of cancer, with the exception of non-melanoma skin cancer
20. Any factor, which would make it unlikely that the patient can comply with the study procedures
21. On any cannabinoid during the past month
22. Body weight > 170 kg
23. Showing suicidal tendency as per the C-SSRS, administered at screening

Differences between study protocol versions 3.4 and 4.XX on the selection criteria impacting on the patients randomized under protocol version 3.4

- Inclusion criterion #1 was previously defined *as males and females aged between 18 and 75 years (inclusive)*
- Inclusion criterion #2 in the protocol version 3.4 *(LVEF< 0.50*) was removed
- Inclusion criterion #3 (equivalent to Inclusion criterion #2 in protocol version v4.0) was as follows in the protocol version 3.4:
  Previously diagnosed with acute myocarditis including:
  a. *Clinical criteria (symptoms of chest pain, arrhythmia or shortness of breath, or history of viral-like illness), preferably followed by elevated troponin in the absence of hemodynamically significant CAD* (defined as a stenosis greater than 50% in a major epicardial coronary artery) within the previous 90 days* ***PLUS***
  b. *CMR diagnosis: (Lake Louise Criteria, Appendix 17.4 of this protocol)* ***OR***
  c. *Endomyocardial biopsy showing either cellular inflammation and/or immunohistochemistry consistent with inflammation*
- Exclusion criterion #9 was not present in protocol version 3.4
- Exclusion criterion #14 was not present in protocol version 3.4

Impact on the Statistical Analysis Plan:

The two patients included under protocol v3.4 will be reviewed during the BDRM to ensure that they comply also with updated / new inclusion/exclusion criteria included in protocol version 4.XX

4.3 Study treatment assignment

Per protocol, study treatment was started in the evening of Day 1 (i.e., day when the patient was randomized), The study treatment dose titration was as follows:

- Week 1 (p.m. dose of Day 1 to a.m. dose of Day 7): 2.5 mg/kg of body weight CardiolRx™ b.i.d. or placebo
- Week 2 (p.m. dose of Day 7 to a.m. dose of Day 14): 5.0 mg/kg of body weight CardiolRx™ b.i.d. or placebo
- Week 3 (p.m. dose of Day 14 to a.m. dose of Day 21): 7.5 mg/kg of body weight CardiolRx™ b.i.d. or placebo
- Week 4 end of treatment period (p.m. dose of Day 21 to a.m. dose of last day of treatment period at week 12): 10.0 mg/kg of body weight CardiolRx™ b.i.d. or placebo
- The morning and evening doses should have been taken within a 6 – 18-hour window of each dose

If the next higher dose after each study drug increase was not tolerated, the dose could have been reduced to the previous tolerated dose.

4.4 Blinding and unblinding

Placebo and active medications were matched in odor, taste, color and appearance to assure proper blinding throughout the trial for all patients.

4.5 Schedule of procedures

Per protocol version 4.0, the procedure/assessment schedule is displayed in Table 4-1.

Table 4-1: Schedule of procedures – Protocol version 4.0

	Days before randomization		Weeks after randomization							
TEST	≤10	≤3	1	2	3	4	6	8	12	13#
Review of diagnostic CMR[1] by Core lab	X								X	
Consent[2]		X								
Clinical assessment		X			X		X		X	X
Demographics		X							X	

	Days before randomization		Weeks after randomization							
TEST	≤10	≤3	1	2	3	4	6	8	12	13#
Medical History		X							X	
Vital signs[3]		X	X	X	X	X	X	X	X	X
ECG		X	X	X	X	X	X	X	X	X
NYHA classification		X					X		X	X
KCCQ		X							X	
C-SSRS		X							X	
Randomization[4]		X								
Study medication[5]	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX									
Study Rx dose adjustment and accountability			X	X	X	X	X	X	X[6]	
Concomitant Rx		X	X	X	X	X	X	X	X	X
AE and SAE recording[7]	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX									

	Days before randomization		Weeks after randomization							
LABORATORY	≤10	≤3	1	2	3	4	6	8	12	13#
Local laboratory[8]										
CBC		X		X			X		X	X
Glucose		X								
ALT/AST		X	X	X	X	X	X	X	X	X
Alkaline Phosphatase		X	X	X			X		X	X
Bilirubin		X	X	X	X	X	X	X	X	X
Creatinine/eGFR		X		X			X		X	X
INR		X		X			X		X	X
Pregnancy Test[9]		X								
Hs-troponin[10]		X								
Central laboratory[11]										
Hs-troponin		X	X	X	X	X	X		X	
NT-proBNP		X	X	X	X	X	X		X	
Ferritin		X	X	X	X	X	X		X	
IL-1 beta, IL-6, IL-10		X	X	X	X	X	X		X	
IL-18		X	X	X	X	X	X		X	

	Days before randomization		Weeks after randomization							
LABORATORY	≤10	≤3	1	2	3	4	6	8	12	13#
TNF-alpha		X	X	X	X	X	X		X	
Hs-CRP		X	X	X	X	X	X		X	
sVCAM-1		X	X	X	X	X	X		X	
TGF-beta (beta 1 and beta 2)		X	X	X	X	X	X		X	
Retention of frozen plasma for CBD levels		X			X		X		X	

 # For French sites, week 13 was performed 30 days after the week 12 visit

[1] Diagnostic CMR in all patients within 10 days of randomization

[2] Patient consent form including CMR for patients diagnosed by EMB, request to use diagnostic CMR and/or biopsy data

[3] Vital signs include heart rate, blood pressure and weight; height at baseline

[4] Randomization after all baseline assessments, including local laboratory tests, have been completed

[5] Start of study drug in the evening of Day 1 after randomization according to treatment schedule

[6] At final visit accountability only

[7] Adverse Event recording starts after informed consent is obtained

[8] All local laboratory assessments at baseline, including hs-troponin, to be performed before randomization

[9] Pregnancy test in women with childbearing potential only.

