STATISTICAL ANALYSIS PLAN

Study Title:	**An Open-Label Pilot Study of KPL-914 in Recurrent Pericarditis**
Protocol Number:	KPL-914-C001
Study Phase:	Phase 2
Product Name:	KPL-914 (rilonacept)
Sponsor:	Kiniksa Pharmaceuticals, Ltd.
	[redacted]
	[redacted]
Version:	Final, Version 1
Date:	04Jun2019

SPONSOR SIGNATURES

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ATC	Anatomic-therapeutic-chemical
BMI	Body Mass Index
CRP	C-Reactive Protein
CS	Corticosteroids
ECG	Electrocardiogram
eCRF	Electronic Case Report From
EP	Extension Period
ESR	Erythrocyte Sedimentation Rate
HBcAB	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HCG	Human chorionic gonadotropin
HCVAb	Hepatitis C Virus Antibody
HEENT	Head, Eyes, Ears, Neck, Throat
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MRI	Magnetic Resonance Imaging
NRS	Numeric Rating Scale
NSAID	Non-Steroid Anti-Inflammatory Drug
PP	Per Protocol
PPS	Post Pericardiotomy Syndrome
PRO	Patient-Reported Outcome
QoL	Quality of Life

Abbreviation	Definition
RIP	Recurrent Idiopathic Pericarditis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SCV1	Screening Visit 1
SCV2	Screening Visit 2
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
WBC	White Blood Cell
WHO	World Health Organization

1. INTRODUCTION

Kiniksa Pharmaceuticals Ltd. (Kiniksa) is developing KPL-914 (rilonacept) for the treatment of recurrent pericarditis due to either idiopathic (RIP) or post pericardiotomy syndrome (PPS) etiologies.

In this first pilot study in subjects with recurrent pericarditis, improvement of pericarditis symptomatology after KPL-914 administration (including inter- and intra-subject variability estimates of key parameters), feasibility of weaning from corticosteroids while receiving KPL-914, as well as the safety and dose relationships will be assessed.

The purpose of this statistical analysis plan (SAP) is to provide all details and specifications for the analysis of the study KPL-914-C001, "An Open-Label Pilot Study of KPL-914 in Recurrent Pericarditis" as set forth in the clinical study protocol, Amendment 3, version 4.0 dated 19 Feb 2019.

2. STUDY DETAILS

2.1. Study Objectives

The study is comprised of 5 Parts.

- Part 1 enrolls symptomatic subjects with recurrent idiopathic pericarditis (RIP) with an elevated marker of systemic inflammation (C-reactive protein [CRP] > 1mg/dL).
- Part 2 enrolls symptomatic subjects with RIP with CRP ≤1 mg/dL which, in the opinion of the investigator, can be attributed to concomitant medications (e.g., corticosteroids) and with pericardial inflammation present on cardiac magnetic resonance imaging (MRI) confirmed by the imaging core lab.
- Part 3 enrolls subjects with corticosteroid-dependent RIP not experiencing symptoms which would meet the diagnostic criteria for a flare of pericarditis.
- Part 4 enrolls symptomatic subjects with recurrent post pericardiotomy syndrome (PPS) with an elevated marker of systemic inflammation (CRP > 1mg/dL).
- Part 5 enrolls subjects with corticosteroid-dependent recurrent PPS not experiencing symptoms which would meet the diagnostic criteria for a flare of pericarditis.

2.1.1. Primary Objective for Parts 1, 2 and 4

- To collect inter- and intra-subject variability data on CRP measurements and the 11-point Numerical Rating Scale (NRS) instrument for assessment of pericardial pain in subjects with RIP or symptomatic recurrent PPS both at baseline and on

treatment with KPL-914 in order to inform power calculations for future trials in pericarditis.

2.1.2. Secondary Objectives for Parts 1, 2 and 4

- To explore the time course to improvement of pericarditis parameters in symptomatic subjects with RIP or recurrent PPS treated with KPL-914.
- To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.
- To evaluate the safety of KPL-914 in symptomatic subjects with RIP or recurrent PPS.

2.1.3. Primary Objective for Parts 3 and 5

- To evaluate feasibility of weaning from corticosteroids while receiving KPL-914 in subjects with corticosteroid-dependent RIP or recurrent PPS.

2.1.4. Secondary Objectives for Parts 3 and 5

- To evaluate the effect of KPL-914 on pericardial inflammation based on cardiac MRI.
- To evaluate the safety of KPL-914 in symptomatic subjects with RIP or recurrent PPS.

2.2. Study Design

This is an open-label single-active-arm pilot study to explore clinical and biochemical endpoints of improvement of pericarditis symptomatology and to collect inter- and intra-subject variability data on both at-baseline and on-treatment parameters. This study consists of 5 distinct Parts, and all subjects will be treated with once-weekly subcutaneously (SC)-administered injections of KPL-914.

Prescreening Period: Prior to enrollment, potential subjects may enter an optional prescreening period, after signing a Prescreening ICF (or prescreening informed assent, if applicable), to confirm the diagnostic workup and to allow monitoring for symptoms and inflammatory markers (CRP, ESR, etc) while concomitant pericarditis medications may be managed by the Investigator or their clinician according to standard of care.

Screening Period: The Screening Period starts with the signing of the full study ICF (or informed assent form, if applicable) (SCV1) and may last for up to 3 days (72 hours) until SCV2. At SCV1, baseline subject and disease characteristics will be determined. At Screening Visit 2 [SCV2]), within the 24 – 72 hour period before subjects advance to the Treatment Period of the study, additional laboratory samples may be drawn to provide additional baseline reference data.

Under special circumstances, the Investigator in consultation with the Sponsor can combine SCV1 and SCV2. The end of the Screening Period coincides with the start of the Treatment Period (Day 0 Visit). For this reason, not all subjects will have all 3 visits SCV1, SCV2 and Day 0.

At the SCV1, subjects will be given a medication diary to record administration of pericarditis medications and rescue (pain) medication use during the Screening Period.

Patient-reported pericardial pain evaluations will be performed on-site at SCV1 and SCV2 using a validated 11-point NRS instrument. A patient-reported QoL questionnaire will be administered as well.

Treatment Period: The first dose of Study Drug will be administered to subjects at the Study site/Clinic at Visit 1 on Day 0. During this visit, subjects and/or caregivers will be trained for outpatient drug administration. At Day 3, the Investigator (or designee) telephone call/virtual visit will occur to evaluate safety (AE evaluations) and patient-reported pericardial pain using a validated 11-point NRS instrument.

Subsequent weekly Study Drug administrations from Weeks 2 to 5 will be self-administered by the subject or administered by an adequately trained caregiver as an outpatient SC administration. A visiting study nurse will assess and record compliance with Study Drug administration at the subject's home as well as provide guidance and training on Study Drug administration as needed. At Week 6/End-of-Trial, Study Drug may be self-administered or administered at the Study site/clinic.

Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit during approximately Weeks 3-4 to assist the Investigator in the clinical management of the subject. However, this visit is not mandatory, and therefore not all subjects will have this visit.

Subjects reporting worsening of pericarditis symptoms or AEs may be brought in for an unscheduled visit at the Study Site/Clinic at any time during the Treatment Period, at the discretion of the Investigator. Any subject who is considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6- week Treatment Period. Subjects identified as "Treatment Failures" may be replaced at the discretion of the Sponsor in order to provide an adequate sampling of subjects completing the active Treatment Period.

During the Treatment Period, subjects will continue documentation of pericarditis treatment medication use as well as rescue (pain) medication use in the medication diary. Subject-reported pericardial pain evaluations will be performed on-site at the Study Site/Clinic and by weekly (and on Day 3) Investigator (or designee) telephone calls/virtual visits using a validated 11-point NRS instrument. A subject-reported QoL questionnaire will be administered at Visit 7 (Study Site/Clinic). Weekly blood samples for central laboratory

testing will be collected at the Study Site/Clinic or at a qualified laboratory site in the vicinity of the subject or by a visiting study nurse.

