STATISTICAL ANALYSIS PLAN
Protocol Cardiol 100-004

I**M**pact of C**A**rdiolRx™ on Recurrent P**ERIC**arditis – An open label **Pilot** Study

Protocol Number: **(Version Date)**	Cardiol 100-004 Amendment 2 (18 January 2023)
Name of Test Drug:	CardiolRx™
Phase:	II
Methodology:	Open label
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1.0	23-May-2024	N/A	Initial release	Emilie Perrin, Sophie de Brouwer
2.0	11-Jul-2024	2.1 Section 7 (SSA) Section 8	Correct typo in protocol number Per Cardiol's request, the following changes were made: - Concomitant medications: added that descriptive analysis will be performed for medications ongoing at enrollment and / or started up to (including) the Week 8 visit date which was prescribed for pain and pericarditis - Qualifying CRP values: Display (descriptive analysis) for data relating to the qualifying CRP values - Baseline CRP values: Provide summary statistics for patients enrolled with a baseline CRP ≥1 mg/dL - Analyses initially requested for the SSA: Remove the analyses requested concerning the N (%) enrolled because of pericardial inflammation assessed by delayed pericardial hyperenhancement on CMR and had qualifying CRP < 1 - section 8.3.10, precision added concerning the imputation of CRP values reported as '<XX' - section 8.5.2, precision added concerning the methodology used to calculate time to CRP normalization; time to normalization to be reported in days and not weeks	Emilie Perrin, Sophie de Brouwer

SIGNATURE PAGE

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Table of Contents

LIST OF IN-TEXT TABLES

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
b.i.d.	Twice daily
CI	Confidence interval
CMR	Cardiac magnetic resonance imaging
CRP	C-reactive protein
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EP	Extension period
FAS	Full Analysis Set
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
IWRS	Interactive Web Response System
ITT	Intention-to-treat
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
NSAID	Non-steroidal anti-inflammatory drug
PP	Per-Protocol
PT	Preferred Term
Q1	First quartile
Q3	Third quartile
SAE	Serious adverse event
SAF	Safety Set
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System Organ Class
SSA	Staged statistical analysis
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods for the analyses of the Cardiol 100-004 trial titled “Impact of CardiolRx™ on Recurrent Pericarditis”. This document was prepared using Protocol, version 1.2, Amendment 2, dated January 18, 2023 but has taken into consideration, where appropriate, protocol version 1.2 (Amendment 1) for patients who were enrolled under this protocol version. Where appropriate, the changes between Protocol amendments 1 and 2 which could potentially impact on the statistical analysis are detailed at the end of the section concerned.

Although not planned for by the study protocol, the statistical analysis for the Cardiol 100-004 trial will be done in a staged manner – i.e. the data collected up to the week 8 visit (i.e. visit 5) will be analyzed after this data is considered clean and complete. The outcomes to be included in this analysis are detailed in section 7. The final analysis will be performed after the last patient, last visit has taken place and the database is declared ‘fit’ (i.e. clean) to be locked.

The SAP will be finalized and signed before the analysis for the data collected up to week 8 starts.

2 OVERALL STUDY DESIGN, OJECTIVES AND OUTCOMES

2.1 Study design

Cardiol 100-004 was designed as a multi-center, open label Pilot Study. The trial protocol planned that approximately 25 patients would be enrolled.

2.2 Study Objectives

The primary objective was to evaluate the effect of treatment with CardiolRx™ on recurrent pericarditis.

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

2.3 Study endpoints

2.3.1 Primary efficacy endpoints

The primary efficacy endpoint was the change in patient-reported pericarditis pain using an 11-point NRS from baseline (highest pain score within the past 7 days of Day 1) to Week 8 (highest pain score during the past 7 days of the Week 8 visit).

2.3.2 Additional efficacy endpoints of interest

Per section 4.1.3 of the study protocol (Amendment 2), additional efficacy endpoints are:

- Pain score using 11-point NRS from baseline (highest pain score within the past 7 days of Day 1) to Week 26 (highest pain score during the past 7 days of Week 26)
- - Percentage of patients with normalized CRP levels at 8 weeks (for patients with CRP ≥ 1.0 mg/dL at baseline)
- - Percentage of patients with pericarditis recurrence during the EP
- - Percentage of patients with normalized CRP levels at 26 weeks (for patients with CRP ≥1.0 mg/dL at baseline)
- - Time to CRP normalization for patients with CRP ≥1.0 mg/dL at baseline
- - CRP change from baseline at 26 weeks (%)

2.3.3 Additional efficacy endpoint of interest in Protocol amendment 2

Compared to protocol version 1, the endpoint 'Percentage of patients with pericarditis recurrence during the extension period (EP)' was added in protocol amendment 2.