[10] Hs-troponin for diagnostic evaluation assessed locally at baseline only

[11] Retention of frozen plasma for central laboratory analyses

Differences between protocol versions 3.4 and 4.0 on the scheduling of study visits/procedures, and the (potential) impact on the Statistical Analysis plan:

- The following biomarkers markers were added under protocol version 4.0: IL-18, sVCAM-1, TGF beta (beta 1 and beta 2).
- The following examinations were removed from baseline and at 12 weeks under protocol version 4.0: 24-hr Holter assessments and the requirement to perform a chest x-ray at baseline and at week 12.

Impact on the Statistical Analysis Plan:

The biomarkers IL-18, sVCAM-1, TGF beta (beta 1 and beta 2) were not analyzed by the central core laboratory.

The 24-hr Holter results and chest x-ray findings performed at baseline and week 12 for the two patients included under protocol version 3.4 will not be analyzed – data collected for the patients concerned will be displayed for information only in the appendix.

5 ANALYSIS POPULATIONS

The study protocol planned for the following analysis populations:

5.1 Modified Intention-to-Treat (mITT)

The modified Intention-to-treat (mITT) analysis set will include all randomized patients who started the IMP and for whom the CMR core laboratory confirmed the diagnosis of Myocarditis on the baseline CMR (see column 'Comments' in the source CMR files recorded as 'Rejected myocarditis diagnosis'). The primary analysis will be done on the mITT analysis population and a sensitivity analysis will be performed on the ITT analysis population - patients will be analyzed in the treatment arm to which they were randomized.

5.2 Intention to Treat (ITT)

The ITT analysis population will include all randomized patients who started the IMP – patients will be analyzed in the treatment arm to which they were randomized.

5.3 Safety analysis set

All randomized patients who started the IMP will be included in the Safety set. Patients will be analyzed in the treatment arm corresponding to the first IMP dose group actually taken. Any (temporary) treatment switch will be reviewed during BDRM.

6 BLIND DATA REVIEW MEETING

The blind data review meeting (BDRM) will take place prior to the locking of the clinical database.

7 DESCRIPTION OF STUDY POPULATION

7.1 Patient disposition

Patient disposition will be summarized in a CONSORT diagram and will include # pre-screened, # signed informed consent, # screening failures and main reasons and per assigned treatment arm, # randomized, # randomized to active and placebo, # started IMP, # who stopped IMP prematurely and # who completed the trial as planned.

Patient enrolment by site will be tabulated by protocol amendment and overall. It will provide the number of patients in the ITT analysis population and the number of patients in the mITT analysis population for each site.

7.2 Description of Demographic and Baseline characteristics

A baseline variable is defined as data obtained / collected prior to or on the same day as randomization but prior to the start of the IMP. Baseline characteristics / demographics will be summarized as either continuous or categorical variables (as appropriate) as described in section 11.1. Baseline information will be summarized for the mITT and ITT analyses populations.

If two baseline values are available for any given variable, the closest value obtained prior to the start of the IMP will be presented as the baseline value. The baseline variables which will be tabulated are shown in the following tables:

7.2.1 Demographics

Variable label:	**Comment / category labels:**
Gender	Tabulate as categorical variable = Male / Female.
Age	Take as (year of randomization – year of birth). Tabulate as continuous variable.
Race	Tabulate as categorical variable = American Indian or Alaska Native / Asian / Black or African American / Native Hawaiian or Other Pacific Islander / White / Unknown or not reported / other / Multiple (if more than one choice has been selected).
Ethnicity	Tabulate as categorical variable = Hispanic or Latino / Non Hispanic or Latino / Unknown or not reported

7.2.2 Diagnosis & disease status

Variable label:	**Comment / category labels:**
Acute myocarditis diagnosed since (days)	Taken as date of randomization – Date of diagnosis. Tabulate as continuous variable.
Confirmed Myocarditis (CMR evaluation)	Tabulate as categorical variable = No / Yes. The source CMR data files will be used to extract this data using column 'Comments' recorded as 'Rejected myocarditis diagnosis' or empty
Did the cardiac biopsy show cellular inflammation and/or immunohistochemistry consistent with inflammation due to acute myocarditis?	Tabulate as categorical variable = Yes / No. N(%) of available values to be taken relative to number of patients for whom EMB was performed.
Hematocrit result from the eCRF (%)	Tabulate as continuous variable. The most recent Hematocrit result performed
Hospitalized for this acute myocarditis episode	Tabulate as categorical variable = Yes / No.
Hospitalization duration (days)	Take as date of discharge – date of admission +1. Tabulate as continuous variable. N(%) of available values to be taken relative to number of hospitalized patients.
ICU duration (days)	Tabulate as continuous variable. N(%) of available values to be taken relative to number of hospitalized patients.