Extension Period (EP): The EP is defined as the 18 weeks following the Treatment Period. Subjects who are considered to be "Treatment Responders" will be, at the discretion of the Investigator, offered participation in an optional 18-week EP, in which weekly administration of open-label KPL-914 may be continued for a total duration of 24 weeks. The weekly KPL-914 doses will be by self-administration or administered by adequately trained caregiver, and study nurse visits to the subject's home as well as Investigator (or designee) telephone calls/virtual visits will continue on a monthly basis. During the EP, the Investigator is encouraged to wean concomitant NSAIDs, and/or colchicine, and/or corticosteroids. It is encouraged that NSAIDs and colchicine be tapered and withdrawn within 15 days after entry into the EP. It is encouraged that corticosteroids be progressively tapered (e.g., by 5 mg prednisone or equivalent every week in adults or 0.2mg/kg every week in subjects <18yo) and discontinued within 6 weeks after entering to EP (i.e., by Study Week 12) unless in the opinion of Investigator, a different corticosteroid weaning schedule is required based on subject's clinical status. Other pericarditis medications may also be initiated at the discretion of the Investigator. All changes to pericarditis-related medications should be captured in the source records and eCRF

Unscheduled clinic visits can be scheduled any time as determined by the Investigator/upon subject request. In addition, Investigators are encouraged to schedule subjects at the Study Site/Clinic for an in-person Interval Evaluation Visit between Weeks 15 to 20 (8 to 13 weeks after Visit 7) to assist the Investigator in the clinical management of the subject. During this visit a physical examination, vital signs, ECG, echocardiogram, and laboratory testing can be performed. However, this visit is not mandatory, and therefore not all subjects will have it.

Subject-reported pericardial pain evaluations using a validated 11-point NRS instrument as well as AE monitoring will be performed during the EP at on-site clinic visits and/or during monthly Investigator (or designee) phone calls/virtual visits. A subject-reported QoL questionnaire will be administered at the Interval Evaluation Visit and the Final Visit of the EP. At the end of the EP, subjects will complete the Week 25/Final Visit.

For detailed schedule of visits and evaluations, refer to study Schedule of Evaluations, Appendix8.1.

3. DATA ANALYSIS CONSIDERATIONS

3.1. Determination of Sample Size

The sample size was chosen on an empirical basis, based on recurrent pericarditis prevalence and number of subjects needed to inform phase 3 planning in this condition.

Approximately up to a total of 40 subjects (age 6 -75 years old) with RIP or recurrent PPS will be enrolled as study subjects across all Parts.

Subjects who discontinue the study (withdrawals and Treatment Failures) may be replaced at the Sponsor's discretion in order to provide an adequate sampling of subjects completing the active Treatment Period.

4. PRIMARY AND SECONDARY ENDPOINTS

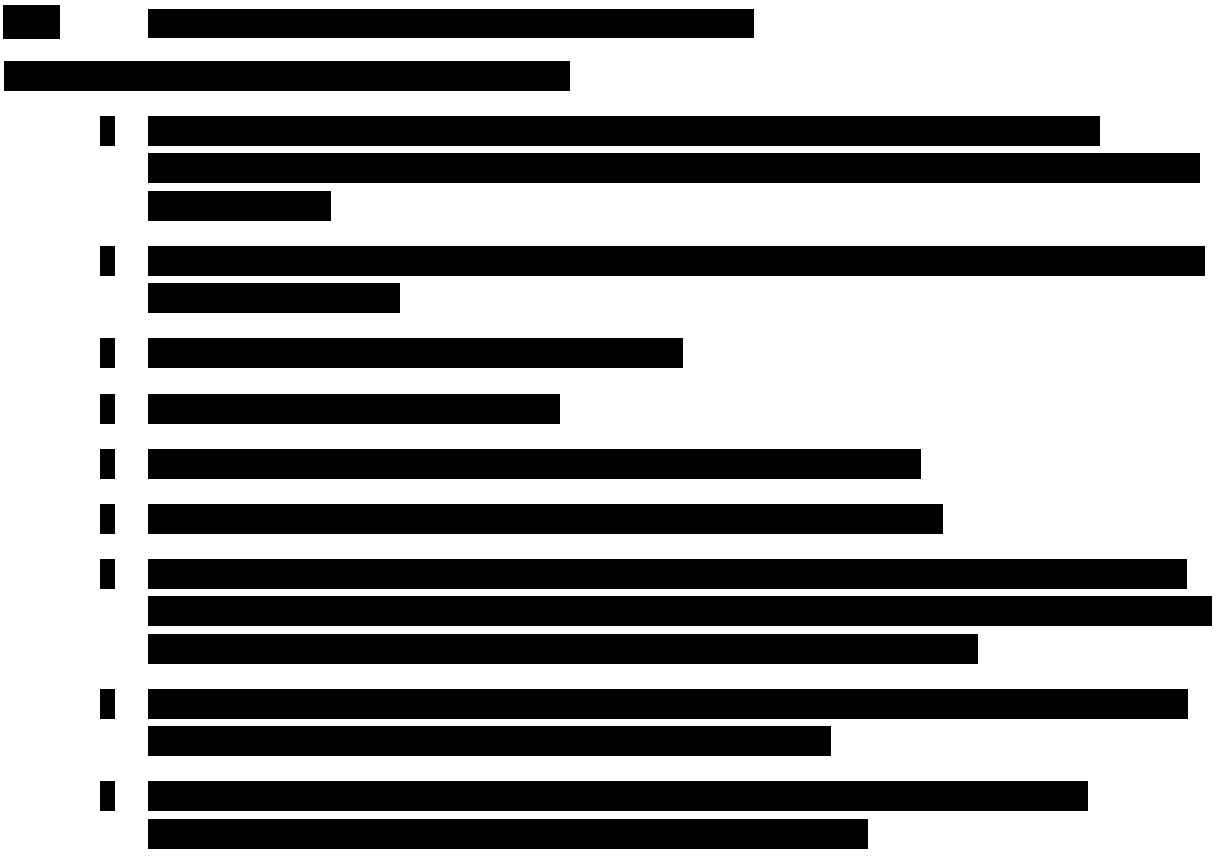
4.1. Primary Efficacy Endpoints for Parts 1, 2 and 4

Primary efficacy endpoints will include:

- inter- and intra-subject variability estimates for CRP and the 11-point NRS instrument in symptomatic subjects with RIP or recurrent PPS both at baseline and while on active KPL-914 treatment in order to inform power calculations for future trials in pericarditis.

4.2. Primary Efficacy Endpoints for Parts 3 and 5

Primary efficacy endpoint will be disease activity after corticosteroid taper in subjects with corticosteroid dependent RIP or recurrent PPS.



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4.4. Safety Endpoints

Safety endpoints will include:

- AEs and SAEs
- Clinical laboratory evaluations
- Vital sign measurements
- ECGs
- Physical examination findings

5. STATISTICAL METHODOLOGY

5.1. General Considerations

All statistical evaluations will be conducted using SAS® version 9.4 or higher (SAS® Institute, Cary, North Carolina). All tables, figures and listings will be produced in landscape format.

Because of the small sample size no inferential statistical analyses or hierarchical testing are planned. Analysis will be descriptive in nature.

Each Part will be analyzed separately. Tables will have columns corresponding to or be stratified by study Parts. Select analyses, as specified in further sections, will be performed for pooled groups of Parts 1, 2 and 4 and Parts 3 and 5, representing similar RIP and PPS populations, i.e. symptomatic and asymptomatic-CS dependent subjects. In general, all data will be listed by study part, subject and visit/time point where appropriate. The total number of subjects under the stated population (N) will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum. In case of $n<2$, where n indicates the number of evaluable subjects at the particular time point, the standard deviation will not be calculated.. The statistic “Missing” will also be presented as the number of missing entries/subjects, if any

at that visit/timepoint, and presented as a summary statistic only when non-zero. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data, whereas the standard deviation will be presented to two more decimal places than the original data.

In summary tables of categorical variables, counts and percentages will be used. The count [n] indicates the actual number of subjects with a particular value of a variable or event, which should always be less than or equal to the total number of subjects with non-missing value of the variable or event [M]. Percentage will be obtained by: % = (n/M)*100. Unless otherwise stated, all percentages will be expressed to one decimal place.