Impact on statistical Analysis Plan:

Given that the data to ascertain this outcome will be available for all enrolled patients, there is no impact on the SAP / analysis for this additional endpoint added per protocol amendment 2.

2.3.4 Safety endpoints

Per section 4.2.2 of the study protocol (Amendment #2), the safety outcomes will encompass the following:

- Occurrence of adverse / serious adverse events as of the start of the IMP through the last study visit.

- Change (from baseline) in C-SSRS at the end of patient follow-up – i.e. either at week 8 or week 26-week study visit.
- Change (from baseline) in laboratory parameters, including liver function parameters and INR at the end of patient follow-up – i.e. either at the week 8 or the week 26 study visit.
- Change (from baseline) in ECG intervals/findings parameters at the end of patient follow-up – i.e. either at the week 8 or the week 26-week study visit.

3 SAMPLE SIZE AND POWER

Please refer to section 11.1 of the study protocol amendment 2.

4 STUDY POPULATION

We present in this section, the inclusion/exclusion criteria as detailed in protocol amendment 2 and compare the changes to protocol amendment 1 to take into consideration the 6 patients enrolled under protocol amendment 1.

4.1 Inclusion Criteria

Per protocol amendment 2, the following inclusion criteria had to be met to be eligible for enrolment:

1. Male or female 18 years of age or older

2. Diagnosis of at least two episodes of recurrent pericarditis

3. At least 1 day with pericarditis pain ≥4 on the 11-point NRS within prior 7 days

4. One of

    a. CRP level ≥1.0 mg/dL within prior 7 days OR

    b. Evidence of pericardial inflammation assessed by delayed pericardial hyperenhancement on cardiac magnetic resonance imaging (CMR)

5. Currently receiving non-steroidal anti-inflammatory drugs (NSAIDs) and/or colchicine and/or corticosteroids for treatment of pericarditis (in any combination) in stable doses

6. Male patients 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.

7. 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 year absence of vaginal bleeding or spotting and confirmed by follicle stimulating hormone [FSH] ≥40 mIU/mL [or ≥ 40 IU/L] if less than 2 years postmenopausal) or be surgically sterile.

4.2 Exclusion Criteria

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

1. Diagnosis of pericarditis that is secondary to specific prohibited etiologies, including tuberculosis (TB); neoplastic, purulent, or radiation etiologies; post-thoracic blunt trauma (e.g., motor vehicle accident); myocarditis

2. Estimated glomerular filtration rate (eGFR) <30 mL/min

3. 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

4. Sepsis, defined as documented bacteremia at the time of screening or other documented active infection

5. Prior history of sustained ventricular arrhythmias

6. History of QT interval prolongation

7. QTc interval > 500 msec (please refer to Section 9.2.3 for bundle branch block, bifascicular block and paced rhythm correction)

8. Current participation in any research study involving investigational drugs or device

9. Inability or unwillingness to give informed consent

10. Ongoing drug or alcohol abuse

11. On any cannabinoid during the past month

12. Women who are pregnant or breastfeeding

13. Current diagnosis of cancer, with the exception of non-melanoma skin cancer

14. Any factor, which would make it unlikely that the patient can comply with the study procedures

15. Showing suicidal tendency as per the C-SSRS, administered at screening

16. On digoxin and/or type 1 or 3 antiarrhythmics

17. On immunosuppressive therapy with any of the following:

    a. Rilonacept

    b. Anakinra

    c. Canakinumab

    d. Methotrexate

    e. Azathioprine

    f. Cyclosporine

    g. IVIG

Difference between protocol amendments 1 and 2 re the selection criteria and the (potential) impact on the statistical Analysis

- Inclusion criterion #5 in Amendment 1 was as follows: Has received NSAIDs and/or colchicine and/or corticosteroids (in any combination) in stable doses for at least 3 days prior to enrolment

- Exclusion criteria 5 and 16 were not present in protocol amendment 1

Potential Impact on statistical Analysis Plan:

Patients included under protocol amendment 1 will be reviewed during Data Review Meeting to ascertain if they complied with protocol amendment 2 with respect to inclusion criterion 5 and exclusion criteria 5 and 16 per protocol amendment 2.

4.3 Study treatment assignment

Per protocol amendment 2, eligible patients would receive open label IMP (i.e. CardiolRx^{TM}). The dosing regimen was as follows:

- Day 1 p.m. to Day 3 a.m. dose: 5 mg/kg of body weight b.i.d. First dose to be taken in the evening of the screening visit (i.e. day 1)
- Day 3 p.m. dose to Day 10 a.m. dose: 7.5 mg/kg of body weight b.i.d. Dose titration if previous dose tolerated
- Day 10 p.m. dose to end of treatment period (a.m. dose at either week 8 or am dose week 26 if patient continued in the EP phase of the trial): 10 mg/kg of body weight b.i.d. Dose titration if previous dose tolerated

The morning and evening doses should be taken minimally 6 and maximally 18 hours apart. If the next higher dose after each study drug increase was not tolerated, the site could reduce the dose to the previous tolerated dose.