Variable label:	Comment / category labels:
Clinical signs / symptoms present when myocarditis was diagnosed • chest pain • Arrhythmia • Shortness of breath • History of viral-like illness • Elevated troponin levels	Tabulate as number of patients with the symptom ticked as 'Yes'
Patients with maximum cTn value above Upper Range Limit	Tabulate as number of patients. N(%) of available values to be taken relative to number of patients with elevated troponin levels.

7.2.3 CMR

Variable label:	Comment / category labels:
ECV	Tabulate as continuous variable in %.
GLS	Tabulate as continuous variable in %.
LVEF	Tabulate as continuous variable in %.
LVEDV	Tabulate as continuous variable in mL.
LVESV	Tabulate as continuous variable in mL.
LAESV	Tabulate as continuous variable in mL.
LV mass	Tabulate as continuous variable in g.
LGE mass	Tabulate as continuous variable in g.
Global LV myocardial T1	Tabulate as continuous variable in milliseconds.
Global LV myocardial T2/ Degree of edema	Tabulate as continuous variable in milliseconds.
Presence of regional T1	Tabulate as categorical variable = Yes / No / Difficult to comment or empty.
Presence of regional T2	Tabulate as categorical variable = Yes / No / Difficult to comment or empty.

The source CMR data files will be used to extract the quantitative CMR data, i.e. all CRM parameters except for presence of regional T1 and presence of regional T2.

7.2.4 Cardiovascular history

Variable label:	**Comment / category labels:**
History of documented acute myocardial infarction (AMI)	Tabulate as categorical variable = Yes / No / Unknown.
Previous diagnosis of heart failure	Tabulate as categorical variable = Yes.
New York Heart Association (NYHA) class	Tabulate as categorical variable = class I / class II / class III / class IV.
History of atrial fibrillation/flutter	Tabulate as categorical variable = Yes.
History of supraventricular tachycardia?	Tabulate as categorical variable = Yes.
History of sustained ventricular arrhythmia?	Tabulate as categorical variable = Yes.
History of peripheral vascular disease?	Tabulate as categorical variable = Yes.
Cardiovascular procedure history	
Previous percutaneous coronary intervention (PCI)	Tabulate as categorical variable = Yes.
Previous coronary artery bypass grafting (CABG)	Tabulate as categorical variable = Yes.
Implantable cardioverter-defibrillator(s) (ICD) implanted	Tabulate as categorical variable = Yes.
Cerebrovascular and Renal history	
History of stroke	Tabulate as categorical variable = Yes.
History of transient ischemic attack (TIA)?	Tabulate as categorical variable = Yes.
Presence of chronic kidney disease defined as eGFR < 60 mL/min/1.73m²	Tabulate as categorical variable = Yes.
Cardiovascular risk factors	
Treated for hypertension	Tabulate as categorical variable = Yes.
Diabetes mellitus	Tabulate as categorical variable = Type 1 / Type 2.
Treated for hyperlipidemia	Tabulate as categorical variable = Yes.
Lifestyle	
Tobacco use	Tabulate as categorical variable = Never / Former / Current
Alcohol consumption	Tabulate as categorical variable = <1 drink/week / 1 - 7 drinks/week / 8 - 14 drinks/week / >14 drinks/week / Does not want to answer
Cannabinoids consumption	Tabulate as categorical variable = Never / Former / Current
Covid-19 History	
Diagnosed with COVID-19	Tabulate as categorical variable = Yes.
Vaccinated for COVID-19	Tabulate as categorical variable = Yes.

7.2.5 Other medical history

Medical history data reported as free text will be coded by system organ class and preferred term, using the MedDRA dictionary. Medical history will be summarized by System Organ class (SOC). Data will be presented in alphabetic order, by system organ class, as well as by incidence of preferred term. The N and % of patients will be presented where: N is the number of patients who present at least one occurrence of diagnosis/symptom concerned and % is the percentage of patients.

7.2.6 Vital signs

Variable label:	**Comment / category labels:**
Body height	Tabulate as continuous variable in meters.
Body weight	Tabulate as continuous variable in kg.
Body Mass Index (BMI)	Tabulate as continuous variable in kg/m^2. Estimated as baseline weight in kilograms divided by the squared baseline height in meters.
Systolic blood pressure	Tabulate as continuous variable in mm Hg.
Diastolic blood pressure	Tabulate as continuous variable in mm Hg.
Heart rate	Tabulate as continuous variable in beats/min

7.2.7 Physical examination

Variable label:	**Comment / category labels:**
Skin	Tabulate as categorical variable = Abnormal (clinically significant).
HEENT	Tabulate as categorical variable = Abnormal (clinically significant).
Chest and respiratory system	Tabulate as categorical variable = Abnormal (clinically significant).
Heart	Tabulate as categorical variable = Abnormal (clinically significant).
Peripheral vascular system	Tabulate as categorical variable = Abnormal (clinically significant).
Abdomen	Tabulate as categorical variable = Abnormal (clinically significant).
Musculo-skeletal system	Tabulate as categorical variable = Abnormal (clinically significant).
Central nervous system	Tabulate as categorical variable = Abnormal (clinically significant).