In by-visit summary tables only scheduled visits/timepoints will be summarized. In listings all visits and timepoints with any data collected, including both scheduled and unscheduled ones and early termination visits, will be included.

In selected NRS and CRP figures overtime, only data from mandatory scheduled visits will be displayed (see sections 5.4.9.1 and 5.4.9.3).

The closest non-missing measurement (whether from scheduled or unscheduled visit) taken prior to the first dose of the study drug will be considered as the baseline value. The change from baseline values will be derived for each subject as the post-baseline evaluation minus the baseline evaluation.

Study days will be calculated as follows:

- For events or findings on or after the date of the first study drug administration:
  - Study Day = Date of the event or finding – Date of the first study drug administration + 1
- For events or findings prior to the date of the first study drug administration:
  - Study Day = Date of the event or finding – Date of the first study drug administration

All dates will be displayed in DDMMMYYYY format. The first dose day is day 0 in protocol, and defined as day 1 to follow SDTM guidance.

Analyses of Dosing Procedure Questionnaire, rilonacept (KPL-914) pharmacokinetics and biomarkers will be conducted separately, outside of this SAP.

5.2. Analysis Populations

The analysis populations defined in this study are as follows:

5.2.1. Safety Population

The safety population will consist of all subjects who received at least one dose of study drug. The safety population will be used for all safety analyses.

Subject 104-0001 enrolled in the study, completed it, and then re-enrolled approximately 4 months later as subject 104-0008. To limit the analyses to unique subjects, the subject 104-0008 will be excluded from the Safety Population, and safety data for this subject will be presented in listings only.

5.2.2. mITT Population

The modified Intention to Treat (mITT) population will consist of all subjects who received at least one dose of Study Drug. The mITT population in this study is the same as the safety population. The mITT population will be the main population for all efficacy analyses.

Subject 104-0008 will be excluded from the mITT Population for reasons described in the Section 5.2.1. Efficacy data for subject 104-0008 will be presented in listings only or in individual graphs.

5.2.3. Per-Protocol Population

The Per Protocol (PP) Population will consist of all subjects who received all 6 doses (with the first dose consisting of two injections) of Study Drug during the active Treatment Period and were maintained at stable dose levels of concomitant pericarditis medications (NSAIDs, colchicine, and/or corticosteroids, if used during screening) according to study protocol without a major protocol deviation with potential impact on efficacy (see section 5.4.7). The Per-Protocol population will be used for sensitivity analyses of pain and CRP over time.

Subject 104-0008 will be excluded from the Per-Protocol Population for reasons described in Section 5.2.1.

5.2.4. Extension Period Population

The Extension Period (EP) Population will consist of all subjects who received at least one dose of the study drug during the Extension Period. This population will be used for analysis of select efficacy endpoints defined at the Final Visit.

Subject 104-0008 will be excluded from the Extension Period Population for reasons described in the Section 5.2.1, and the data collected during Extension Period for this subject will be presented in listings only.

5.3. Coding Dictionaries Used

Adverse event and medical history verbatim terms provided by the investigator will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA, version 20.1). The resultant primary system organ class and preferred term will be used for AE summaries.

Prior and concomitant medication provided by the investigator will be coded according to WHO Drug Dictionary Sep-2017 and classified by preferred terms and ATC classes using generic terms. The resultant ATC class and preferred term will be used for prior and concomitant medication summaries and listings.

5.4. Analysis Methods

5.4.1. Study Subjects Disposition

Subject disposition will be summarized by presenting the number of subjects who were:

- Signed pre-screening informed consent
- Signed screening informed consent
- Screened (signed either pre-screening or screening informed consent)
- Screen failures
- Enrolled (passed screening and found eligible)
- Included into the safety population
- Included into the mITT population
- Included into the PP population
- Completed the study prior to Extension Period
- Prematurely discontinued prior to Extension Period, with breakdown by reason for early discontinuation.
- Entered the Extension Period (i.e. signed re-consent for Extension Period)
- Included into the Extension Period population (i.e. treated in Extension Period).
- Completed the study in Extension Period
- Prematurely discontinued in Extension Period, with breakdown by reason for early discontinuation.

Number of subjects pre-screened, screened and screen failures will be presented without percentages. For all other numbers percentages will be based on the number of enrolled subjects.

This analysis will be performed by study part, but also for pooled groups of Parts 1, 2 and 4 and Parts 3 and 5.

A listing will be presented to describe whether the subject entered Extension Period, completed the study, date of completion or early withdrawal, and the reason for early discontinuation, if applicable. A listing will also be provided to describe when informed consent was obtained and if the subject meets all inclusion/exclusion criteria. Reason for entry criteria violation, if any, will be presented. A listing also will be provided for subjects excluded from safety, mITT and PP populations with reasons for exclusion.

5.4.2. Demographic and Baseline Characteristics

Demographic and baseline characteristics such as age, sex, childbearing potential (for female subjects only), race, ethnicity, height (cm), weight (kg) and BMI (kg/m^2) as well as baseline Pain Rating Scale score, whether this score is >=4, number of prior RIP or PPS recurrences , whether subjects are taking pericarditis medications of the following categories at baseline: analgesics, aspirin, NSAIDs, colchicine or systemic corticosteroids and number of different pericarditis medication categories at baseline will be summarized. Number of prior RIP and PPS recurrences is excluding the index and current episodes, if any, thus for Part 1, 2 and 4 will be total number of episodes minus 2 and for Parts 3 and 5, minus 1.

In addition, the following statistics will be summarized:

- Disease duration, defined as the number of years from the start of index episode to the day of signing informed consent.
- Annual incidence of episodes, defined as total number of episodes, including index, recurrence and current episodes, divided by disease duration.

The analysis will be based on the safety, PP and EP populations.

Pericarditis medications (analgesics, aspirin, NSAIDs, colchicine and corticosteroids) will be identified among subjects' prior and concomitant medications through medical review.

Descriptive statistics will be presented for age, height, weight, BMI and pain rating scale score. Frequency counts and percentage will be presented for sex, childbearing potential, race, ethnicity and use of pericarditis medications at baseline.

This analysis will be performed by study part, but also for pooled groups of Parts 1, 2 and 4 and Parts 3 and 5, and total

The demographic and baseline characteristic data will also be presented as a data listing.

5.4.3. Medical History

Medical history will be summarized by MedDRA system organ class and preferred term. One subject will be counted only once within one preferred term and one system organ class. The summary will be sorted in the alphabetic order of system organ classes and preferred terms.

Medical history details as collected on the eCRF such as body system, description, the date of onset, stop date and the current status of the condition will be presented in a by-subject data listing.

5.4.4. Pericarditis History

Information collected on the eCRF regarding index pericarditis episode and recurring episode(s) will be presented in a by-subject listing, including criteria for diagnosis, dates and duration of the episode.

5.4.5. Vaccination History

Vaccination history details collected on the eCRF, such as dates and names of vaccines, will be presented in a by-subject listing.

5.4.6. Prior and Concomitant Medications

Prior medications are defined as those taken before the date of the first study drug administration, i.e. started before the start of the study drug. Concomitant medications are defined as any non-study medication taken during the course of the study i.e. on or after the date of the first dose. Additionally, the medications will be considered concomitant if the stop date of the medication is missing (not available). A medication that started prior to the first dose of the study drug and continued after that date will be considered as both prior and concomitant.

Prior and concomitant medications will be summarized separately by anatomical-therapeutic-chemical (ATC) class (highest level available) and WHO Drug Dictionary preferred term. One subject will be counted once within one preferred term and one ATC class. The summary will be sorted in the alphabetic order of ATC classes and preferred terms.

Prior and concomitant medication information will be presented in a by-subject listing with ATC class (highest level available) and WHO Drug Dictionary preferred term, start and stop date, dosage, route, frequency and indication.

5.4.7. Protocol Deviations

Protocol deviations will be derived programmatically as well as reported by sites.

Protocol deviations are considered major if based on Sponsor assessment they can impact study integrity or interpretability of study results.

All major protocol deviations will be summarized by deviation category (including Inclusion Criteria, Exclusion Criteria, ICF, Concomitant Medication, and other if applicable).