Difference between protocol amendments 1 and 2 and the (potential) impact on the statistical Analysis

Protocol amendment 1: Administration of IMP was planned as follows¨:

- Day 1 p.m. dose to Day 3 a.m. dose: 2.5 mg/kg of body weight b.i.d.
- Day 3 p.m. dose to Day 7 a.m. dose: 5.0 mg/kg of body weight b.i.d.
- Day 7 p.m. dose to Day 14 a.m. dose: 7.5 mg/kg of body weight b.i.d.
- Day 14 p.m. dose to end of treatment period (a.m. dose at week 26, i.e Day 181): 10.0 mg/kg of body weight b.i.d

Impact on the statistical Analysis Plan:

The difference in the overall dose is an increase of 5% (i.e. starting dose was 2.5 mg/kg of body weight b.i.d for protocol amendment 1 and 5 mg/kg of body weight b.i.d for amendment 2). This may potentially impact on the primary endpoint at 8 weeks and on the total dose taken over the study duration.

4.4 Blinding and unblinding

Not applicable as it is an open label study

4.5 Schedule of procedures

The schedule of procedures in amendment 2 is as follows

Table 4-1 – Schedule of procedures – Protocol amendment 2

VISIT	1	2	3		4		5	6	7	8	9
DAYS	Within 72 hours of Day 1	3	10								
WEEKS					3		8[8,9]	12	16	20	26
		Virtual visit if feasible and not possible in person	Virtual visit if feasible and not possible in person		Virtual visit if feasible and not possible in person			Virtual visit		Virtual visit	
Informed Consent	X										
Demographics	X										
Medical History	X										
Clinical assessment	X						X		X		X
Vital signs[1]	X	X	X		X		X		X		X
Highest NRS pain score within the past 7 days recorded[11]	X		X		X		X	X	X	X	X
Review/Collection of NRS Pain Scores		X	X		X		X	X	X	X	X
12-lead ECG[2]	X	X	X		X		X		X		X
C-SSRS	X						X				X
Study medication[3]	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX										
Start of EP (weaning of concomitant Rx)							X				
Study Rx adjustment and accountability[4]		X	X		X		X	X	X	X	X
Concomitant medication recording	X	X	X		X		X	X	X	X	X
AE and SAE recording[5]	X	X	X		X		X	X	X	X	X
Laboratory	DAYS			WEEKS							
Local Laboratory	1[6]	3	10		3		8	12	16	20	26
CRP[10]	X				X		X		X		X
CBC	X				X		X		X		X
ALT/AST	X				X		X		X		X
Alkaline Phosphatase	X				X		X		X		X
Bilirubin	X				X		X		X		X
Creatinine/ eGFR	X				X		X		X		X
INR	X				X		X		X		X
Pregnancy Test[7]	X										

Table legend: Source: section 17.2 of protocol amendment 2

Difference between protocol amendments 1 and 2 and the (potential) impact on the statistical Analysis:

There is difference in the timing when visit 3 and week 4 visits should be performed.

Schedule of procedures was the following in Protocol amendment 1 - Table 4-2 below.

Table 4-2 – Schedule of procedures – Protocol amendment 1

VISIT	1	2	3	4	5	6	7	8	9	10	11
DAYS	Within 72 hours of Day 1	3	7								
WEEKS			1	2	3	4	8[8,9]	12	16	20	26
					Phone Contact			Phone Contact		Phone Contact	
Informed Consent	X										
Demographics	X										
Medical History	X										
Clinical assessment	X			X		X	X		X		X
Vital signs[1]	X	X	X	X		X	X		X		X
Highest NRS pain score within the past 7 days recorded[11]	X		X	X	X	X	X	X	X	X	X
NRS Pain Score collection	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[2]	X	X	X	X		X	X		X		X
C-SSRS	X						X				X
Study medication[3]	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX										
Start of EP (weaning of concomitant Rx)							X				
Study Rx adjustment and accountability[4]		X	X	X	X	X	X	X	X	X	X
Concomitant medication recording	X	X	X	X	X	X	X	X	X	X	X
AE and SAE recording[5]	X	X	X	X	X	X	X	X	X	X	X
Laboratory	DAYS			WEEKS							
Local Laboratory	1[6]	3	7	2	3	4	8	12	16	20	26
CRP[10]	X	X	X	X		X	X		X		X
CBC	X			X			X		X		X
ALT/AST	X	X	X	X		X	X		X		X
Alkaline Phosphatase	X	X	X	X		X	X		X		X
Bilirubin	X	X	X	X		X	X		X		X
Creatinine/ eGFR	X			X			X		X		X
INR	X			X			X		X		X
Pregnancy Test[7]	X										

Impact on statistical Analysis Plan:

Due to the difference if timing when visit 3 and the week 4 visits were planned to be performed between protocol amendment 1 and 2, this impacts on the timing when the laboratory blood draws and ECGs were performed at these visits between patients enrolled under Amendment 1 and Amendment 2 and thus may impact the following endpoints.