7.2.8 12-lead Electrocardiogram (ECG)

Variable label:	**Comment / category labels:**
Ventricular rate	Tabulate as continuous variable in beats/min.
RR interval	Tabulate as continuous variable in milliseconds.
PR interval	Tabulate as continuous variable in milliseconds.
QRS interval	Tabulate as continuous variable in milliseconds.
QT interval	Tabulate as continuous variable in milliseconds.
QTc interval (Fridericia's formula)	Tabulate as continuous variable in milliseconds.
Patients with abnormal ECG	Tabulate as categorical value = Yes. A Listing of ECG abnormalities considered clinically significant will be provided.

7.2.9 Laboratory test results

The date and time when the laboratory tests were performed in addition to the laboratory test results as entered in eSOCDAT will be used. A baseline laboratory sample is defined as a blood sample where the blood draw date / time is < the start of IMP. All available, baseline laboratory test results will be presented for:

7.2.9.1 Chemistry:

Creatinine, eGFR, Total bilirubin, Aspartate-Amino-Transferase (AST), Alanine Transaminase (ALT), Alkaline phosphatase, Glucose.

The e-GFR will be calculated using the abbreviated CKD-EPI Creatinine Equation (2021) formula:

If Scr >= k: $eGFR\ (mL/min/1.73m2) = 142 \times (Scr/k)^{-1.2} \times 0.9938^{Age} \times 1.012$ [if female]

Else: $eGFR\ (mL/min/1.73m2) = 142 \times (Scr/k)^{\alpha} \times 0.9938^{Age} \times 1.012$ [if female]

where:

Scr = serum creatinine in mg/dL

k = 0.7 (females) or 0.9 (males)

Age (years)

α = -0.241 (female) or -0.302 (male)

7.2.9.2 Hematology:

Red Blood Cell Count, Hemoglobin, Hematocrit, Platelets count, White Blood Cell count (WBC), Monocytes, Lymphocytes, Neutrophils, Eosinophils, Basophils and International Normalized Ratio (INR)

7.2.9.3 Cardiac Biomarkers:

hs-Troponin I, hs-Troponin T analyzed by the local hospital laboratories will also be presented.

The local laboratory test results will be converted into SI units as displayed in Table 7-1

Table 7-1: SI units to be used

Assay	**SI unit**
Creatinine	mg/dL
eGFR	mL/min/1.73m^2
Total bilirubin	mg/dL
Aspartate-Amino-Transferase (AST)	U/L
Alanine Transaminase (ALT)	U/L
Alkaline phosphatase	U/L
Glucose	mg/dL
Red Blood Cell Count	10^6/µL
Hemoglobin	g/dL
Hematocrit	%
Platelets count	10^3/µL
White Blood Cell count (WBC)	10^3/µL
Monocytes	10^3/µL
Lymphocytes	10^3/µL
Neutrophils,	10^3/µL
Eosinophils	10^3/µL
Basophils	10^3/µL
International Normalized Ratio (INR)	No unit
Hs-Troponin I	ng/L
Hs-Troponin T	ng/L

The local laboratory normal ranges will be used to identify assays for which the results are either within, above or below the local normal range.

Assays reported as '<XXX' will be imputed to 0 (e.g. hs-Troponin T <14 ng/L → value imputed as 0).

7.2.9.4 Additional laboratory tests analyzed by a central laboratory:

Altasciences is the central core laboratory tasked to perform the analyses for the following blood samples: CBD, hs-troponin T, NT-proBNP, inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10)

The central laboratory normal ranges as defined in Table 7-2 below will be used to identify assays for which the results are either within, above or below the local normal range.

Table 7-2: Central laboratory normal ranges

Assay	**Gender**	**Age (years)**	**Laboratory normal ranges**
hs-troponinT	M/F		≤14 ng/L
hs-CRP	M/F		≤ 3 mg/L
NT-proBNP	M/F		≤125 pg/mL
TNF-alpha	M/F		0 – 2.2 pg/mL
interleukin 1-beta	M/F		< 1.0 pg/mL
interleukin 6	M/F		0 – 13 pg/mL
interleukin 10	M/F		4.8 – 9.8 pg/mL (ELISA)
Ferritin	M	18 – 29	30 – 334 µg/L
	M	30 – 39	30 – 453 µg/L
	M	40 – 49	30 – 537 µg/L
	M	50 – 59	30 – 543 µg/L
	M	60 – 69	30 – 517 µg/L
	M	≥70	30 – 441 µg/L
Ferritin	F	18 – 29	30 – 105 µg/L
	F	30 – 39	30 – 109 µg/L
	F	40 – 49	30 – 125 µg/L
	F	50 – 59	30 – 223 µg/L
	F	60 – 69	30 – 289 µg/L
	F	≥70	30 – 287 µg/L

The results for these assays will be available in early June 2025.

The central laboratory normal ranges will be used to identify assays for which the results are either within, above or below the local normal range.

Assays reported as '<XXX' will be imputed to 0 (e.g. hs-Troponin T< LLOQ → value imputed as 0).