Major protocol deviations will be identified as either deviations with potential impact on efficacy or deviations without potential impact on efficacy. Major protocol deviations with potential impact on efficacy will be used to exclude subjects from PP population set.

Specific deviation and their severity are defined in the separate Protocol Deviations List document.

The protocol deviations data with the verbatim description, the reason for deviation will also be presented as a by-subject data listing.

5.4.8. Study Drug Administration

The study drug administration details including the administration date and time, dose, site of injection and comments will be presented in a by-subject listing.

The following parameters related to study drug administration will be summarized:

- Number of injections in the Treatment Period and in the Extension Period.
- Compliance percentage, calculated as [Number of injections]/[Planned number of injections]*100%, where Planned number of injections is 7 for the Treatment Period and 18 for the Extension Period.
- Total rilonacept dose administered in the Treatment Period and in the Extension Period, defined as the sum of all doses (in mg) received by the subject in the corresponding period. For subjects receiving a fixed-dose regiment (e.g. 160 mg) it will be assumed that the entire planned dose was injected. For subjects receiving weight-adjusted dose (e.g. 2.2 mg/kg) their weight collected at Screening Visit 1 will be used to calculate the amount of the study drug received for the entire duration of the trial.
- Percentage of injections self-administered by the subject, defined as [Number of self-administered injections] / [Total number of injections received by the subject except the very 1st one that is always administered by the site personnel] * 100%.

The parameters above for the Treatment Period will be summarized descriptively for the safety population. Separately these parameters for the Extension Period will be summarized descriptively for the Extension Period population. The parameters over both Treatment Period and Extension Period will also be summarized for the safety population.

Additionally the number and percentage of subjects who self-administered all their injections (except the very 1st one that is always administered by the site personnel) will be presented for the Treatment Period, Extension Period and the entire study.

5.4.9. Efficacy Analysis

5.4.9.1. CRP

Samples for CRP assessment will be obtained and sent to the central laboratory at each visit. CRP levels will be summarized descriptively by visit. Change from baseline will also be summarized for all post-baseline scheduled visits. This analysis will be performed by study part, but also for pooled groups of Parts 1, 2 and 4 and Parts 3 and 5.

Number and percentage of subjects with normal CRP (defined as ≤0.5 mg/dL) as well as with CRP ≤ 1 mg/dL will be presented by visit.

A subject with abnormal baseline CRP level (>0.5 mg/dL) will be considered to have a *persistent CRP normalization in the Treatment Period* if she/he has at least two consecutive normal CRP results in the Treatment Period with no abnormal results in the Treatment Period after these normal results.

Similarly, a subject will be defined to have a *persistent CRP normalization in the study* if she/he has at least two consecutive normal CRP results at any time after the baseline (in either the Treatment Period or the Extension period) with no abnormal results after these normal results.

Number and percentage of subjects with persistent CRP normalization in the Treatment Period and in the entire study will be presented. The denominator for percentages will be the number of subjects with abnormal CRP at baseline.

A summary of number and percentage of subjects in the following categories among those with normal CRP at baseline (<=0.5 mg/dL) will be presented:

- who did not have abnormal post-baseline CRP (>0.5 mg/dL)
    - in the Treatment Period
    - in entire study (Treatment and Extension Period combined)
- who did not have more than one abnormal post-baseline CRP (>0.5 mg/dL)
    - in the Treatment Period
    - in entire study (Treatment and Extension Period combined)

The denominator for percentages will be the number of subjects with normal baseline CRP.

Time to CRP normalization will be defined only for subjects with abnormal CRP at baseline as the study day of the first visit when normal CRP is observed. For subjects who never achieve normal CRP this time will be censored at the day of the last available CRP assessment. Kaplan-Meier estimates of the median, 25% and 75% percentiles of time to CRP normalization will be provided with 95% confidence intervals (estimated using the method of Brookmeyer and Crowley with loglog transformation for the survival function, PROC LIFETEST in SAS).

CRP changes over time will also be presented graphically. A line plot of mean CRP with ± SE error bars will be created with X axis representing scheduled study visits and Y axis representing CRP level. A separate plot will be created for each study part. Baseline and all post-baseline visits will be included, except the two Interval Evaluation visits, End of Treatment visit as well as Early Termination and Unscheduled visits, since they do not have fixed planned weeks when they are scheduled to occur.

Individual subjects' CRP levels will be plotted over time. A plot will be created per study part. Actual study day of assessment will be used as X-axis and CRP level as Y-axis. Data from all visits will be used.

The same graph will be created for subjects 104-0001 and 104-0008 (the second enrollment of subject 104-0001).

Inter- and intra-subject variability of CRP changes under treatment will be estimated as follows. A mixed model for repeated measures will be fit separately for each study part with change from baseline in CRP level as the outcome, repeated effect of visit and random effect of subject. Variance Components covariance structure will be assumed. The data from all scheduled post-baseline visits will be used. Inter-subject standard deviation (SD) will be estimated as the square root of the variance component associated with the subject effect and

intra-subject SD as the square root of the variance component associated with the visit effect Total variance will be the sum of the inter- and intra-subject variances. Additional details are provided in Section 8.2.

The same approach will be used to estimate the inter- and intra-subject variability of CRP values prior to treatment. This analysis will use the same model as for the changes under treatment, but using actual CRP value (rather than change from baseline) as the outcome and using the data from all available scheduled pre-treatment assessments.

These analyses will be performed on the mITT and PP populations.

5.4.9.2. Echocardiogram

Echocardiograms (ECHOs) including assessment of pericardial effusion will be performed at screening (SCV1), at Study Site/Clinic visits during the Treatment Period (Interval Evaluation Visit [if applicable] and Visit 7/End-of-Trial), at the Interval Evaluation Visit during the EP [if applicable], and at the Final Study Visit/Visit 8.

For the purposes of the analysis, the results of local ECHO evaluations at the site for presence or absence of pericardial effusion will be used.

Presence of pericardial effusion may include any size of pericardial effusion, and may range from trivial/trace/physiologic to very large.

Size of pericardial effusion, if available, will be noted in individual subject listings.

Number and percentage of subjects with pericardial effusion will be presented by visit.

A shift table will be created presenting shifts between presence and absence of the pericardial effusion from baseline to Visit 7 (end of Treatment Period) and Visit 8 (end of Extension Period). At each post-baseline visit the denominator for percentages will be the number of subjects with assessment of pericardial effusion at both baseline and the current visit.

These analyses will be performed on the mITT population.

At the end of or after the study, ECHO images may be assessed by a central reader.

5.4.9.3. Pain Numerical Rating Scale

Average level of pericarditis pain over previous 24 hours will be assessed by subjects at each visit using 11-point pain Numerical Rating Scale (where “0” indicates “no pain” and “10” indicates pain ”as bad as it could be”). The pain level will be summarized descriptively by visit. Change from baseline will also be summarized for all post-baseline scheduled visits. This analysis will be performed by study part, but also for pooled groups of Parts 1, 2 and 4 and Parts 3 and 5.

Number and percentage of subjects with NRS ≤ 1 will be presented by visit.

NRS changes over time will also be presented graphically. A line plot of mean NRS with +/- SE error bars will be created with X axis representing scheduled study visits and Y

axis representing NRS. Separate plot will be created for each study part. Baseline and all post-baseline visits will be included, except the two Interval Evaluation visits, End of Treatment visit as well as Early Termination and Unscheduled visits, since they do not have fixed planned weeks when they are schedule to occur.

Individual subjects' NRS scores will be plotted over time. A plot will be created per study part. Actual study day of assessment will be used as X-axis and NRS score as Y-axis. Data from all visits will be used.

The same graph will be created for subjects 104-0001 and 104-0008 (the second enrollment of subject 104-0001).

Inter- and intra-subject variability of NRS measurements will be estimated in the same manner as for CRP (see Section 5.4.9.1).

These analyses will be performed on the mITT and PP populations.

5.4.9.4. Pericarditis Manifestation

Presence of pericardial rub will be assessed as part of physical examination at screening (SCV1 and SCV2), at Study Site/Clinic visits during the Treatment Period (Interval Evaluation Visit [if applicable] and Visit 7/End-of-Trial), at the Interval Evaluation Visit during the EP [if applicable], and the Final Study Visit/Visit 8. If applicable, assessment of pericarditis signs will also be performed at unscheduled visits.