Efficacy endpoint

- Time to CRP normalization for patients with CRP ≥1.0 mg/dL at baseline

Safety endpoints

- changes in laboratory parameters, including liver function parameters and INR during the 26-week study period.
- changes in ECG parameters during the 26-week study period.

The laboratory test results, vital signs and ECG data for visit 4 (week 2) protocol amendment 1 and visit 4 (week 3), protocol amendment 2 will be combined and labelled as Week 2-3.

5 ANALYSIS POPULATIONS

5.1 Full analysis set (FAS)

All patients who were enrolled and who started the IMP will be included in the Full Analysis set.

5.2 Safety analysis set

All patients who were enrolled and who started the IMP will be included in the safety analyses set.

6 DATA REVIEW MEETINGS

Two data review meetings (DRM) will take place for this trial. The first DRM will take place to review/evaluate the data collected up to (and including) the week 8 visit and the second DRM will take place after the LPLV has taken place and prior to the locking of the clinical database.

After the DRM for the week 8, the data will be 'locked' for data collected up to this visit and will not be subsequently changed.

7 STAGED STATISTICAL ANALYSIS (SSA)

As mentioned in section 1, the analyses for this trial will be done in a staged manner – i.e. the first analysis will per performed for data collected up to the week 8 visit and the second analysis will be done when the last patient last visit is performed and the database is declared ready for complete database lock. The following data will be presented in the SSA:

- Baseline data for all patients enrolled:
    - Patient demographics: age, gender, race, ethnicity
    - Past medical history: N (%) of patients by previous episodes of pericarditis category (i.e., 2, 3, 4, or >4);
    - N (%) of patients for whom medications at baseline was prescribed for pain and pericarditis: analgesics, opiates, NSAIDs, colchicine and corticosteroids. The medications concerned will be identified as those with following

Anatomical Therapeutic Chemical (ATC) classification: H02 (Corticosteroids for systemic use), M01 (anti-inflammatory and antirheumatic products), M04 (antigout preparations), N02A (Opioids), N02B (other analgesics and antipyretics)

- N (%) of patients prescribed medications for pain and pericarditis i.e. medications which were started up to and including the Week 8 visit date and for which the stop date was either empty or > enrolment date at the time of enrolment
- CRP value at baseline will be summarized as a continuous variable
- NRS scores at baseline will be summarized as a continuous variable

- Primary efficacy endpoint, i.e. the change in patient-reported pericarditis pain using an 11-point NRS from baseline to 8 weeks – see section 8.5.1.
- Additional efficacy endpoints (see section 8.5.2):
  - Patients with normalized CRP levels (i.e. with a CRP ≤ 0.5 mg/dL) at 8 weeks (for patients with CRP ≥1.0 mg/dL at baseline) will be summarized as a categorical variable.
  - Time to CRP normalization (in days – see section 8.5.2) up to the Week 8 visit date for patients with CRP ≥1.0 mg/dL at baseline will be summarized as a continuous variable. If CRP had not normalized at the timepoint assessed in the analysis (e.g. week 8), the patients concerned was not included in the analysis - Time to CRP normalization
  - CRP change from baseline at 8 weeks will be summarized as a continuous variable.
- Study drug exposure:
  - N (%) of patients with highest tolerated dose of (up to Week 8 visit date):
    - 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.
  - N (%) of patients by dose taken at Week 8:
    - 10 mg/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.

- 0 mg/kg of body weight – i.e. study treatment (temporarily) stopped

Table 7-1 – Highest tolerated dose for complex cases

Subject ID	Study treatment dose planned as of this visit					
	Screening	**Day 3**	**Day 10**	**Week 3**	**Week 8**	**Highest tolerated dose per Cardiol team**
US-0007-0001	**15-Jun-2023**	**19-Jun-2023**	**26-Jun-2023**	**07-Jul-2023**	**09-Aug-2023**	5 mg/kg
	5.0 mg/kg b.i.d.	7.5 mg/kg b.i.d.	5.0 mg/kg b.i.d.	0 mg/kg		
			Reduced from 7.5 to 5 due to AE then temporarily interrupted then finally stopped on 20-Jul-2023			
US-0005-0002	**01-Sep-2023**	**05-Sep-2023**	**11-Sep-2023**	**19-Sep-2023**	**25-Oct-2023**	10 mg/kg
	5.0 mg/kg b.i.d.	7.5 mg/kg b.i.d.	10 mg/kg b.i.d.	10 mg/kg b.i.d.	Patient started on rilonacept treatment prior to entering the EP. They decided not to continue taking the IP and final visit is Visit 5.	
US-0010-0004	**27-Dec-2023**	**30-Dec-2023**	**05-Jan-2024**	**16-Jan-2024**	**20-Feb-2024**	10 mg/kg
	5.0 mg/kg b.i.d.	7.5 mg/kg b.i.d.	10 mg/kg b.i.d.	10 mg/kg b.i.d.	Permanently stopped due to AE	

Table 7-1 displays the highest tolerated dose which should be used for three 'complex' cases, as discussed during the first Data review meeting.