Only the unblinded statistician will have access to this data prior to DB lock and unblinding because of the potential of unblinding.

7.2.9.5 Laboratory test results at baseline

For all assays listed above, the results will be tabulated as follows:

- Standard descriptive statistics for continuous variables.
- Standard descriptive statistics for categorical variables for values that are below the lower limit of normal / within normal range / above the upper limit of normal.
- For all baseline laboratory test data which are gender dependent – i.e. Alkaline phosphatase, ALT, AST, Basophils, creatinine, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Platelets count, INR, HGB, HCT, RBC and WBC – standard descriptive statistics for continuous variables will be tabulated separately for men and women.

7.2.10 Concomitant medications

Concomitant medications/treatments will be coded using the WHO Drug dictionary with the primary Anatomical Therapeutic Chemical (ATC) classification selected based on the route and indication.

All medication prescribed prior to the first dose of IMP intake, i.e. concomitant treatments with a stop date/time before the date/time of first IMP intake will be classified as medications prescribed prior to the first dose of IMP intake.

For the purpose of classify medication, incomplete medication start and stop date will be imputed as detailed in Section 11.6.2.

Prior, baseline and concomitant medications will be summarized by providing the N and percentage of patients by therapeutic class (ATC second level, e.g. C03: Diuretics) sorted in alphabetical order of the therapeutic class.

All prior, baseline and medications prescribed as of the first IMP intake will be listed by study center, and patient number.

7.2.11 KCCQ Questionnaires

The KCCQ item response is coded 1, 2, 3, etc. with 1 denoting the 'worst' response (most severe/limited/etc.). The intermediate scores and the overall summary score (from 0 – worst score to 100 - best score) will be calculated in the following manner (as taken from the KCCQ documentation):

Score label	**Value**	**remark**
Physical limitation (0-100)	PL = 100*(mean(Q1a,Q1b,Q1c,Q1d,Q1e,Q1f)-1)/4	At least 3 non-null sub-questions, score is null otherwise.
Symptom stability (0-100)	SS = 100*(Q2-1)/4	If Q2 value is 6 then use 3 as value.
Symptom frequency (0-100)	SF = 100* (mean((Q3-1)/4,(Q5-1)/6,(Q7-1)/6,(Q9-1)/4))	At least 2 non-null sub-questions, score is null otherwise.
Symptom burden (0-100)	SB = 100*(mean(Q4,Q6,Q8)-1)/4	If Q4, Q6 or Q8 value is 6 then use 5 as corresponding value.
Self-efficacy (0-100)	SE = 100*(mean(Q10,Q11)-1)/4	
Quality of Life (0-100)	QL = 100*(mean(Q12,Q13,Q14)-1)/4	
Social limitation (0-100)	SL = 100*(mean(Q15a,Q15b,Q15c,Q15d)-1)/4	At least 2 non-null sub-questions, score is null otherwise.
Total symptom score (0-100)	TS = mean (SF,SB)	
Clinical summary score (0-100)	CS = mean (PL,TS)	
Overall summary score (0-100)	OS = mean(PL,TS,QL,SL)	

The baseline KCCQ summary scores, i.e Total symptom score, Clinical summary score and Overall summary score, will be summarized as a continuous variable.

7.2.12 C-SSRS Questionnaires

Variable label:	**Comment / category labels:**
C-SSRS – Suicidal Ideation in Lifetime	Count of patients with Yes to any question 1-5 in C-SSRS questionnaire in Lifetime
C-SSRS – Most severe ideation in Lifetime	Tabulate as continuous variable (1-5)
C-SSRS – Suicidal behavior	Count of patients with Yes to any suicidal behavior questions in C-SSRS questionnaire in Lifetime

8 EFFICACY ANALYSES

The primary and secondary efficacy analyses will be performed on the mITT analysis population. In addition, a sensitivity analysis will be performed on the ITT analysis population for the primary outcome.

For all primary and secondary efficacy outcomes, statistical descriptive statistics will be provided by visit on the absolute value and on the change from baseline.

8.1 Primary efficacy analysis

For each of the primary outcomes, i.e. Extracellular volume (ECV) and Global Longitudinal Strain (GLS), the respective value at 12 weeks will be compared between the active and the placebo groups, applying an ANCOVA analysis adjusted for the respective baseline value.

SAS-code:

```
proc glm data=labdata;
      class trt;
      model val_12w = val_bl trt / solution;
      lsmeans trt /pdiff ;
run;
```

where:

trt = 1 (Active) or 0 (Placebo)

val_12w = Value at 12 weeks (ECV or GLS)

val_bl = Value at baseline (ECV or GLS)

The two primary outcomes will be considered statistically significant following the Hochberg Procedure.(Benjamini and Hochberg 1995):

- The p-values for the two tests (for ECV and GLS, respectively) will be ordered in size (p1 ≤ p2. Let H1 and H2 the corresponding Alternative Hypotheses). p2 will be compared to a significance level of 5%.
- If p2 ≤ 5%, both Alternative Hypotheses will be proven (H1 and H2)
- If p2 >5% and p1 ≤ 2.5%, the corresponding Alternative Hypothesis of the smaller p-value (H1) will be proven.