Electrocardiographic signs of pericarditis, namely widespread ST-elevation or PR depression will be assessed as part of 12-lead ECG at screening (SCV1 and SCV2), at Study Site/Clinic visits during the Treatment Period (Interval Evaluation Visit [if applicable] and Visit 7/End-of-Trial), at the Interval Evaluation Visit during the EP [if applicable], and at the Final Study Visit/Visit 8, based on local site ECG assessment.

Fever will be assessed as part of vital signs at Study Site/Clinic visits. Fever will be defined as body temperature > 37.5 degrees C.

Number and percentage of subjects with pericardial rub, widespread ST-elevation and PR depression based on local ECG read, with fever and with pericardial effusion per Echocardiogram based on a local read will be presented by visit. This analysis will be performed by study part, but also for pooled groups of Parts 1, 2 and 4 and Parts 3 and 5.

These analyses will be performed on the mITT.

5.4.9.5. Magnetic Resonance Imaging (MRI)

Cardiac MRI is an optional assessment for Parts 1, 3, 4 and 5 and may be performed at study entry (SCV1) and at the final study visit (Visit 8) to assess any changes in pericardial inflammation. For Part 2, cardiac MRI to determine subject's eligibility based on presence of pericardial inflammation is a mandatory assessment.

For the purposes of the analysis of treatment response in all subjects at the end of the study, all cardiac MRI images will be assessed by a central reader for presence or absence of inflammation

Number and percentage of subjects with following MRI parameters will be presented by visit:

- presence of pericardial inflammation as measured by pericardial delayed hyperenhancement (normal, mild, moderate, severe)
- presence of myocardial inflammation as measured by myocardial delayed hyperenhancement (yes/no)
- presence of pericardial effusion by category:
  - Trivial/Physiological
  - Small (<10 mm)
  - Moderate (10-20 mm)
  - Large (>20 mm)
  - Very large (>25 mm)

These analyses will be performed by study part, but also for pooled groups of Parts 1, 2 and 4 and Parts 3 and 5.

These analyses will be performed on the mITT population.

5.4.9.6. Quality of Life

A validated Quality of Life Questionnaire PROMIS Scale v.1.2-Global Health will be used to assess changes in the subject's physical and mental well-being. The subject will fill the PROMIS questionnaire at screening (SCV1), at Visit 1 (Day 0), at the Interval Evaluation Visit (Week 3-4), at the end of the Treatment Period (Visit 7/End-of-Trial), at the Interval Evaluation Visit during the EP, and at the Final Visit (Visit 8).

Responses to each of the QoL questionnaire questions will be summarized descriptively by visit and question. Change from baseline will also be summarized for post-baseline scheduled visits.

Additionally, Global Physical Health and Global Mental Health scores will be calculated as described in Appendix 8.3. These scores will also be summarized descriptively by visit along with their change from baseline.

This analysis will be performed by study part, but also for pooled groups of Parts 1, 2 and 4 and Parts 3 and 5 on the mITT population.

5.4.9.7. Correlation Analysis

Correlations between CRP levels and pericardial 11-point Numerical Pain Rating Scale will be explored graphically. A scatter-plot will be created for each Study Part separately with X-axis representing CRP level and Y-axis representing pericardial pain NRS. Data points from all subjects of the Study Part from all available visits will be used. The regression line will be superimposed on the scatter-plot, and the regression equation with the R^2 coefficient will be presented.

Relationship between CRP levels and presence of pericardial effusion per Echocardiography local read will also be explored. For each study part and each visit when Echocardiogram is performed CRP levels will be summarized descriptively separately side-by-side for the subjects with pericardial effusion and subjects without pericardial effusion. A p-value from the two-sample t-test comparing the CRP levels between these two groups will be provided.

These analyses will be performed on the mITT population.

5.4.9.8. Prednisone Use

The following characteristics of prednisone use throughout the study will be summarized descriptively. Prednisone use will be identified via medical review of baseline and concomitant medications.

- Daily dose of prednisone at study baseline (mg/day) in subjects who were treated with study drug in TP and who were taking prednisone at baseline
- Daily dose of prednisone at the start of extension period (mg/day) in subjects who were treated in EP with study drug and received prednisone at EP start
- For each subject with prednisone use at baseline, the subject's average daily dose in the Treatment Period (mg/day), defined as total cumulative dose of prednisone taken in the Treatment Period divided by the duration of the Treatment Period in days. For the purposes of this analysis the Treatment Period ends on the day of Week 6/End of Trial/Visit 7 for subjects who proceed to the Extension Period; for subjects who do not enter the Extension Period, the Treatment Period ends on the day of the last study drug dose.
- For each subject with prednisone use at the start of the extension period, the subject's average daily dose in the Extension Period (mg/day), defined as total cumulative dose of prednisone taken in the Extension Period divided by the duration of treatment in the Extension Period in days. For the purposes of this analysis the Extension Period starts on the day of Week 6/End of Trial/Visit 7.
- For each subject with prednisone use at baseline, the subject's average daily dose in the Treatment and Extension Periods combined (mg/day), defined as total cumulative dose of prednisone taken in both the Treatment and Extension Periods

divided by the duration of periods in days (from the first dose in the Treatment Period to the last dose in the Extension Period).

This analysis will be performed by study part, but also for pooled groups of Parts 1, 2 and 4 and Parts 3 and 5.

To evaluate disease activity after discontinuation of corticosteroids, selected efficacy parameters including CRP will be analysed in subjects who received prednisone at baseline and discontinued it by the end of EP.

5.4.9.9. Concomitant Pericarditis Medications

Pericarditis medications will be identified among subjects' concomitant medications and classified as analgesics, aspirin, NSAIDs, colchicine or corticosteroids through medical review.

For the purposes of these analyses, medications taken on as needed basis (PRN) will not be accounted for due to difficulty in assessing the actual dose. Only medications with a fixed daily use frequency (QD, BID, TID, etc.) will be used, so that their daily dose can be calculated.

For the purposes of these analyses, the Treatment period ends and the Extension Period starts on the day of Visit 7 for subjects who proceed to the Extension Period. For subjects who do not enter the Extension Period, the Treatment Period ends on the day of the last study drug dose.

Each category of pericarditis medications will be analyzed for changes in the Treatment Period, Extension Period and the study as a whole as follows and categorized as follows:

1. New Medication: a new medication of the given category is taken at the end of the period compared to the start of the period.
2. Dose Increase: no new medications of the given category are taken, but the total daily dose of one of the medications increased by the end of the period compared to the start of the period.
3. Dose Decrease: there are no new medications and no dose increases, and the total daily dose of one of the medications decreased by the end of the period compared to the start of the period.
4. Stopped: a medication of the given category was taken at the start of the period, and none is taken at the end of the period.
5. Stable Dosing: none of the above.

Number and percentage of subjects with each of the above outcomes will be presented by the pericarditis medication category and study period (Treatment, Extension and study as a whole). The population will be mITT for the Treatment Period and EP for the Extension

Period and the study as a whole. The denominator for percentages for the "New Medication" outcome will be the total number of subjects in the appropriate population. For all other outcomes it will be the number of subjects who take any medication of the given category at the start of the period.

This analysis will be performed by study part, but also for pooled groups of Parts 1, 2 and 4 and Parts 3 and 5.

Use of Pain/Rescue medications will be also analysed (see section5.4.10.7).

5.4.9.10. Recurrent episodes of RIP and PPS during the study

The numbers of subjects with recurrent pericarditis episodes will be summarized by the number of recurrent episodes during the study. Duration-adjusted number of episodes will be defined for each subject as the number of recurrent episodes during the study divided by the study duration (from the first dose of the study drug to study completion/discontinuation) in years. Duration-adjusted number of episodes will be summarized descriptively. This analysis will be performed for the mITT population.

5.4.9.11. Clinical Response

Clinical Response is a composite endpoint defined at the visits when both pain NRS and CRP are assessed. A subject is defined to have clinical response if pain NRS assessment is ≤ 2 and CRP is normal (≤ 0.5 mg/dL) at the same time.