- Safety endpoints:
  - ALT, AST absolute value and change from baseline up to the Week 8 visit date will be summarized as a continuous variable.
  - QTc absolute value and change from baseline at each visit where ECG was done up to the Week 8 visit date will be summarized as a continuous variable.
  - Individual listings as well as the number of events and percentage of patients with at least one event will be presented for the following events reported up to and including Week 8 visit date:
    - Gastro-intestinal related, identified as any event from the MedDRA System Organ Class 'Gastrointestinal disorders'
    - Rash and related events, identified as any event from the MedDRA System Organ Class 'Skin and subcutaneous tissue disorders'
    - AEs leading to study drug discontinuation

        - SAEs
        - TEAEs
    - Suicidal ideation i.e. N (%) of patients for whom reply to “1. Wish to be Dead” (Q1) and/or “2. Non-Specific Active Suicidal Thoughts” (Q2) was ‘Yes’
- Exploratory endpoints not foreseen by the protocol:
    - N (%) of patients who did not complete 8 weeks on study medication
    - NRS score at baseline for patients still under medication at week 8 will be described as continuous variable
    - NRS score at baseline for patients still under medication at week 8 AND were enrolled with qualifying CRP ≥ 1.0mg/kg will be described as continuous variable
    - N (%) patients enrolled with CRP ≥ 1.0mg/dl at baseline
    - CRP value at baseline for patients enrolled with qualifying CRP ≥ 1.0mg/dl will be summarized as a continuous variable
    - Qualifying CRP (mg/dL) will be summarized as a continuous variable for all enrolled patients
    - For patients with a baseline CRP value ≥1 mg/dL, the CRP values obtained at each visit in addition to the change from baseline at each visit will be summarized as a continuous variable. The qualifying CRP value will also be presented for the patients concerned.

8 STATISTICAL ANALYSES

The complete set of tables, figures and listings planned to be generated by this SAP is displayed in section 10.

8.1 Deviations

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

8.2 Patient enrolment and disposition

Patient enrolment by site will be tabulated by protocol amendment and overall.

Patient disposition will be summarized by protocol amendment and overall. This will include # screened (i.e. with informed consent), # screening failures with reason, # enrolled and # who started IMP. The summary will include the number and percentage of patients in each of the defined analysis populations in Section 5. In addition, frequency counts and percentages of patients' reported reasons for ending the study will be summarized.

8.3 Description of Demographic and Baseline characteristics

A baseline variable is defined as data obtained / collected prior to or on the same day as enrollment 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 9.1. Baseline information will be summarized for the FAS dataset only.

All demographic and baseline characteristics will be listed by study center, and patient number.

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:

8.3.1 Demographics

Variable label:	**Comment / category labels:**
Age	Take as (year of enrollment – year of birth). Tabulate as continuous variable.
Gender	Tabulate as categorical variable = male/female.
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.
Ethnicity	Tabulate as categorical variable = Hispanic or Latino / Non Hispanic or Latino / Unknown or not reported

8.3.2 Pericarditis History

Variable label:	**Comment / category labels:**
Days since current pericarditis episode was diagnosed prior to IMP start	Take as date of first study treatment dose – date current pericarditis diagnosed. Tabulate as continuous variable.
Symptoms present at time of diagnosis • Pericarditic chest pain • Pericardial rub • New widespread ST-segment elevation or PR segment depression according to ECG findings • Pericardial effusion (new or worsening)	Tabulate as number of patients with the symptom ticked
CRP level ≥1.0 mg/dL within prior 7 days of screening?	Tabulate as categorical variable = Yes./No
Confirmation of Pericarditis diagnosis	Tabulate as categorical variable = CRP level ≥1.0 mg/dL within prior 7 days and Pericarditis confirmed by CMR or CRP level ≥1.0 mg/dL within prior 7 days only or Pericarditis confirmed by CMR only (CRP < 1.0 mg/dL) Source: reply to inclusion criteria 4.a and 4.b as 'Yes'
Number of previous episodes of pericarditis	Tabulate as categorical variable = 2 episodes,3 episodes,4 episodes or >4 episodes.