8.2 Secondary efficacy analysis

The secondary analysis will be done on the mITT analysis population - patients will be analyzed in the treatment arm to which they were randomized.

Contrary to what stated in the protocol amendment 2 no sensitivity analysis will be performed for the secondary analysis.

For the secondary efficacy analysis, the Left ventricular ejection fraction (LVEF) at 12 weeks will be compared between the active and the placebo groups, applying an ANCOVA analysis, adjusted for the baseline LVEF value.

8.3 Other efficacy analyses

The other efficacy analyses will be done on the mITT analysis population - patients will be analyzed in the treatment arm to which they were randomized.

8.3.1 CMR related

The changes from baseline at the week 12 visit for the following CMR data will be compared between the active and placebo groups: Left ventricular end-diastolic volume (LVEDV), Left ventricular end-systolic volume (LVESV), Left atrial end-systolic volume (LAESV), Left ventricular mass (LV mass), Late gadolinium enhancement (LGE mass) and degree of edema (T2). The data will be analyzed using the same ANCOVA analysis as that for the primary analysis.

8.3.2 KCCQ

The change in KCCQ summary scores from baseline at the week 12 visit between the two treatment groups will be analyzed using the same ANCOVA analysis as that for the primary analysis.

8.3.3 NYHA class

The number and percentage of patients in each of the NYHA class ranks at each visit (baseline, week 6, week 12 and final study visit) will be tabulated by treatment group.

The overall effect of treatment on NYHA rank at 12 weeks will be evaluated by ordered polytomous regression using treatment and baseline NYHA class (separated into dummy binary variables, NYHA class I being the reference) as covariate.

Example SAS-code:

```
proc logistic data=categdata;
      class trt (ref='Placebo') nyha2_bl nyha3_bl   / param=reference ;
      model nyha_w12 = drug nyha2_bl nyha3_bl  ;
      ods output OddsRatios=Odds Globaltests=pvalue
      ParameterEstimates=model;
run;
```

where:

trt = Active or Placebo

nyha2_bl = 1 if baseline NYHA is Class II 0 otherwise

nyha3_bl = 1 if baseline NYHA is Class III 0 otherwise

nyha_w12 = NYHA class at Week 12

8.3.4 Efficacy laboratory assays

The changes from baseline and up to the week 12 visit for the following assays analyzed by the central blood core laboratory will be analyzed using the area under the curve value (AUC) analysis: CBD, hs-troponin T, NT-proBNP, inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10)

The area under the curve (AUC in laboratory unit * weeks) of each laboratory assay will be calculated using the trapezoid rule – i.e. as the sum of the areas of the trapezoids above zero up to the 12 weeks visit. Nominal time points (baseline as T=0 and week 1,2,3,4,6,12 as T=1,2,3,4,6,12) will be used to calculate the AUCs. The AUC

will only be calculated for each assay for the patients who have at least the baseline and the week 12 visit values.

The effect of treatment will be done using an ANCOVA analysis adjusted for the baseline value. The results for these assays will be available by mid-June 2025.

8.3.5 Time to event analysis

For all events defined below, the time to event estimated as the time from IMP start up to the first occurrence of the event concerned will be summarized as a continuous variable.

For each event, the hazard ratio (relative to placebo) and the p-value from the log-rank test will be given. In the case of no event, the patient will be censored at the last study visit performed.

The events of interest defined in the protocol are:

- Time to the first major event. A major event of interest is defined as cardiac transplant identified with MedDRA PT code 10019314 Heart transplant, LVAD identified with MedDRA PT code 10052371 Ventricular assist device insertion, any hospitalization for heart failure identified with MedDRA SMQ code 20000004 Cardiac Failure.
- Time to normalization of high sensitivity troponin (hs-troponin T), N-terminal pro B-type naturetic peptide (NT-proBNP) and inflammatory markers: high sensitivity C reactive protein (hs-CRP), ferritin, tumour necrosis factor alpha (TNF-alpha), interleukin 1-beta (IL-1 beta), interleukin 6 (IL-6), interleukin 10 (IL-10). This applies only to patients with an abnormal corresponding assay at baseline. Time to normalization will be estimated in days as the time between IMP start date up to the first blood draw date when laboratory results normalized. Normalization will be defined as follows:

Table 8-1: Normalization

Assay	**Gender**	**Age (years)**	**Normalization criteria**
hs-troponinT	M/F		≤14 ng/L
hs-CRP	M/F		≤ 3 mg/L
NT-proBNP	M/F		≤125 pg/mL

Assay	Gender	Age (years)	Normalization criteria
TNF-alpha	M/F		≤ 2.2 pg/mL
interleukin 1-beta	M/F		< 1.0 pg/mL
interleukin 6	M/F		≤ 13 pg/mL
interleukin 10	M/F		4.8 – 9.8 pg/mL (ELISA)
Ferritin	M	18 – 29	30 – 334 µg/L
	M	30 – 39	30 – 453 µg/L
	M	40 – 49	30 – 537 µg/L
	M	50 – 59	30 – 543 µg/L
	M	60 – 69	30 – 517 µg/L
	M	≥70	30 – 441 µg/L
Ferritin	F	18 – 29	30 – 105 µg/L
	F	30 – 39	30 – 109 µg/L
	F	40 – 49	30 – 125 µg/L
	F	50 – 59	30 – 223 µg/L
	F	60 – 69	30 – 289 µg/L
	F	≥70	30 – 287 µg/L

If laboratory result had not normalized at 12 week visit date patients concerned will be censored at the last study visit performed.