Number and percentage of subjects with Clinical Response will be presented by visit through end of the study for the mITT population.

5.4.10. Safety Analysis

All safety data will be listed and tabulated. The analysis will be performed on the safety population.

Safety parameters include adverse events, selected laboratory parameters collected at the sites local laboratory or at central study laboratory, vital signs, ECG, and physical examination findings.

Subject 104-0008 will be excluded from all safety assessments, and the safety data for this subject will be presented in listings.

5.4.10.1. Adverse Events

Adverse Events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA version 20.1) AE coding system for purpose of summarization.

An AE will be defined as treatment-emergent (TEAE) if its date/time of onset falls within the interval from the date/time of the first study drug administration until the end of study. If the date of AE onset coincides with the date of the first study drug administration and AE time is

not captured, AE will be considered treatment-emergent, unless the eCRF field "Did event start prior to first dose of study drug?" is checked as "Yes".

An AE will be defined as treatment-related if its relationship to the study drug is recorded as Possibly Related or Related on the eCRF.

An overall summary of number and percentage of subjects with at least one AE, TEAE, serious TEAE, treatment-related TEAE, serious treatment-related TEAE, TEAE leading to discontinuation and TEAE leading to death will be presented. It will also include a summary of subjects by the highest severity of TEAE reported in the study.

A summary of the frequency (number and percentage of subjects) of TEAEs will be presented by system organ class and preferred term. Adverse events will also be analyzed by their severity (mild, moderate or severe) and relationship to study drug (related or not related).

A subject experiencing the same AE multiple times will be counted only once for that preferred term. Similarly, if a subject experiences multiple AEs (preferred terms) within the same system organ class then that subject will be counted only once for that system organ class. When summarizing by severity and relationship, only event with highest severity or relationship will be counted. All AEs will be presented in the descending order of total frequency by SOC and preferred terms within SOC.

These analyses will be performed by study part, but also for pooled groups of Parts 1, 2 and 4 and Parts 3 and 5 and total (all Parts combined)

All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim term given by the investigator, preferred term, system organ class, start date, stop date, severity, outcome, action taken and drug relatedness. Separate listings will be created for Serious TEAEs and TEAEs leading to study drug discontinuation.

5.4.10.2. Clinical Laboratory Parameters

The following laboratory analyses will be performed at the Study Site/Clinic laboratories and recorded on the eCRF:

- Serology: HCVAb, HBsAg, HBcAb, HBsAb and HIV tests (SCV 1 only)
- Urine Drug Screen**:** Alcohol, amphetamines, cocaine, or phencyclidine (SCV1 only)
- Screening for tuberculosis (QuantiFERON test) at SCV1 only (optional)
- Screening for pregnancy (urine β-HCG) at SCV1 only.

The Study Site/Clinic laboratories will also perform Hematology, Clinical Chemistry and Urinalysis tests to support clinical management and decision-making, but these tests will not be recorded on the eCRF and will not be analyzed as part of this SAP.

The following tests will be performed by the central lab in peripheral blood samples:

- CRP
- Lipid panel (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides)
- Anti-rilonacept (anti-KPL-914) antibody
- KPL-914 drug levels
- Biomarkers

CRP testing will be performed for the purposes of efficacy analyses described in the Section 5.4.9.1 above.

Analysis of anti-rilonacept antibodies is described in the section 5.4.10.3 below.

Laboratory evaluation results for lipid panel, as well as changes from baseline will be summarized descriptively by visit. Only subjects with both non-missing baseline and time point values will be summarized at each time point.

Lipid panel results will be summarized both in the conventional units (mg/dL) and SI units (mmol/L).

Shifts among normal, low and high results (as determined by laboratory normal ranges) from baseline to last available post-baseline assessment in the Treatment Period and in the Extension Period will be summarized.

All individual subject clinical laboratory evaluation results that are captured in the study database will be presented in listings subject and visit.

Results of serology tests, drug screen, anti-rilonacept antibodies, tuberculosis screening, pregnancy test will be listed.

5.4.10.3. Anti-rilonacept (anti-KPL-914) antibodies

Anti-rilonacept antibodies will be measured in blood samples collected at SCV1/Day 0, Visit 2, Visit 3, Visit 4, Visit 7, EP Month 2, and Visit 8.

Number and percentage of subjects with positive and negative anti-rilonacept antibodies will be presented overall, and by visit for subjects in each Part and for all Parts combined. For subjects with at least 1 positive sample, number and percentage of subjects with each observed titer will be presented.

In addition, a listing with anti-rilonacept antibody status (positive, negative), and antibody titer (for subjects with positive anti-rilonacept antibodies) will be provided by visit.

Additional analyses may be performed, including anti-rilonacept antibodies transience, persistence, or temporal association with efficacy or safety measures.

5.4.10.4. Vital Signs

Vital signs will be recorded at Study Site/Clinic visits in a standardized manner, i.e., after the subject has rested in the sitting position for 5 minutes.

The following measurements will be taken: oral temperature, respiratory rate, blood pressure, and pulse. Overall interpretation (normal, abnormal not clinically significant or abnormal clinically significant) will also be recorded.

Body weight and height will be determined and BMI will be calculated at SCV1 and at the final study visit.

Actual values of vital signs (including weight and BMI) and changes from baseline will be summarized using descriptive statistics by visit. Only subjects with both non-missing baseline and visit values will be summarized at each visit.

Overall interpretation will be summarized categorically by visit.

All vital signs data will be provided as a by-subject listing.

5.4.10.5. Electrocardiogram (ECG)

Twelve-lead ECGs will be performed at screening (SCV1 and SCV2), at Study Site/Clinic visits during the Treatment Period (Interval Evaluation Visit [if applicable] and Visit 7/End-of-Trial), at the Interval Evaluation Visit during the EP [if applicable], and at the Final Study Visit/Visit 8.

Analysis based on central read

Heart rate (bpm), PR Interval, RR Interval, QRS Interval, QT Interval, QTcB Interval, QTcF Interval (msec) and the overall interpretation (normal, abnormal) will be captured.

Actual values and changes from baseline for the ECG intervals and heart rate will be summarized using descriptive statistics by time point using central ECG reads.

Number and percentage of subjects with normal and abnormal overall interpretation, with further breakdown by abnormal findings (such as conduction, rhythm, ST segment and T wave findings) will be presented by visit.

Analysis based on local read

Frequency table for interpretation (normal, abnormal not clinically significant, and abnormal clinically significant) will be generated.

Shift table for shifts from baseline to the last post-baseline assessment in the treatment period and extension period in the overall interpretation based on local read will be created.

All ECG data will be provided as a by-subject listing.

5.4.10.6. Physical Examination

Physical examinations will be performed at screening (SCV1 and SCV2), at Study Site/Clinic visits during the Treatment Period (Interval Evaluation Visit [if applicable] and Visit 7/End-of-Trial), at the Interval Evaluation Visit during the EP [if applicable], and the Final Study Visit/Visit 8.

Physical examination will include assessment of the following systems: HEENT, Neck/Thyroid, Respiratory/Chest, Cardiovascular, Abdominal, Urological, Lymph Nodes, Skin, Musculoskeletal/Extremities and Neurological. Additional body systems may be evaluated at the investigator's discretion. Each body system will be characterized as Normal, Abnormal Not Clinically Significant or Abnormal Clinically Significant.

Physical examination findings will be summarized by visit. The number and percentage of subjects with normal, abnormal not clinically significant and abnormal clinically significant findings will be presented for each body system.

All physical examination data will be provided in a listing.

5.4.10.7. Pain/Rescue Medication Use

Number and percentage of subjects who used Pain/Rescue medication at least once will be presented for the Treatment Period, Extension Period and entire study broken down by the medication type as captured on the eCRF (opioid analgesics, non-opioid analgesics, acetaminophen, other). Medication used at fixed doses and as needed (PRN) will be counted in analyses.

Time to first Pain/Rescue medication will be defined as the earliest study day when a rescue medication is taken post-baseline. For subjects who never took any rescue medication post-baseline, it will be censored at the study day of study completion/discontinuation. Kaplan-Meier estimates of the median, 25% and 75% percentiles of time to first rescue medication will be provided with 95% confidence intervals using the same methods as for time for CRP normalization (see Section 5.4.9.1).