8.3.3 Cardiovascular History

Variable label:	**Comment / category labels:**
History of documented acute myocardial infarction (AMI)?	Tabulate as categorical variable = Yes.
Previous diagnosis of heart failure?	Tabulate as categorical variable = Yes.
History of supraventricular tachycardia	Tabulate as categorical variable = Yes.

Variable label:	Comment / category labels:
History of sustained ventricular arrhythmia?	Tabulate as categorical variable = Yes. Only available for protocol amendment 2
Any other clinically relevant rhythm disorder?	Tabulate as categorical variable = Yes.
Cardiovascular risk factors	
Treated for hypertension	Tabulate as categorical variable = Yes.
Diabetes mellitus	Tabulate as categorical variable = No / Type 1 / Type 2
Treated for hyperlipidemia	Tabulate as categorical variable = Yes.
Diagnosed with chronic kidney disease?	Tabulate as categorical variable = Yes. (Unknown if any is grouped with No)
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	Never / Former / Current
Covid-19 History	
Diagnosed with COVID-19	Tabulate as categorical variable = Yes.
Vaccinated for COVID-19	Tabulate as categorical variable = Yes.

8.3.4 Other medical history

Medical history data will be coded by system organ class and preferred term, using the MedDRA dictionary. Medical history will be summarized by body system. The table will be sorted by alphabetic order, by system organ class, as well as by incidence of preferred term. The N and % will be presented where: N is the number of patients who present at least one occurrence of the medical history and % is the percentage of patients.

8.3.5 Concomitant medications

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

For the purpose of classify medication, incomplete medication start and stop date will be imputed as detailed in Section 9.5.2.

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.

8.3.6 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

8.3.7 Physical examination

Variable label:	**Comment / category labels:**
Skin	Tabulate as categorical variable = Abnormal (clinically significant).
HEENT	Tabulate as categorical variable = Abnormal (clinically significant).

Variable label:	Comment / category labels:
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).

8.3.8 Questionnaires

Variable label:	Comment / category labels:
NRS	Highest NRS pain score within the past 7 days of Day 1 (documented on the visit 1, page 9) - Tabulate as continuous variable.
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

8.3.9 Standard 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.

Variable label:	Comment / category labels:
Patients with abnormal ECG	Tabulate as categorical value = Yes. A Listing of ECG abnormalities considered clinically significant will be provided l

8.3.10 Laboratory tests

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:

8.3.10.1 Chemistry:

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

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)

8.3.10.2 Hematology:

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

The laboratory test results will be converted into SI units as displayed in Table 8-1

Table 8-1: 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
C-Reactive Protein (CRP)	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

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. CRP <0.3 mg/dL → value imputed as 0 mg/dL).

For all assays, 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.

8.4 Study drug exposure

The study drug exposure will be presented using the variables listed below:

Variable	Formula
Total dose planned per protocol for patients enrolled under protocol amendment 1 (mL) [PLANNED_DOSE]	Weight (in kg) * 3.68 mL/kg for patients who agreed to do the extension Where 3.68 mL/kg= (2 days * 2.5 mg/kg bid * 2 + 4 days * 5 mg/kg bid * 2 + 7 days * 7.5 mg/kg bid * 2 + 167 days * 10 mg/kg bid * 2) / 950 mg/mL Or Weight (in kg) * 1.07 mL/kg for patients who stopped the study at 8 weeks Where 1.07 mL/kg= (2 days * 2.5 mg/kg bid * 2 + 4 days * 5 mg/kg bid * 2 + 7 days * 7.5 mg/kg bid * 2 + 43 days * 10 mg/kg bid * 2) / 950 mg/mL
Total dose planned for patients enrolled under protocol amendment 1 (mL) based on visits actually performed	$\text{weight (in kg)} * \sum_{i=1}^{10} \text{planned dose (mg/kg bid) documented at visit i} * 2 * \left(\text{visit date (i + 1)} - \text{visit date (i)}\right)$
Total dose planned for patients enrolled under protocol amendment 2 (mL) [PLANNED_DOSE]	Weight (in kg) * 3.73 mL/kg for patients who agreed to do the extension Where 3.73 mL/kg= (2 days * 5 mg/kg bid * 2 + 7 days * 7.5 mg/kg bid * 2 + 171 days * 10 mg/kg bid * 2) / 950 mg/mL Or

Variable	Formula
	Weight (in kg) * 1.11 mL/kg for patients who stopped the study at 8 weeks Where 1.11 mL/kg= (2 days * 5 mg/kg bid * 2 + 7 days * 7.5 mg/kg bid * 2 + 47 days * 10 mg/kg bid * 2) / 950 mg/mL
Total dose planned for patients enrolled under protocol amendment 2 (mL) based on visits actually performed	$\text{weight (in kg)} * \sum_{i=1}^{8} \text{planned dose (mg/kg bid) documented at visit i} * 2 * (\text{visit date (i + 1)} - \text{visit date (i)})$
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', 'Unknown' must be reviewed during DRM.
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 8 weeks on IMP	# of patients with Premature withdrawal of study treatment form completed before the Week 8 visit date
# patients who stopped the IMP prematurely (i.e. prior to or at week 8)	# of patients with Premature withdrawal of study treatment form with a premature withdrawal date <= Week 8 visit date

Variable	Formula
# patients with highest tolerated IMP dose up to Week 8	# of patients for whom the maximum dose taken up to the week 8 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.
# patients with highest tolerated IMP dose over the complete follow-up period	# of patients for whom the maximum dose taken up to the last IMP intake 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.