The results for these assays will be available in early June 2025.

- The biomarkers IL-18, sVCAM-1, TGF beta (beta 1 and beta 2) were not analyzed by the central core laboratory.
- Time to resolution of clinical symptoms, including chest pain, arrhythmias, shortness of breath will not be analyzed.
- Time to normalization of electrocardiogram (ECG) abnormalities which applies only to patients with an abnormal ECG at baseline will not be analyzed.

8.4 Subgroup analyses

Subgroup analyses will be performed for the following baseline variables:

- NYHA class (I vs. II + III)
- Treated for Hyperlipidemia (Yes vs. No)
- Treated for Hypertension (Yes vs. No)

The sub-group analyses will be performed on the mITT analysis population for the primary endpoint and the main secondary endpoint, i.e LVEF.

For each subgroup variable, a statistical test of interaction will be performed to test whether there is evidence of heterogeneity between subgroups.

9 SAFETY ANALYSIS

The Safety analysis set will be used for all safety analysis

9.1 Adverse events (AEs)

The number of adverse events and percentage of patients with at least one adverse event will be summarized per treatment group by system organ class and by preferred terms (MedDRA). Difference in proportion between the treatment groups will be compared using a chi-square test.

AEs will be considered as treatment - emergent adverse events (TEAE) if the event onset date and time is > start date and time of the IMP.

9.2 Serious Adverse events (AEs)

The number of Serious Adverse Events (SAE) and percentage of patients with at least one SAE be summarized per treatment group by system organ class and by preferred terms (MedDRA). Difference in proportion between the treatment groups will be compared using a chi-square test.

9.3 Change in C-SSRS

The number of patients and percentage of patients with worsening C-SSRS ideation and behavior scores compared to baseline will be summarized. The difference in proportions between the treatment groups will be compared using a chi-square test.

9.4 Laboratory parameters.

Descriptive statistics of absolute values and change from baseline for laboratory test results from local lab, including liver function parameters and INR, will be presented per treatment group and by follow-up time points during the entire study period (i.e. up to the final visit). Differences between the treatment groups will be done on the absolute value up to the 12 weeks visit using a mixed-model for repeated-measures including terms for treatment, baseline, time and treatment-by-time with an unstructured covariance matrix to model the within-patient variability.

The number and percentage of patients with changes in laboratory test values above or below the site normal ranges over the follow-up period i.e. within normal range at baseline and during the trial above or below the normal range using the site local reference ranges will be summarized per treatment group and by assay concerned.

9.5 ECG parameters.

Descriptive statistics of absolute values and change from baseline of ECG intervals and rhythm during the entire study period (i.e. up to the final visit) will be provided. Differences between the treatment groups up to the 12 weeks visit will be done on the QTc absolute value using a mixed-model for repeated-measures including terms for treatment, baseline, time and treatment-by-time with an unstructured covariance matrix to model the within-patient variability.

9.6 Vital signs.

Descriptive statistics of absolute values and change from baseline will be presented by follow-up time point during the entire study period (i.e. up to the final visit).

10 COMPLIANCE

10.1 Compliance with inclusion/exclusion criteria

The patients who were randomized and for whom protocol deviation as “Inclusion/exclusion criteria not respected” has been reported be presented as a summary table and listing.

10.2 Overall IMP exposure

The overall IMP exposure will be presented using the variables listed below:

Variable	Formula
Total dose planned (mL) based on visits actually performed [PLANNED_DOSE]	weight *[kg]* * $\sum_{i=1}^{7}$ (planned dose *[in mg/kg bid]* documented at visit i * 2 * (visit date (i+1)-visit date (i))) / 950 *[mg/mL]*

Total dose taken (mL)
 	
[DOSE_TAKEN]
	$\sum_{j=1}^{\#\ bottles\ returned} \frac{78\ \text{g} - \text{bottle weight in g (j)}}{0.95\ [\text{g/mL}]}$
	If there is no bottle weight and the reason is:
	• 'Bottle broken', imputed weight to 48g
	• 'Unused bottle', imputed weight to 78g
	Note: 'Already weighted' should not be considered.
	
	$+ \sum_{k=1}^{\#\ bottles\ unreturned} \frac{78\ \text{g} - \text{imputed bottle weight (k)}}{0.95\ [\text{g/mL}]}$
	Imputed weight if the status of the unreturned IMP bottle is:
	• 'Unused', imputed weight to 78g
	• 'Empty', imputed weight to 48g
	• Other reasons, i.e., 'Used per instructions', 'Not used per instructions' (none reported), 'Unknown' have been reviewed during BDRM held on 08-Apr-2025 and the bottle weight will be imputed as follows:
	  • 'Used per instructions', imputed weight to 48g
	  • 'Unknown', imputed weight to 78g