All Pain/Rescue medications will be listed.

6. CHANGES IN ANALYSIS FROM PROTOCOL

There are no changes to the analyses specified in the KPL-914-C001, "An Open-Label Pilot Study of KPL-914 in Recurrent Pericarditis" clinical study protocol, Amendment 3, version 4.0 dated 19 Feb 2019.

7. REFERENCES

1. Study protocol: "An Open-Label Pilot Study of KPL-914 in Recurrent Pericarditis" as set forth in the clinical study protocol version 4.0 dated Feb. 19, 2019.

8. APPENDICES

8.1. Study Schedule of Evaluations

Table 1: Schedule of Evaluations

Trial Period →	**Pre-screening Period**	**Run-In Period (Up to 3 days)**		**Treatment Period (6 weeks)**								**Extension Period (18 weeks)**			
Visit Days/Weeks →		**Day -3 to Day 0[a]**		**Day 0[b]**	**Week 2[c]**	**Week 3[c]**	**W3-W4[d]**	**Week 4[c]**	**Week 5[c]**	**Week 6[cc]**	**Week 6/ End-of-Trial[c]**			**W15-W20[t]**	**Week 25 (Week 7 +18 weeks)**
Visit Number →		**SC Visit 1**	**SC Visit 2**	**Visit 1 Clinic**	**Visit 2 (Outpt)**	**Visit 3 (Outpt)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 4 (Outpt)**	**Visit 5 (Outpt)**	**Visit 6 (Outpt)**	**Visit 7 Clinic**	**Monthly Visits (Outpt)**	**Un-scheduled Visits (Clinic)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 8 (Final, Clinic)**
Dose Number →				**Dose 1**	**Dose 2**	**Dose 3**	**N/A**	**Dose 4**	**Dose 5**	**Dose 6**					
Trial Procedure ↓					**Unscheduled Visits[u]**										
Signature of ICF	X	X													
Inclusion and exclusion criteria verification		X	X												
Demographics	X	X													
Medical history [e]	X	X													
Study Drug admin. – On site [f]				X							(X[f])				
Study Drug admin. - Outpatient [f]					X	X		X	X	X	X[f]	X[w] (weekly)			

Trial Period →	**Pre-screening Period**	**Run-In Period (Up to 3 days)**		**Treatment Period (6 weeks)**								**Extension Period (18 weeks)**			
Visit Days/Weeks →		**Day -3 to Day 0[a]**		**Day 0[b]**	**Week 2[c]**	**Week 3[c]**	**W3-W4[d]**	**Week 4[c]**	**Week 5[c]**	**Week 6[cc]**	**Week 6/ End-of-Trial[c]**			**W15-W20[t]**	**Week 25 (Week 7 +18 weeks)**
Visit Number →		**SC Visit 1**	**SC Visit 2**	**Visit 1 Clinic**	**Visit 2 (Outpt)**	**Visit 3 (Outpt)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 4 (Outpt)**	**Visit 5 (Outpt)**	**Visit 6 (Outpt)**	**Visit 7 Clinic**	**Monthly Visits (Outpt)**	**Un-scheduled Visits (Clinic)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 8 (Final, Clinic)**
Dose Number →				**Dose 1**	**Dose 2**	**Dose 3**	**N/A**	**Dose 4**	**Dose 5**	**Dose 6**					
Trial Procedure ↓					**Unscheduled Visits[u]**										
Physical examination [g]		X	X				X				X		X	X	X
Body weight and height		X													X
Vital Signs [h]		X	X				X				X		X	X	X
ECG/ECHO [i]		X	X (ECG)				X				X			X	X
MRI [j]	X	X													X
Prior and concomitant medicines [k]	X	X	X				X				X	X	X	X	X
Drug and alcohol test		X													
QuantiFERON TB test [j]		X													

Trial Period →	**Pre-screening Period**	**Run-In Period (Up to 3 days)**		**Treatment Period (6 weeks)**								**Extension Period (18 weeks)**			
Visit Days/Weeks →		**Day -3 to Day 0[a]**		**Day 0[b]**	**Week 2[c]**	**Week 3[c]**	**W3-W4[d]**	**Week 4[c]**	**Week 5[c]**	**Week 6[cc]**	**Week 6/ End-of-Trial[c]**			**W15-W20[t]**	**Week 25 (Week 7 +18 weeks)**
Visit Number →		**SC Visit 1**	**SC Visit 2**	**Visit 1 Clinic**	**Visit 2 (Outpt)**	**Visit 3 (Outpt)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 4 (Outpt)**	**Visit 5 (Outpt)**	**Visit 6 (Outpt)**	**Visit 7 Clinic**	**Monthly Visits (Outpt)**	**Un-scheduled Visits (Clinic)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 8 (Final, Clinic)**
Dose Number →				**Dose 1**	**Dose 2**	**Dose 3**	**N/A**	**Dose 4**	**Dose 5**	**Dose 6**					
Trial Procedure ↓					**Unscheduled Visits[u]**										
Clinical laboratory tests (incl CRP)– Central laboratory [l]		X	X	(X)[x]	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests (lipid panel) – Central Laboratory				X								X[aa]			X
Clinical laboratory tests (incl CRP) – Study Site/Clinic laboratory [m]	X[y]	X	X	(X)[x]			X				X		X	X	X
Biomarker testing, PK, and anti-rilonacept antibody – Central Laboratory [l]		X		(X)	X	X	X	X	X	X	X	X	X	X	X

Trial Period →	**Pre-screening Period**	**Run-In Period (Up to 3 days)**		**Treatment Period (6 weeks)**								**Extension Period (18 weeks)**			
Visit Days/Weeks →		**Day -3 to Day 0[a]**		**Day 0[b]**	**Week 2[c]**	**Week 3[c]**	**W3-W4[d]**	**Week 4[c]**	**Week 5[c]**	**Week 6[cc]**	**Week 6/ End-of-Trial[c]**			**W15-W20[t]**	**Week 25 (Week 7 +18 weeks)**
Visit Number →		**SC Visit 1**	**SC Visit 2**	**Visit 1 Clinic**	**Visit 2 (Outpt)**	**Visit 3 (Outpt)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 4 (Outpt)**	**Visit 5 (Outpt)**	**Visit 6 (Outpt)**	**Visit 7 Clinic**	**Monthly Visits (Outpt)**	**Un-scheduled Visits (Clinic)**	**Optional Interval Evaluation Visit (Clinic)**	**Visit 8 (Final, Clinic)**
Dose Number →				**Dose 1**	**Dose 2**	**Dose 3**	**N/A**	**Dose 4**	**Dose 5**	**Dose 6**					
Trial Procedure ↓					**Unscheduled Visits[u]**										
Pregnancy test [n]		X													
AE evaluations [o]				X	X	X	X	X	X	X	X	X	X	X	X
Medication diary dispensing [p]		X													
Medication diary compliance verification and reminder [q]			X	(X)[x]			X				X				X
Pericardial pain (11-pt Numerical Rating Scale)[r]	X	X	X	(X)[x]	X	X	X	X	X	X	X	X	X	X	X
PGA (QoL questionnaire) [s]		X		X			X				X			X	X
Dosing Procedure Questionnaire [z]						X				X				X	
Investigator (or designee) phone call/virtual visit [v]					X	X		X	X	X		X (monthly)			