8.5 Efficacy analysis

Given the small sample size and the design of the study, no inferential statistical analyses are planned. All data collected during a scheduled visit (except the NRS score which was collected daily) will be included in the descriptive statistics.

8.5.1 Primary efficacy analysis

The 11-point NRS value for a specific week will be determined by the worst NRS score collected on the daily NRS questionnaire for the seven days prior (day – 7 to day -1) to the week 8 visit (or planned visit date if week 8 visit not performed). If the daily NRS questionnaire is not completed for 7 consecutive days prior to the week 8 visit, the worst NRS score between the eCRF (Item: What is the highest NRS score over the past 7 days according to the patient?) and the NRS questionnaire completed by the patient will be used. The change in patient-reported pericarditis pain using an 11-point NRS from baseline to 8 weeks will be presented as a continuous variable.

8.5.2 Additional efficacy analysis

- The change in patient-reported pericarditis pain using an 11-point NRS from baseline to 26 weeks will be summarized as a continuous variable.
- The change in patient-reported pericarditis pain using an 11-point NRS from baseline to other intermediate weeks (i.e. visits 3,4,5,6,7) will be summarized as a continuous variable.
- Patients with normalized CRP levels (i.e with a CRP≤ 0.5 mg/dL) at 8 weeks (for patients with CRP ≥1.0 mg/dL at baseline) will be summarized as a categorical variable
- Patients with normalized CRP levels (i.e with a CRP≤ 0.5 mg/dL) at 26 weeks (for patients with CRP ≥1.0 mg/dL at baseline) will be summarized as a categorical variable
- Patients with pericarditis recurrence during the extension period (EP), i.e with an adverse event occurring between week 8 and week 26 and coded with the following LLT code 10087207 (Recurrent pericarditis) will be summarized as a categorical variable

- Time to CRP normalization (in days) (i.e time between IMP start date up to the first blood draw date when CRP≤ 0.5 mg/dL) for patients with CRP ≥1.0 mg/dL at baseline will be summarized as a continuous variable. If CRP had not normalized at the timepoint assessed (i.e 8 week visit date (for SSA) or 26 weeks visit date for the final analysis), the patients concerned will not be included in the analysis for this outcome.
- CRP change from baseline at 26 weeks (%) will be summarized as a continuous variable.

8.5.3 Further exploratory analyses

- Evaluate the NRS for patients with qualifying CRP ≥1.0 mg/dL
- Evaluate the NRS for patients who qualified for the trial on basis of past CMR findings and had qualifying CRP < 1.0 mg/dL
- Examine the correlation between medications used to treat pericarditis and the NRS score at different time points.
- Perform a numerical comparison with the historical data from the rilonacept phase 2 and RHAPSODY trials for the patients with similar eligibility criteria. The methodology to do this analysis will be addressed in a separate SAP.

8.6 Safety analysis

The Safety analysis set will be used for all safety analysis.

8.6.1 Adverse events (AEs)

The number of adverse events and percentage of patients with at least one adverse event will be summarized by system organ class and by preferred terms (MedDRA).

AEs will be considered as treatment - emergent adverse events (TEAE) if the event onset time (and date) is > start of the IMP. Adverse events with incomplete onset dates will be summarized as TEAE regardless of severity and relationship to the IMP.

8.6.2 Serious Adverse events (AEs)

The number of Serious Adverse Events (SA) and percentage of patients with at least one SAE be summarized by system organ class and by preferred terms (MedDRA).

8.6.3 Change in C-SSRS

The number of patients with C-SSRS ideation and behaviour scores compared to baseline will be summarized.

8.6.4 Laboratory parameters.

Descriptive statistics of absolute value and change from baseline for laboratory values, including liver function parameters and INR, will be presented by follow-up time points.

The number and percentage of patients with changes in laboratory test results during the course of the study, i.e. change from normal to high or low, based on the local reference ranges will be summarized by assay concerned.

8.6.5 ECG parameters.

Descriptive statistics of absolute value and change from baseline of ECG intervals and rhythm during the 26-week study period.

8.6.6 Vital signs.

Descriptive statistics of absolute value and change from baseline will be presented by follow-up time points.