Compliance global (%)	[DOSE_TAKEN] / [PLANNED_DOSE]
# days during which patients were taking the IMP	Last date under medication – first date under medication – the sum of all temporary interruption (end date of interruption – start date of interruption +1)
# patients who did not complete 12 weeks on IMP	# of patients with Premature withdrawal of study treatment form completed before the Week 12 visit date
# patients with highest tolerated IMP dose up to Week 12	# of patients for whom the highest tolerated IMP dose taken up to the week 12 visit date was: • 10mg/kg of body weight b.i.d. • 7.5mg/kg of body weight b.i.d. • 5.0mg/kg of body weight b.i.d. • 2.5mg/kg of body weight b.i.d. As discussed during the BDRM held on 8-Apr-2025, if any dose reduction occurred within 7 days then the last lower dose will be

Variable	Formula
	considered as the highest tolerated dose. This will be the case for all patients listed in tables 5.6 and 5.7 of the BDRM report v2.0

10.3 Deviations

The total number of deviations will be reported and in addition, deviations will be presented by Important / non-important deviations.

11 GENERAL STATISTICAL PRINCIPLES

11.1 Standard descriptive statistics

The analyses will be presented/reported using summary tables, figures, and data listings – see section 12.

For continuous variables:

- Normally distributed data will be summarized by study group with counts, means, standard deviations, medians, Interquartile range, minimums, and maximums.
- Non-normally distributed continuous variables: only median, 25%- and 75%-quartiles will be presented.
- In case of log-transformation due to non-normal data continuous variables will be presented with geometric means and its 95% confidence interval.

Categorical variables will be summarized by study group with counts and percentage of patients.

All analyses and tabulations will be performed using SAS Version 9.4 on a PC platform. Table, listings, and figures will be presented in RTF or Microsoft Word format. Upon completion, primary endpoints results will be validated by an independent programmer. In addition, all program output will undergo a senior level statistical review.

11.2 Models' feasibility check

If the model assumptions are not met, log transformations or a non-parametric test will be considered.

11.3 Handling of missing data

No imputation will be performed for missing data. Missing data will be considered as missing at random.

11.4 Precision

The precision of original measurements will be maintained in summaries. Where possible means, medians and standard deviations will be presented with an increased level of precision; means and medians will be presented to one more decimal place compared to the raw data, and the standard deviations will be presented to two more decimal places compared to the raw data.

Percentages will be presented based on available data and denominators will not include missing values.

For frequency counts of categorical variables, categories where counts are zero will be displayed for the sake of completeness. For example, if none of the patients discontinue due to "lost to follow-up," this reason will be included in the table with a count 0. Categories with zero counts will not have zero percentages displayed.

11.5 Standard Calculations

Variables requiring calculation will be derived using the following formulas:

Study day – For a given date (date), study day is calculated as days since the date of first dose of IMP (firstdose):

- Study day = date – firstdose + 1, where date ≥ firstdose
- Study day = date – firstdose, where date < firstdose

Days – Durations, expressed in days between one date (date1) and another later date (date2), are calculated using the following formula: duration in days = (date2-date1). This is because study intake starts during the afternoon and ends in the morning.

Weeks – Durations, expressed in weeks between one date (date1) and another later date (date2), are calculated using the following formula: duration in weeks = (date2-date1)/7.

Months – Durations, expressed in months between one date (date1) and another later date (date2), are calculated using the following formula: duration in months = (date2-date1)/30.4.

11.6 Imputation of Dates

11.6.1 Adverse events

If year is present and month and day are missing (e.g XX-XXX-2020)

- If year = year of first dose, then set month and day to month and day of first dose unless end date is before date of first dose, in which case the onset date is set to 28 days prior to end date.
- If year < year of first dose, then set month and day to December 31st.
- If year > year of first dose, then set month and day to January 1st.

If month and year are present and day is missing (e.g XX-Jun-2022)

- If year = year of first dose and if month = month of first dose then set day to day of first dose date unless end date is before date of first dose, in which case the onset date is set to 28 days prior to end date.
- if month < month of first dose then set day to last day of month
- if month > month of first dose then set day to 1st day of month
- if year < year of first dose then set day to last day of month
- if year > year of first dose then set day to 1st day of month

11.6.2 Concomitant Medications

- If start date is completely missing: start date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing): set month and day to January 1.

Any partial dates will be displayed in data listings without imputation.

12 TABLES FIGURES AND LISTINGS

12.1 List of tables

Other efficacy endpoints

Subgroup analyses for the primary outcome

Safety related

Compliance related

12.2 List of figures

*XXX=Central blood core laboratory parameters i.e. CBD, hs-troponin T, NT-proBNP, inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10

Figure 6 – XXX up to Week 12 – mean change from baseline (SD)

*XXX=Central blood core laboratory parameters i.e. CBD, hs-troponin T, NT-proBNP, inflammatory markers (hs-CRP, ferritin, TNF-alpha, IL-1 beta, IL-6, IL-10

Figure 7 – XXX up to Week 13 – mean (SD)

*XXX=Local laboratory assay, ECG intervals and vital signs parameters

Figure 8 – XXX up to Week 13 – mean change from baseline (SD)

*XXX=Local laboratory assay, ECG intervals and vital signs parameters

Figure 9 – Subgroup analyses – Forest plot

12.3 List of listings

Listing 1 – ECG abnormalities considered clinically significant reported at enrolment

Listing 2 – Inclusion/Exclusion criteria not met