ECHO = echocardiogram, ECG = electrocardiogram, ICF = informed consent form, MRI = magnetic resonance imaging, Outpt = outpatient, PGA = patient global assessment, pt = point, TB = tuberculosis, HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; HIV = human immunodeficiency virus

a. A second Screening visit (SCV2) should be performed within ~24h to 72h. Under special circumstances, the Investigator, in consultation with the Sponsor, can combine SCV1 and SCV2. The last Screening and Day 0 procedures may be performed on the same day, but SCR procedures must be completed prior to Study Drug administration.
b. Subjects who do not complete the Treatment Period (withdraw consent or are discontinued before they have completed 6 weeks treatment), must be asked to complete the procedures specified at the EoT Visit.
c. Weekly intervals refer to 7 ± 1 days. The interval between Study Drug administrations must be at least 5 days.
d. Subjects should return for an optional Interval Evaluation Visit at the clinic between approximately Week 3 and 4, as determined by the Investigator.
e. Including age at first attack, number of previous attacks, and duration of attacks.
f. Drug administration training of subjects is performed at Visit 1. Study Drug will be administered in the Study Site/Clinic at Visit 1. Study Drug administrations are performed by the subjects (self-administration) on Visits (Outpatient) 2, 3, 4, 5, and 6. Participation in the Extension Phase (optional) is determined at the Week 6/EoT Visit 7 by the Investigator. Subjects who are eligible and who are willing to participate will be consented during EoT Visit 7 at the Study Site/Clinic. Only subjects continuing treatment into the Extension Phase will receive Study Drug at Visit 7; Study Drug can be self-administered either as an outpatient or at the Study Site/Clinic (Site to provide Study Drug) depending on the logistics/timing of the EoT Visit 7 relative to the timing of weekly dosing. Timing for dose administration is per direction of the Investigator based upon the prescribing information and study-specified dosing intervals. Continued weekly Study Drug treatment during the EP will be outpatient administration.
g. Full physical examination including assessment of pericardial rub.
h. Vital signs must be obtained in the seated position and include oral temperature, respiratory rate, blood pressure, and pulse.
i. Central 12-lead ECG and echocardiogram reading (including assessment of pericardial effusion). At SCV2 only the ECG will be obtained. The Study Site/Clinic reading of the ECG and the ECHO at the time of the examination will be used by the Investigator for clinical decision-making. In addition, both the ECG and ECHO will be sent to a core laboratory for additional analysis.
j. Optional in Group 1 and 3. Required for Group 2.
k. At the SCV1, information related to concomitant medicine that subjects were taking during at least the 2 weeks prior to the visit will be captured. During the Treatment Period, changes in concomitant medication since the last Study Site/Clinic visit will be documented. During the EP, changes in pericarditis/concomitant medication will be assessed at Study Site/Clinic Visits and in monthly outpatient phone calls/virtual visits.
l. Biomarker, pharmacokinetics (PK) and anti-rilonacept antibody analysis samples will be drawn in all subjects and archived for future testing. . During each Visit at the Study Site/Clinic a sample for CRP will be obtained and sent to the central laboratory (or designated qualified laboratory) for analysis; at each Outpatient Visit; blood for central laboratory measurement of CRP will be obtained as described in the Laboratory Manual.
m. Hematology, chemistry, and urinalysis will be performed at the Study Site/Clinic laboratories, and results when available will be entered into the eCRF with appropriate reference values. Serology (HCVAb, HBsAg, HBcAb, HBsAb and HIV) and urine drug screen will be performed at SCV1 only.
n. To be eligible to continue in the trial, a negative urine pregnancy test must be documented at the SCV1. If the urine test is positive, additional Study Site/Clinic and/or central serum tests may be performed.
o. All AEs occurring after the subject receives the first dose of Study Drug will be captured in source records and eCRF.
p. At the SCV1, the Investigator or designee will instruct the subject about the use of the medication diary. The subject will be asked to complete entries into the medication diary during the Screening Period and Treatment Period. Only information on pain/rescue medication will be collected. Other concomitant treatments/medications are not required to be captured.

q. At the SCV2 and all subsequent visits at the Study Center, the Investigator or designee will review the Diary entry information to verify subject compliance. If the last screening visit occurs at a different day than Visit 1, the review will also be performed at Visit 1. Diary documentation will end at the End-of-Trial visit (Visit 7).
r. Subject assessment of pericardial pain using a validated 11-point Numerical Rating Scale. The assessment will be performed on-site during clinic visits and as part of a telephone call/virtual visit during outpatient treatment weeks. If the last screening visit occurs at a different day than Visit 1, the assessment will also be performed at Visit 1, prior to Study Drug treatment.
s. Adult subjects only. Subject global assessment of overall well-being will be assessed using a validated QoL Questionnaire (see Section 8.3). The assessment will be performed on-site during clinic visits. If SCV2 occurs at a different day than Visit 1 (Day 0), the global assessment will also be performed at Visit 1, prior to Study Drug administration.
t. Subjects may return for an optional EP Interval Evaluation Visit at the clinic between Week 15 and 20 (8 to 13 weeks after Visit 7), as determined by the Investigator.
u. Subjects reporting worsening of pericarditis symptoms or AEs may be brought in at the discretion of the Investigator for an Unscheduled Visit at any time during the Treatment Period. Any subject who is not responding to treatment (e.g., no reduction in pericardial pain compared to baseline, no decrease in CRP levels, etc.) and who is therefore considered by the Investigator to be a "Treatment Failure" may be withdrawn from further Study Drug treatment at the discretion of the Investigator and receive rescue therapy for their pericarditis according to standard of care as per Investigator decision; these subjects will be followed for safety for the remainder of the 6-week Treatment Period.
v. At weekly Investigator (or designee) phone calls/virtual visits during the Treatment Period, Study Drug compliance, medication diary compliance, and laboratory sample collection will be checked. The subjects will be asked using non-leading questions about any AEs occurring since the last contact (phone call/virtual visit or site visit), and NRS pain assessment will be performed. Investigator (or designee) phone calls/virtual visits will be performed monthly during the during the EP to perform NRS pain assessments, collect AE information, and review pericarditis/concomitant medications. If scheduled, in-person Study Site/Clinic Visits (Unscheduled Visits or Evaluation Visits) can replace the phone calls/virtual visits.
w. During the Extension Period, Study Drug treatment is weekly by self-administration, and the study nurse visits to the home and Investigator (or designee) phone calls/virtual visits are monthly.
x. Visit 1 will coincide with SCV2. In case Visit 1 is separated from SCV2, SCV2 clinical laboratory blood sampling and subject NRS pericardial pain rating must be repeated prior to Study Drug dosing.
y. Per Standard of Care.
z. Adult subjects only. The dosing preparation and administration questionnaire must be completed in the presence of Study Staff (via virtual visit) or visiting nurse.
aa. This lab will be drawn only during the first monthly Extension Period visit.

8.2. Code Fragments

Estimation of intra- and inter-subject variability of changes from baseline in CRP or NRS:

```
proc mixed data=…;
  by partno;
  class avisitn usubjid;
  model chg = avisitn;
  repeated avisitn / subject=usubjid type=VC;
  random usubjid;
run;
```

The input dataset will have the results from all scheduled post-baseline visits.

For estimates of intra- and inter-subject variability of CPR and NRS prior to treatment use a similar model replacing CHG with AVAL as the model outcome. The input dataset will have the results from all scheduled pre-baseline visits.

Variance components are then found in the ODS dataset CovParms. Inter-subject variance corresponds to the covariance parameters USUB JID and intra-subject, to parameter AVISITN. Square root must be taken of the estimate to arrive at the Standard Deviation.

8.3. Calculation of Global Physical and Global Mental scores for the QoL Questionnaire

This study employs PROMIS v1.2 questionnaire that is scored as follows.

1. Recode the response to question 10 (How would you rate your pain on average) as follows:

Response	Recoded Response
0	5
1, 2, 3	4
4, 5, 6	3
7, 8, 9	2
10	1

2. Calculate the Global Physical Health raw score by summing the responses for questions 3, 7, 10, and 9. If not all of these questions are answered, the score will be missing.
3. Calculate the Global Mental Health raw score by summing the responses for 2, 4, 5, and 8. If not all of these questions are answered, the score will be missing.

Global Physical Health	
Raw summed score	**T-score**
4	16.2
5	19.9
6	23.5
7	26.7
8	29.6
9	32.4
10	34.9
11	37.4
12	39.8
13	42.3
14	44.9

15	47.7
16	50.8
17	54.1
18	57.7
19	61.9
20	67.7

4. Use the following tables to convert the global raw scores to the T-scores that will be used in analysis:

Global Mental Health	
Raw summed score	**T-score**
4	21.2
5	25.1
6	28.4
7	31.3
8	33.8
9	36.3
10	38.8
11	41.1
12	43.5
13	45.8
14	48.3
15	50.8
16	53.3
17	56.0
18	59.0
19	62.5
20	67.6