9 GENERAL PRINCIPLES

9.1 Standard descriptive statistics

The analyses will be presented/reported using summary tables, figures, and data listings. Continuous variables will be summarized with counts, means, standard deviations, medians, Interquartile range, minimums, and maximums.

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

All analyses and tabulations will be performed using SAS Version 9.3 or higher 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.

9.2 Handling of missing data

Missing data will be treated as missing, not imputed, unless otherwise stated.

9.3 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 than the raw data, and the standard deviations will be presented to two more decimal places than the raw data.

Percentages will be based on available data and denominators will exclude 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.

9.4 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 study drug (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.

Minutes – Durations, expressed in minutes between one timepoint (time1) and another later timepoint (time2), are calculated using the following formula: duration in minutes = (time2-time1)/60.

9.5 Imputation of Dates

9.5.1 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

9.5.2 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.

10 TABLES, FIGURES AND LISTINGS

10.1 List of tables

Table 1 – Protocol deviations summary overview

Table 2 – Demographics

Table 3 – Pericarditis History

Table 4 – Cardiovascular History

Table 5 – Other medical history by MedDRA System Organ Class

Table 6 – Other medical history by MedDRA Preferred Term

Table 7 – Baseline medication by WHO Anatomical Therapeutic Chemical (ATC) Classification

Table 8 – Anthropometric assessment and vital signs at baseline – Descriptive statistics

Table 9 – Physical examination at baseline – Descriptive statistics

Table 10 –Questionnaire at baseline: NRS and C-SSRS – Descriptive statistics

Table 11 – Standard 12-lead Electrocardiogram (ECG) at baseline – Descriptive statistics

Table 12 –Laboratory tests results at baseline – Descriptive statistics

Table 13 –Laboratory tests results at baseline – Descriptive statistics by gender

Table 14 –Laboratory tests results at baseline below, within and above the normal range

Table 15 – Study drug exposure

Primary efficacy endpoint

Table 16 – Primary endpoint – Worst 11-point NRS score at Week 8 and 11-point NRS change from baseline to Week 8 – Descriptive statistics

Additional efficacy endpoints

Table 17 – Worst 11-point NRS score and change from baseline by week up to 26 weeks – Descriptive statistics

Table 18 – Patients with normalized CRP levels (i.e with a CRP≤ 0.5 mg/dL) at 8 weeks and 26 weeks (for patients with CRP ≥1.0 mg/dL at baseline)

Table 19 – Time to CRP normalization (in weeks) for patients with CRP ≥1.0 mg/dL at baseline

Table 20 – CRP change from baseline at 26 weeks – Descriptive statistics

Table 21 – Patients with pericarditis recurrence during the extension period (EP),

Further exploratory endpoints

Table 22 – Worst 11-point NRS score and change from baseline by week up to 26 weeks for patients enrolled with qualifying CRP ≥1.0 mg/dL – Descriptive statistics

Table 23 – Worst 11-point NRS score and change from baseline by week up to 26 weeks for patients for patients who qualified for the trial on basis of past CMR findings and had qualifying CRP < 1.0 mg/dL – Descriptive statistics

Safety related

Table 24 – Overview of reported adverse events

Table 25 – Non-serious adverse events by MedDRA System Organ Class

Table 26 – Non-serious adverse events by MedDRA Preferred Term

Table 27 – Serious adverse events by MedDRA System Organ Class

Table 28 – Serious adverse events by MedDRA Preferred Term

Table 29 – Patients with a worsening of C-SSRS ideation and behaviour scores compared to baseline

Table 30 – Laboratory tests results (absolute and change from baseline) during the 26-week study period – Descriptive statistics

Table 31 – Patients who experience changes in laboratory parameters during the 26-week study period

Table 32 – ECG intervals (absolute and change from baseline) during the 26-week study period– Descriptive statistics

Table 33 – Vital signs (absolute and change from baseline) during the 26-week study period – Descriptive statistics

10.2 List of figures

Figure 1 – Consort

Figure 2 – Worst NRS score by week – mean (SD)

Figure 3 – Laboratory test results by week – mean (SD) – Graphical representation for each parameter

Figure 4 – Laboratory test results by week – mean change from baseline (SD) – Graphical representation for each parameter

Figure 5 – Patients who experience changes in laboratory parameters during the course of the study – bar chart over time (for each parameter)

10.3 List of listings

Listing 1 – Patient disposition: Informed consent signature date, date of enrolment, death date, premature withdrawal from follow-up, premature withdrawal from study treatment

Listing 2 – Demographics and Baseline Characteristics

Listing 3 – ECG abnormalities considered clinically significant reported at enrolment

Listing 4 – Prior, baseline and concomitant medications

Listing 5 – Serious and non-serious adverse events reported during study